guna
medical device

GUNA COLLAGEN MEDICAL DEVICES

Injection treatment of osteo-arthro-myofascial pathologies [1]

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1. Milani L. Physiological Regulating Medicine 2010; 3-15

OSTEO-ARTHRO-MYOFASCIAL PATHOLOGIES IN EUROPE

It has been estimated that **15-20%** of the general population is affected by **pathologies of the Musculo-Skeletal System**, better defined as arthro-rheumatic disorders, representing **70%** of the patients with chronic pain. [1,2]

These numbers are **expected to increase in the following years** because of many factors, including [1]:

- **longer life expectancy**
- **general average increase in body weight**
- **greater propensity to be sedentary in the over-50s**
- **higher incidence of amateur sporting activity and resulting injuries** (mainly between 20 and 45 years of age)
- **abuse of NSAIDs**
- **unbalanced diet**, usually **high in proteins**

Osteo-arthro-myofascial pathologies are primarily characterized by a **collagen deficiency**. The physiological structure, qualitative and quantitative composition of collagen determine the characteristics of the connective tissues. [1]

1. Milani L. Physiological Regulating Medicine 2013; 21-36
2. Jordan KM. et al. Ann Rheum Dis 2003; 62: 1145-1155

MUSCULOSKELETAL DISORDERS

- Musculoskeletal disorders constitute a **heterogeneous group of diseases of the osteoarticular apparatus**, associated with pain symptoms and functional limitations. This group includes acute and short-term diseases, as well as chronic pathologies such as low back pain (lumbago), osteoarthritis, osteoporosis, and rheumatoid arthritis. (1)

- Musculoskeletal disorders can have a **significant impact on an individual's social life and lead**, in different ways and at different times, **to disability and inability to work**. (1)

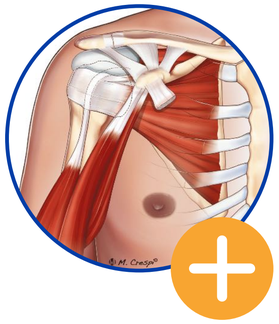
- The **high incidence** of these diseases **causes high costs** for national health systems. (2)

- **Over the past twenty years**, there has been increasing interest and success of **conservative treatments** of musculoskeletal diseases, including those **interventions aimed at repairing and regenerating musculoskeletal tissues**, which are collectively referred to as **Functional Tissue Engineering.** (3)

- More recently, in the field of **Functional Tissue Engineering**, a new approach is represented by the use of **bio-scaffolds of the extracellular matrix containing type I collagen and ancillary substances, to be administered by injection (Guna Collagen Medical Devices).**

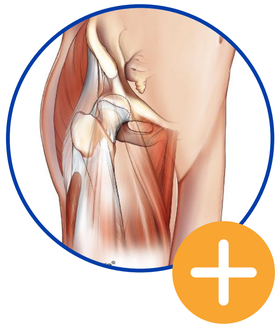
1. Epicentro Istituto Superiore di Sanità. https://www.epicentro.iss.it/muscolo-scheletriche/
2. Strategia nazionale « Malattie muscolo-scheletriche » 2017-2022 Elaborato ed edito dalla Lega svizzera contro il reumatismo (LSR). Available online at https://www.rheumaliga.ch/assets/doc/CH_Dokumente/ueber-uns/Strategia_nazionale_Mallatie_musculo-scheletriche_Versione_breve.pdf
3. Butler DL, et al. J Biomech Eng 2000; 122 (6): 570-575

MOST FREQUENT PATHOLOGIES OF UPPER AND LOWER LIMBS



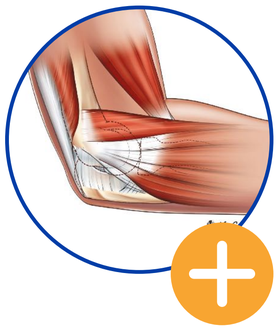
SHOULDER

Osteoarthritis: 16.1%-20.1% prevalence in adults over 65 years [1]
Rotator cuff lesions: 51% in individuals over 80 years [2]



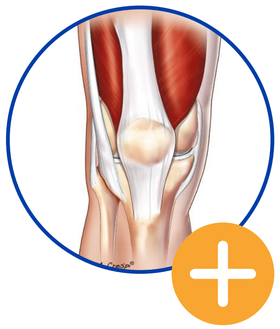
HIP

Coxarthrosis: 11% prevalence [6,7]



ELBOW

Epicondylitis: 1-3% prevalence [3]

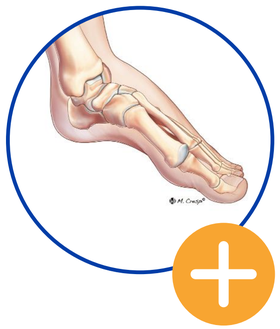


KNEE

Gonarthrosis: 24% prevalence [6,7]

HAND/WRIST

Osteoarthrosis: 19% prevalence [4]
Rhizoarthrosis: 20% prevalence in the adult population [5]

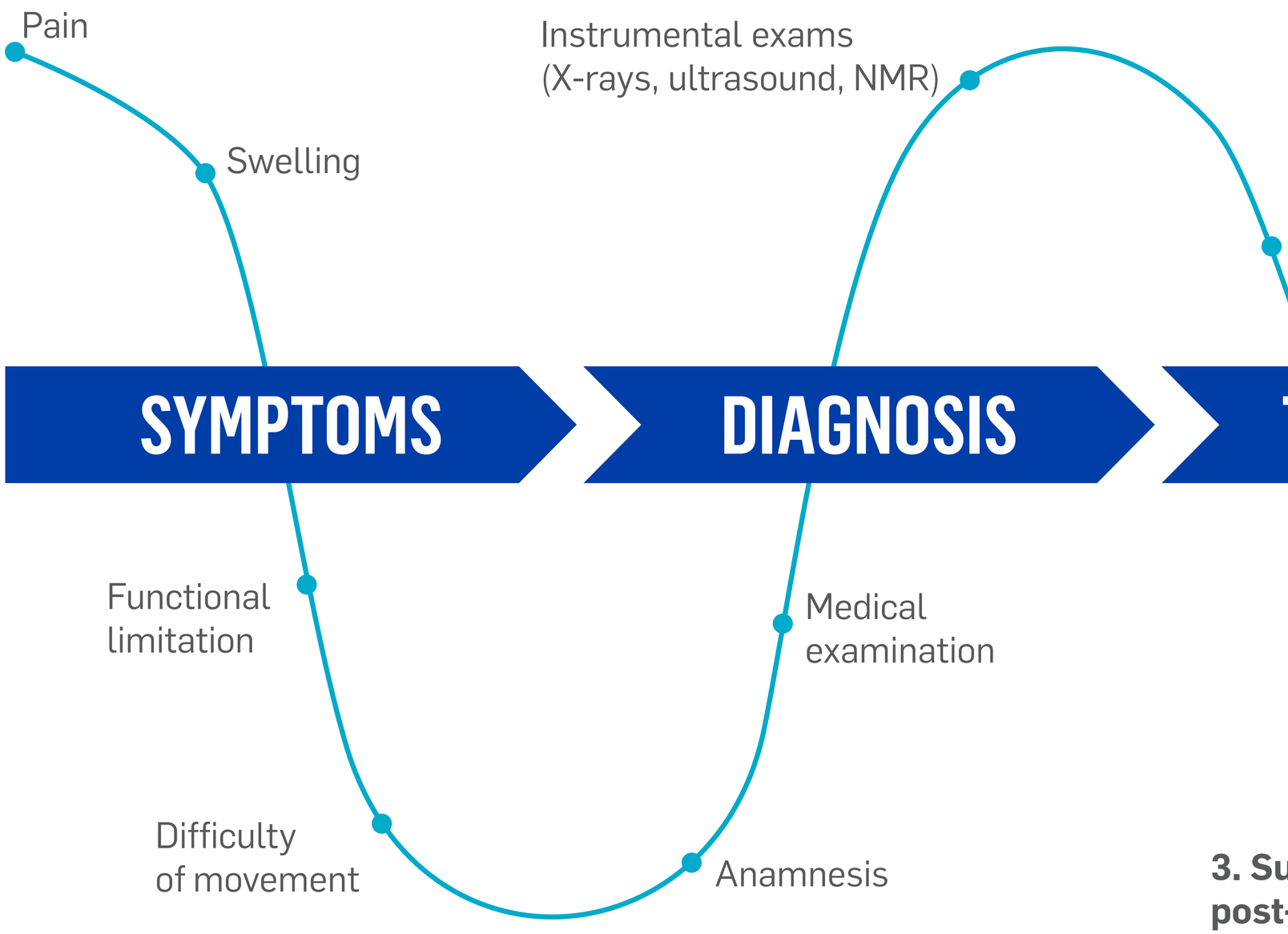


ANKLE/FOOT

Osteoarthritis: 9% prevalence [8]

1. Ansok CB., Muh SJ. Orthopedic Research and Reviews 2018; 10: 9-18
2. Castagna A. et al. Giornale Italiano di Ortopedia e Traumatologia 2015; 41: 6-14
3. Corrado B. et al. Muscles, Ligaments and Tendons Journal 2019; 9 (4): 584-589
4. Ramonda R. et al. Artrosi: aspetti epidemiologici, clinici e classificativi. Rheumalab. https://www.rheumalab.it/site/artrosi-aspetti-epidemiologici-clinici-e-classificativi
5. Brunato F. Physiological Regulating Medicine 2021; 3-12
6. Migliore A., Ravasio R. Physiological Regulating Medicine 2020; 3-7
7. Fernandes L. et al. Ann Rheum Dis 2013; 72: 1125-1135
8. DiStefano J.G., Pinney S. Semin Arthro 2010; 21: 218-222

PATIENT JOURNEY
MUSCULO-TENDINOUS & OSTEOARTICULAR DISEASES



1. Reduction of inflammation and pain (NSAIDs, cortisone and/or hyaluronic acid injections, collagen injections, food supplements, mesotherapy, ultrasound, ionophoresis, etc.)

2. Recovery of strength and mobility (physiotherapy, shock waves, etc.)

3. Surgical approach + post-surgery therapy (when conservative treatments fail and/or in cases of tendon ruptures)

TREATMENT

Muscle pain (myalgia). https://www.my-personaltrainer.it/salute/dolore-muscolare-mialgia.html

Currently, available treatments for **arthro-rheumopathies** are numerous and diverse, including both **conservative and non-conservative treatments, to be carried out individually or associated one with each other:**

1. **MEDICAL DEVICES/EQUIPMENTS** (e.g., ultrasound therapy, magnetotherapy, laser therapy, TENS, acupuncture, moxibustion, Oxygen-Ozone therapy, shock waves, injections of hyaluronic acid, **collagen**)

2. **PHARMACOLOGICAL THERAPIES** [e.g., COX-2 inhibitors, NSAIDs, salicylic acid, paracetamol, corticosteroids (including intra-articular or mesotherapy injections)]

3. **PHYSICAL REHABILITATION**

4. **PROSTHETIC IMPLANTS**, mobile (mainly hip, knee, shoulder implants) or fixed (arthrodesis)

CONSERVATIVE

NON-CONSERVATIVE

Among the treatments of painful and degenerative pathologies of the musculo-skeletal apparatus, we can find the previously-mentioned **injectable Guna Collagen Medical Devices (conservative treatment)**.

Milani L. Physiological Regulating Medicine 2013; 21-36

COLLAGEN:
WHAT IT IS, WHAT IT DOES

Collagen is the most abundant protein in the body [1] and it represents:

- **5-6%** of adult human body weight [1]
- **30%** of the total protein mass of higher animals [2,3]
- **90%** of the body's collagen is type I collagen [4]
- **Location:** skin, tendons, joint capsules, ligaments, cartilage, bones, muscles, teeth, extracellular matrix [1,3,4]
- **Properties:** strength, rigidity, resistance, and flexibility [5]

Collagen acts as a bio-scaffold that SUPPORTS, STRUCTURES and STABILISES the somatic scaffolding [4]

1. Ruiu DE. Advanced Therapies 2012; 1: 30-39
2. Verzàr F. International Review of Connective Tissue Research 1964; 2: 243-300
3. Martin Martin LS. et al. BMC Musculoskelet Disord 2016; 17: 94
4. Milani L. Physiological Regulating Medicine 2019; 3-18
5. Milani L. Physiological Regulating Medicine 2010; 3-15

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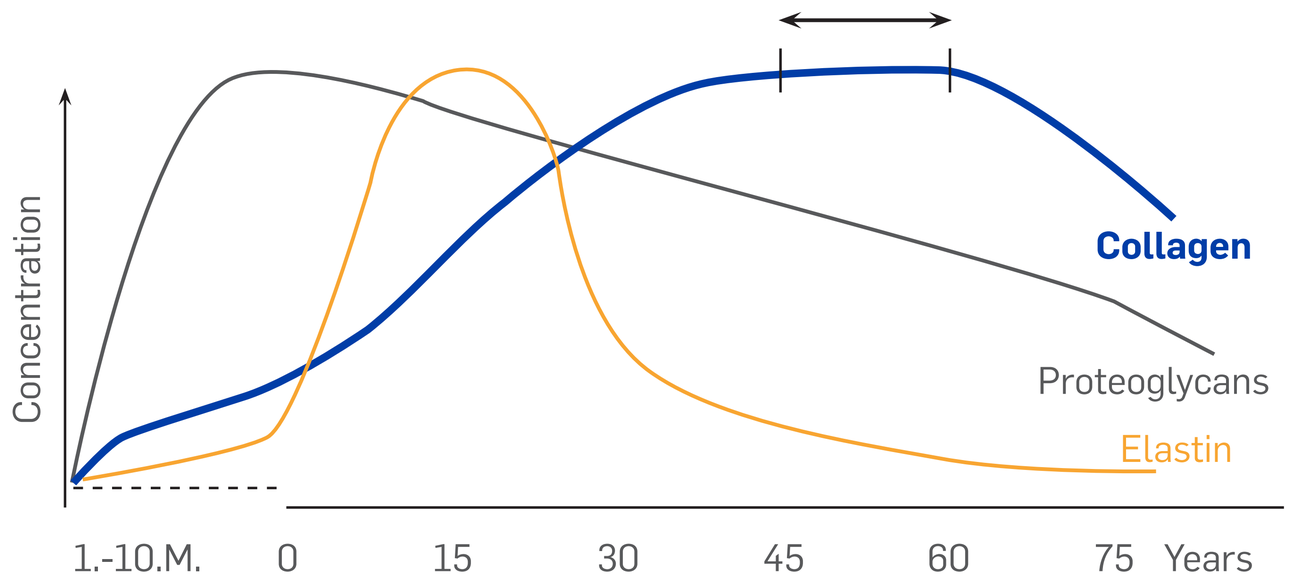
COLLAGEN BIOSYNTHESIS DURING THE AGING PROCESS

In humans, collagen biosynthesis starts decreasing from 55-60 years of age



At a locomotor apparatus level, **thinning and degeneration of cartilage surface appears, generating arthrosis**, while **tendon and ligament structures** lose elasticity, which leads to and **tendinosis and tendinopathies** of various grade.

Biosynthesis of collagen, proteoglycans and elastin correlated to aging.

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Ottaviani M. Physiological Regulating Medicine 2018; 19-28

GUNA COLLAGEN MEDICAL DEVICES

A range of 13 different medical devices containing:

Collagen of swine (porcine) origin

- **Swine tissues** contain **high amounts of collagen**, about 50% [1,2]
- Swine collagen is **structurally more similar to human collagen**, compared to other sources [3,4]
- **Each vial of Guna Collagen Medical Device (2 ml)** contains **100 µg of collagen** [5]

Ancillary substances of plant or mineral origin

- **Support the mechanical action of collagen**
- They have a specific **tropism for those anatomical regions** they are intended to be applied to, ensuring **greater effectiveness and specificity** of each product. [3]

Guna Collagen Medical Devices act as **bio-scaffolds** of the **extracellular matrix. They support tissue repair and regeneration processes** when the connective component is degraded by overuse, ageing or injuries, which are frequently the cause of musculoskeletal pain. [6]

Guna Collagen Medical Devices are Class III Medical Devices
1. Milani L. Physiological Regulating Medicinel 2010; 3-15
2. Martin Martin LS. et al. BMC Musculoskelet Disord 2016; 17: 94
3. Bernardini G. La Med Biol 2018; 2: 15-23
4. Silvipriya KS. et al. Journal of Applied Pharmaceutical Science 2015; 5 (03): 123-127
5. Guna Collagen Medical Devices. IFU
6. Randelli PS. GIOT 2010; 36: 211-222

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BENEFITS OF
GUNA COLLAGEN MEDICAL DEVICES

GUNA COLLAGEN MEDICAL DEVICES are administered via injections in the **intra-articular or extra-articular joint compartments**.

- **They improve the histological structure** of collagen in the anatomical area where injected. (1)
- **They provide a mechanical support reducing joint hypermobility and pain, improving movement and quality of life.** (1)
- They provide **structural support**. (1)
- They help **limit the physiological degeneration of joints and tissues** and **counterbalance the damage** caused by ageing processes, postural defects, concomitant chronic diseases, trauma and injury, and pollutants. (1)
- **Safety and tolerability are guaranteed** by **collagen biocompatibility** as well as by the **intrinsic biodegradability** of endogenous collagenases, which makes **exogenous collagen ideal for biomedical applications**. (2,3)

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1. Bernardini G. La Med Biol 2018; 2: 15-23
2. Chattopadhyay S., Raines RT. Biopolymers 2014; 101: 821-833
3. Deshmukh SN. et al. J Oral Maxillofac Pathol 2016; 20 (2): 276-283

QUALITY AND SAFETY OF
GUNA COLLAGEN MEDICAL DEVICES

- The extraction and sterilisation processes developed and carried out at Guna S.p.a. production plant ensure a **pure product with standardised chemical and physical characteristics**.

- **The injection of Guna Collagen Medical Devices is proven to be safe and well tolerated.**

It acts in accordance with physiology as it does **not induce micro-inflammatory processes and consequent fibrotic reactions**, as in the case of prolotherapy.

Milani L. Physiological Regulating Medicine 2010; 3-15

GUNA COLLAGEN MEDICAL DEVICES:
A TAILOR-MADE TREATMENT

Treatment with GUNA COLLAGEN MDs can be **customised** based on the **anatomical area to be treated**

9 specific
COLLAGEN MEDICAL DEVICES

- **MD-SHOULDER**
- **MD-HIP**
- **MD-KNEE**
- **MD-SMALL JOINTS**
- **MD-LUMBAR**
- **MD-ISCHIAL**
- **MD-NECK**
- **MD-POLY**
- **MD-THORACIC**

4 non-specific
COLLAGEN MEDICAL DEVICES

- **MD-TISSUE**
- **MD-MUSCLE**
- **MD-NEURAL**
- **MD-MATRIX**

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Milani L. Physiological Regulating Medicine 2010; 3-15

BASICS OF INJECTION TECNIQUE

GUNA COLLAGEN MEDICAL DEVICES

GENERAL RULES

- Obtain **patient's informed consent**.
- **Replace the needle** used to draw the product from the vial with the specific needle for the injection to be performed.
- **Identify landmarks, to be marked** using a dermographic pen if necessary.
- **Disinfect the skin thoroughly** with iodopovidone or chlorhexidine, starting from the entry point to be used, progressively enlarging the disinfected area with eccentric movements.
- **Use sterile gloves** in case of intra-articular injections.
- Apply a **medicated patch onto the injection site**.
- The injection **may cause symptoms such as burning/pain in the injection site**, which generally **disappear within 5-10 minutes after the injection**.

SYRINGES

• 2.5 ml • 5 ml • 10 ml

NEEDLES

• 26G x 13 mm • 22G x 32 mm • Spinal needle 20G x 90 mm

PROTOCOLS

- When required by the specific clinical situation, **different Collagen Medical Devices can be mixed together in one syringe**.
- According to the clinical experience of many users, **5 weekly infiltrations** are **sufficient** to achieve a **significant improvement in symptoms.**
- **In acute cases**, the injections can be carried out **twice a week** for the first two weeks.

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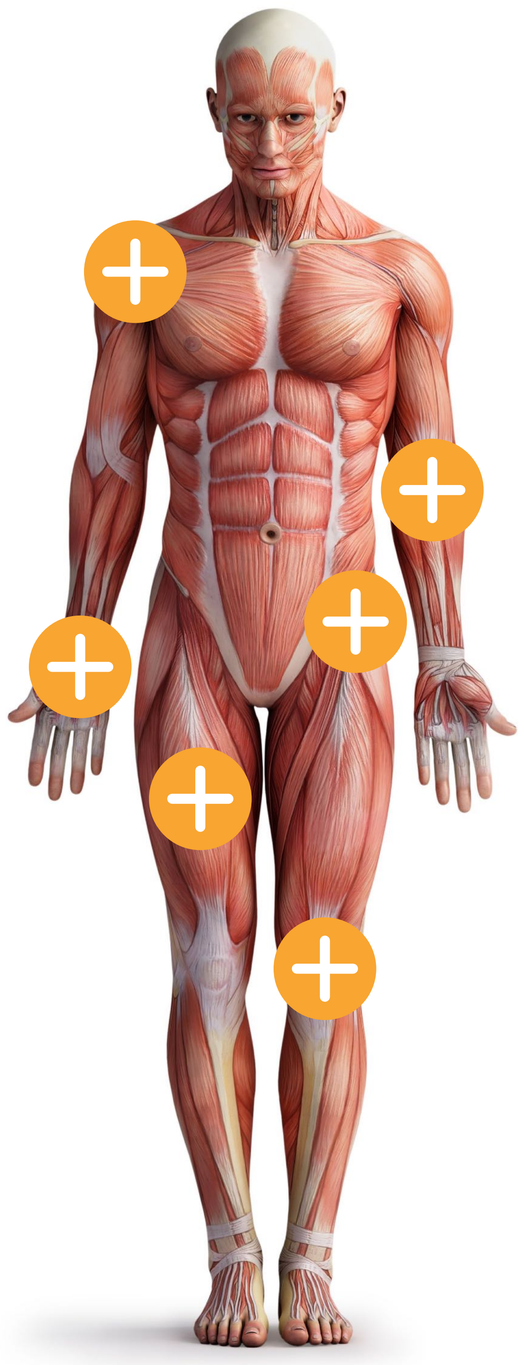
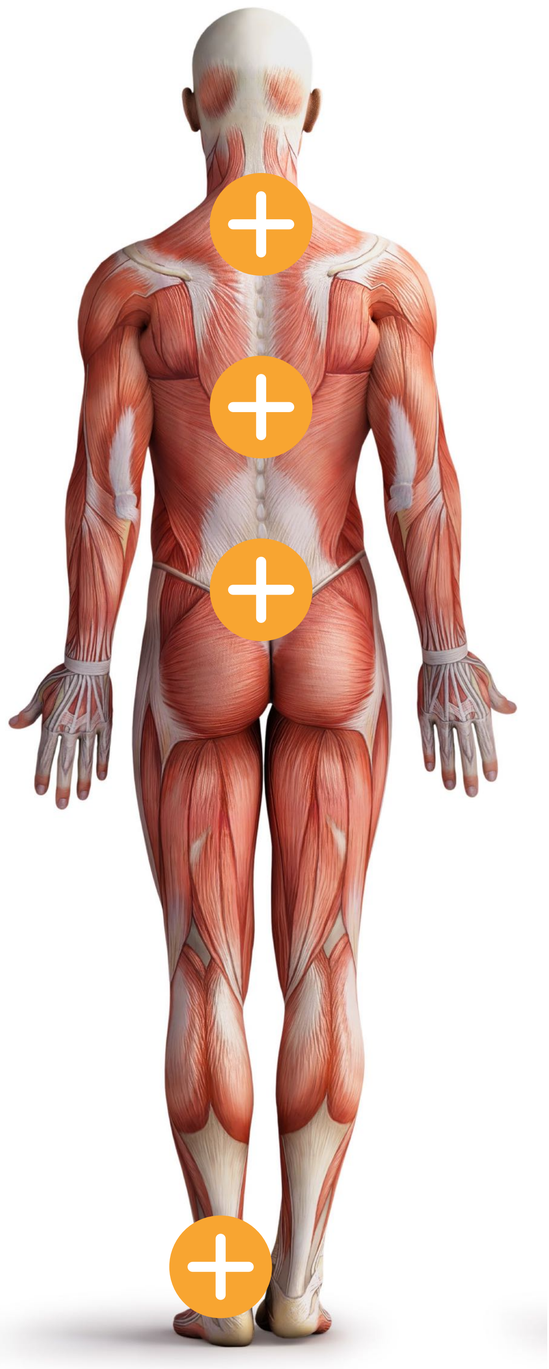
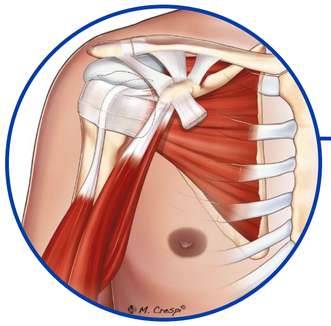
MAIN INDICATIONS OF
GUNA COLLAGEN MEDICAL DEVICES





MAIN INDICATIONS OF
GUNA COLLAGEN MEDICAL DEVICES



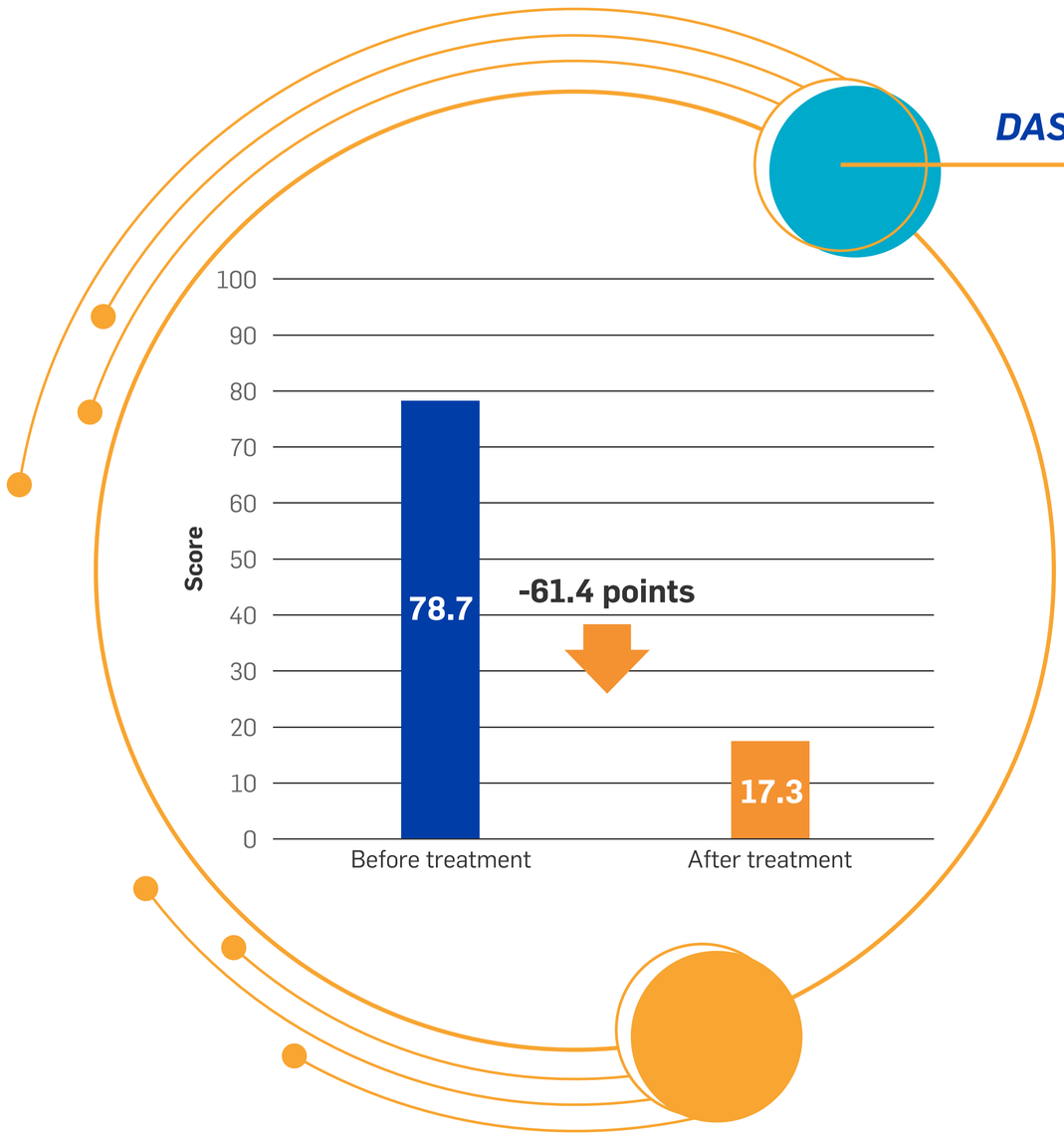
SHOULDER

PATHOLOGIES	*GUNA COLLAGEN MEDICAL DEVICES*
Osteo-articular pathologies	
Glenohumeral osteoarthritis	**MD-SHOULDER** ⊕
Acromioclavicular osteoarthritis	**MD-SHOULDER** ⊕
Sternoclavicular osteoarthritis	**MD-SHOULDER** ⊕
Soft tissue disorders	
Rotator cuff tendinopathy	**MD-TISSUE** ⊕
Tendinopathy of the long head of the biceps brachii	**MD-TISSUE** ⊕
Capsulitis	**MD-TISSUE** ⊕ *(with* **MD-NEURAL** ⊕ *in case of acute pain)*

GUNA COLLAGEN MEDICAL DEVICES:

Efficacy in the treatment of rotator cuff syndrome

Disability reduction after injection treatment with **MD-SHOULDER**



- The vast majority of patients appreciated **greater joint mobility** after the first 3-4 administrations.
- The **effectiveness on pain** was **quite rapid**.
- All patients have significantly **reduced consumption of other drugs**.
- **No side effect after administration was reported**.

The study was conducted on 124 patients with disorders strictly localised in the shoulder region (rotator cuff impingement syndrome with possible tendon lesions). The patients received intra-articular injections of MD-SHOULDER twice a week for 5 consecutive weeks. A specific questionnaire was administered at the first visit and at the end of the treatment.

DASH = Disability for Arm, Shoulder and Hand

Download the study

Graph elaborated from text.

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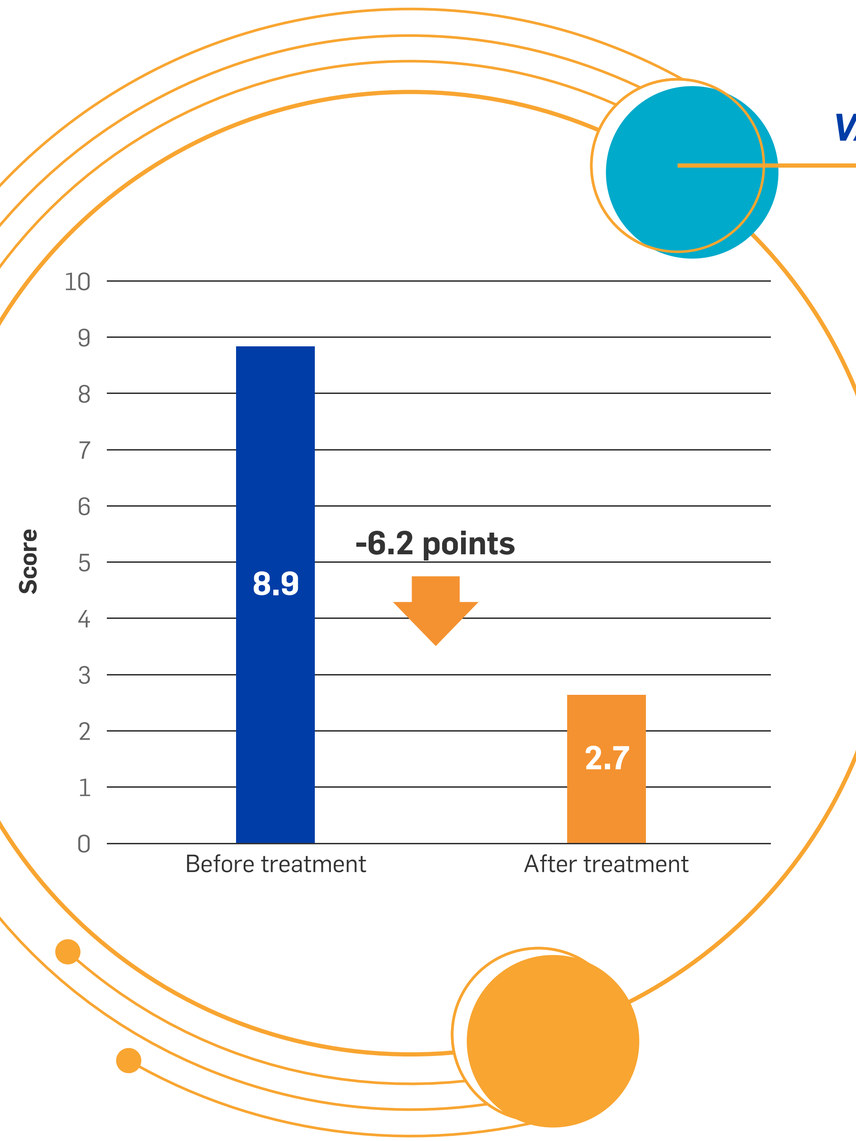
Ottaviani M. Physiological Regulating Medicine 2018; 19-28

GUNA COLLAGEN MEDICAL DEVICES:

Efficacy in the treatment of calcific supraspinatus tendinitis

Pain reduction after treatment with **MD-SHOULDER**

VAS scale before and after treatment



Study conducted on 10 patients with calcific tendinopathy of the supraspinatus tendon. Patients received weekly MD-SHOULDER ultrasound-guided infiltrations for 4 consecutive weeks. Evaluations were conducted before the treatment and 2 weeks after the last infiltration.

VAS = Visual Analogue Scale

Graphic elaboration from Tab.1

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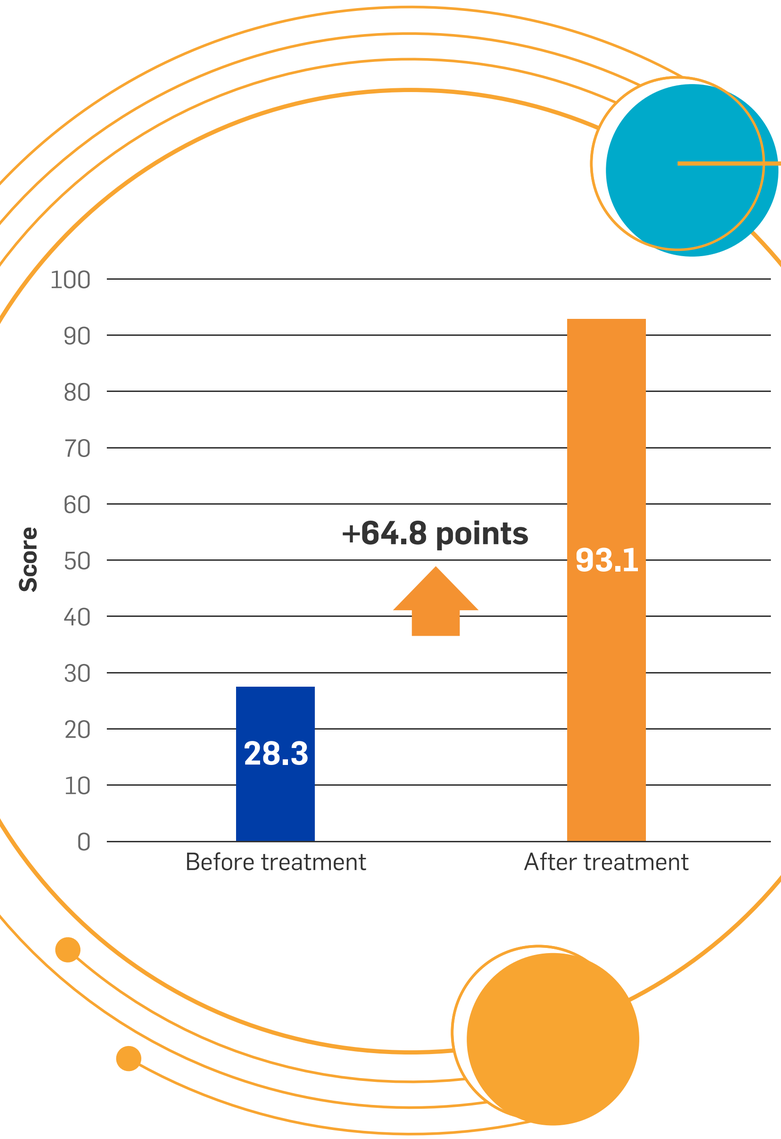
Zurita Uroz N. Physiological Regulating Medicine 2016-2017; 15-17

GUNA COLLAGEN MEDICAL DEVICES:

Efficacy in the treatment of calcific supraspinatus tendinitis

Joint functionality improvement after treatment with **MD-SHOULDER**

Constant-Murley score before and after treatment



Overall, reduction and disappearance of calcifications were observed after treatment with MD-SHOULDER.

Study conducted on 10 patients with calcific supraspinatus tendinitis. Patients received weekly MD-SHOULDER ultrasound-guided infiltrations for 4 consecutive weeks. Evaluations were conducted before treatment and 2 weeks after the last infiltration.

Graphic elaboration from Tab.2.

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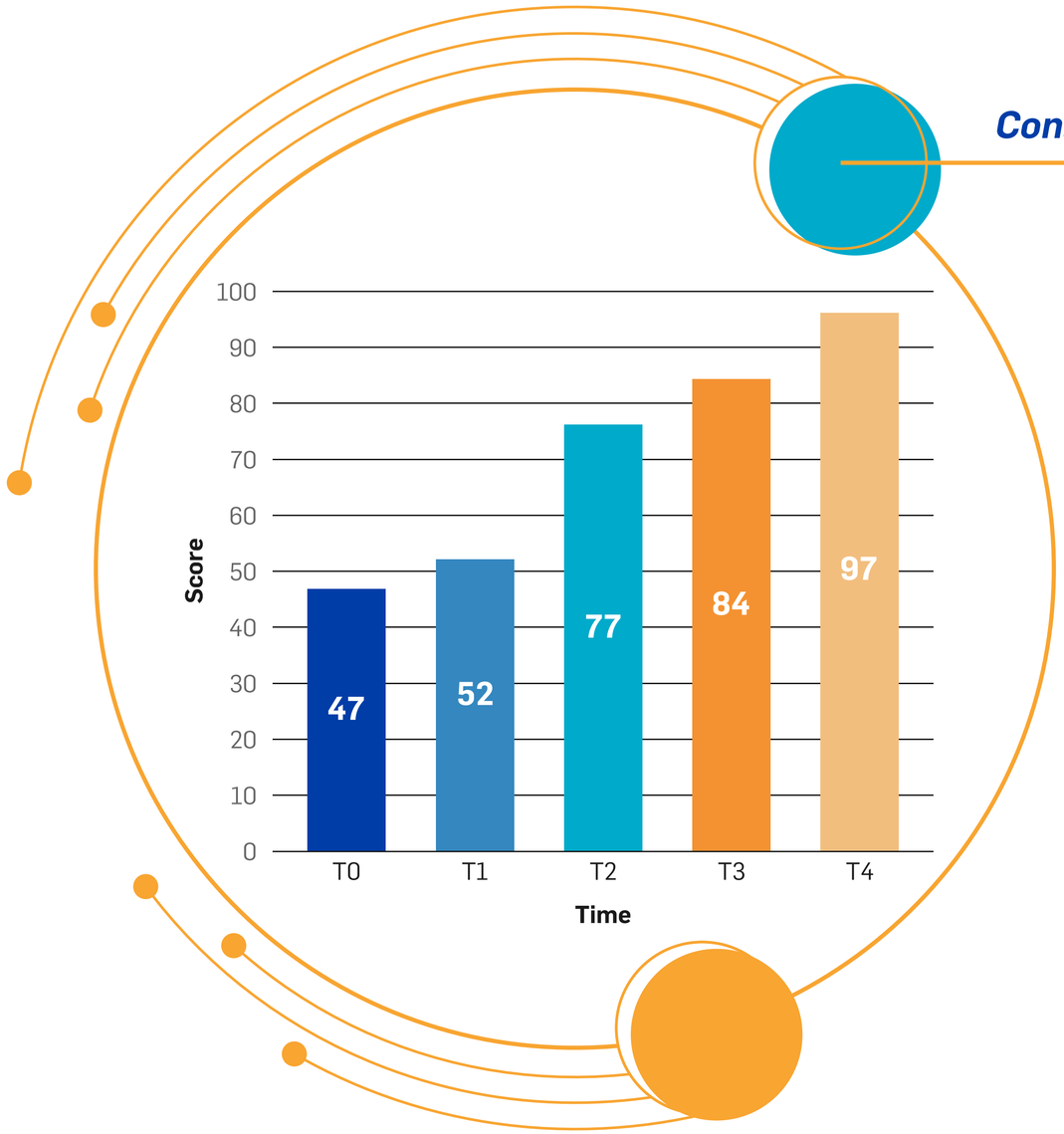
Zurita Uroz N. Physiological Regulating Medicine 2016-2017; 15-17

GUNA COLLAGEN MEDICAL DEVICES:

Efficacy in partial-thickness tears of the supraspinatus tendon

Pain and disability improvement after treatment with **MD-TISSUE**



Constant-Murley score evaluated during treatment

The patient observed in this clinical case was **fully compliant. No adverse events** have been reported after collagen injections.

Study conducted on 1 patient with partial-thickness tears of the supraspinatus tendon. The patient was treated with a series of four intra-tendinous, ultrasound-guided injections of type I collagen at weekly intervals, in combination with physical therapy. The patient was evaluated at the time of enrolment (T0), right before the third injection (T1), and 1 month (T2), 3 months (T3) and 18 months (T4) after the fourth injection.

Graphic elaboration of Fig.1 and Tab.1.

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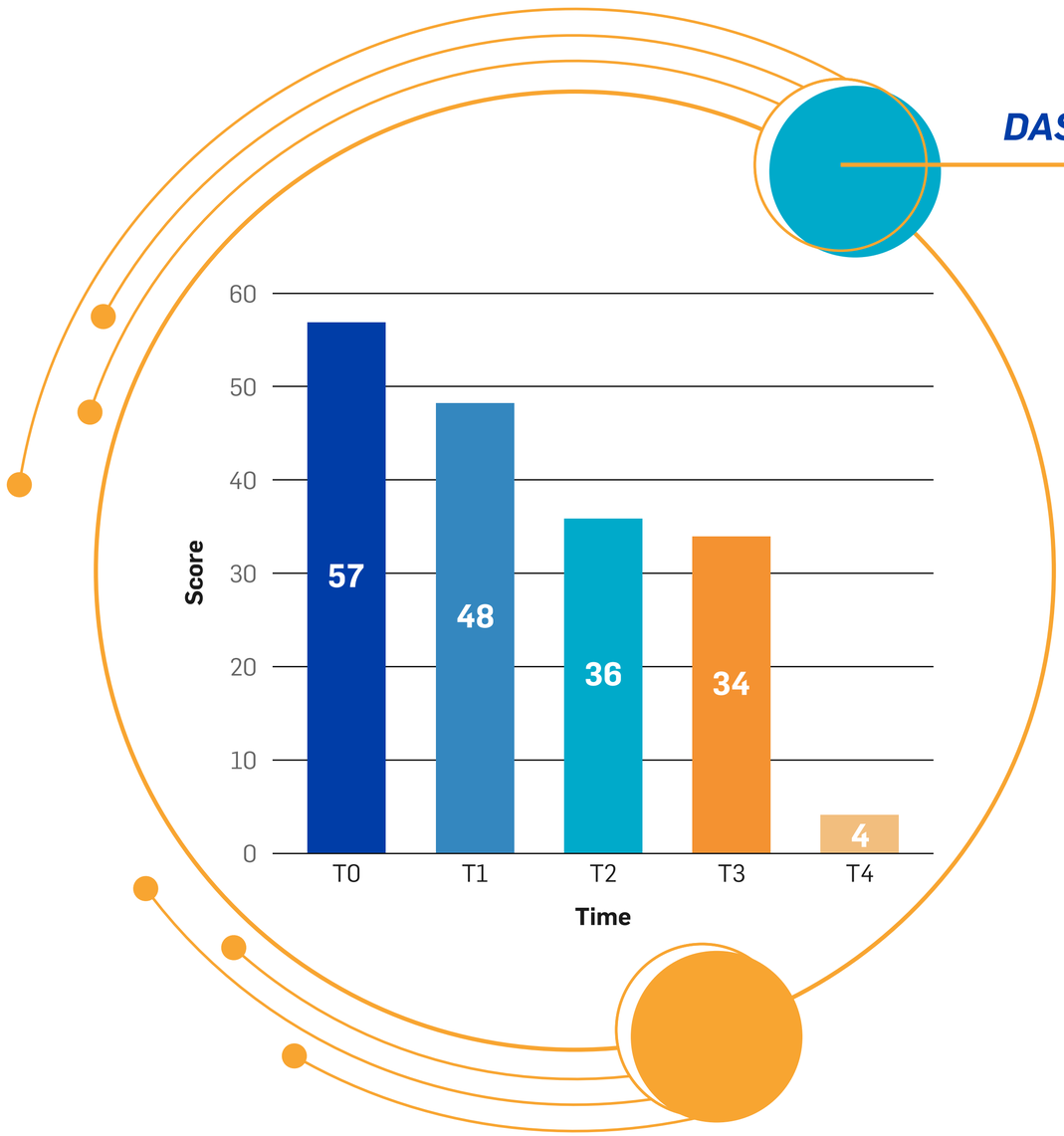
Corrado B. et al. Oxford Medical Case Reports 2020; 11: 408–410

GUNA COLLAGEN MEDICAL DEVICES:

Efficacy in partial-thickness tears of the supraspinatus tendon

Disability reduction after treatment with **MD-TISSUE**



DASH Questionnaire used during the treatment

Ultrasound scanning showed **gradual healing of the injury and regeneration of the tendon structure.**

Study conducted on 1 patient with partial-thickness tears of the supraspinatus tendon. The patient was treated with a series of four intra-tendinous, ultrasound-guided injections of type I collagen at weekly intervals, in combination with physical therapy. The patient was evaluated at the time of enrolment (T0), right before the third injection (T1), and 1 month (T2), 3 months (T3) and 18 months (T4) after the fourth injection.

DASH = Disability for Arm, Shoulder and Hand

Graphic elaboration of Fig.1 and Tab.1.

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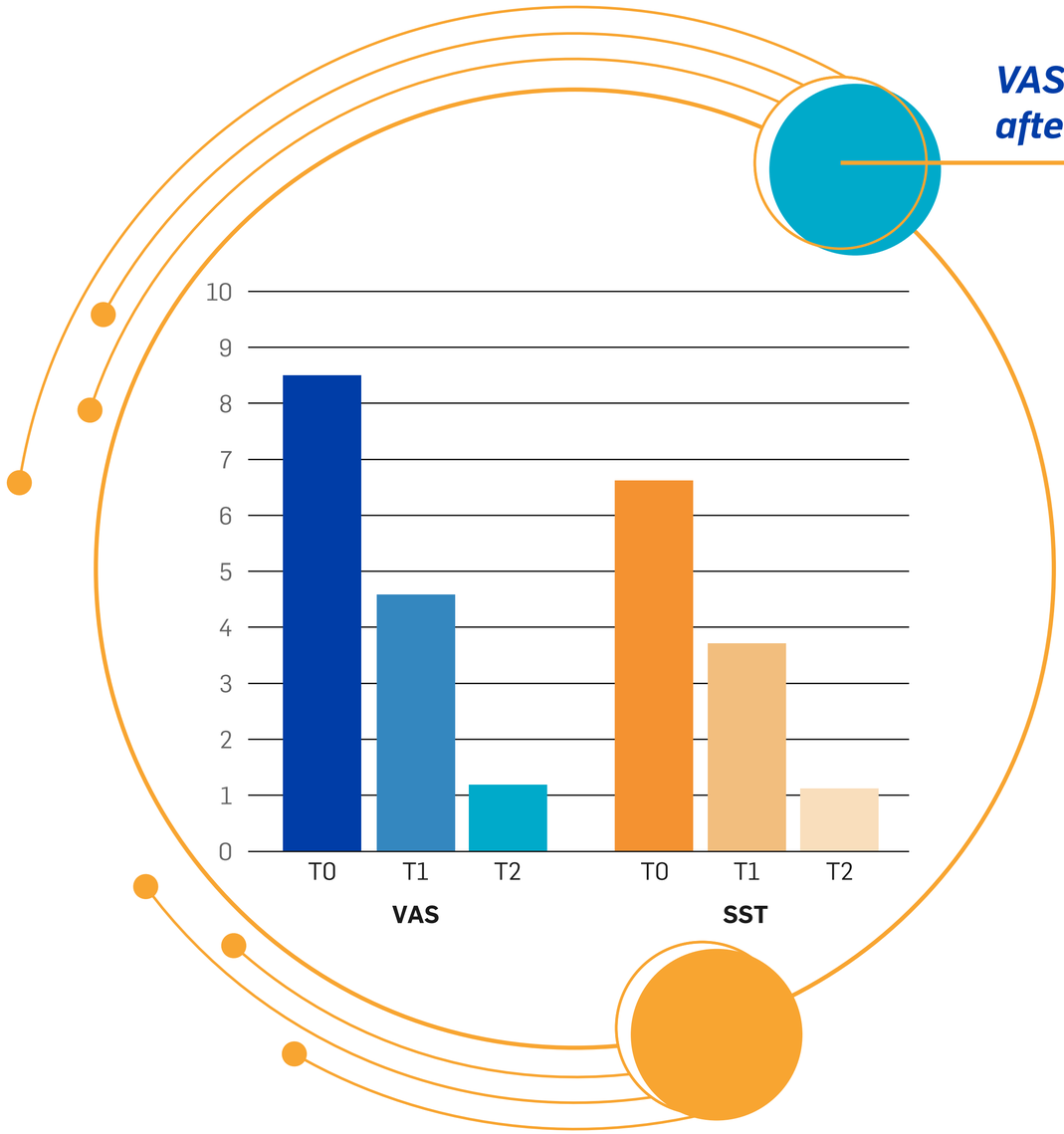
Corrado B. et al. Oxford Medical Case Reports 2020; 11: 408–410

GUNA COLLAGEN MEDICAL DEVICES:

Efficacy in the treatment of shoulder osteo-articular pain

Pain and joint functionality improvement starting from the first month of treatment with **MD-SHOULDER + CHELT therapy**



VAS scale and SST score at baseline and 1 and 4 months after beginning of treatment

The combination of the two methods reduced pain by 50% on average after the first month of treatment. This result is maintained without relapses, even after 4 months.

This observational study was conducted on 20 patients with osteo-articular pain in the shoulder. The patients were treated with MD-SHOULDER, and after each injection they received a CHELT therapy session. The complete therapeutic cycle was constituted by 6-10 injections spread over 4-6 weeks. Evaluations were conducted at T0 (initial evaluation), at T1 (after 1 month) and at T2 (4 months after starting the treatment).

VAS = Visual Analogue Scale
SST = Simple Shoulder Test
CHELT =Cryo High Energy Laser Therapy

Graphic elaboration of Tab.3.

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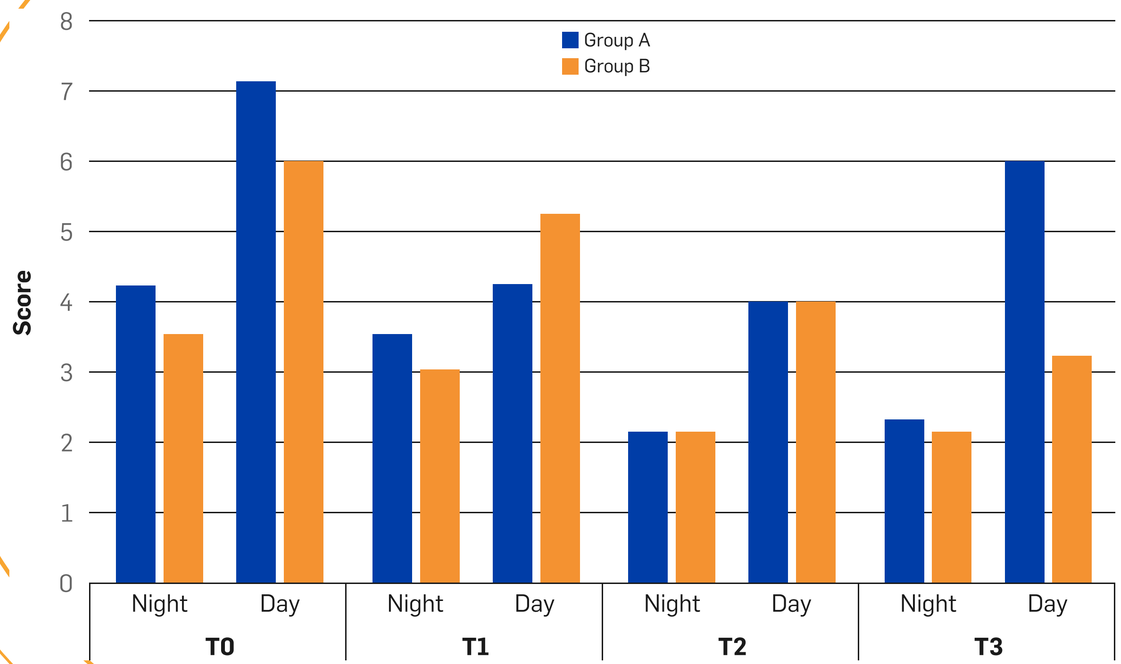
Feninno D., Bonacina A. La Med Biol 2017; 2: 37-42

GUNA COLLAGEN MEDICAL DEVICES:

Efficacy in the treatment of shoulder pain in post-stroke hemiplegic patients

Reduction of daytime and night time pain after treatment with **MD-SHOULDER**

WBS scale at 1, 6 and 10 months



Study conducted on 40 patients aged 55-75 years with recent ischemic stroke; clinical and instrumental diagnosis of painful shoulder on the hemiplegic side due to adhesive capsulitis, less than 3 months after the cerebral ischemic event; WBS (Wong-Baker Scale) > 5, without NSAID, cortisone or opioid intake.
Patients were randomly divided into 2 treatment groups stratified by age, gender, and pain intensity. Group A was treated with intra-articular infiltration of Triamcinolone 40 mg 1 vial and Ropivacaine 2% 3 ml (for a total volume of 4 ml) weekly for the first 2 weeks. The third treatment was performed 15 days after the second one. Group B was treated with MD-SHOULDER: 3 vials (for a total volume of 6 ml) injected intra-articularly (4 ml) and pericapsularly (2 ml). Outcomes were assessed at 1, 6 and 10 months.

WBS = Wong-Baker Scale

Graphic elaboration of Fig.4

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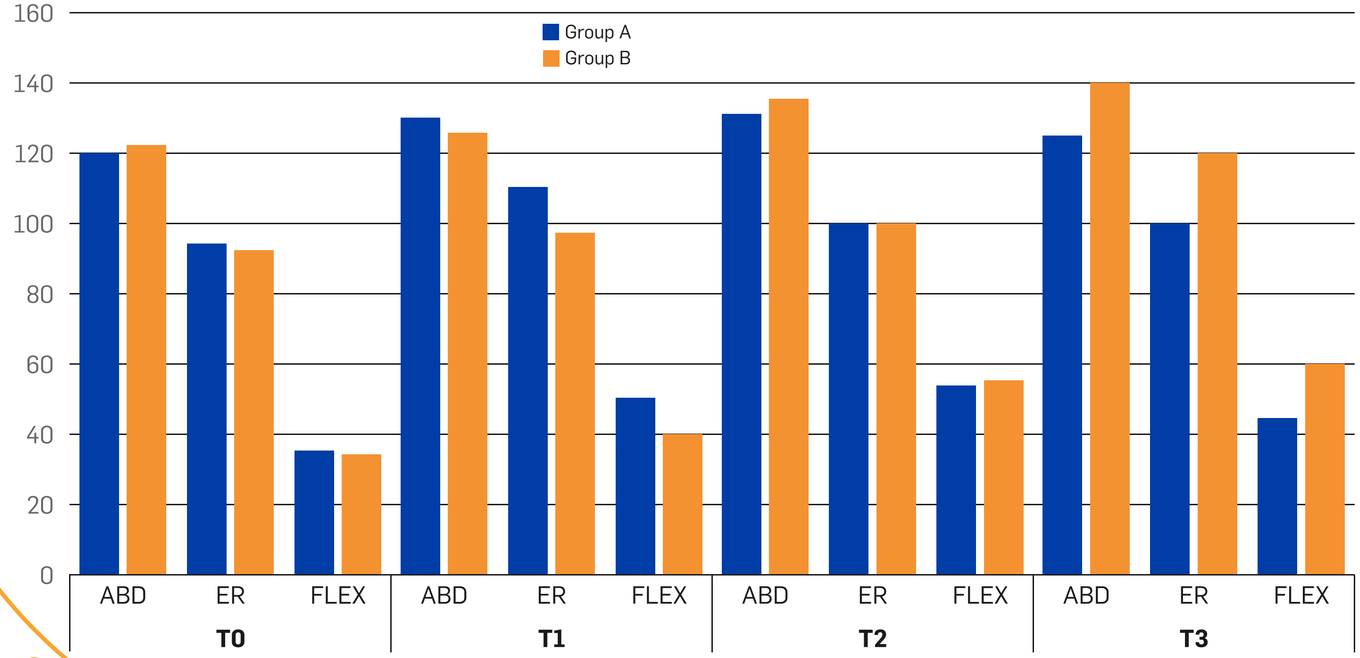
Milano E. Physiological Regulating Medicine 2021; 31-35

GUNA COLLAGEN MEDICAL DEVICES:

Efficacy in the treatment of shoulder pain in post-stroke hemiplegic patients

Passive joint mobility improvement with treatment with **MD-SHOULDER**

PROM shoulder of the paretic limb at 1, 6 and 10 months



ABD - Abduction
ER - External rotation
FLEX - Frontal flexion

Study conducted on 40 patients aged 55-75 years with recent ischemic stroke; clinical and instrumental diagnosis of painful shoulder on the hemiplegic side due to adhesive capsulitis, less than 3 months after the cerebral ischaemic event; WBS (Wong-Baker Scale) > 5, without taking NSAIDs, corticosteroids or opioids. Patients were randomly divided into 2 treatment groups, stratified by age, gender, and pain intensity.
Group A was treated with intra-articular infiltration of Triamcinolone 40 mg 1 vial and Ropivacaine 2% 3 ml (total volume 4 ml) weekly for the first 2 weeks; the third treatment was given 15 days after the second one. Group B was treated with Guna MD-Shoulder 3 vials (for a total volume of 6 ml) intra-articularly (4 ml) and in the peri-capsule area (2 ml). Outcomes were assessed at 1, 6 and 10 months.

PROM = Passive Range Of Motion

Graphic elaboration of Fig.2

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Milano E. Physiological Regulating Medicine 2021; 31-35

GUNA COLLAGEN MEDICAL DEVICES:

Efficacy in the treatment of shoulder pain in post-stroke hemiplegic patients

The treatment with MD-SHOULDER allowed to obtain an **effect of biological reconditioning of the impaired anatomical structures**, allowing a **positive result on the stabilisation of the glenohumeral joint,** its range of motion and, consequently, on the daytime and night-time pain symptoms, **not only in the early stage, but especially in the weeks after the treatment, with a continuous improvement in the outcomes recorded at the follow-up time-points.** (1)

Treatment with MD-SHOULDER did not cause any adverse reactions, thus **resulting completely safe**. (1)

Injection treatment with MD-SHOULDER also seems to **better control the progression of the shoulder pathology, reducing the frequency of relapses over time**. (1)

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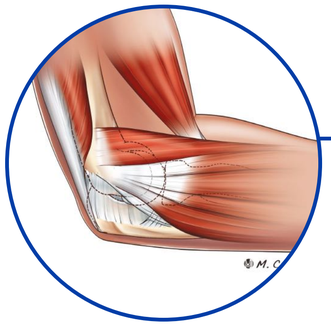
1. Milano E. Physiological Regulating Medicine 2021; 31-35

MAIN INDICATIONS OF
GUNA COLLAGEN MEDICAL DEVICES



ELBOW

PATHOLOGIES	*GUNA COLLAGEN MEDICAL DEVICES*
Soft tissue disorders	
Epicondylitis	**MD-TISSUE** ⊕
Medial epicondylitis	**MD-TISSUE** ⊕

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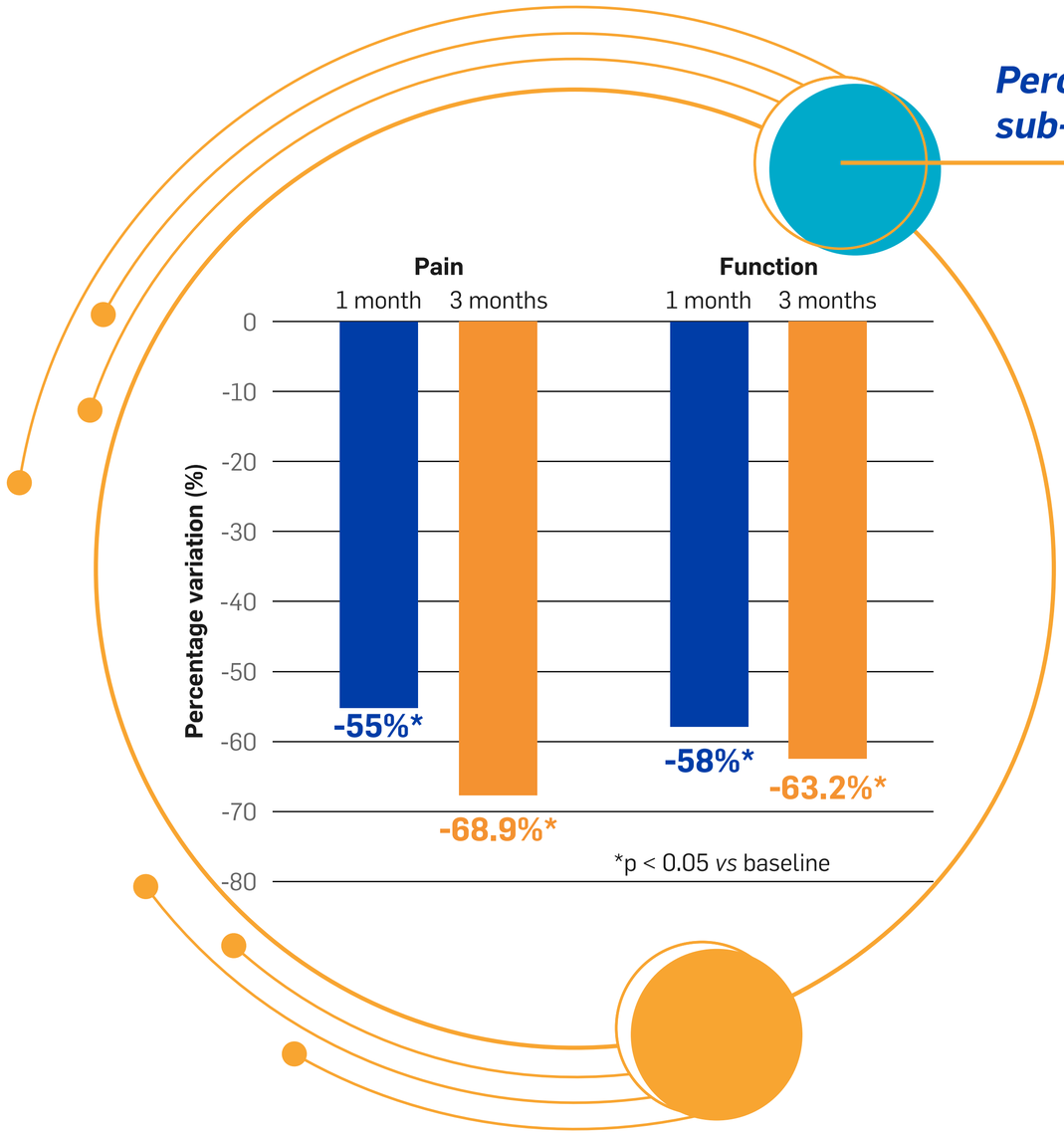
GUNA COLLAGEN MEDICAL DEVICES:
Efficacy in the treatment of epicondylitis

Statistically significant improvement in pain and function after injection treatment **with MD-TISSUE**



Percentage variation of the PRTEE score in the sub-scales of pain and function

- **Positive effects** appeared in a **short time** (1 month) and **further occurred in the following two months even after the end of treatment**.
- Compared to other regenerative injection therapies, **collagen injections seemed to be one of the most effective and fast-acting**.

Prospective, observational and pilot study conducted on 50 subjects affected by tennis elbow for at least 6 months. The patients were treated once a week, for 5 consecutive weeks. The results were evaluated by administering the PRTEE questionnaire, before the first injection, and one month and three months after the last injection.

PRTEE = Patient-Rated Tennis Elbow Evaluation

Graph elaborated form text.

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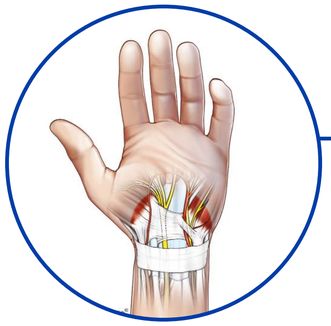
Corrado B. et al. Muscles, Ligaments and Tendons Journal 2019; 9 (4): 584-589

MAIN INDICATIONS OF
GUNA COLLAGEN MEDICAL DEVICES



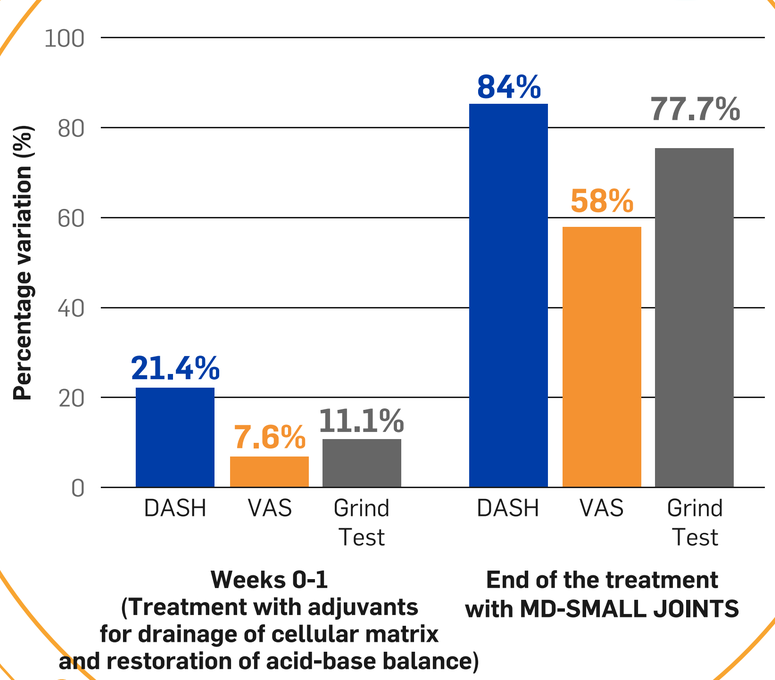
HAND/WRIST

PATHOLOGIES	*GUNA COLLAGEN MEDICAL DEVICES*
Osteoarticular pathologies	
Rhizoarthrosis (trapeziometacarpal osteoarthritis)	**MD-SMALL JOINTS** ⊕
Metacarpophalangeal osteoarthritis	**MD-SMALL JOINTS** ⊕
Proximal interphalangeal osteoarthritis	**MD-SMALL JOINTS** ⊕
Soft tissue disorders	
De Quervain's tenosynovitis	**MD-TISSUE** ⊕
Trigger finger (stenosing flexor tenosynovitis)	**MD-TISSUE** ⊕
Carpal tunnel syndrome	**MD-NEURAL** ⊕ **+ MD-TISSUE** ⊕

GUNA COLLAGEN MEDICAL DEVICES:
Efficacy in the treatment of rhizoarthrosis

Pain, function, and capsular-ligamentous laxity improvement with **MD-SMALL JOINTS**

Percentage variations of DASH, VAS and Grind test values before and after the treatment



The study showed that MD-SMALL JOINTS is **effective in delaying surgical intervention**, guaranteeing the patient a **rapid clinical improvement** and an expectation of **slowing down the pathology, without side effects** and with **excellent tolerability**.

Study conducted on 22 patients suffering from rhizoarthrosis. Patients were administered MD-SMALL JOINTS, 3 or 4 intra-articular injections at weekly intervals, with the 4th or 5th injection being given after 2 weeks.

DASH = Disability for Arm, Shoulder and Hand
VAS = Visual Analogue Scale

Graph elaborated from text.

Download the study

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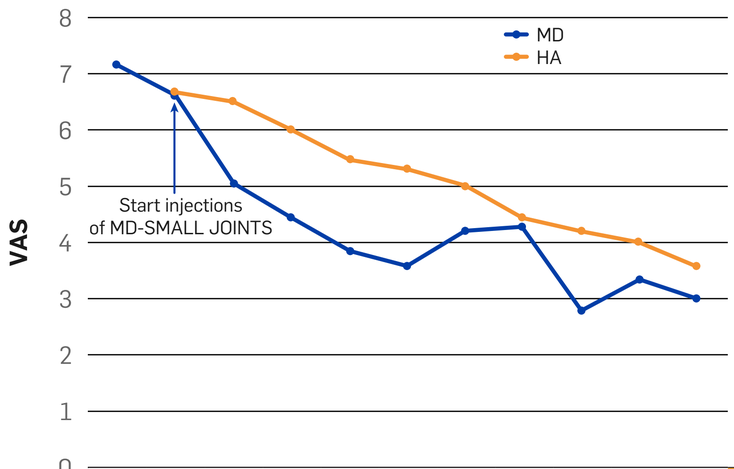
Brunato F. Physiological Regulating Medicine 2021; 3-12

GUNA COLLAGEN MEDICAL DEVICES:
Efficacy in the treatment of rhizoarthrosis

Comparison of pain management with **MD-SMALL JOINTS vs hyaluronic acid**

VAS scale at 11 weeks:
MD-SMALL JOINTS vs hyaluronic acid (HA)



	1	2	3	4	5	6	7	8	9	10	11	Diff.	%
MD	7.14	6.60	5.06	4.44	3.85	3.60	4.20	4.29	2.80	3.33	3.00	**4.14**	**57.98**
HA		6.67	6.50	6.00	5.45	5.30	5.00	4.43	4.20	4.00	3.57	**3.10**	**46.47**

Diff. 11.51

Compared to hyaluronic acid, MD-SMALL JOINTS showed an **early and significant decrease in pain from the first weeks of treatment.**

Comparison of the results obtained from two studies:
- *Study conducted on 22 patients suffering from rhizoarthrosis, treated with MD-SMALL JOINTS, 3 or 4 intra-articular injections at weekly intervals, with the 4th or 5th injection being given after 2 weeks.*
- *Study conducted on 51 patients with rhizoarthrosis, who received 3 intra-articular injections of hyaluronic acid, administered at intervals of 3 weeks.*

VAS = Visual Analogue Scale

Graphic elaboration of Fig.9

Download the study

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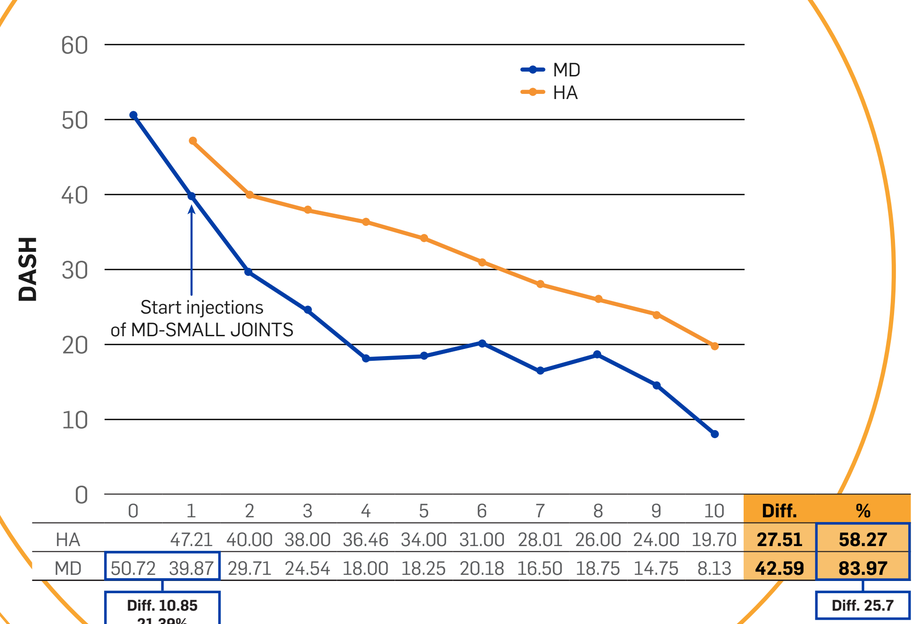
Brunato F. Physiological Regulating Medicine 2021; 3-12

GUNA COLLAGEN MEDICAL DEVICES:
Efficacy in the treatment of rhizoarthrosis

Greater improvement of hand function with **MD-SMALL JOINTS compared to hyaluronic acid**

DASH Questionnaire at 10 weeks:
MD-SMALL JOINTS (MD) vs hyaluronic acid (HA)



	0	1	2	3	4	5	6	7	8	9	10	Diff.	%
HA		47.21	40.00	38.00	36.46	34.00	31.00	28.01	26.00	24.00	19.70	**27.51**	**58.27**
MD	50.72	39.87	29.71	24.54	18.00	18.25	20.18	16.50	18.75	14.75	8.13	**42.59**	**83.97**

Diff. 10.85 21.39%

Diff. 25.7

DASH questionnaire results show that treatment with MD-SMALL JOINTS allowed to carry out **daily work activities with significantly less pain**.

Comparison of the results obtained from two studies:
- *Study conducted on 22 patients suffering from rhizoarthrosis, treated with MD-SMALL JOINTS, 3 or 4 intra-articular injections at weekly intervals, with the 4th or 5th injection being given after 2 weeks.*
- *Study conducted on 51 patients with rhizoarthrosis, who received 3 intra-articular injections of hyaluronic acid, administered at intervals of 3 weeks.*

DASH = Disability for Arm, Shoulder and Hand

Graphic elaboration of Fig.10

Download the study

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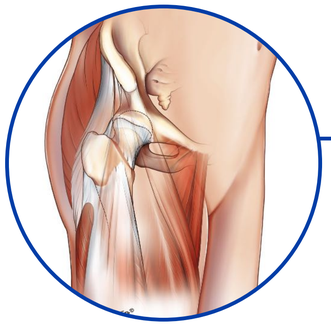
Brunato F. Physiological Regulating Medicine 2021; 3-12

MAIN INDICATIONS OF
GUNA COLLAGEN MEDICAL DEVICES



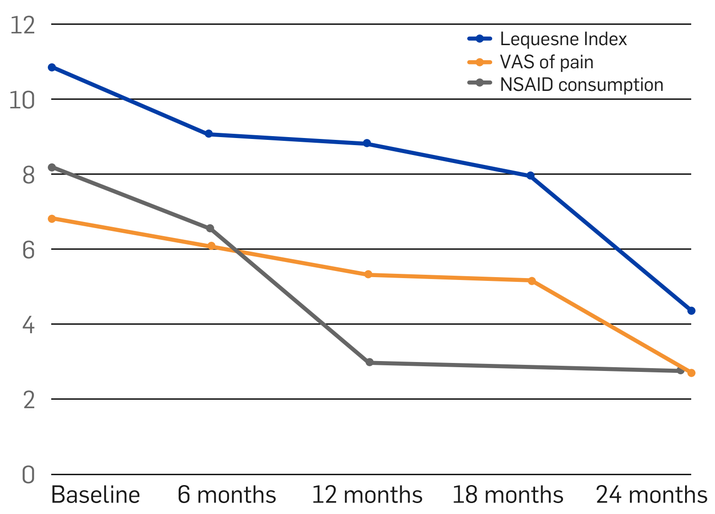
HIP

PATHOLOGIES	*GUNA COLLAGEN MEDICAL DEVICES*
Osteoarticular pathologies	
Coxarthrosis	**MD-HIP** ⊕
Soft tissue disorders	
Greater trochanteric pain syndrome	**MD-TISSUE** ⊕
Trochanteric bursitis	**MD-TISSUE** ⊕
Adductor enthesitis	**MD-TISSUE** ⊕

GUNA COLLAGEN MEDICAL DEVICES:
Efficacy in the treatment of hip osteoarthritis

Pain and functionality improvement and NSAIDs consumption reduction after treatment with **MD-HIP**

VAS scale, Lequesne Index and NSAIDs consumption (number of days)



The **beneficial effects** obtained with MD-HIP occurred as early as after the **first injection and are maintained for 24 months** with repeated intra-articular injections every 6 months.

Study conducted on 24 patients with symptomatic hip osteoarthritis (grades 1-3 according to the Kellgren-Lawrence Scale). The patients received ultrasound-guided injection of 4 ml (2 vials) of MD-HIP. Outcomes were measured at baseline and every 6 months after the first injection. Follow-up was at 24 months.

VAS = Visual Analogue Scale

Graphic elaboration of Fig.1.

Download the study

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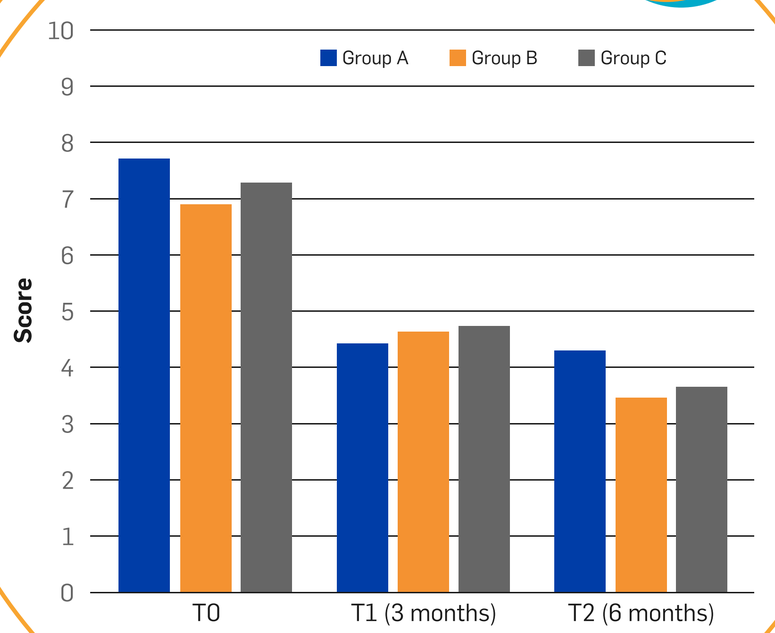
Giovannangeli F. et al. Physiological Regulating Medicine 2016-2017; 31-32

GUNA COLLAGEN MEDICAL DEVICES:

Efficacy in the treatment of hip osteoarthritis

Greater pain reduction with hyaluronic acid +MD-HIP combined treatment compared to treatment with hyaluronic acid only

NRS scale in the 3 groups at 3 and 6 months after the first treatment



Study conducted on 60 patients diagnosed with primary hip osteoarthritis for more than 12 months, who were randomised into three treatment groups:

- ***Group A**, a cycle of 3 intra-articular injections of high molecular weight **HA** at 10-day intervals.*
- ***Group B**, a cycle of 3 intra-articular injections of high molecular weight **HA** and peri-capsular injections of **MD-HIP** (4ml, 2 vials) at T0, T14 e T35, alternated with 2 peri-intracapsular injections of 4 ml **MD-HIP** at T7 and T21.*
- ***Group C**, a cycle of 2 intra-articular high molecular weight injections of **HA** and peri-capsular **MD-HIP** injections (4 ml) at T7 and T14, alternated with peri-intracapsular **MD-HIP** injections (4 ml) at T0, T14 and T35. Clinical and functional outcomes were assessed at 3 and 6 months after the first treatment.*

NRS = Numeric Rating Scale
HA = Hyaluronic acid

Graphic elaboration of Tab.3.

Download the study

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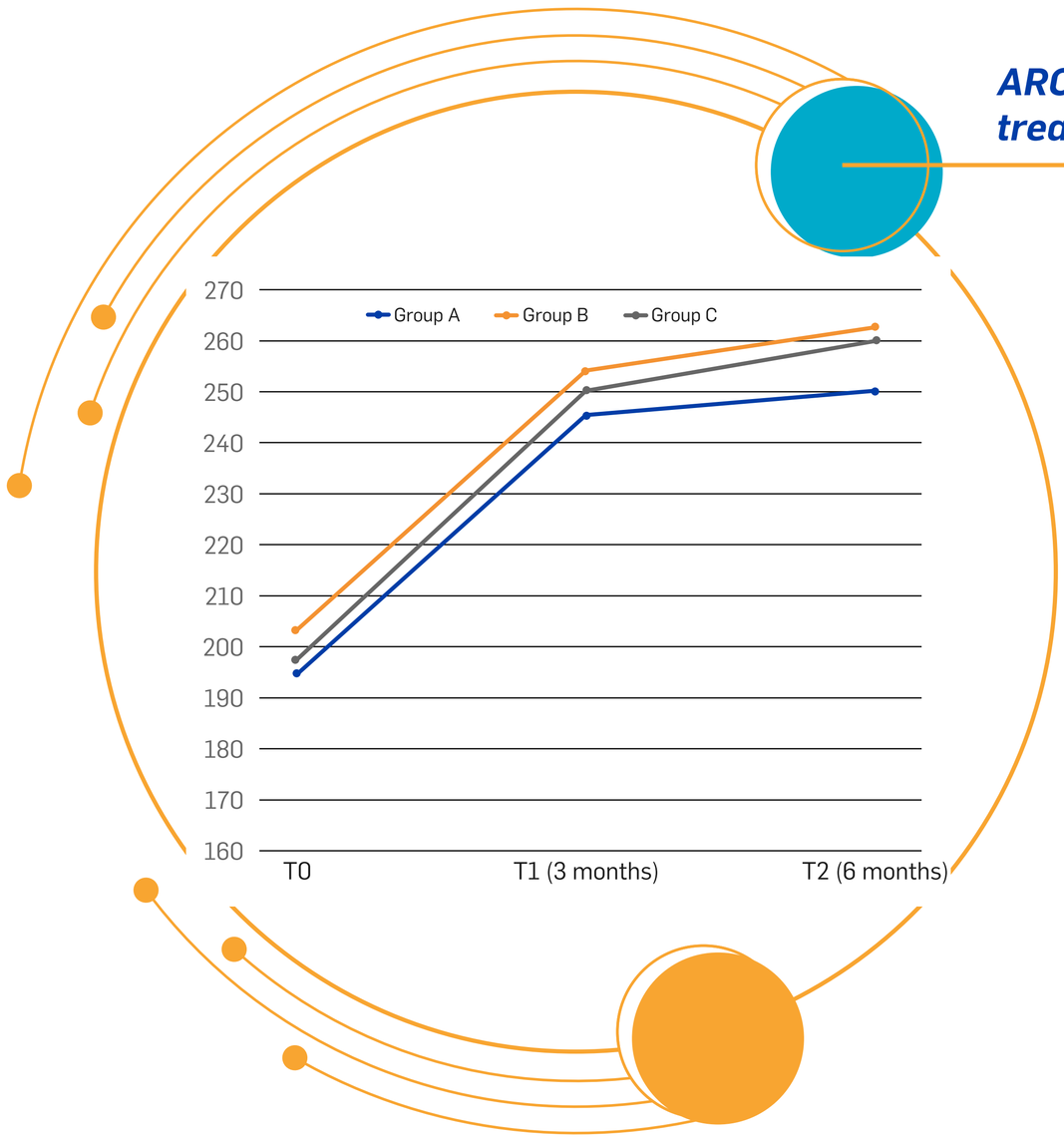
Milano E. Physiological Regulating Medicine 2018; 3-8

GUNA COLLAGEN MEDICAL DEVICES:

Efficacy in the treatment of hip osteoarthritis

Greater overall improvement of hip mobility with **HA+MD-HIP combined treatment** compared to treatment with HA only

AROM in the 3 groups at 3 and 6 moths from the first treatment



Study conducted on 60 patients diagnosed with primary hip osteoarthritis for more than 12 months, randomised into three treatment groups:

- ***Group A**, a cycle of 3 intra-articular injections of high molecular weight **HA** at 10-day intervals.*
- ***Group B**, a cycle of 3 intra-articular injections of high molecular weight **HA** and peri-capsular injections of **MD-HIP** (4 ml) at T0, T14 e T35, alternated with 2 peri-intracapsular infiltrations of **MD-HIP**, 2 vials at T7 and T21.*
- ***Group C**, a cycle of 2 intra-articular high molecular weight injections of **HA** and peri-capsular **MD-HIP** injections (4 ml) at T7 and T14, alternated with peri-intracapsular **MD-HIP** injections (4 ml) at T0, T14 and T35. Clinical and functional outcomes were assessed at 3 and 6 months after the first treatment.*

AROM = Active Range of Motion
HA = Hyaluronic acid

Graphic elaboration of Tab.5.

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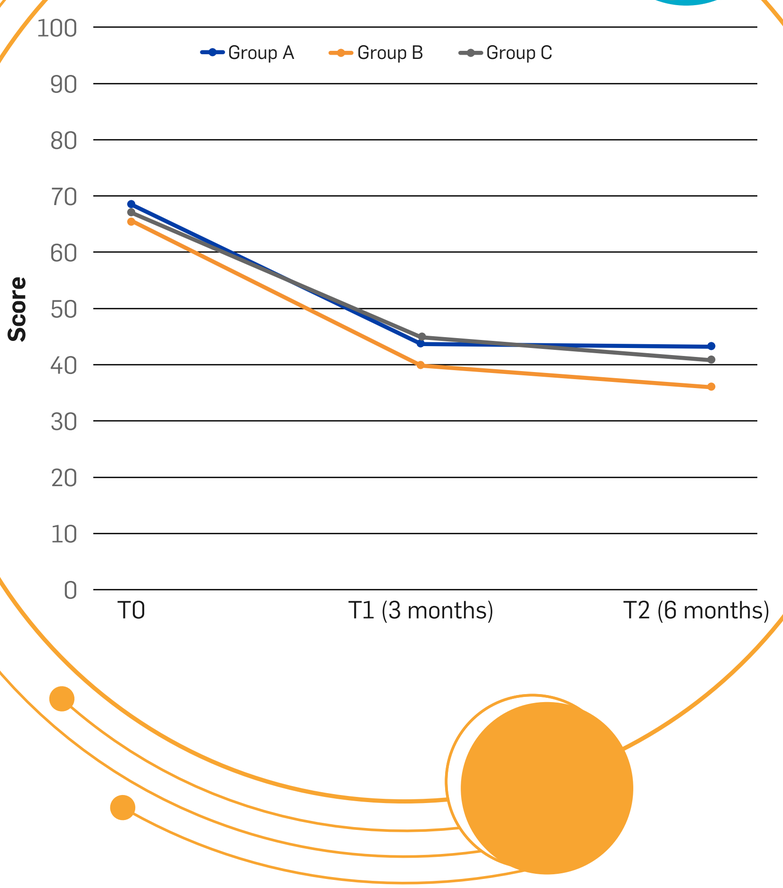
Milano E. Physiological Regulating Medicine 2018; 3-8

GUNA COLLAGEN MEDICAL DEVICES:
Efficacy in the treatment of hip osteoarthritis

Greater overall improvement of hip functionality with **HA+MD-HIP combined treatment** compared to treatment with HA only

WOMAC score in the three groups at 3 and 6 months from the first treatment



Study conducted on 60 patients diagnosed with primary hip osteoarthritis for more than 12 months, randomised into three treatment groups:

- ***Group A**, a cycle of 3 intra-articular injections of high molecular weight **HA** at 10-day intervals.*
- ***Group B**, a cycle of 3 intra-articular injections of high molecular weight **HA** and peri-capsular injections of **MD-HIP** (4 ml) at T0, T14 e T35, alternated with 2 peri-intracapsular infiltrations of **MD-HIP**, 2 vials at T7 and T21.*
- *Group C, a cycle of 2 intra-articular injections of high molecular weight **HA** and peri-capsular **MD-HIP** injections (4 ml) at T7 and T14, alternated with peri-intracapsular **MD-HIP** injections (4 ml) at T0, T14 and T35. Clinical and functional outcomes were assessed at 3 and 6 months after the first infiltrative treatment.*

WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index
HA = Hyaluronic acid

Graphic elaboration of Tab.6.

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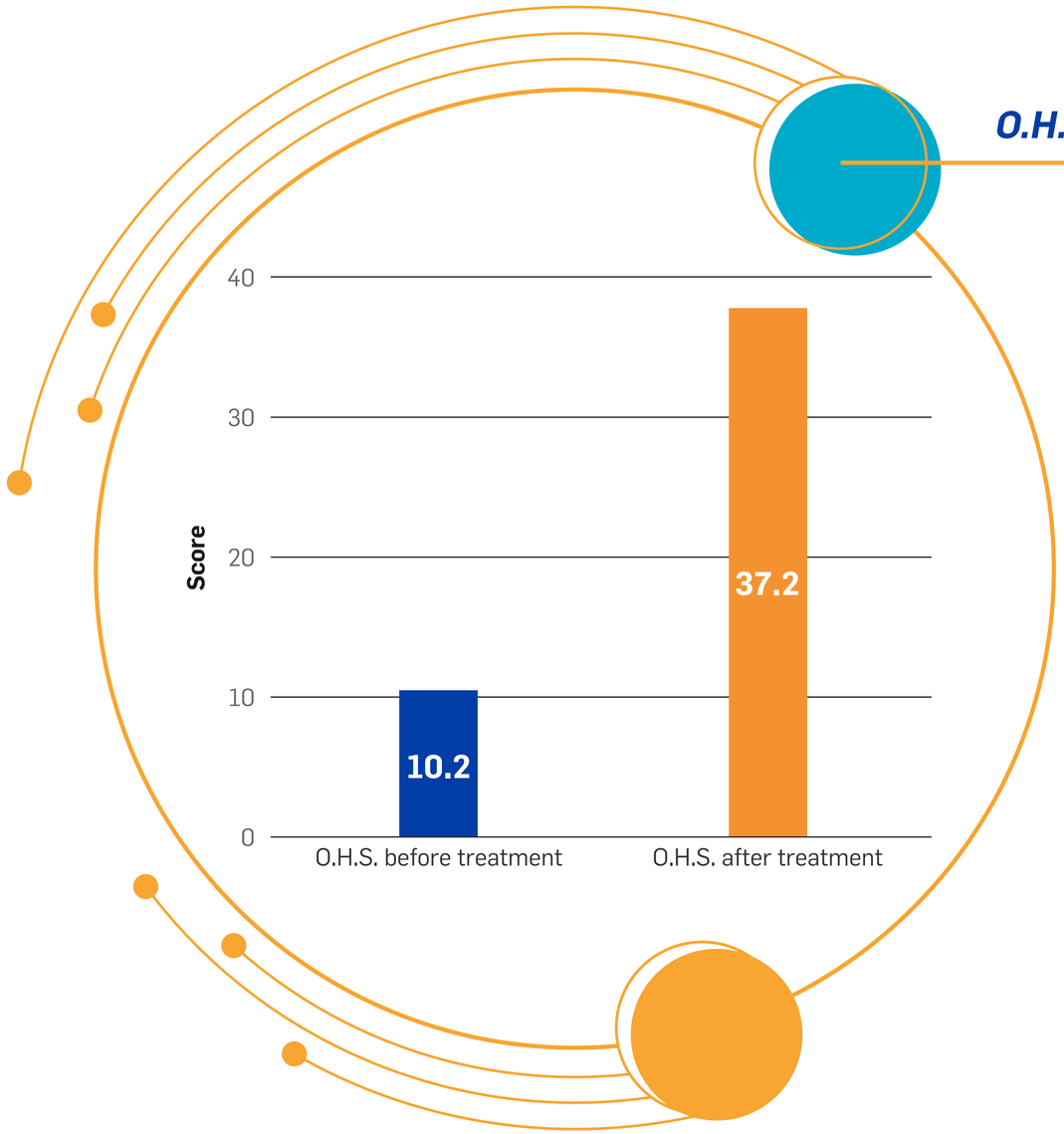
Milano E. Physiological Regulating Medicine 2018; 3-8

GUNA COLLAGEN MEDICAL DEVICES:

Efficacy in the treatment of hip osteoarthritis

Reduction in functional impairment after injection treatment with **MD-HIP**



O.H.S. scale before and after treatment

- Patients reported a **feeling of increased joint excursion after the first 2-3 sessions.**
- The **effect on pain** was **quite rapid**.
- All patients significantly **reduced** their **consumption of drugs**.
- **No patient** reported **any side effects** after administration.

Study conducted on 30 patients with mild to moderate primary coxarthrosis (stage I and II). Patients received peri-capsular injections of MD-HIP twice a week for 5 consecutive weeks. The dedicated questionnaire was given at the first visit and at the end of the treatment.

O.H.S. = Oxford Hip Score

Graph elaborated from text

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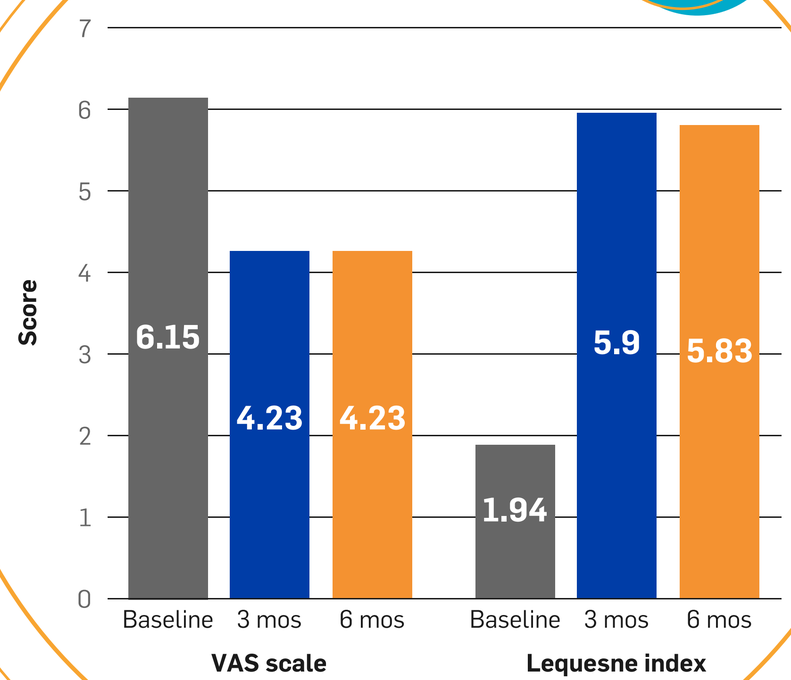
Ottaviani M. Physiological Regulating Medicine 2018; 19-28

GUNA COLLAGEN MEDICAL DEVICES:

Efficacy in the treatment of hip osteoarthritis

Pain and joint function improvement after treatment with **MD-HIP,** in patients not responsive to visco-supplementation with hyaluronic acid

VAS scale and Lequesne Index during the study



- **NSAIDs consumption was reduced** from 7.57 (before treatment) to 4.25 (after 3 months), to 5.78 (after 6 months).
- **MD-HIP** demonstrated **efficacy and safety**.
- The data suggest that the **results obtained can be seen from the first injection and are maintained for 6 months.**

Study conducted on 7 patients with Rx stage I-III Kellgren Lawrence osteoarthritis of the coxo-femoral joint unresponsive to visco-supplementation with hyaluronic acid. Patients were treated with MD-HIP (2 vials, 4 ml), 1 ultrasound-guided intra-articular infiltration. The study lasted 6 months.

VAS = Visual Analogue Scale

Graph elaborated from text.

Download the study

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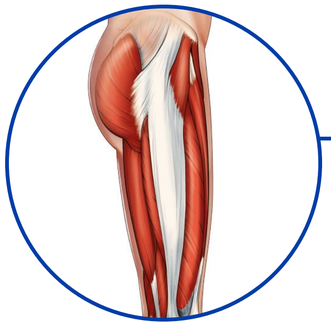
Migliore A. et al. Physiological Regulating Medicine 2013; 31

MAIN INDICATIONS OF
GUNA COLLAGEN MEDICAL DEVICES



THIGH

PATHOLOGIES	*GUNA COLLAGEN MEDICAL DEVICES*
Soft tissue disorders	
Fascia lata disorders	**MD-TISSUE** ⊕
Quadriceps muscle injury/inflammation	**MD-TISSUE** ⊕ **or MD-MUSCLE** ⊕
Flexor muscle injury/inflammation	**MD-TISSUE** ⊕ **or MD-MUSCLE** ⊕
Piriformis syndrome	**MD-MUSCLE** ⊕

GUNA COLLAGEN MEDICAL DEVICES:

Efficacy in the treatment of the piriformis syndrome

*In clinical practice, **Piriformis Syndrome is usually latent**. The **diagnosis** is **often supported by X-ray, CT scan or MRI scan** showing spondylosis and osteochondrosis of the lumbosacral spine or herniated disk.*

AVAILABLE TREATMENTS FOR PIRIFORMIS SYNDROME

- ***Non-invasive treatments:*** *physiotherapy (exercises, yoga, stretching, massage, etc.); electrotherapy (magnetotherapy, laser, ultrasound, etc.); hydrotherapy, etc.*
- ***Semi-invasive treatments:*** *acupuncture, injection techniques.*
- ***Injection therapies used to treat PS:*** *lidocaine (marcaine), steroids, combination of the two drugs, botulinum toxin under CT control, Guna Collagen MDs*
- ***Injection therapies includes:***
  - ***MD-MUSCLE or MD-MATRIX***
  - *20G needle, 0.9 x 70-90 mm*
  - *Gentle manipulation of the needle: identification of the sacrum*
  - *Aspiration: hematoma in the piriformis muscle*
  - *Risk: ischiatic nerve damage, bleeding*

28 patients with Piriformis syndrome were treated with MD-MUSCLE or MD-MATRIX

•No one worsened after the treatment

•No one underwent surgery after the treatment

The **application of Guna MDs** in patients with Piriformis Syndrome is **safe and effective**

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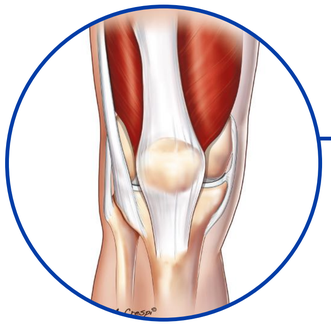
Staňa J. Physiological Regulating Medicine 2016-2017;19-20

MAIN INDICATIONS OF
GUNA COLLAGEN MEDICAL DEVICES



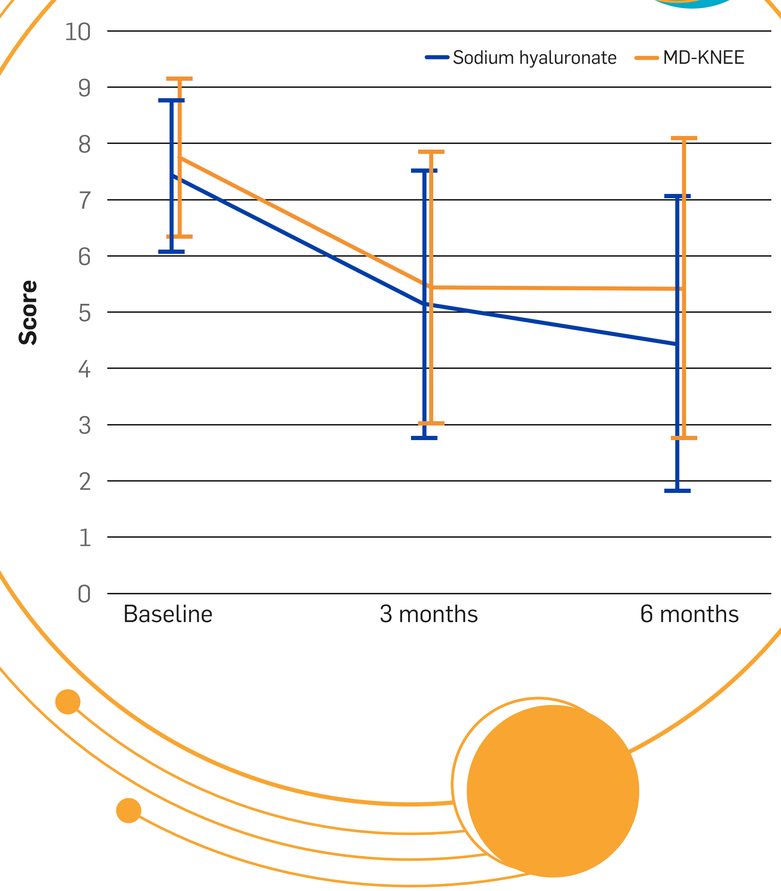
KNEE

PATHOLOGIES	*GUNA COLLAGEN MEDICAL DEVICES*
Osteoarticular pathologies	
Femorotibial/ patellofemoral osteoarthritis of the knee	**MD-KNEE** ⊕
Patellofemoral chondropathy	**MD-KNEE** ⊕
Arthrosynovitis	**MD-KNEE** ⊕
Soft tissue disorders	
Iliotibial band syndrome	**MD-TISSUE** ⊕
Tendinopathy (quadriceps/ patellar - hamstrings)	**MD-TISSUE** ⊕
Ligament injury	**MD-KNEE** ⊕
Meniscal disorders	**MD-KNEE** ⊕

GUNA COLLAGEN MEDICAL DEVICES:
Efficacy in the treatment of gonarthrosis

Pain improvement after treatment **with MD-KNEE, with results comparable to treatment with HA**

VAS scale at baseline and 3 and 6 months after treatment



The consumption of analgesics did not differ between the two groups, confirming the hypothesis of non-inferiority of MD-KNEE treatment.

Prospective, double blind, multicentric, randomized clinical trial with active control. The study was conducted on 60 patients with grade II-III gonarthrosis according to the Kellgren-Lawrence Scale. 29 patients received 5 intra-articular injections of MD-KNEE at weekly intervals, while 31 patients were treated with 5 intra-articular injections of sodium hyaluronate at weekly intervals. Outcomes were assessed at baseline and 3 and 6 months after treatment.

VAS = Visual Analogue Scale

Graphic elaboration of Fig.3.

Download the study

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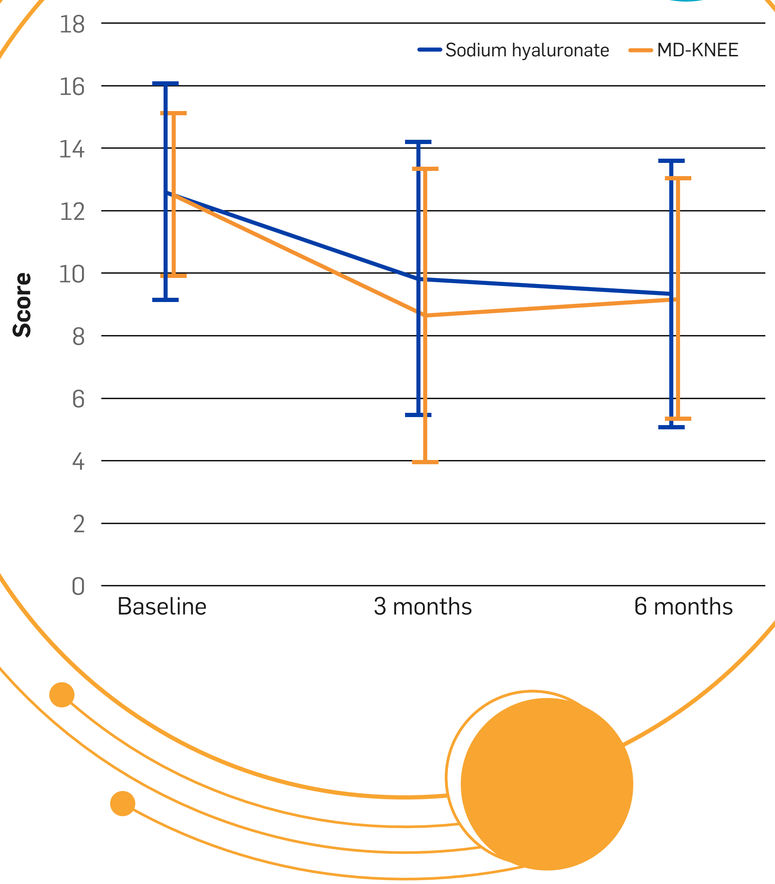
Martin Martin L.S. et al. BMC Musculoskeletal Disorders 2016; 17-94

GUNA COLLAGEN MEDICAL DEVICES:
Efficacy in the treatment of gonarthrosis

Functionality improvement after treatment **with MD-KNEE, with results comparable to treatment with HA**

Lequesne Index at baseline and 3 and 6 months after treatment



MD-KNEE has demonstrated a **good tolerability, at both local and systemic level, and it was not inferior to HA.** It also showed a **high safety profile.**

Prospective, double blind, multicentric, randomized clinical trial with active control. The study was conducted on 60 patients with grade II-III gonarthrosis according to the Kellgren-Lawrence Scale. 29 patients received 5 intra-articular injections of MD-KNEE at weekly intervals, while 31 patients were treated with 5 intra-articular injections of sodium hyaluronate at weekly intervals. Outcomes were assessed at baseline and at 3 and 6 months after treatment.

Graphic elaboration of Fig.2.

Download the study

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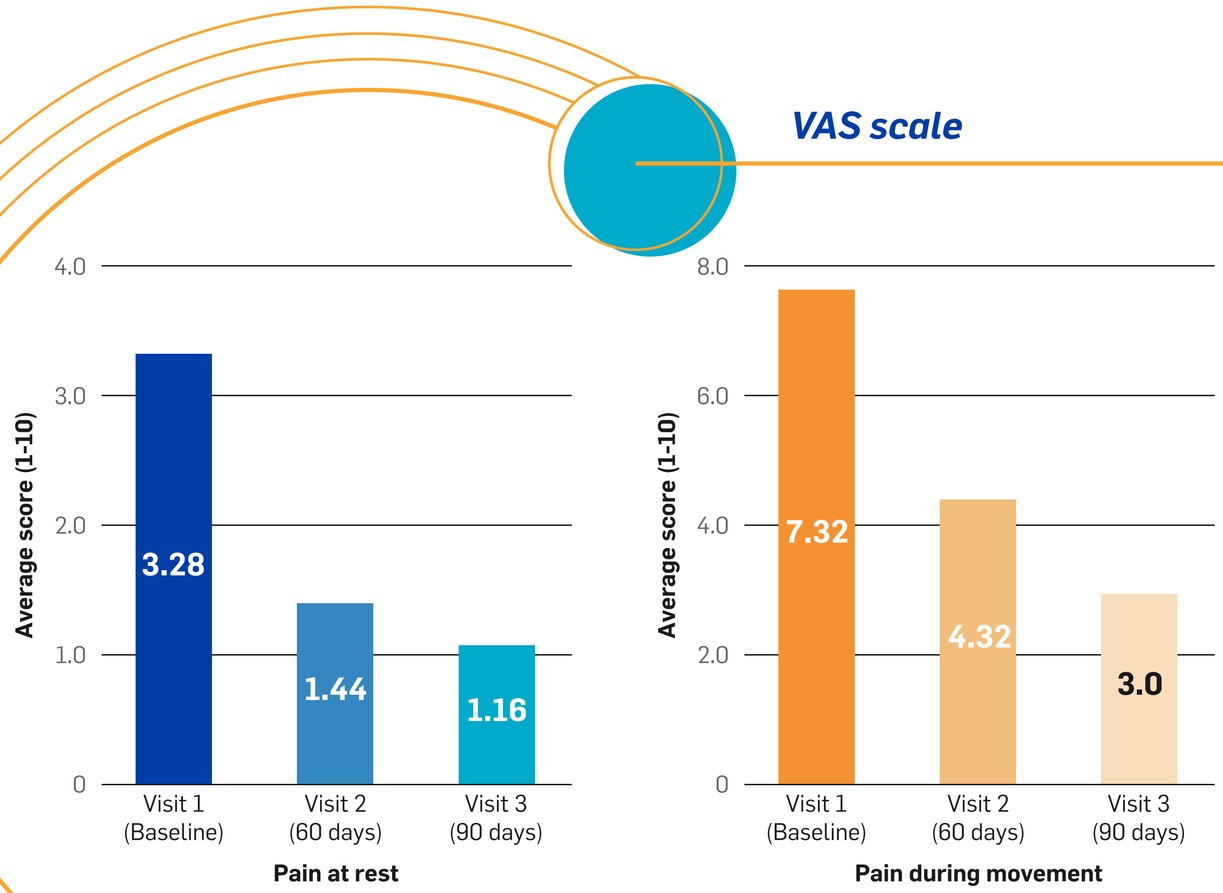
Martin Martin L.S. et al. BMC Musculoskeletal Disorders 2016; 17-94

GUNA COLLAGEN MEDICAL DEVICES:
Efficacy in the treatment of gonarthrosis

Pain reduction at rest and during movement after treatment with
MD-KNEE + MD-MATRIX



The effectiveness of treatment is maintained even after end of treatment.

Study conducted on 25 patients with radiological stage III-IV gonarthrosis according to the Kellgren-Lawrence Scale. The patients were treated peri-articularly with MD-KNEE + MD-MATRIX, for a total of 10 vials each product, according to the following scheme: 2 injections per week for the first 2 weeks and 1 injection per week for the following 6 weeks, for a total treatment cycle of 8 weeks.

VAS = Visual Analogue Scale

Graphic elaboration of Fig.1-2.

Download the study

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Nestorova R. et al. Physiological Regulating Medicine 2012; 37-39

GUNA COLLAGEN MEDICAL DEVICES:
Efficacy in the treatment of gonarthrosis

Functionality improvement after treatment with **MD-KNEE + MD-MATRIX**

90 days after starting treatment

- **Morning stiffness** — Reduction by **over 2 times**
- **Pain when standing** — Reduction by **3 times**
- **Pain when walking** — Reduction by **1.5 times**
- **Maximum walking distance** — Increase by **1.5 times**

Study conducted on 25 patients with radiological stage III-IV gonarthrosis according to the Kellgren-Lawrence Scale. The patients were treated peri-articularly with MD-KNEE + MD-MATRIX, for a total of 10 vials each product, according to the following scheme: 2 injections per week for the first 2 weeks and 1 injection per week for the following 6 weeks, for a total treatment cycle of 8 weeks.

Ultrasound assessment of knee oedema, conducted **30 days after treatment** with MD-KNEE+ MD-MATRIX, shows that **60% of patients had no oedema and 30% showed oedema reduction**.

Download the study

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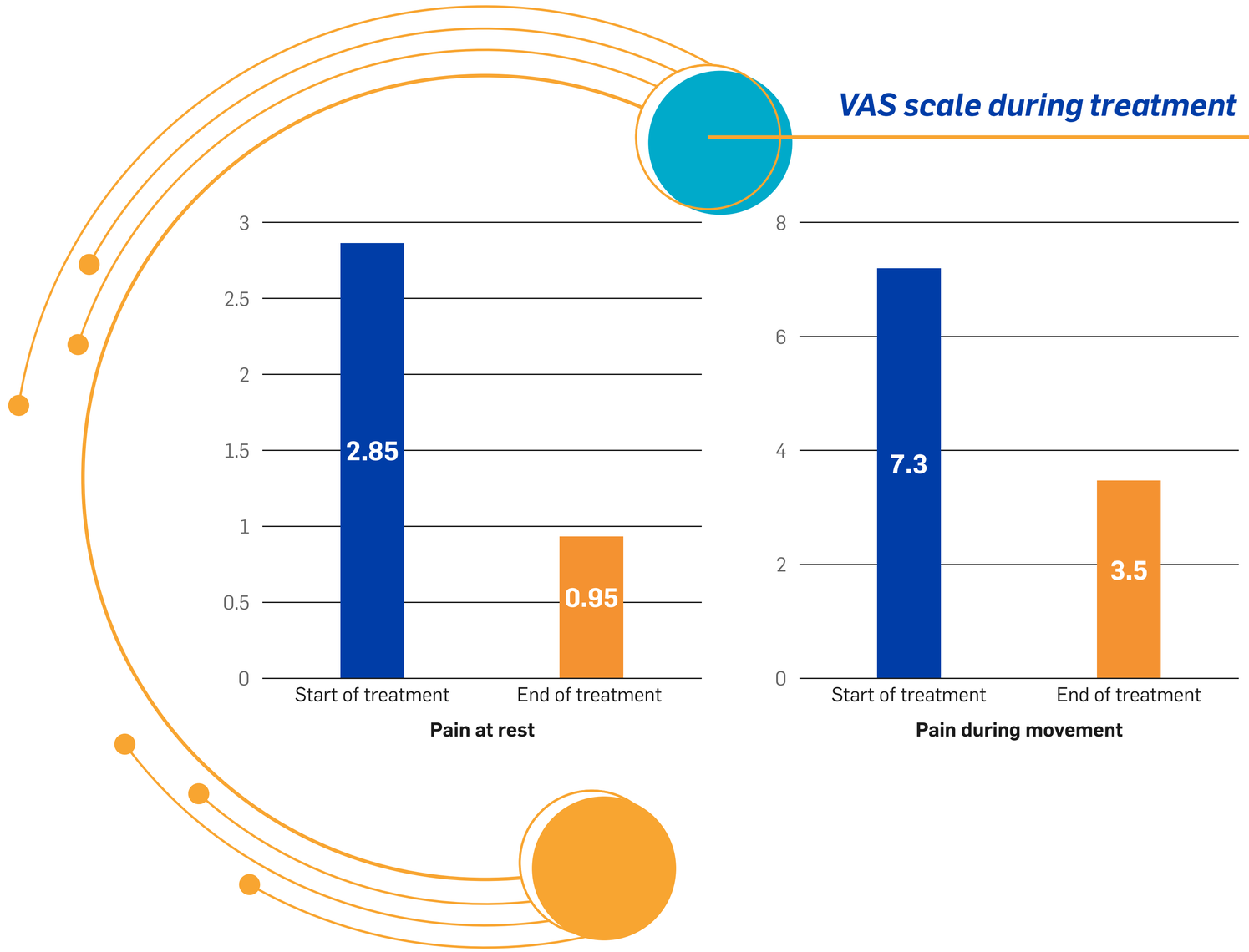
Nestorova R. et al. Physiological Regulating Medicine 2012; 37-39

GUNA COLLAGEN MEDICAL DEVICES:
Efficacy in the treatment of gonarthrosis

Pain reduction at rest and during movement after treatment with
MD-KNEE + MD-MUSCLE



Study conducted on 14 patients with gonarthrosis treated with MD-KNEE + MD-MUSCLE: 2 intra-articular and peri-articular injections/week for 2 consecutive weeks + 1 intra-articular and peri-articular injection per week for the following 6 weeks (total 10 treatments in 8 weeks).

VAS = Visual Analogue Scale

Graphic elaboration of Tab.9-10.

Download the study

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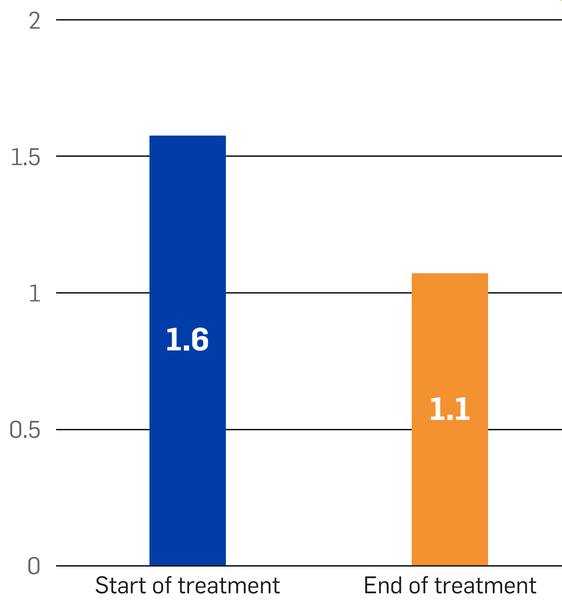
Boshnakov D. Physiological Regulating Medicine 2013; 29-30

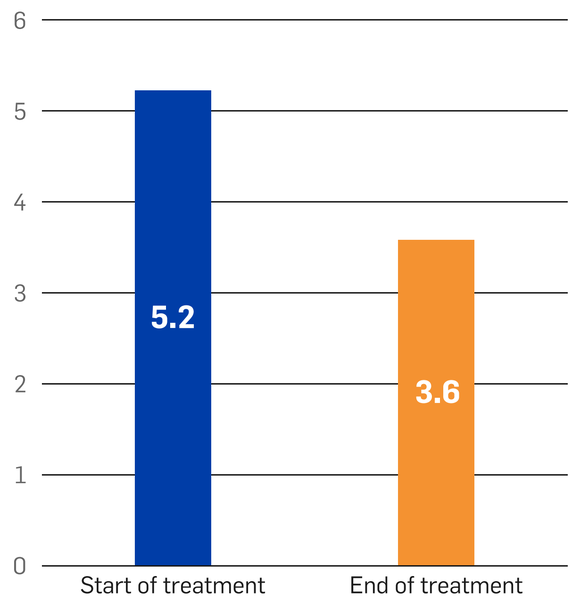
GUNA COLLAGEN MEDICAL DEVICES:
Efficacy in the treatment of gonarthrosis

Improvement of joint mobility and functionality after treatment with **MD-KNEE + MD-MUSCLE**

Lequesne Index during the treatment



Pain during movement



Maximum walking distance

Collagen MDs represent an **innovative approach and an effective treatment of gonarthrosis.**

Study conducted on 14 patients with gonarthrosis treated with MD-KNEE + MD-MUSCLE: 2 intra-articular and peri-articular injections/week for 2 consecutive weeks + 1 intra-articular and peri-articular injection per week for the following 6 weeks (total 10 treatments in 8 weeks).

Graphic elaboration of Tab.11-12.

Download the study

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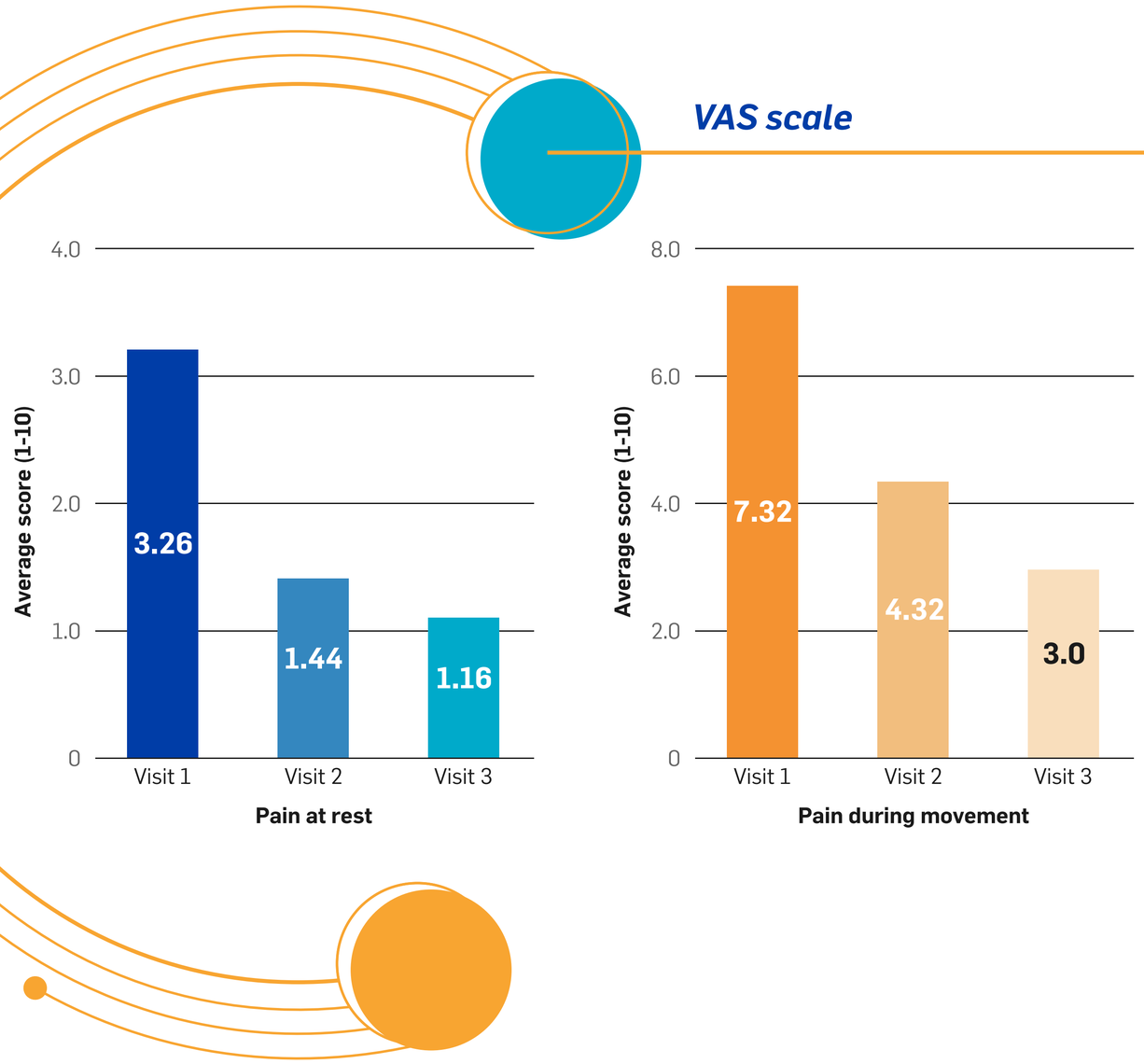
Boshnakov D. Physiological Regulating Medicine 2013; 29-30

GUNA COLLAGEN MEDICAL DEVICES:
Efficacy in the treatment of gonarthrosis

Reduction of pain at rest and during movement after treatment with **MD-KNEE + MD-MUSCLE**



Pain reduction continued even 30 days after the end of treatment.

Study conducted on 30 patients with radiological stage II-III gonarthrosis according to the Kellgren-Lawrence Scale. They were treated with intra-articular injections of MD-KNEE + MD-MUSCLE: 1 injection twice a week for 2 weeks and 1 injection a week for 6 weeks. The patients were evaluated at baseline (visit 1) and at 8 (visit 2) and 12 (visit 3) weeks. The treatment lasted 8 weeks.

VAS = Visual Analogue Scale

Graphic elaboration of Fig.1.

Download the study

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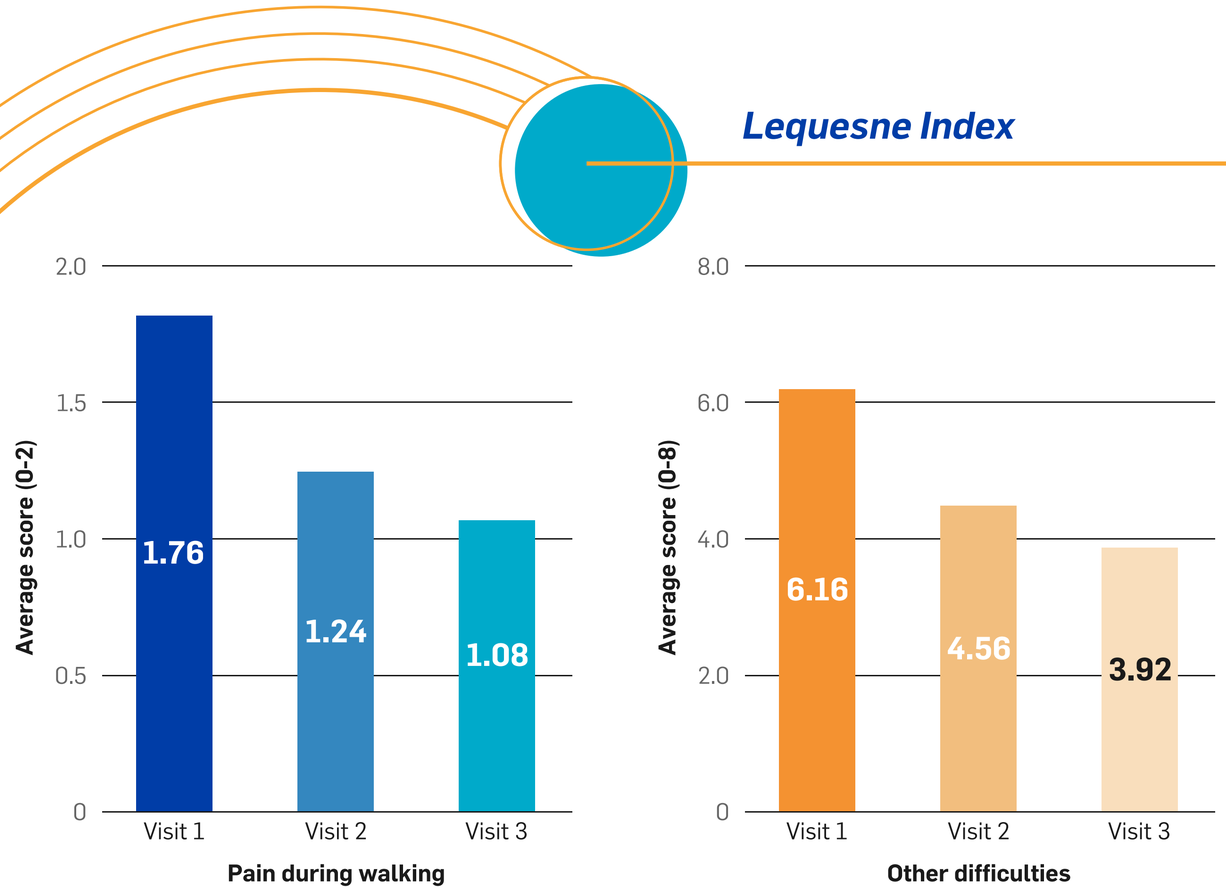
Reshkova V. et al. Physiological Regulating Medicine 2016-2017; 27-29

GUNA COLLAGEN MEDICAL DEVICES:
Efficacy in the treatment of gonarthrosis

Joint functionality improvement after treatment with **MD-KNEE + MD-MUSCLE**



No adverse reactions were reported during follow-up.

Study conducted on 30 patients with radiological stage II-III gonarthrosis according to the Kellgren-Lawrence Scale. They were treated with intra-articular injections of MD-KNEE + MD-MUSCLE: 1 injection twice a week for 2 weeks and 1 injection a week for 6 weeks. The patients were evaluated at baseline (visit 1) and at 8 (visit 2) and 12 (visit 3) weeks. The treatment lasted 8 weeks.

Graphic elaboration of Fig.2.

Download the study

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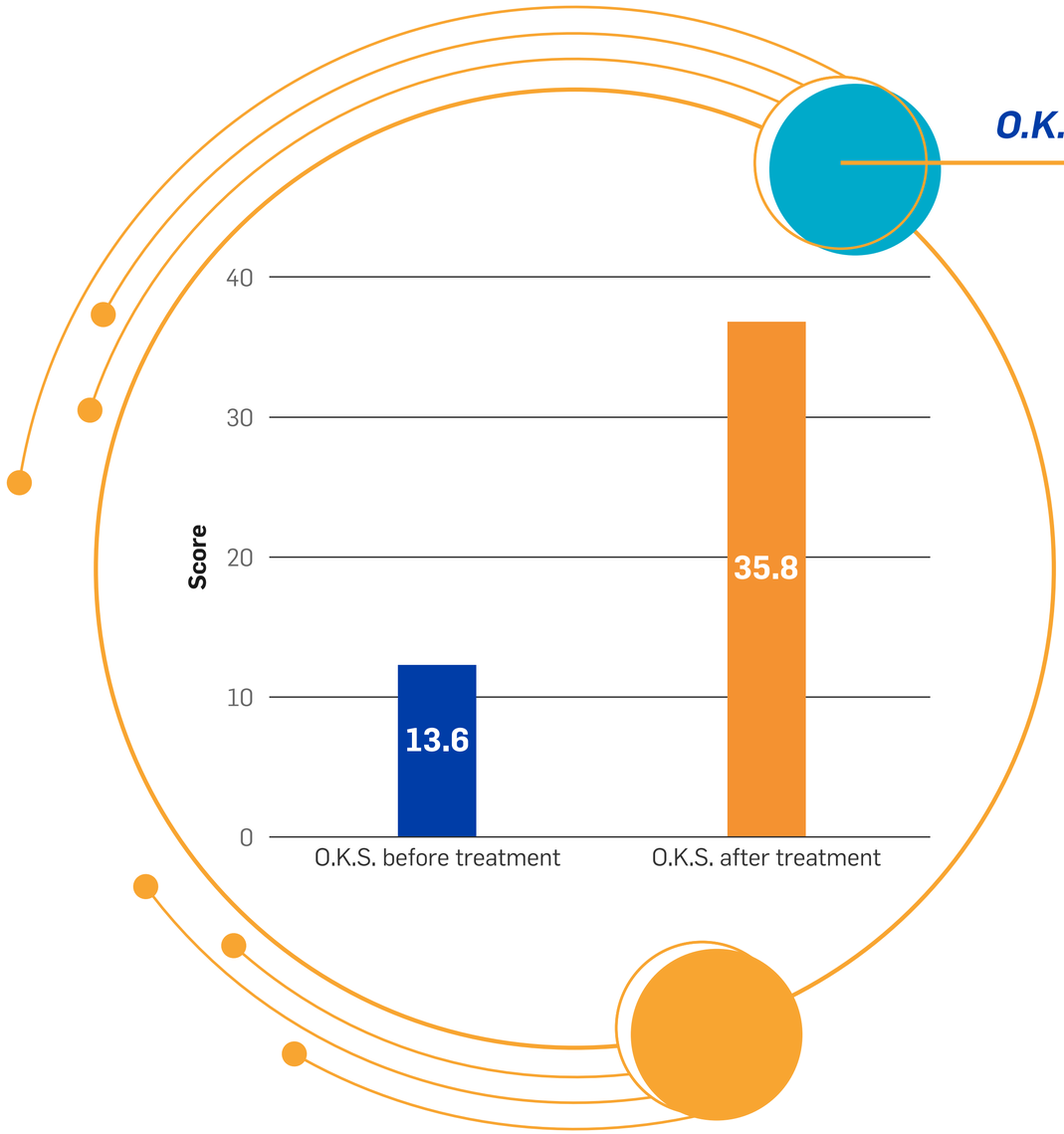
Reshkova V. et al. Physiological Regulating Medicine 2016-2017; 27-29

GUNA COLLAGEN MEDICAL DEVICES:
Efficacy in the treatment of gonarthrosis

Functionality improvement after the treatment with **MD-KNEE**



O.K.S. questionnaire before and after treatment

- Patients reported a **feeling of greater joint excursion after the first 2-3 sessions.**
- The **effect on pain** was **quite rapid.**
- All patients significantly **reduced consumption of analgesics.**
- **No patient reported any side effects** after the administration.

Study conducted on 53 patients with gonarthrosis stage I, II and III according to the Kellgren-Lawrence Scale. The patients were given intra-articular injections of MD-KNEE twice a week for 5 consecutive weeks. The dedicated questionnaire was administered at the first visit and at the end of the treatment.

OKS = Oxford Knee Score

Graph elaborated from text.

Download the study

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Ottaviani M. Physiological Regulating Medicine 2018; 19-28

GUNA COLLAGEN MEDICAL DEVICES:
Efficacy in the treatment of knee pain

The treatment with **MD-KNEE + MD-MATRIX showed:**

- **fast recovery**
- **excellent management of acute transient pain**
- **VAS scale ≤ 1 after 2 weeks of treatment**
- **no need to use NSAIDs**

Study conducted on 10 patients with a knee sprain associated with clinically negative involvement of the intra-articular ligaments and without significant intra-articular effusion. They were regularly treated with systemic NSAIDs for 4 days, but still had severe epicondylar pain at the end of this treatment. The patients then received periarticular injections of MD-KNEE + MD-MATRIX twice a week for 3 consecutive weeks.

Download the study

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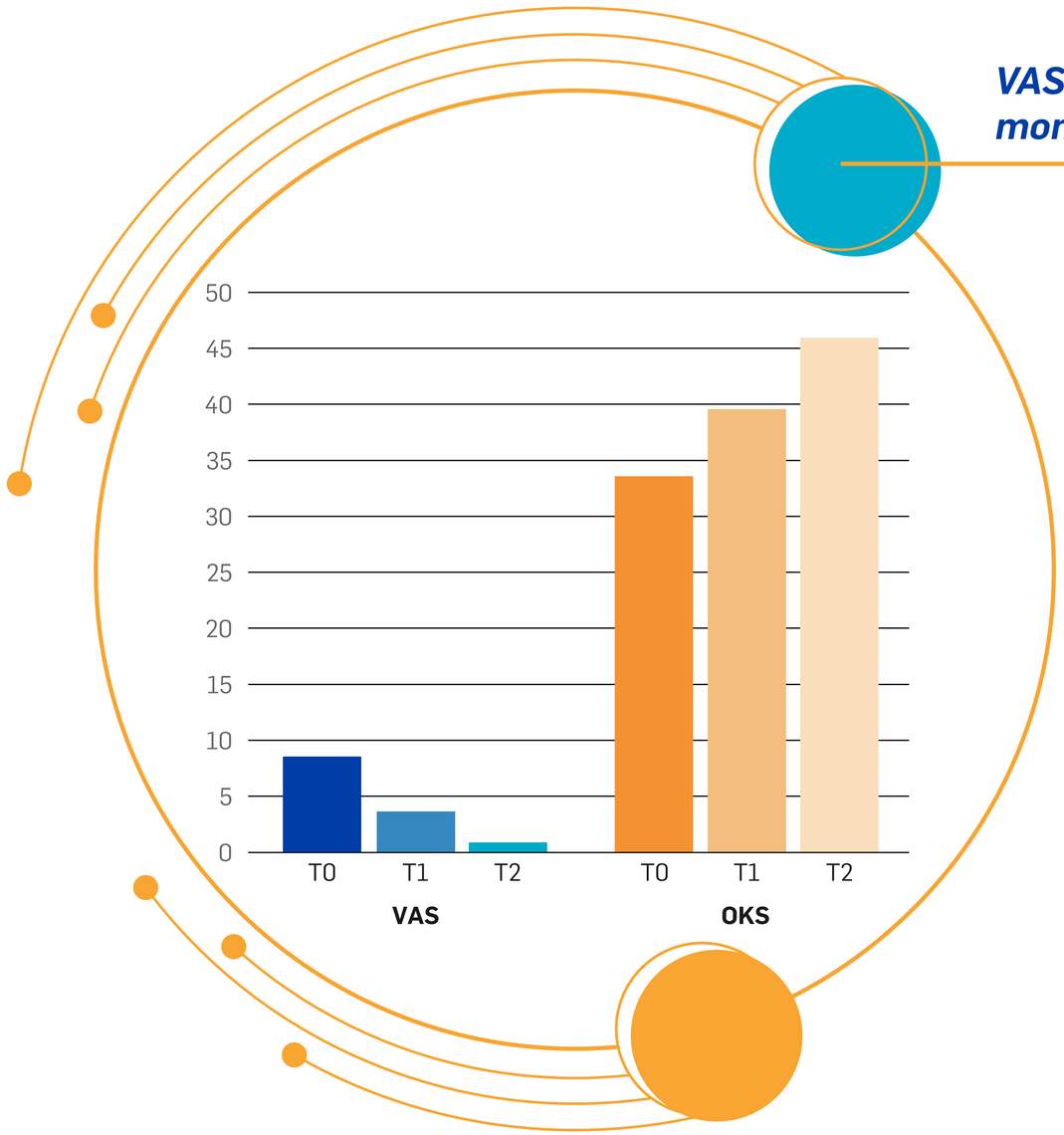
Mariconti P. Physiological Regulating Medicine 2016-2017; 39-40

GUNA COLLAGEN MEDICAL DEVICES:

Efficacy in the treatment of knee osteoarticular pain

Improvement of pain and joint functionality from the first month of treatment with **MD-KNEE + CHELT**

VAS scale and OKS score at baseline and 1 and 4 months after the start of the treatment



The combination of the two methods reduces pain by an average of 50% within the first month of treatment, maintaining and implementing this result without relapses even after 4 months.

Observational study conducted on 20 patients with osteoarticular knee pain. The patients were treated with MD-KNEE and received a CHELT application after each administration. The complete course of therapy consisted of a total of 6-10 injections spread over 4-6 weeks. Efficacy evaluations were carried out at T0 (initial evaluation), T1 (1 month) and T2 (4 months after the start of treatment).

VAS = Visual Analogue Scale
OKS = Oxford Knee Score
CHELT = Cryo High Energy Laser Therapy

Graphic elaboration of Tab.4.

Download the study

Replace Reinforce Repair

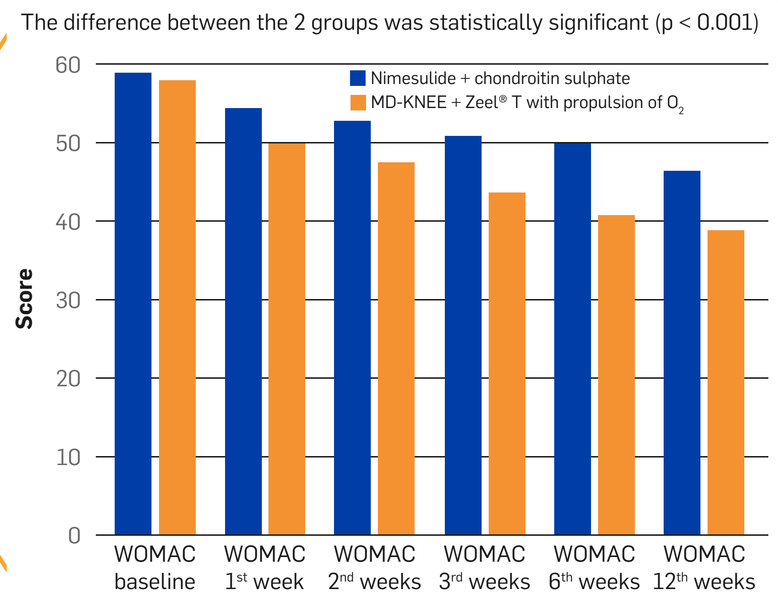
Feninno D., Bonacina A. La Med Biol 2017; 2: 37-42

GUNA COLLAGEN MEDICAL DEVICES:

Efficacy in the treatment of patello-femoral chondropathy

Greater reduction of WOMAC score for lower limb pain, stiffness, and function with **MD-KNEE + Zeel® T transmitted with propulsion of O_2** than with nimesulide + chondroitin sulphate

Progressive differences in mean WOMAC in the 2 patient groups



The **improvement of the clinical and functional picture is faster** in patients treated with MD-KNEE + Zeel® T transmitted with propulsion of O_2.

Controlled, randomised study conducted on 40 patients with patello-femoral chondropathy. 20 patients received a daily oral administration of nimesulide + chondroitin sulphate; the other 20 patients received a weekly administration of MD-KNEE + Zeel® T transmitted with O_2 propulsion. Efficacy evaluations were carried out before the start of treatment and 1, 2, 3, 6 and 12 weeks after the first administration.

WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Graphic elaboration of Tab.7.

Download the study

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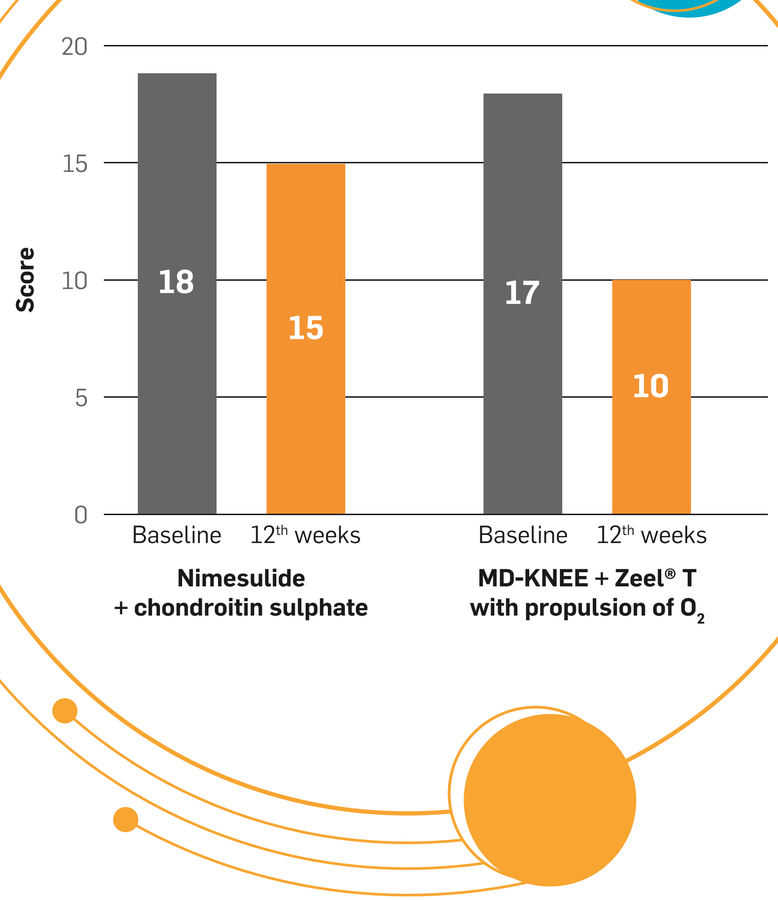
Posabella G. Physiological Regulating Medicine 2011; 3-10

GUNA COLLAGEN MEDICAL DEVICES:

Efficacy in the treatment of patello-femoral chondropathy

Greater reduction of function limitation with MD-KNEE + Zeel® T transmitted with propulsion of O_2 than with nimesulide + chondroitin sulphate

Lequesne Index before and after 12 weeks of treatment



The complete **absence of side effects** recorded in the patients of the group treated with **MD-KNEE + Zeel® T** transmitted with O_2 propulsion and the use of a **non-invasive, painless, and easy-to-use therapy** have led to **better acceptance and** to a **more advantageous economic cost.**

Controlled, randomised study conducted on 40 patients with patello-femoral chondropathy. 20 patients received nimesulide + chondroitin sulphate daily; the other 20 patients received a weekly administration of MD-KNEE + Zeel® T delivered with O_2 propulsion. Efficacy evaluations were carried out before the start of treatment and at 1, 2, 3, 6 and 12 weeks after the first administration.

Graph elaborated from text.

Download the study

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Posabella G. Physiological Regulating Medicine 2011; 3-10

GUNA COLLAGEN MEDICAL DEVICES:
Cost-effectiveness analysis in the treatment of gonarthrosis

Significant cost saving with the entire treatment cycle with **MD-KNEE in comparison with hyaluronic acid**

Results of the cost-minimisation analysis

Parameters	A	B
	MD-Knee	**SUPARTZ®**
Dose for each administration	4 mL	2.5 mL
No. total administrations	5	5
Difference (A-B)	**- € 110.00**	

MD-KNEE represents a more efficient option compared to a medium molecular weight hyaluronic acid such as SUPARTZ®: it has demonstrated to have a **lower average treatment cost over a 6-month time horizon,** while maintaining the same safety and efficacy.

Cost-minimisation analysis aimed at comparing, over a six-month horizon, the benefit and cost of treatment associated with MD-KNEE versus SUPARTZ® from a hospital perspective.

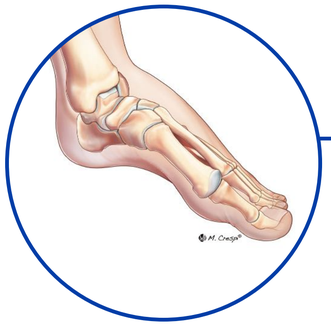
Graphic elaboration of Tab.2.

Download the study

Replace Reinforce Repair

Migliore A., Ravasio R. Physiological Regulating Medicine 2020; 3-7

MAIN INDICATIONS OF
GUNA COLLAGEN MEDICAL DEVICES



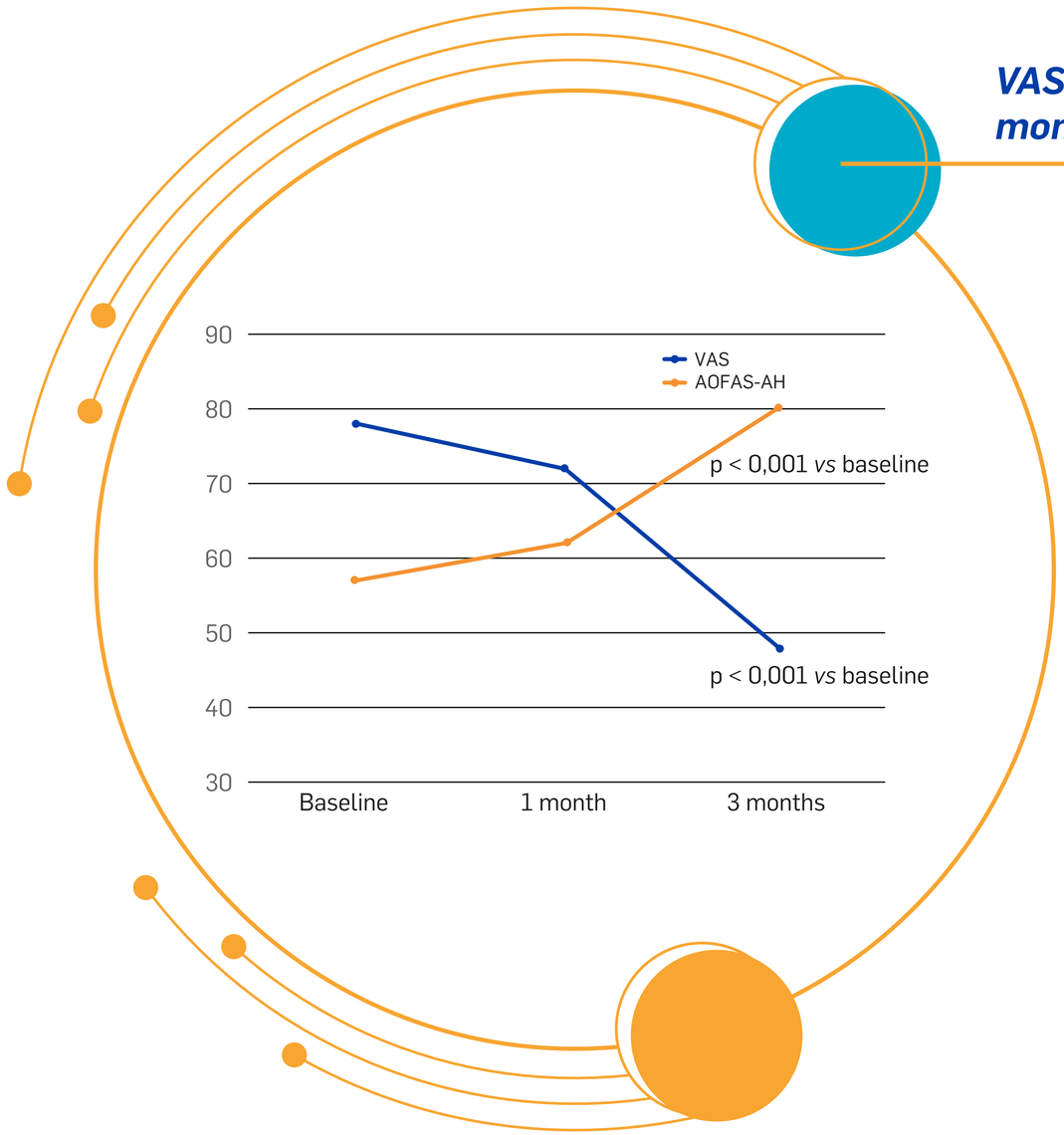
ANKLE/FOOT

PATHOLOGIES	*GUNA COLLAGEN MEDICAL DEVICES*
Osteoarticular pathologies	
Osteoarthritis	**MD-SMALL JOINTS** ⊕
Metatarsophalangeal joint pain	**MD-SMALL JOINTS** ⊕
Soft tissue disorders	
Achilles' tendonitis/tendinosis	**MD-TISSUE** ⊕
Lateral and medial capsuloligamentous injury/inflammation	**MD-TISSUE** ⊕
Anterior tibial tendinopathy	**MD-TISSUE** ⊕
Posterior tibial tendinopathy	**MD-TISSUE** ⊕
Peroneal tendinopathy	**MD-TISSUE** ⊕
Plantar fasciitis and calcaneal spurs	**MD-TISSUE** ⊕
Retrocalcaneal bursitis	**MD-TISSUE** ⊕
Morton's neuroma	**MD-NEURAL** ⊕

GUNA COLLAGEN MEDICAL DEVICES:

Efficacy in the treatment of plantar fasciopathy

Statistically significant improvement of pain and function after treatment with **MD TISSUE**



VAS scale and AOFAS-AH score at 1 month- and 3 months- follow-up

- **Adverse events were not observed** neither during nor after the treatment.
- **Since collagen is a structural protein of the plantar fascia, injectable collagen works not just healing, but also restoring the tissue's physiological function. Endogenous collagen synthesis, maturation, and secretion are also stimulated by injecting collagen, thus favouring plantar fascia repair.**

Prospective observational pilot study conducted on 10 non-professional marathon runners suffering from plantar fasciopathy for at least 6 months. The patients were treated with ultrasound-guided injections once a week for 4 weeks. Patients were evaluated at the time of enrolment (T0), one month (T1) and three months (T2) after the last injection.

VAS = Visual Analogue Scale
AOFAS-HF = American Orthopedic Foot Ankle Society - Hind Foot

Graphic elaboration of Fig.1.

Download the study

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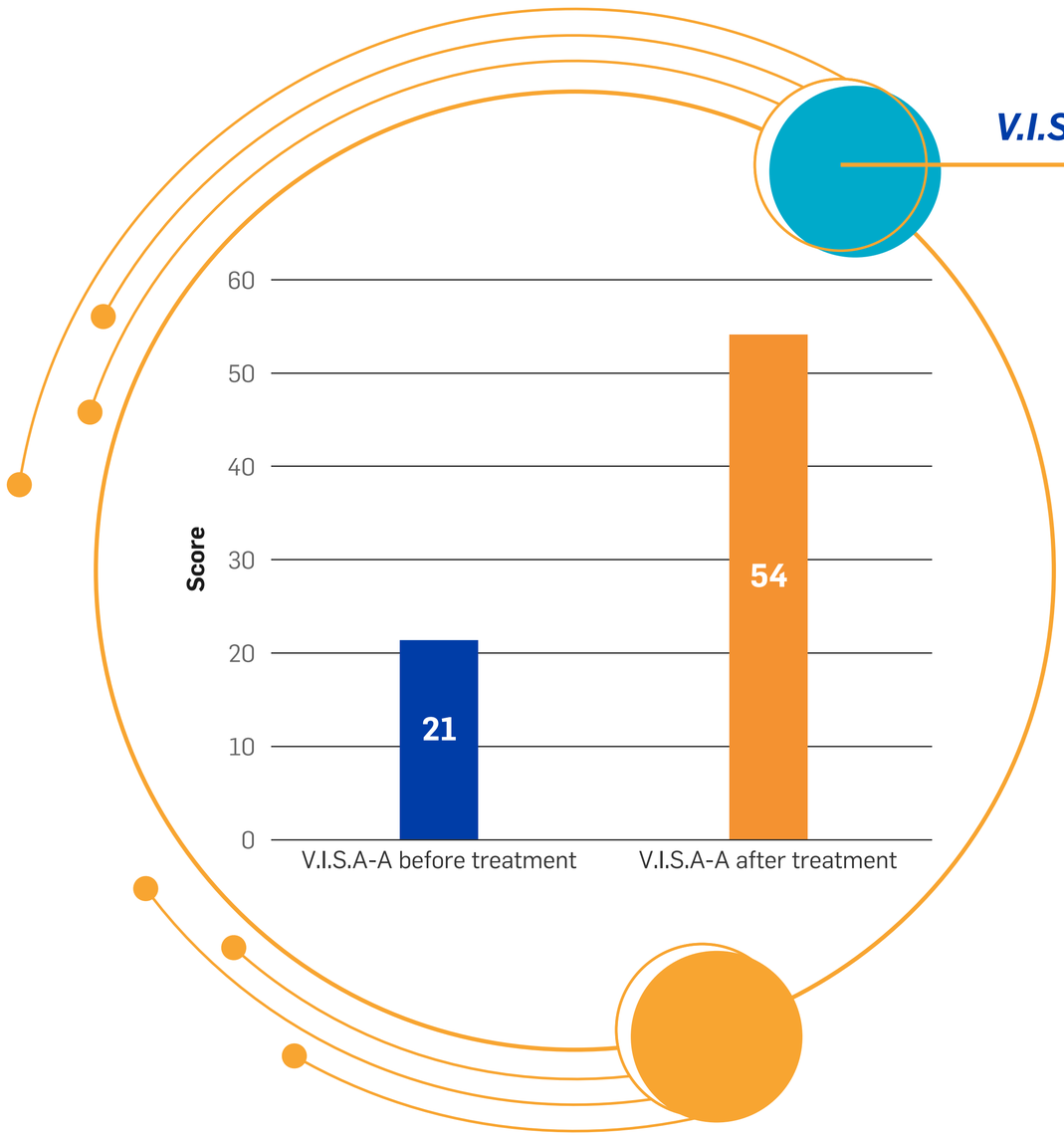
Corrado B. et al. Journal of Human Sport and Exercise 2020; 15 (3proc): S793-S805

GUNA COLLAGEN MEDICAL DEVICES:

Efficacy in the treatment of Achilles' tendinopathy

Function improvement after treatment with **MD TISSUE**



V.I.S.A.-A questionnaire before and after treatment

- **Efficacy on pain** was quite **rapid.**
- Patients underwent ultrasound examination **at the end of treatment, which showed reabsorption of the edema.**
- All patients significantly **reduced consumption of analgesics.**
- **No side effects** were **reported** after the administration of **MD TISSUE.**

Study conducted on 27 patients with mono- and/or bilateral Achilles tendinopathy, including 11 cases of tendinitis with ultrasound-documented exudate. The patients were given local injections of Collagen MD twice a week for 5 consecutive weeks. The dedicated questionnaire was given at the first visit and at the end of the treatment.

VISA-A = Victorian Institute of Sport Assessment – Achilleus

Graph elaborated from text.

Download the study

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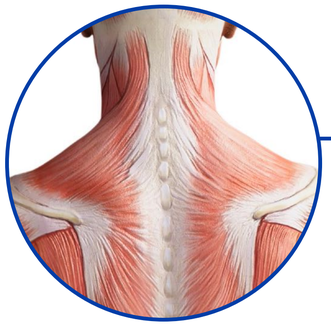
Ottaviani M. Physiological Regulating Medicine 2018; 19-28

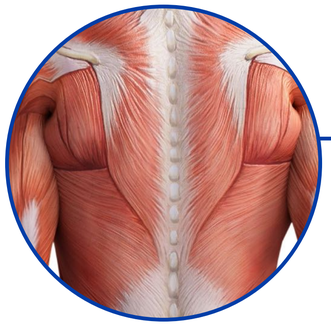
MAIN INDICATIONS OF
GUNA COLLAGEN MEDICAL DEVICES



SPINE – CERVICAL TRACT

PATHOLOGIES	*GUNA COLLAGEN MEDICAL DEVICES*
Cervical osteoarthritis	**MD-NECK** ⊕
Neck pain due to cervical muscular trigger points	**MD-NECK** ⊕ **+ MD-MUSCLE** ⊕
Torticollis	**MD-MUSCLE** ⊕ **or MD-NEURAL** ⊕
Muscle-tension cervicalgia	**MD-MUSCLE** ⊕
Whiplash	**MD-NECK** ⊕ **+ MD-NEURAL** ⊕
Cervicalgia due to bad posture	**MD-NECK** ⊕ **+ MD-MUSCLE** ⊕
Alterations of the cervical axis (Facet joint syndrome)	**MD-NECK** ⊕
Cervical spinal ligament syndrome	**MD-NECK** ⊕ **+ MD-NEURAL** ⊕
Cervical spinal nerve root pain	**MD-NECK** ⊕ **+ MD-NEURAL** ⊕

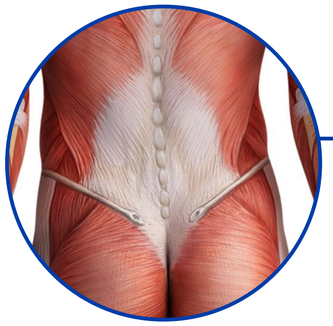
MAIN INDICATIONS OF
GUNA COLLAGEN MEDICAL DEVICES



SPINE – DORSAL TRACT

PATHOLOGIES	*GUNA COLLAGEN MEDICAL DEVICES*
Dorsal osteoarthrosis	**MD-THORACIC** ⊕
Thoracic pain due to scoliosis	**MD-MUSCLE** ⊕ **+ MD-NEURAL** ⊕
Thoracic pain due to thoracic long muscle trigger points	**MD-MUSCLE** ⊕
Pain due to thoracic spine osteophytosis	**MD-NEURAL** ⊕ **+ MD-LUMBAR** ⊕
Pain from spinal osteoporosis	**MD-NEURAL** ⊕ **+ MD-MUSCLE** ⊕
Alterations of the dorsal axis (costo-vertebral facet joint syndrome)	**MD-LUMBAR** ⊕
Thoracic spinal ligament syndrome	**MD-TISSUE** ⊕
Thoracic spinal nerve root pain	**MD-NEURAL** ⊕

MAIN INDICATIONS OF
GUNA COLLAGEN MEDICAL DEVICES



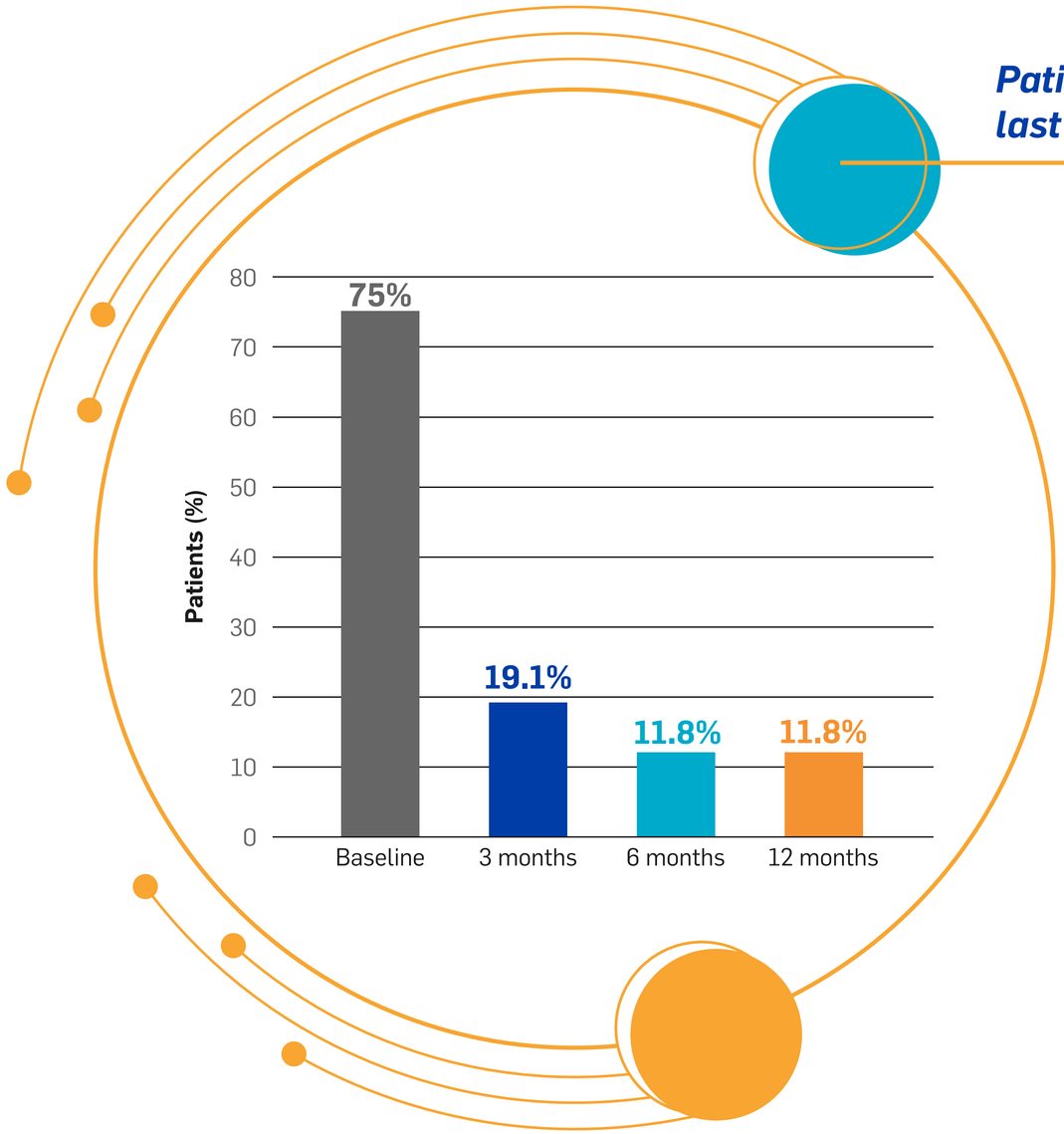
SPINE – LUMBAR TRACT

PATHOLOGIES	*GUNA COLLAGEN MEDICAL DEVICES*
Lumbar and lumbosacral osteoarthritis	**MD-LUMBAR ⊕**
Lumbar vertebral osteophytosis	**MD-LUMBAR ⊕**
Low-back pain secondary to musculo-tendinous trigger points	**MD-LUMBAR ⊕ + MD-MUSCLE ⊕**
Postural low-back aches	**MD-LUMBAR ⊕ + MD-MUSCLE ⊕ or MD-NEURAL ⊕**
Lumbar and lumbar-sacral mechanical imbalance	**MD-LUMBAR ⊕**
Lumbar and lumbar-sacral spinal ligament syndrome	**MD-LUMBAR ⊕ + MD-TISSUE ⊕**
Sacro-iliac syndrome	**MD-LUMBAR ⊕ + MD-NEURAL ⊕**
Spinal lumbar and lumbar-sacral nerve root pain	**MD-LUMBAR ⊕ + MD-NEURAL ⊕**
Sciatica	**MD-ISCHIAL ⊕ + MD-NEURAL ⊕**
Lumbar sciatica	**MD-ISCHIAL ⊕ or MD-LUMBAR ⊕ + MD-NEURAL ⊕**
Sciatica following surgery of herniated discs L4-L5, L5-S1	**MD-LUMBAR ⊕ + MD-NEURAL ⊕**

GUNA COLLAGEN MEDICAL DEVICES:

Efficacy in the treatment of vertebral pain [1-4]

Pain reduction after injection treatment with **MD-LUMBAR in association with manipulative treatment and acupuncture** [1]



Patients with severe pain at 3, 6 and 12 months after last treatment [1]

Functional disorders of the lumbosacral hinge were found in **46.2% of cases at the first visit, in 30.8% after 3 and 6 months and in 38.5% after 12 months.** [1,2]

Observational study conducted on 60 patients with vertebral disorders for at least 6 months, who were not responsive to pharmacological and physical therapy. The patients were treated with cycles of 3 consecutive weeks of manipulative therapy, acupuncture and MD-LUMBAR once a week for 10 weeks. The effects were evaluated 3, 6 and 12 months after the last treatment. [1,2]

Graph elaborated from text of (1).

Download the study

Replace
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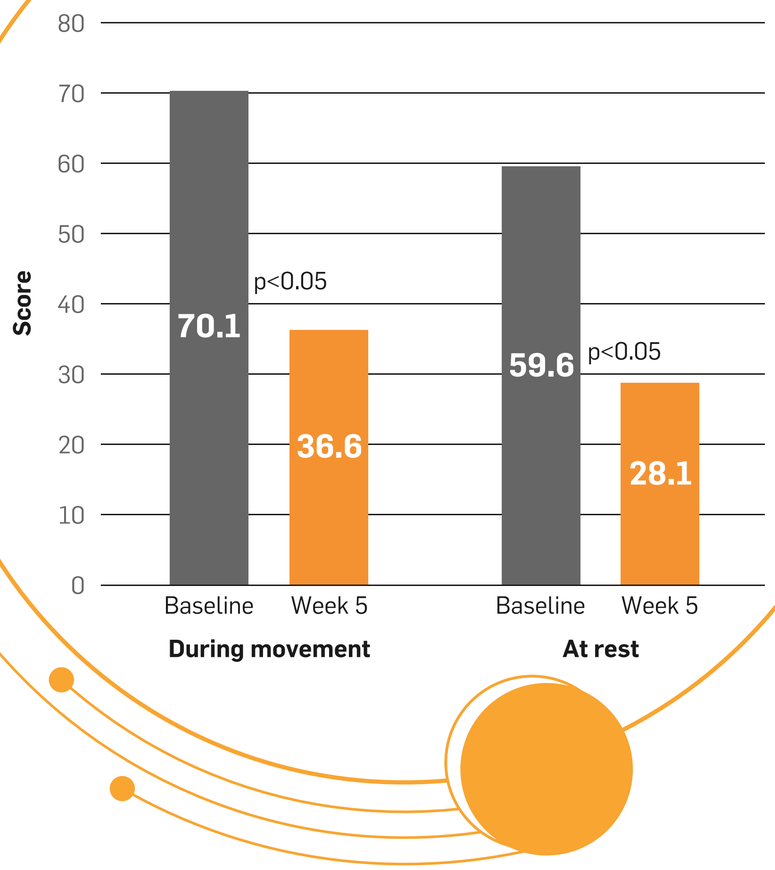
1. Ruiu DE. Advanced Therapies 2012; 1: 30-39
2. Zocco R. et al. Physiological Regulating Medicine 2012; 41
3. Raychev I. Movement Disorders Bulgaria 2013/2; 28-32
4. Milano E. Physiological Regulating Medicine 2020; 39-44

GUNA COLLAGEN MEDICAL DEVICES:

Efficacy in the treatment of low back pain [1,2]

Pain reduction at rest and during movement after treatment with **MD-LUMBAR + MD-MUSCLE + MD-NEURAL** [1]

VAS scale at baseline and at the 5th week (2 weeks after the last injection) [1]



Single-blind study conducted on 100 patients with acute lumbar pain. 75 patients were treated with injections of MD-MUSCLE (1 ml) + MD-LUMBAR (2 ml) + MD-NEURAL (1 ml) at 8 predefined sites (0.5 ml at each site). 25 patients were treated with 4 ml mesocaine 1% at the same 8 predefined sites (control group). Five applications were performed (2 per week in the first 2 weeks, followed by the fifth one). The evaluation of the primary outcome took place at week 5, 2 weeks after the last injection. [1]

VAS = Visual Analogue Scale

Graph elaborated from text (1).

Download the study

Replace
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1. Pavelka K. et al. Physiological Regulating Medicine 2012; 3-6
2. Pavelka K. et al. Physiol Res 2019; 68 (Suppl. 1): S65-S74

GUNA COLLAGEN MEDICAL DEVICES:

Efficacy in the treatment of low back pain [1,2]

- **Pain relief** was quite fast, **less than 2 weeks**. [1]

- **The analgesic efficacy** of Collagen MDs **was not inferior to that of mesocaine.** [1]

- The **tolerability** was **very good**. [1]

- **In a long-term perspective, injections of Collagen MDs** are a much **more physiological treatment option** compared to local anesthetics, which induce only a temporary effect. [1]

- **The effect** of local collagen administration **is structural, functional, analgesic and antioxidant.** [2]

- Collagen MDs represent a **new strategy in the treatment of pain**. They are based on the **reinforcement of the collagen matrix** underlying the structures of the musculoskeletal system (bio-scaffold) which provides **analgesic effects**. [2]

Replace
Reinforce
Repair

1. Pavelka K. et al. Physiological Regulating Medicine 2012; 3-6
2. Pavelka K. et al. Physiol Res 2019; 68 (Suppl. 1): S65-S74

GUNA COLLAGEN MEDICAL DEVICES:
Efficacy in the treatment of low back pain

CASE STUDY 1

- Female, 26 years old, practising horse riding and hurdle jumping.
- In June 2014 she **fell while jumping during a competition**, due to a technical error.
- The patient complained of **intense low back pain, which worsened in the following days**, forcing her to stop horse riding.
- **MRI negative for herniated discs**.
- The patient was treated with **manipulative therapy** and **returned to training after two sessions**.
- After one month of residual pain and discomfort, the patient agrees to **associate the manipulative therapy with injection therapy** with Guna Collagen Medical Devices: **MD-LUMBAR + MD-MATRIX**, 2 injections per week for 2 consecutive weeks; then 1 injection per week for 6 consecutive weeks.
- **Even though pain had completely disappeared after just 3 treatments, the patient completed the entire therapy cycle.**

The local administration of **MD-LUMBAR + MD-MATRIX** induced the **deposition of collagen fibres in the damaged area**, thus leading to **complete healing**.

Download the study

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Massullo C. Physiological Regulating Medicine 2016-2017; 3-7

GUNA COLLAGEN MEDICAL DEVICES:
Efficacy in the treatment of low back pain

CASE STUDY 2

- Male, 28 years old, football player in the role of striker.
- In September 2014 an **acute lumbar joint block** occurred after a training session in the gym, leading to immediate interruption of sport activity.
- Treatment prescribed by the sports club doctor: **NSAIDs for 5 days, 3 osteopathic sessions + 8 applications of Tecar therapy.**
- The player **resumed training after 15 days**, although not completely recovered.
- Symptoms worsened: MRI shows **“moderate disc protrusion in the posterior median L4-L5 and L5-S1”.** There are no disc herniations.
- Treatment continued with **muscle stretching** of ischio-crural muscles, intra- and extra-rotators muscles, iliopsoas muscles + injection therapy with **MD-LUMBAR + MD-MUSCLE + MD-MATRIX** at a frequency of 3 sessions per week for 1 week; 2 sessions per week for 2 consecutive weeks; 1 session per week for 5 consecutive weeks.
- **After 3 applications the patient gradually returns to training; after 7 applications (3 weeks) he plays a game for the full 90 minutes. “Discomfort” in the first morning movements remained until the 9th session.**

Vertebral manipulative therapy alone had not been enough to remove the primary cause of the lumbar block, resulting in an amplification of the lesion. Muscle stretching therapy is aimed at vertebral biomechanical recovery. Injection **therapy with MD-LUMBAR + MD-MATRIX + MD-MUSCLE enabled to neutralise the concomitant inflammation and disc degeneration.**

Download the study

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Massullo C. Physiological Regulating Medicine 2016-2017; 3-7

HOW TO USE
GUNA COLLAGEN MEDICAL DEVICES

- Guna Collagen Medical Devices come in boxes of 10 of 5 **vials of 2 ml** solution for **intradermal, subcutaneous, periarticular, intra-articular and intramuscular** injection.

- Guna Collagen Medical Devices **can be used singularly or one associated with another** (2 or 3 MDs in the same syringe), according to the specific needs of the patient.

- Guna Collagen Medical Devices **can be used even if patient is undergoing other treatments, such as corticosteroids, NSAIDs, chondroprotectors. There are no contraindications in cases concomitant of physical therapies** (manipulative therapy, acupuncture, electroacupuncture, massages, etc.), **instrumental therapies** (magnetotherapy, ultrasound therapy, laser therapy, electrotherapy, Oxygen-Ozone Therapy, shock waves, etc.) **or thermal therapy.**

Download the study

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Reinforce
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Milani L. Physiological Regulating Medicine 2010; 3-15

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MD-HIP. IFU

MD-ISCHIAL. IFU

MD-KNEE. IFU

MD-LUMBAR. IFU

MD-MATRIX. IFU

MD-MUSCLE. IFU

MD-NECK. IFU

MD-NEURAL. IFU

MD-POLY. IFU

MD-SHOULDER. IFU

MD-SMALL JOINTS. IFU

MD-THORACIC. IFU

MD-TISSUE. IFU

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Milani L. Physiological Regulating Medicine 2019; 3-18

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INSIGHTS

Internal code: 7SM010
Bureau Veritas Certification body.
The following information is intended exclusively for professionals.

COLLAGEN CHARACTERISTICS OF GUNA COLLAGEN MEDICAL DEVICES

- The **tropocollagen** present in Guna Collagen Medical Devices provides a mechanic support which constitutes an effective **bio-scaffold** [1]

- Its **effectiveness** can **be attributed to the induction of endogenous collagen synthesis by fibroblasts.**

- **Fibroblasts** generate and exert **force on the extracellular matrix during repair.** These forces are expressed in the contraction of fibroblasts, which **are essential for repairing damages.** An optimal level of contractile capacity of fibroblasts is necessary to facilitate repair processes and reduce scar formation. [2]

1. Milani L. Physiological Regulating Medicine 2010; 3-15
2. Massoud EIE. World J Orthop 2013; 4(4): 229–240

Replace
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EFFECTS OF MD-TISSUE ON CULTURED HUMAN TENOCYTES: *IN VITRO STUDY*

The addition of **MD-TISSUE** to a culture of human tenocytes produces the following effects:

- **increased levels of type I collagen**
- **stimulation of tenocyte migration for wound healing**, mediated by a mechanical input
- **improvement of tenocyte binding to the extracellular matrix and of the ability to form more efficient focal adhesions** to promote cell migration

MD-TISSUE, acting as **a mechanical scaffold,** could be an **effective medical device** to promote **tendon healing** in tendonitis with **a regenerative and rehabilitative approach.**

Download the study

Randelli F. Cells 2020; 9 (12): 2641

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HYALURONIC ACID

- **It is a** joint cavity **lubricant, acting** exclusively **in the intra-articular compartment and mainly in large joints** [1]
- It has a **medium to high lubricating viscosity**, with **visco-induction or visco-supplementation** action depending on molecular weight [2-4]
- It is effective in **cases of moderate to medium clinical severity** [1]
- **More frequent side effects** [5]
  - Pain and temporary local inflammatory reaction
- **Less frequent side effects** [5]
  - Allergic reactions

VS

TYPE I COLLAGEN

- It **acts on** the structures of **the extra-articular compartment (capsules, ligaments, tendons) of small, medium and large joints**, in addition to the intra-articular compartment [1]
- **It strengthens the support structures of lax joints,** with **regenerative and antalgic effect** [1,6]
- It is effective **not only in cases of moderate to medium clinical severity, but also in more severe conditions of disease and related disability** [1]
- Unlike hyaluronic acid, **it does not have visco-supplementation properties** [2-4]
- **It is composed of three alpha chains of amino acids organized in a triple helix forming a linear protein structure.** The glycoprotein sequences of α1 and α2 chains of human type I collagen have 97% and 94% homology with porcine type I collagen
- **It acts as a bio-scaffold** [7]
- **It has a very high safety profile for the patient** [8]

1. Ottaviani M. Physiological Regulating Medicine 2018; 19-28
2. Ganesan VV. et al. Biophysical Chemistry 2018; 240: 15-24
3. Ferreira AM. et al. Acta Biomaterialia 2012; 8 (9): 3191-3200
4. Campbell KA. et al. Arthroscopy 2015; 31 (10): 2036-45.e14
5. Lazzaro F. La terapia infiltrativa nell'Apparato locomotore, pag. 41
6. Hauser R.A., Dolan E.E. Journal of Prolotherapy 2011; 3 (4): 836-846
7. Randelli PS. GIOT 2010; 36: 211-222
8. Milani L. Physiological Regulating Medicine 2010; 3-15

Replace
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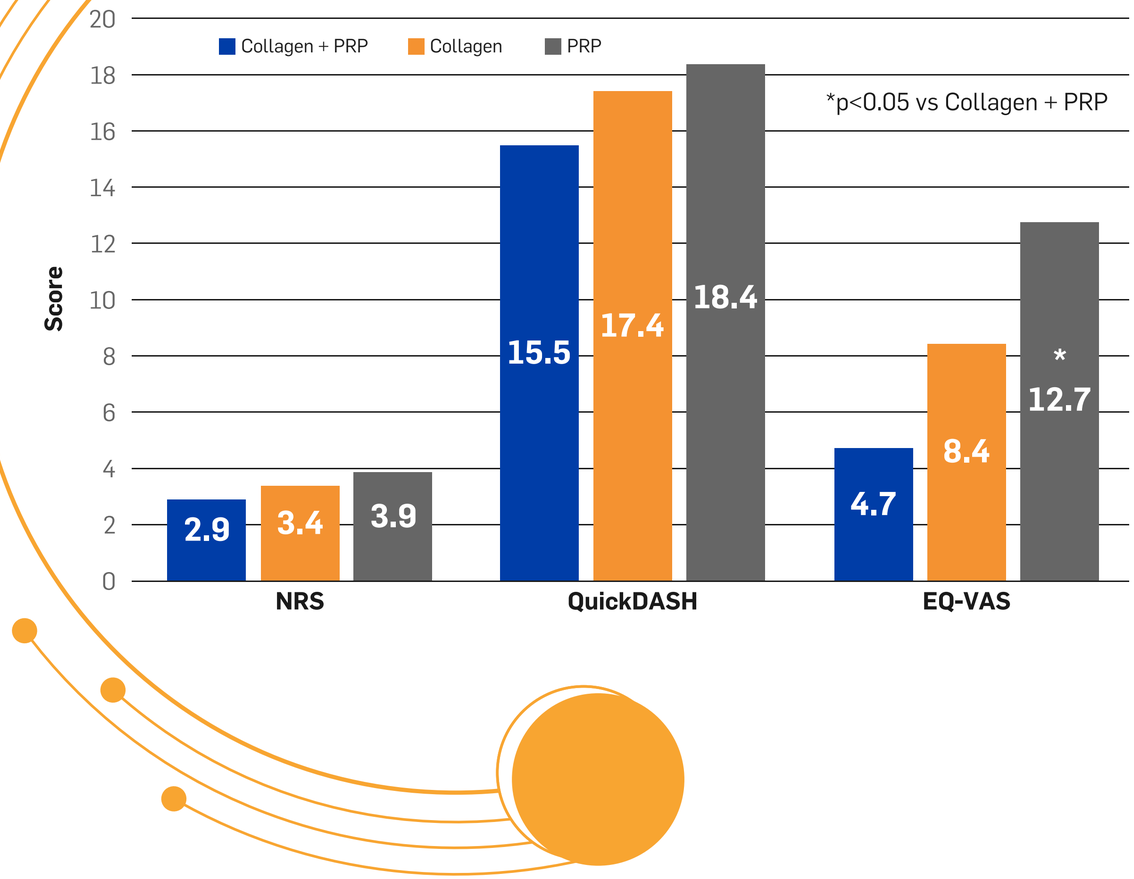
Repair

NO DIFFERENCE BETWEEN THE USE OF COLLAGEN AND PRP, ALONE OR IN ASSOCIATION, IN PARTIAL THICKNESS ROTATOR CUFF INJURIES

Mean variation in NRS scale and QuickDASH and EQ-VAS questionnaires between baseline and week 12 in the three treatment groups



Randomised, controlled, open-label, single-centre, outpatient study conducted on 90 patients with ultrasound-confirmed partial thickness rotator cuff injury (53% men; mean age 53.8 years), randomised to three treatment groups:

- *Group A (n=30): collagen (3 vials MD-SHOULDER, 6 ml) + PRP (2 ml)*
- *Group B (n=30): collagen (3 vials MD-SHOULDER, 6 ml)*
- *Group C (n=30): PRP*

Each group was treated by three ultrasound-guided injections into the shoulder bursa, one per week. All patients were allowed to continue physical rehabilitation therapy. Assessment was made at baseline, 6, 12 and 24 weeks after the last injection treatment.

PRP = Platelet-rich plasma
NRS = Numeric Rating Scale
DASH = Disability of the Arm, Shoulder and Hand
EQ-VAS = EuroQol-Visual Analogue Scales

Graph elaborated from text.

Download the study

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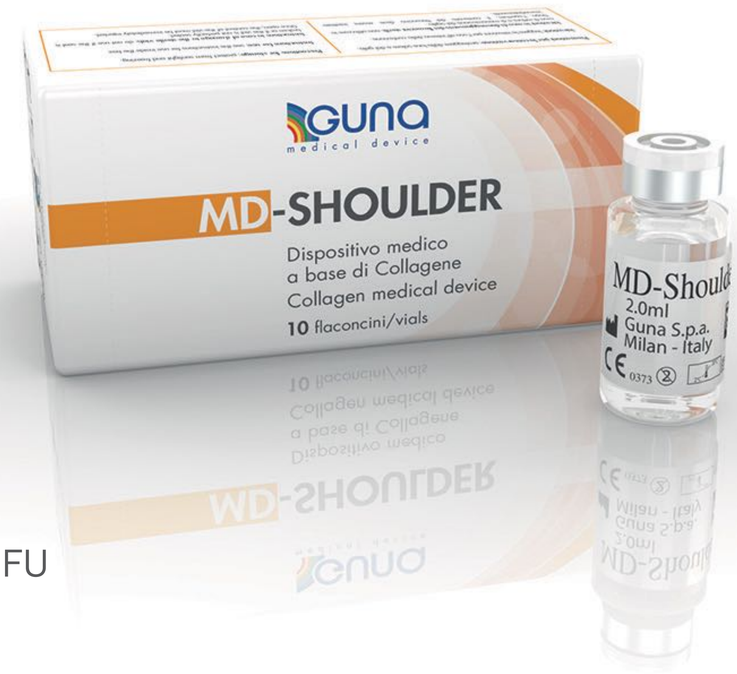
Godek P. et al. Research Square 2021

GUNA COLLAGEN MEDICAL DEVICES

«SPECIFIC»

MD - SHOULDER

Composition: Collagen of porcine origin, Iris, NaCl, Water for injection.



- Effectively reduces pain and improves joint mobility of the shoulder

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

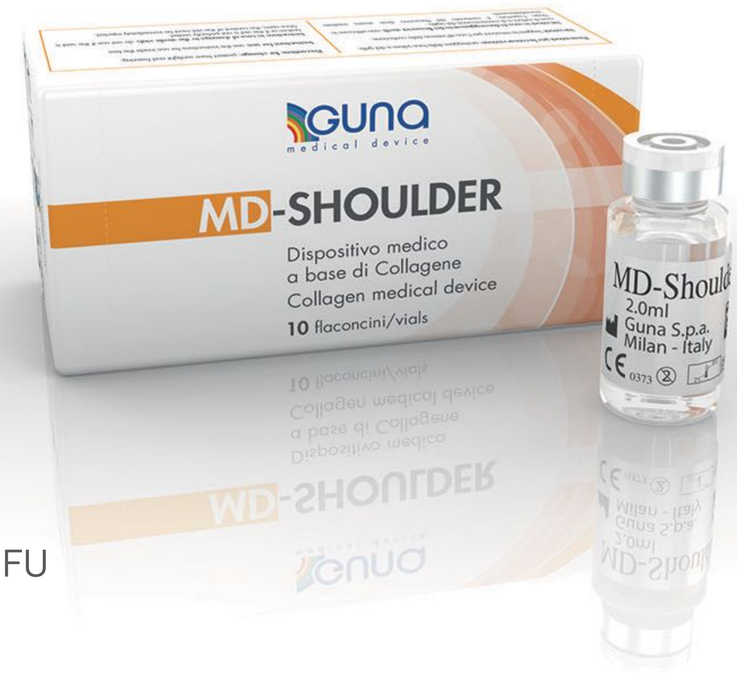
MD-SHOULDER. IFU

GUNA COLLAGEN MEDICAL DEVICES

«SPECIFIC»

MD - SHOULDER

Composition: Collagen of porcine origin, Iris, NaCl, Water for injection.



- Effectively reduces pain and improves joint mobility of the shoulder

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

MD-SHOULDER. IFU

GUNA COLLAGEN MEDICAL DEVICES

«SPECIFIC»

MD - HIP

Composition: Collagen of porcine origin, Calcium Phosphate, NaCl, Water for injection.

- Improves mobility of the hip joint
- Supports peri-articular muscle tissue
- Soothes pain at rest or pain due to joint movement or bad posture

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

MD-HIP. IFU

GUNA COLLAGEN MEDICAL DEVICES

«SPECIFIC»

MD - HIP

Composition: Collagen of porcine origin, Calcium Phosphate, NaCl, Water for injection.

- Improves mobility of the hip joint
- Supports peri-articular muscle tissue
- Soothes pain at rest or pain due to joint movement or bad posture

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

MD-HIP. IFU

GUNA COLLAGEN MEDICAL DEVICES

«SPECIFIC»

MD - KNEE

Composition: Collagen of porcine origin, Arnica, NaCl, Water for injection.

- Effectively improves knee pain and mobility

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

MD-KNEE. IFU

GUNA COLLAGEN MEDICAL DEVICES

«SPECIFIC»

MD - KNEE

Composition: Collagen of porcine origin, Arnica, NaCl, Water for injection.

- Effectively improves knee pain and mobility

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

MD-KNEE. IFU

GUNA COLLAGEN MEDICAL DEVICES

«SPECIFIC»

MD - SMALL JOINTS

Composition: Collagen of porcine origin, Viola, NaCl, Water for injection.

- Effectively reduces pain and improves the mobility of small joints

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

MD-SMALL JOINTS. IFU

GUNA COLLAGEN MEDICAL DEVICES

«SPECIFIC»

MD - SMALL JOINTS

Composition: Collagen of porcine origin, Viola, NaCl, Water for injection.

- Effectively reduces pain and improves the mobility of small joints

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

MD-SMALL JOINTS. IFU

GUNA COLLAGEN MEDICAL DEVICES

«SPECIFIC»

MD - SMALL JOINTS

Composition: Collagen of porcine origin, Viola, NaCl, Water for injection.

- Effectively reduces pain and improves the mobility of small joints

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

MD-SMALL JOINTS. IFU

GUNA COLLAGEN MEDICAL DEVICES

«SPECIFIC»

MD - LUMBAR

Composition: Collagen of porcine origin, Hamamelis, NaCl, Water for injection.

- Effectively improves mobility of the lumbosacral area of the spine

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

MD-LUMBAR. IFU

GUNA COLLAGEN MEDICAL DEVICES

«SPECIFIC»

MD - LUMBAR

Composition: Collagen of porcine origin, Hamamelis, NaCl, Water for injection.

- Effectively improves mobility of the lumbosacral area of the spine

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

MD-LUMBAR. IFU

GUNA COLLAGEN MEDICAL DEVICES

«SPECIFIC»

MD - LUMBAR

Composition: Collagen of porcine origin, Hamamelis, NaCl, Water for injection.

- Effectively improves mobility of the lumbosacral area of the spine

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

MD-LUMBAR. IFU

GUNA COLLAGEN MEDICAL DEVICES

«SPECIFIC»

MD - ISCHIAL

Composition: Collagen of porcine origin, Rhododendron, NaCl, Water for injection.

- Improves leg mobility
- Supports leg muscle tissue
- Soothes the pain due to inflammation/ compression of the great sciatic and sciatic nerve

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

MD-ISCHIAL. IFU

GUNA COLLAGEN MEDICAL DEVICES

«SPECIFIC»

MD - ISCHIAL

Composition: Collagen of porcine origin, Rhododendron, NaCl, Water for injection.

- Improves leg mobility
- Supports leg muscle tissue
- Soothes the pain due to inflammation/ compression of the great sciatic and sciatic nerve

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

MD-ISCHIAL. IFU

GUNA COLLAGEN MEDICAL DEVICES

«SPECIFIC»

MD - NECK

Composition: Collagen of porcine origin, Silica, NaCl, Water for injection.

- Improves mobility of the cervical region of the spine
- Promotes cervical muscle stretching
- Supports cervical muscle tissue in bad posture disorders
- Soothes cervical column pain due to movement

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

MD-NECK. IFU

GUNA COLLAGEN MEDICAL DEVICES

«SPECIFIC»

MD - NECK

Composition: Collagen of porcine origin, Silica, NaCl, Water for injection.

- Improves mobility of the cervical region of the spine
- Promotes cervical muscle stretching
- Supports cervical muscle tissue in bad posture disorders
- Soothes cervical column pain due to movement

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

MD-NECK. IFU

GUNA COLLAGEN MEDICAL DEVICES

«SPECIFIC»

MD - POLY

Composition: Collagen of porcine origin, Drosera, NaCl, Water for injection.

- Improves small joint mobility
- Promotes muscle stretching
- Supports muscle tissue in bad posture disorders
- Soothes local pain and pain due to joint movement or bad posture

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

MD-POLY. IFU

GUNA COLLAGEN MEDICAL DEVICES

«SPECIFIC»

MD - THORACIC

Composition: Collagen of porcine origin, Cimicifuga, NaCl, Water for injection.

- Improves mobility of the thoracic tract of the spine
- Promotes muscle stretching
- Supports muscle tissue in bad posture disorders
- Soothes pain due to movement

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

MD-THORACIC. IFU

GUNA COLLAGEN MEDICAL DEVICES

«SPECIFIC»

MD - THORACIC

Composition: Collagen of porcine origin, Cimicifuga, NaCl, Water for injection.

- Improves mobility of the thoracic tract of the spine
- Promotes muscle stretching
- Supports muscle tissue in bad posture disorders
- Soothes pain due to movement

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

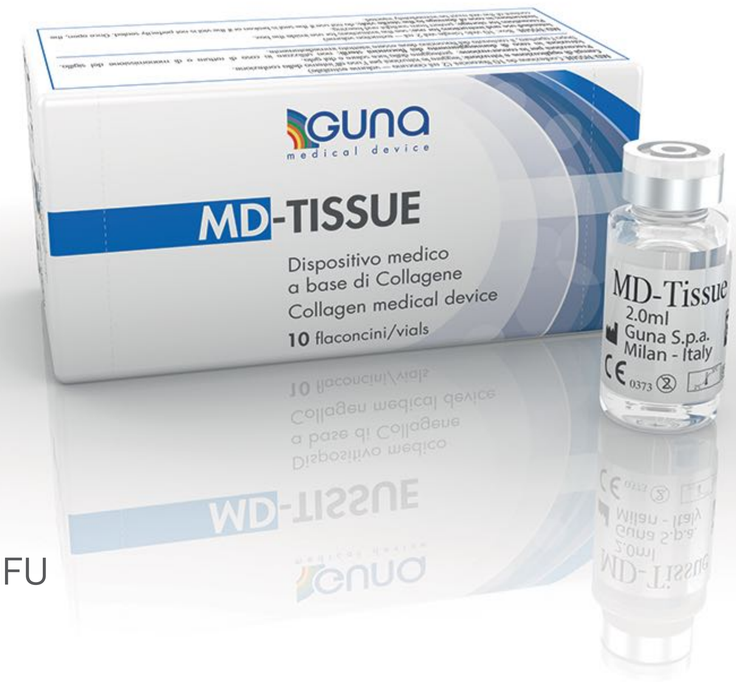
MD-THORACIC. IFU

GUNA COLLAGEN MEDICAL DEVICES

«NON-SPECIFIC»

MD - TISSUE

Composition: Collagen of porcine origin, Ascorbic acid, Magnesium gluconate, Pyridoxine hydrochloride, Riboflavin, Thiamine hydrochloride, NaCl, Water for injection.



- Effectively reduces pain and improves joint and tissue movement (tendons and ligaments)

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

MD-TISSUE. IFU

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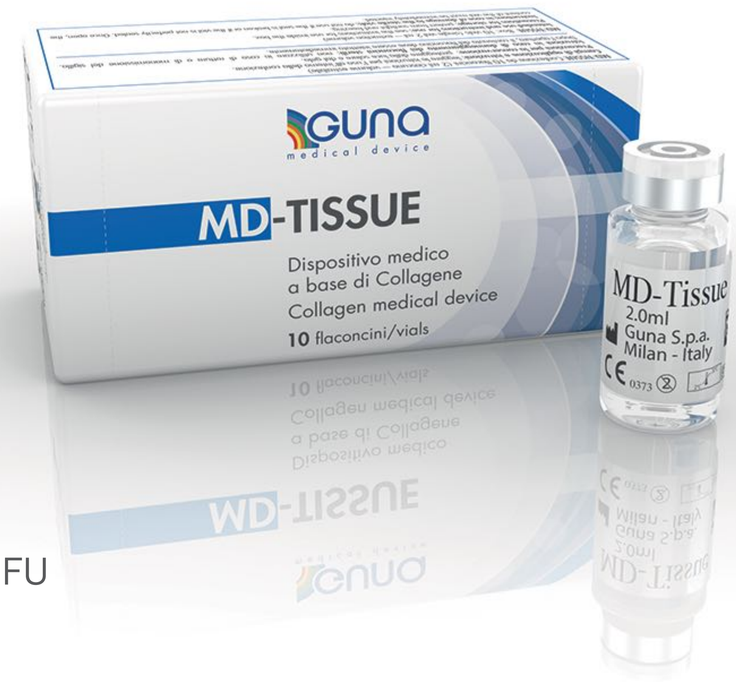

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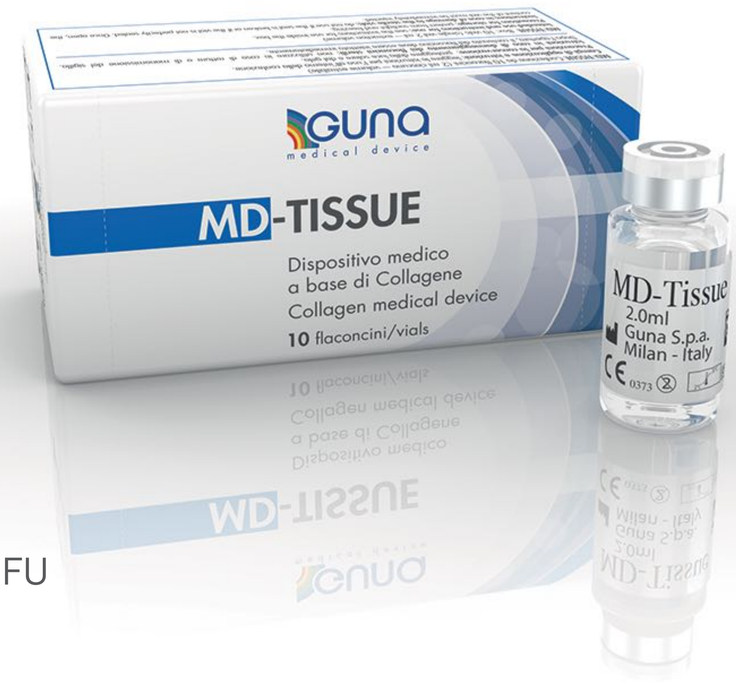

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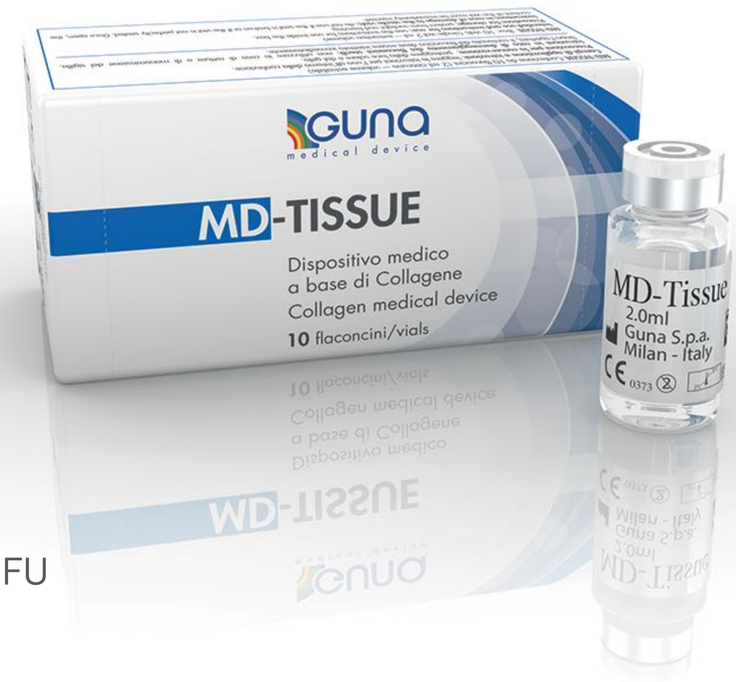

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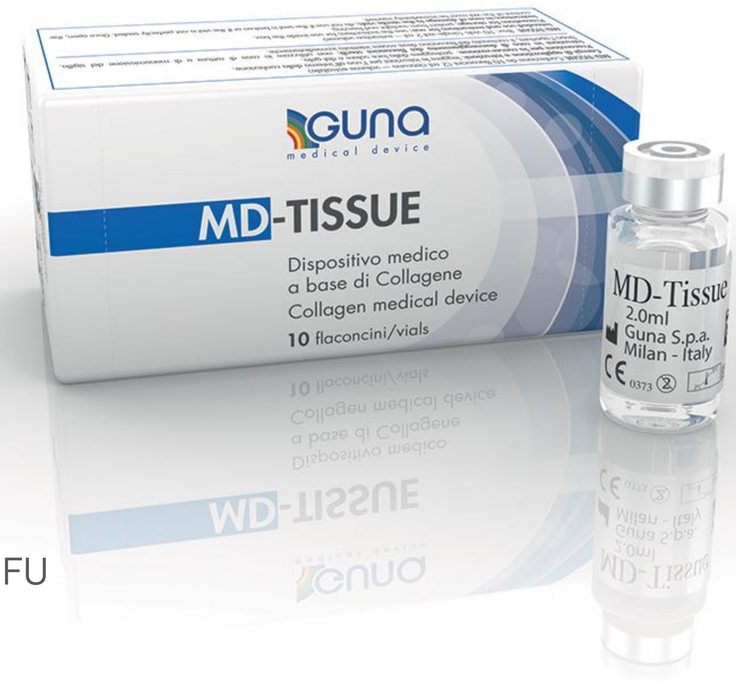


- Effectively reduces pain and improves joint and tissue movement (tendons and ligaments)

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

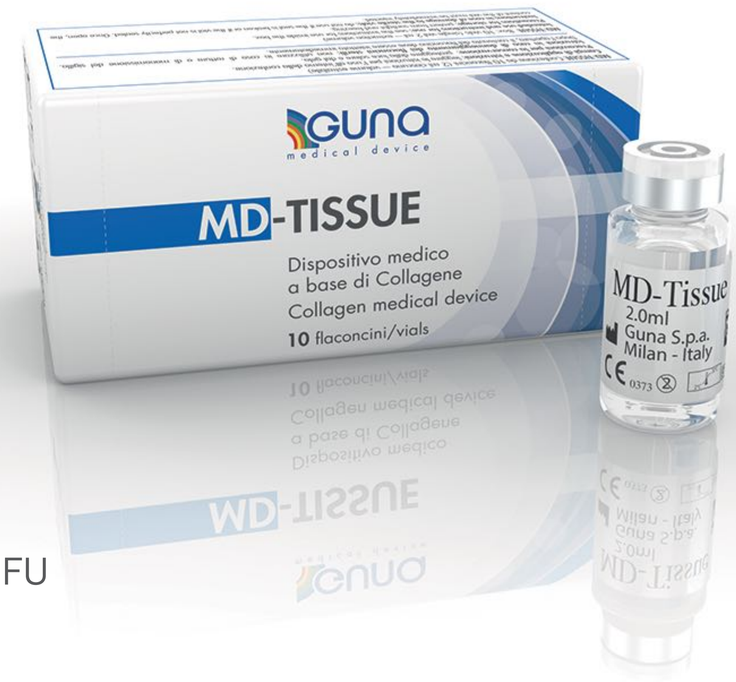
MD-TISSUE. IFU

GUNA COLLAGEN MEDICAL DEVICES

«NON-SPECIFIC»

MD - TISSUE

Composition: Collagen of porcine origin, Ascorbic acid, Magnesium gluconate, Pyridoxine hydrochloride, Riboflavin, Thiamine hydrochloride, NaCl, Water for injection.



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MD-TISSUE. IFU

GUNA COLLAGEN MEDICAL DEVICES

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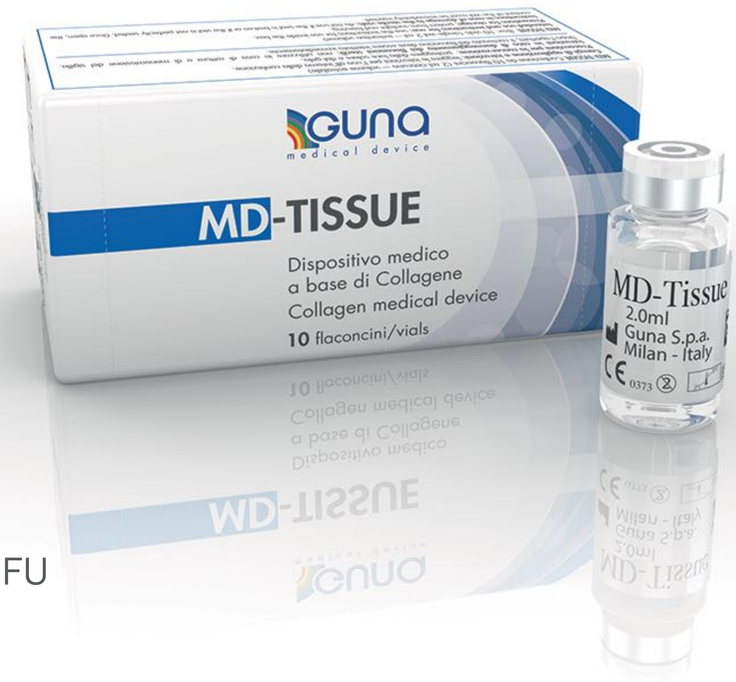
MD - TISSUE

Composition: Collagen of porcine origin, Ascorbic acid, Magnesium gluconate, Pyridoxine hydrochloride, Riboflavin, Thiamine hydrochloride, NaCl, Water for injection.



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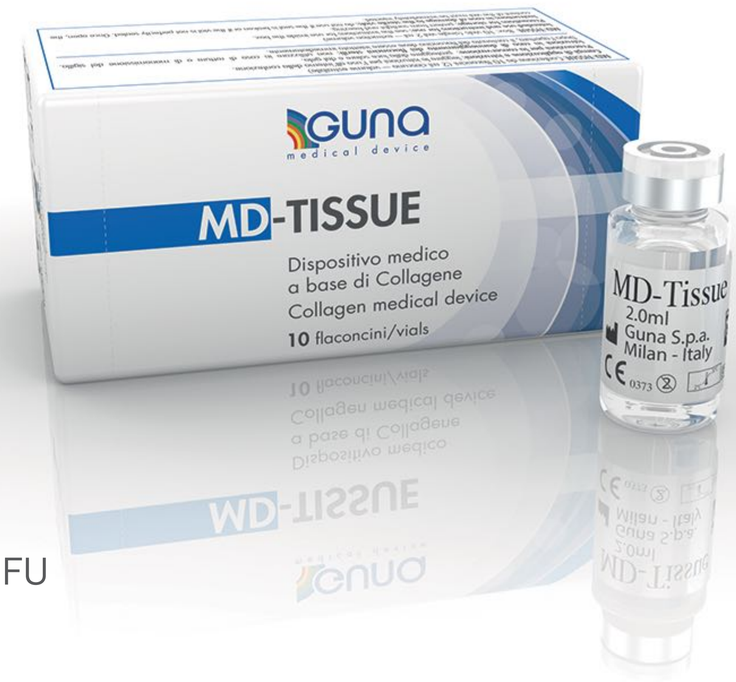

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MD-TISSUE. IFU

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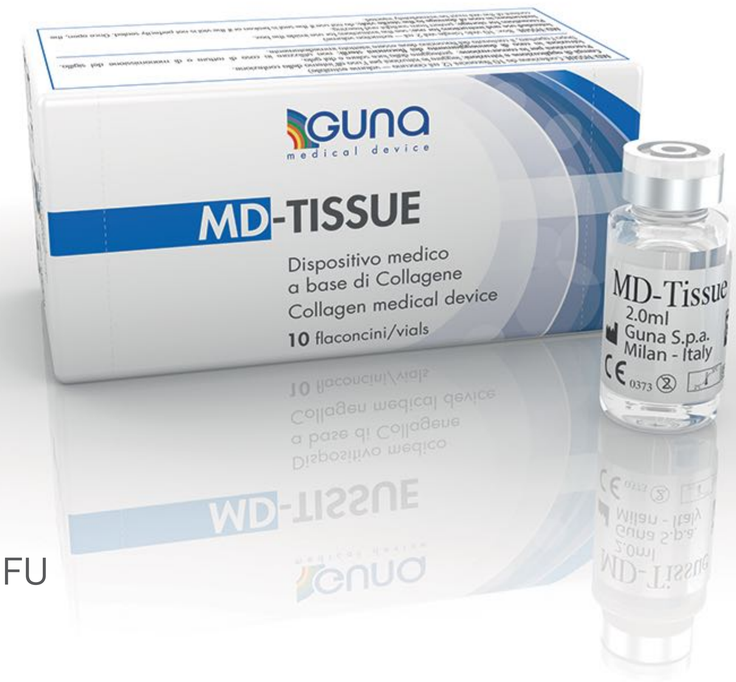
Composition: Collagen of porcine origin, Ascorbic acid, Magnesium gluconate, Pyridoxine hydrochloride, Riboflavin, Thiamine hydrochloride, NaCl, Water for injection.



- Effectively reduces pain and improves joint and tissue movement (tendons and ligaments)

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

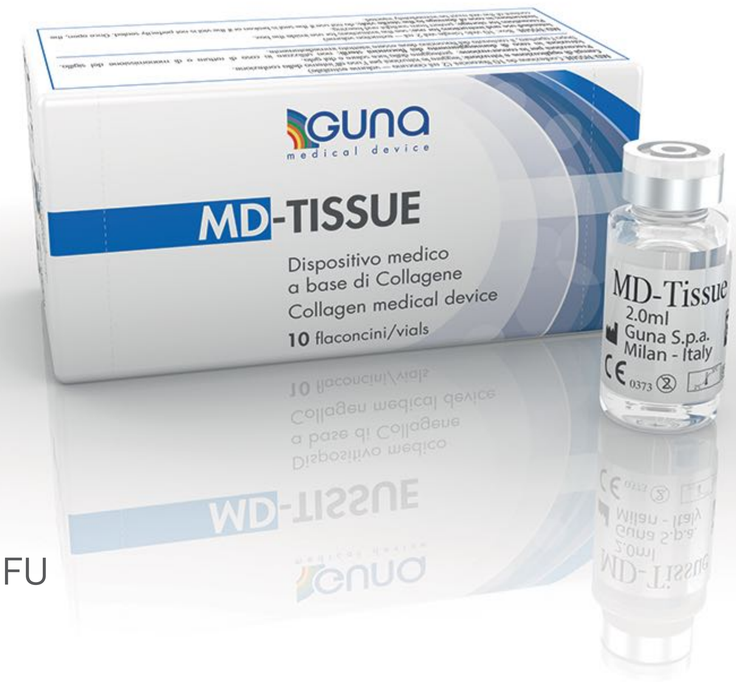
MD-TISSUE. IFU

GUNA COLLAGEN MEDICAL DEVICES

«NON-SPECIFIC»

MD - TISSUE

Composition: Collagen of porcine origin, Ascorbic acid, Magnesium gluconate, Pyridoxine hydrochloride, Riboflavin, Thiamine hydrochloride, NaCl, Water for injection.



- Effectively reduces pain and improves joint and tissue movement (tendons and ligaments)

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

MD-TISSUE. IFU

GUNA COLLAGEN MEDICAL DEVICES

«NON-SPECIFIC»

MD - MUSCLE

Composition: Collagen of porcine origin, Hypericum, NaCl, Water for injection.

- Enhances muscle relaxation and functioning
- Supports the muscle tissue in bad posture disorders
- Improves joint mobility
- Soothes local pain or pain due to movement or bad posture

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

MD-MUSCLE. IFU

GUNA COLLAGEN MEDICAL DEVICES

«NON-SPECIFIC»

MD - MUSCLE

Composition: Collagen of porcine origin, Hypericum, NaCl, Water for injection.

- Enhances muscle relaxation and functioning
- Supports the muscle tissue in bad posture disorders
- Improves joint mobility
- Soothes local pain or pain due to movement or bad posture

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

MD-MUSCLE. IFU

GUNA COLLAGEN MEDICAL DEVICES

«NON-SPECIFIC»

MD - MUSCLE

Composition: Collagen of porcine origin, Hypericum, NaCl, Water for injection.

- Enhances muscle relaxation and functioning
- Supports the muscle tissue in bad posture disorders
- Improves joint mobility
- Soothes local pain or pain due to movement or bad posture

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

MD-MUSCLE. IFU

GUNA COLLAGEN MEDICAL DEVICES

«NON-SPECIFIC»

MD - MUSCLE

Composition: Collagen of porcine origin, Hypericum, NaCl, Water for injection.

- Enhances muscle relaxation and functioning
- Supports the muscle tissue in bad posture disorders
- Improves joint mobility
- Soothes local pain or pain due to movement or bad posture

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

MD-MUSCLE. IFU

GUNA COLLAGEN MEDICAL DEVICES

«NON-SPECIFIC»

MD - MUSCLE

Composition: Collagen of porcine origin, Hypericum, NaCl, Water for injection.

- Enhances muscle relaxation and functioning
- Supports the muscle tissue in bad posture disorders
- Improves joint mobility
- Soothes local pain or pain due to movement or bad posture

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

MD-MUSCLE. IFU

GUNA COLLAGEN MEDICAL DEVICES

«NON-SPECIFIC»

MD - NEURAL

Composition: Collagen of porcine origin, Colocynthis, NaCl, Water for injection.

- Mechanical support in case of other on-going therapies
- Strengthens the connective tissue layer of the perineurium improves mobility and reduces pain symptoms, specifically due to bad posture.

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

GUNA COLLAGEN MEDICAL DEVICES

«NON-SPECIFIC»

MD - NEURAL

Composition: Collagen of porcine origin, Colocynthis, NaCl, Water for injection.

- Mechanical support in case of other on-going therapies
- Strengthens the connective tissue layer of the perineurium improves mobility and reduces pain symptoms, specifically due to bad posture.

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

GUNA COLLAGEN MEDICAL DEVICES

«NON-SPECIFIC»

MD - NEURAL

Composition: Collagen of porcine origin, Colocynthis, NaCl, Water for injection.

- Mechanical support in case of other on-going therapies
- Strengthens the connective tissue layer of the perineurium improves mobility and reduces pain symptoms, specifically due to bad posture.

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

GUNA COLLAGEN MEDICAL DEVICES

«NON-SPECIFIC»

MD - NEURAL

Composition: Collagen of porcine origin, Colocynthis, NaCl, Water for injection.

- Mechanical support in case of other on-going therapies
- Strengthens the connective tissue layer of the perineurium improves mobility and reduces pain symptoms, specifically due to bad posture.

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

GUNA COLLAGEN MEDICAL DEVICES

«NON-SPECIFIC»

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Composition: Collagen of porcine origin, Colocynthis, NaCl, Water for injection.

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IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

GUNA COLLAGEN MEDICAL DEVICES

«NON-SPECIFIC»

MD - NEURAL

Composition: Collagen of porcine origin, Colocynthis, NaCl, Water for injection.

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Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

GUNA COLLAGEN MEDICAL DEVICES

«NON-SPECIFIC»

MD - NEURAL

Composition: Collagen of porcine origin, Colocynthis, NaCl, Water for injection.

- Mechanical support in case of other on-going therapies
- Strengthens the connective tissue layer of the perineurium improves mobility and reduces pain symptoms, specifically due to bad posture.

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

GUNA COLLAGEN MEDICAL DEVICES

«NON-SPECIFIC»

MD - MATRIX

Composition: Collagen of porcine origin, Citric acid, Nicotinamide, NaCl, Water for injection.

- Strengthens the extracellular matrix tissues

IFU

Directions for use

1-2 injections per week to limit the physiological deterioration of joints and tissues (tendons and ligaments).
Results are evident from the third or fifth week.

MD-MATRIX. IFU

MD-HIP

Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Calcium Phosphate, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-HIP is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-HIP is a medical device that helps hip movement. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-HIP is intended to be used by a qualified staff in private or public health Facilities to:
- ⇨ Improve the movement of the hip joint.
- ⇨ Help muscle stretching of the lumbosacral area.
- ⇨ Support the periarticular muscle tissue.
- ⇨ Soothe local pain, pain caused by joint movement or bad posture.

Directions for use
Therapeutic protocol:
1 treatment weekly for 10 consecutive weeks.

Periarticular injection technique (the site of application must be aseptic; insert the needle at 6-8 mm depth)
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Intraarticular injection technique
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.

The application of a topical anaesthetic on the skin area to be treated is recommended.
- Needles: sterile 22 G.
- Syringes: 2 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
Patients treated with anticoagulants or with recognized vessel fragility should be carefully monitored during the therapy.
There is no history of hypersensitivity to MD-HIP. It contains animal-derived collagen from porcine source. Patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

Warnings and precautions
Hip pain requires differential diagnosis for primary or metastatic cancer pain, referred nerve pain of lumbar origin, inguinal hernia.
A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.

KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

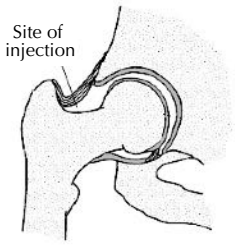
Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-HIP may be used as a single treatment or mixed with other medical devices of the same range in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for acute pain, MD-HIP can be associated with MD-NEURAL, MD-POLY and MD-MUSCLE (together with one or more than one of these).
Moreover, when a supportive treatment is needed for the connective tissue matrix or when the physiological aging process is needed to be slowed down, MD-HIP can be associated with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:
- Hip joint osteoarthritis.
- Hip joint capsule inflammation.
- Hip joint osteoarthritis with rheumatoid arthritis (in association with MD-POLY).
- Hip joint pain of muscle origin (in association with MD-MUSCLE).
- Hip joint pain of nerve origin (*burning hip*, in association with MD-NEURAL).
- Hip joint pain due to prolonged bed rest.

Administration may vary according to individual needs.

Instructions in case of damage to the sterile vials
Do not use if the seal is broken or if the vial is not perfectly sealed. Once open, the content of the vial must be immediately injected. Do not use if the package is damaged.



The trochanteric bursa is located over the lateral prominence of the greater trochanter of the femur. There can be an anterior or a lateral approach to the hip.
The patient is lying supine. The anatomic landmark is located 2 cm below the superior border of the greater trochanter in between its anterior and posterior borders. The skin overlying this location is marked and prepared in a sterile way. A 22 gauge needle is injected parallel to the floor and perpendicular to the femoral shaft.

Hip – Intraarticular injection

CE 0373

Information reserved for healthcare professionals

7EX100

GUNA medical device

Guna S.p.a. • Milan - Italy
collagenmd.guna.com

MD-HIP

Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Calcium Phosphate, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-HIP is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-HIP is a medical device that helps hip movement. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-HIP is intended to be used by a qualified staff in private or public health Facilities to:
⇨ Improve the movement of the hip joint.
⇨ Help muscle stretching of the lumbosacral area.
⇨ Support the periarticular muscle tissue.
⇨ Soothe local pain, pain caused by joint movement or bad posture.

Directions for use
Therapeutic protocol:
1 treatment weekly for 10 consecutive weeks.

Periarticular injection technique (the site of application must be aseptic; insert the needle at 6-8 mm depth)
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Intraarticular injection technique
For this purpose the use of the following materials and accessories is recommended:
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The application of a topical anaesthetic on the skin area to be treated is recommended.
- Needles: sterile 22 G.
- Syringes: 2 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
Patients treated with anticoagulants or with recognized vessel fragility should be carefully monitored during the therapy.
There is no history of hypersensitivity to MD-HIP. It contains animal-derived collagen from porcine source. Patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

Warnings and precautions
Hip pain requires differential diagnosis for primary or metastatic cancer pain, referred nerve pain of lumbar origin, inguinal hernia.
A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.

KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

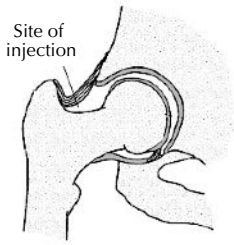
Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-HIP may be used as a single treatment or mixed with other medical devices of the same range in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for acute pain, MD-HIP can be associated with MD-NEURAL, MD-POLY and MD-MUSCLE (together with one or more than one of these).
Moreover, when a supportive treatment is needed for the connective tissue matrix or when the physiological aging process is needed to be slowed down, MD-HIP can be associated with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:
- Hip joint osteoarthritis.
- Hip joint capsule inflammation.
- Hip joint osteoarthritis with rheumatoid arthritis (in association with MD-POLY).
- Hip joint pain of muscle origin (in association with MD-MUSCLE).
- Hip joint pain of nerve origin (*burning hip*, in association with MD-NEURAL).
- Hip joint pain due to prolonged bed rest.

Administration may vary according to individual needs.

Instructions in case of damage to the sterile vials
Do not use if the seal is broken or if the vial is not perfectly sealed. Once open, the content of the vial must be immediately injected. Do not use if the package is damaged.



The trochanteric bursa is located over the lateral prominence of the greater trochanter of the femur. There can be an anterior or a lateral approach to the hip.
The patient is lying supine. The anatomic landmark is located 2 cm below the superior border of the greater trochanter in between its anterior and posterior borders. The skin overlying this location is marked and prepared in a sterile way. A 22 gauge needle is injected parallel to the floor and perpendicular to the femoral shaft.

Hip – Intraarticular injection

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Information reserved for healthcare professionals

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Guna S.p.a. • Milan - Italy
collagenmd.guna.com

MD-ISCHIAL

Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Rhododendron, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-ISCHIAL is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-ISCHIAL is a medical device designed to help movement, specifically the low back area of the vertebral spine. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-ISCHIAL is intended to be used by a qualified staff in private or public health Facilities to:
- ⇨ Improve leg movement.
- ⇨ Help leg muscle stretching.
- ⇨ Help to support the leg muscle tissue.
- ⇨ Soothe leg pain while starting to move legs again, after a period of prolonged inactivity.

Directions for use
Therapeutic protocol:
1 treatment weekly for 10 consecutive weeks.

Periarticular injection technique (the site of application must be aseptic; insert the needle near the sacroiliac joint at 2-4 mm depth)
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
There is no history of hypersensitivity to MD-ISCHIAL. It contains animal-derived collagen from porcine source. Patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

Warnings and precautions
Sciatic pain requires differential diagnosis for secondary muscle pain, full-blown disc herniation, vertebral canal stenosis, Cauda equine syndrome.
A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-ISCHIAL may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for acute pain, MD-ISCHIAL can be associated with MD-NEURAL, MD-POLY and MD-MUSCLE (together with one or more than one of these).
Moreover, when a supportive treatment is needed for the connective tissue matrix or when the physiological aging process should be slowed down, MD-ISCHIAL can be associated with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:
- Sciatic pain.
- Lumbar-sciatic pain (in association with MD-LUMBAR and MD-NEURAL).
- Nerve pain in the lower lumbar spine (in association with MD-MUSCLE).
- Leg nerve pain due to post-surgery treatment of disc herniation L4-L5, L5-S1.
- Morton neuroma (in association with MD-NEURAL).

Instructions in case of damage to the sterile vials
Do not use if the seal is broken or if the vial is not perfectly sealed. Once open, the content of the vial must be immediately injected. Do not use if the package is damaged.

7EX101

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Information reserved for healthcare professionals

GUNA medical device
Guna S.p.a. • Milan - Italy
collagenmd.guna.com

MD-ISCHIAL

Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Rhododendron, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-ISCHIAL is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-ISCHIAL is a medical device designed to help movement, specifically the low back area of the vertebral spine. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-ISCHIAL is intended to be used by a qualified staff in private or public health Facilities to:
- ⇨ Improve leg movement.
- ⇨ Help leg muscle stretching.
- ⇨ Help to support the leg muscle tissue.
- ⇨ Soothe leg pain while starting to move legs again, after a period of prolonged inactivity.

Directions for use
Therapeutic protocol:
1 treatment weekly for 10 consecutive weeks.

Periarticular injection technique (the site of application must be aseptic; insert the needle near the sacroiliac joint at 2-4 mm depth)
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
There is no history of hypersensitivity to MD-ISCHIAL. It contains animal-derived collagen from porcine source. Patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

Warnings and precautions
Sciatic pain requires differential diagnosis for secondary muscle pain, full-blown disc herniation, vertebral canal stenosis, Cauda equine syndrome.
A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-ISCHIAL may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for acute pain, MD-ISCHIAL can be associated with MD-NEURAL, MD-POLY and MD-MUSCLE (together with one or more than one of these).
Moreover, when a supportive treatment is needed for the connective tissue matrix or when the physiological aging process should be slowed down, MD-ISCHIAL can be associated with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:
- Sciatic pain.
- Lumbar-sciatic pain (in association with MD-LUMBAR and MD-NEURAL).
- Nerve pain in the lower lumbar spine (in association with MD-MUSCLE).
- Leg nerve pain due to post-surgery treatment of disc herniation L4-L5, L5-S1.
- Morton neuroma (in association with MD-NEURAL).

Instructions in case of damage to the sterile vials
Do not use if the seal is broken or if the vial is not perfectly sealed. Once open, the content of the vial must be immediately injected. Do not use if the package is damaged.

7EX101

CE 0373

Information reserved for healthcare professionals

GUNA medical device
Guna S.p.a. • Milan - Italy
collagenmd.guna.com

MD-KNEE

Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Arnica, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-KNEE is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-KNEE is a medical device designed to help knee movement. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-KNEE is a medical device intended to be used by a qualified staff in private or public health Facilities to:
⇨ Improve the knee movement.
⇨ Help muscle stretching.
⇨ Soothe pain while moving legs and knee.

Directions for use
Therapeutic protocol:
1 treatment weekly for 10 consecutive weeks.

Periarticular injection technique (the site of application must be aseptic; insert the needle at 2-4 mm depth)
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Intraarticular injection technique
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.

The application of a topical anaesthetic on the skin area to be treated is recommended.
- Needles: sterile 22 G.
- Syringes: 2 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
There is no history of hypersensitivity to MD-KNEE. It contains animal-derived collagen from porcine source. Patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

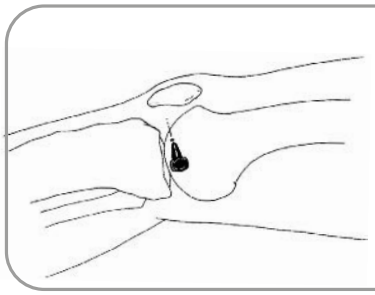
Warnings and precautions
Knee pain requires differential diagnosis for collateral or cruciate ligament injuries, prepatellar bursitis, hip joint pathologies, osteochondritis dissecans, inflammatory arthropathy, gout, pseudo gout, septic arthritis.
A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-KNEE may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for acute pain, MD-KNEE can be associated with MD-NEURAL, MD-POLY and MD-MUSCLE (together with one or more than one of these).
Moreover, when a supportive treatment is needed for the connective tissue matrix or when the physiological aging process should be slowed down, MD-KNEE can be associated with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:
- Knee arthrosis (in association with MD-POLY).
- Patello-femoral arthrosis.
- Knee localization of rheumatoid arthritis or of other autoimmune diseases (in association with MD-POLY).
- Knee acute and chronic arthrosynovitis secondary to arthrosis or to rheumatoid arthritis (in association with MD-POLY).
- Post-traumatic or post-surgery acute and chronic arthrosynovitis.
- Traumatic lesions of cruciate or collateral ligaments of the knee.
- Meniscal lesions (in association with MD-MUSCLE).
- Knee joint preparation to meniscectomy (in association with MD-MUSCLE).
- Maintenance therapy after knee surgery (in association with MD-MUSCLE and MD-NEURAL).

Instructions in case of damage to the sterile vials
Do not use if the seal is broken or if the vial is not perfectly sealed. Once open, the content of the vial must be immediately injected. Do not use if the package is damaged.



The patient should lay supine with the knee comfortably extended. A 22 G needle is inserted in a direction parallel to the plane of the posterior surface of the patella in a medial and lateral position.

Knee – Intraarticular injection technique (internal side)

7EX094

CE 0373

Information reserved for healthcare professionals

Guna S.p.a. • Milan - Italy
collagenmd.guna.com

MD-KNEE

Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Arnica, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-KNEE is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-KNEE is a medical device designed to help knee movement. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-KNEE is a medical device intended to be used by a qualified staff in private or public health Facilities to:
⇨ Improve the knee movement.
⇨ Help muscle stretching.
⇨ Soothe pain while moving legs and knee.

Directions for use
Therapeutic protocol:
1 treatment weekly for 10 consecutive weeks.

Periarticular injection technique (the site of application must be aseptic; insert the needle at 2-4 mm depth)
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Intraarticular injection technique
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.

The application of a topical anaesthetic on the skin area to be treated is recommended.
- Needles: sterile 22 G.
- Syringes: 2 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
There is no history of hypersensitivity to MD-KNEE. It contains animal-derived collagen from porcine source. Patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

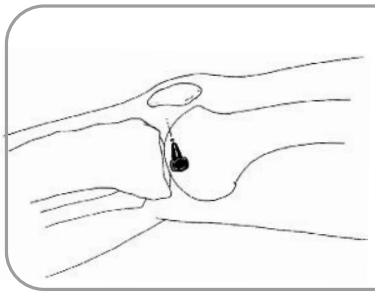
Warnings and precautions
Knee pain requires differential diagnosis for collateral or cruciate ligament injuries, prepatellar bursitis, hip joint pathologies, osteochondritis dissecans, inflammatory arthropathy, gout, pseudo gout, septic arthritis.
A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-KNEE may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for acute pain, MD-KNEE can be associated with MD-NEURAL, MD-POLY and MD-MUSCLE (together with one or more than one of these).
Moreover, when a supportive treatment is needed for the connective tissue matrix or when the physiological aging process should be slowed down, MD-KNEE can be associated with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:
- Knee arthrosis (in association with MD-POLY).
- Patello-femoral arthrosis.
- Knee localization of rheumatoid arthritis or of other autoimmune diseases (in association with MD-POLY).
- Knee acute and chronic arthrosynovitis secondary to arthrosis or to rheumatoid arthritis (in association with MD-POLY).
- Post-traumatic or post-surgery acute and chronic arthrosynovitis.
- Traumatic lesions of cruciate or collateral ligaments of the knee.
- Meniscal lesions (in association with MD-MUSCLE).
- Knee joint preparation to meniscectomy (in association with MD-MUSCLE).
- Maintenance therapy after knee surgery (in association with MD-MUSCLE and MD-NEURAL).

Instructions in case of damage to the sterile vials
Do not use if the seal is broken or if the vial is not perfectly sealed. Once open, the content of the vial must be immediately injected. Do not use if the package is damaged.



The patient should lay supine with the knee comfortably extended. A 22 G needle is inserted in a direction parallel to the plane of the posterior surface of the patella in a medial and lateral position.

Knee – Intraarticular injection technique (internal side)

7EX094

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Information reserved for healthcare professionals

Guna S.p.a. • Milan - Italy
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MD-LUMBAR

Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Hamamelis, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-LUMBAR is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-LUMBAR is a medical device designed to help movement, specifically the lumbosacral area of the vertebral spine. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-LUMBAR is a medical device intended to be used by a qualified staff in private or public health Facilities to:
⇨ Help lumbar movement.
⇨ Help muscle stretching of the lumbosacral area of the spine.
⇨ Help to support the lumbar muscle tissue.
⇨ Soothe local pain, pain at rest or caused by movement and bad posture.

Directions for use
Periarticular therapeutic protocol:
2 treatments weekly for the first 2 weeks; 1 treatment until improvement of symptoms (average 8-10 sessions). Chronic pathologies: go on with 1 treatment weekly for one month until improvement of symptoms, then with 1 treatment monthly or – according to individual needs – every 45-50 days.
The site of application must be aseptic. Insert the needle near the lumbar and lumbosacral joints at 3-4 mm depth.

For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
There is no history of hypersensitivity to MD-LUMBAR. It contains animal-derived collagen from porcine source. Patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

Warnings and precautions
Spinal pain requires differential diagnosis for herniated disk, primary or secondary cancer pain; reflex or referred pain from internal organs.
A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-LUMBAR may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for acute pain, MD-LUMBAR can be associated with MD-NEURAL, MD-POLY and MD-MUSCLE (together with one or more than one of these).
Moreover, when a supportive treatment is needed for the connective tissue matrix or when the physiological aging process should be slowed down, MD-LUMBAR can be associated with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:

- Lumbar pain secondary to cartilage degenerative lumbar spine disorders (lumbar and lumbar-sacral arthrosis).
- Lumbar vertebral osteophytosis.
- Low-back pain secondary to musculo-tendinous trigger points (in association with MD-MUSCLE).
- Postural low-back aches (in association with MD-NEURAL and MD-MUSCLE).
- Lumbar and lumbar-sacral mechanical imbalance.
- Lumbar and lumbar-sacral spinal ligament syndrome.
- Sacro-iliac syndrome.
- Spinal lumbar and lumbar-sacral nerve root pain (in association with MD-NEURAL and MD-ISCHIAL).

Instructions in case of damage to the sterile vials
Do not use if the seal is broken or if the vial is not perfectly sealed. Once open, the content of the vial must be immediately injected. Do not use if the package is damaged.

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Composition: Collagen of porcine origin.

Excipients: Hamamelis, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-LUMBAR is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-LUMBAR is a medical device designed to help movement, specifically the lumbosacral area of the vertebral spine. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-LUMBAR is a medical device intended to be used by a qualified staff in private or public health Facilities to:
⇨ Help lumbar movement.
⇨ Help muscle stretching of the lumbosacral area of the spine.
⇨ Help to support the lumbar muscle tissue.
⇨ Soothe local pain, pain at rest or caused by movement and bad posture.

Directions for use
Periarticular therapeutic protocol:
2 treatments weekly for the first 2 weeks; 1 treatment until improvement of symptoms (average 8-10 sessions). Chronic pathologies: go on with 1 treatment weekly for one month until improvement of symptoms, then with 1 treatment monthly or – according to individual needs – every 45-50 days.
The site of application must be aseptic. Insert the needle near the lumbar and lumbosacral joints at 3-4 mm depth.

For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
There is no history of hypersensitivity to MD-LUMBAR. It contains animal-derived collagen from porcine source. Patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

Warnings and precautions
Spinal pain requires differential diagnosis for herniated disk, primary or secondary cancer pain; reflex or referred pain from internal organs.
A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-LUMBAR may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for acute pain, MD-LUMBAR can be associated with MD-NEURAL, MD-POLY and MD-MUSCLE (together with one or more than one of these).
Moreover, when a supportive treatment is needed for the connective tissue matrix or when the physiological aging process should be slowed down, MD-LUMBAR can be associated with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:

- Lumbar pain secondary to cartilage degenerative lumbar spine disorders (lumbar and lumbar-sacral arthrosis).
- Lumbar vertebral osteophytosis.
- Low-back pain secondary to musculo-tendinous trigger points (in association with MD-MUSCLE).
- Postural low-back aches (in association with MD-NEURAL and MD-MUSCLE).
- Lumbar and lumbar-sacral mechanical imbalance.
- Lumbar and lumbar-sacral spinal ligament syndrome.
- Sacro-iliac syndrome.
- Spinal lumbar and lumbar-sacral nerve root pain (in association with MD-NEURAL and MD-ISCHIAL).

Instructions in case of damage to the sterile vials
Do not use if the seal is broken or if the vial is not perfectly sealed. Once open, the content of the vial must be immediately injected. Do not use if the package is damaged.

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MD-LUMBAR

Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Hamamelis, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-LUMBAR is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-LUMBAR is a medical device designed to help movement, specifically the lumbosacral area of the vertebral spine. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-LUMBAR is a medical device intended to be used by a qualified staff in private or public health Facilities to:
⇨ Help lumbar movement.
⇨ Help muscle stretching of the lumbosacral area of the spine.
⇨ Help to support the lumbar muscle tissue.
⇨ Soothe local pain, pain at rest or caused by movement and bad posture.

Directions for use
Periarticular therapeutic protocol:
2 treatments weekly for the first 2 weeks; 1 treatment until improvement of symptoms (average 8-10 sessions). Chronic pathologies: go on with 1 treatment weekly for one month until improvement of symptoms, then with 1 treatment monthly or – according to individual needs – every 45-50 days.
The site of application must be aseptic. Insert the needle near the lumbar and lumbosacral joints at 3-4 mm depth.

For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
There is no history of hypersensitivity to MD-LUMBAR. It contains animal-derived collagen from porcine source. Patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

Warnings and precautions
Spinal pain requires differential diagnosis for herniated disk, primary or secondary cancer pain; reflex or referred pain from internal organs.
A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-LUMBAR may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for acute pain, MD-LUMBAR can be associated with MD-NEURAL, MD-POLY and MD-MUSCLE (together with one or more than one of these).
Moreover, when a supportive treatment is needed for the connective tissue matrix or when the physiological aging process should be slowed down, MD-LUMBAR can be associated with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:

- Lumbar pain secondary to cartilage degenerative lumbar spine disorders (lumbar and lumbar-sacral arthrosis).
- Lumbar vertebral osteophytosis.
- Low-back pain secondary to musculo-tendinous trigger points (in association with MD-MUSCLE).
- Postural low-back aches (in association with MD-NEURAL and MD-MUSCLE).
- Lumbar and lumbar-sacral mechanical imbalance.
- Lumbar and lumbar-sacral spinal ligament syndrome.
- Sacro-iliac syndrome.
- Spinal lumbar and lumbar-sacral nerve root pain (in association with MD-NEURAL and MD-ISCHIAL).

Instructions in case of damage to the sterile vials
Do not use if the seal is broken or if the vial is not perfectly sealed. Once open, the content of the vial must be immediately injected. Do not use if the package is damaged.

7EX096

CE 0373

Information reserved for healthcare professionals

Guna S.p.a. • Milan - Italy
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MD-MATRIX

Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Citric acid, Nicotinamide, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-MATRIX is a medical device designed to help movement by limiting a physiological degeneration of joints and connective tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

Due to its special function, MD-MATRIX is also intended for firming the subcutaneous and microvascular connective tissue layer of localized adiposities and cellulite in the connective tissue, especially those at the root of the thighs and in the inner area of the knee.

MD-MATRIX is a medical device designed to help movement, by strengthening the supportive tissue of the joints, and of the skin and its subcutaneous tissue.
Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-MATRIX is a medical device intended to be used by a qualified staff in private or public health Facilities to:
⇨ Strengthen the extra-cellular matrix tissues where the collagen is applied.
⇨ Act as a defensive barrier against free radicals.

Directions for use
Therapeutic protocol:
2 treatments weekly for the first 2 weeks, 1 treatment weekly until improvement of symptoms (average 8-10 sessions). It is possible to go on with 1 treatment every other week for 10 weeks at most. For chronic pathologies: go on with 1 treatment weekly for 1 month until improvement of symptoms, then 1 treatment monthly.

- *Intradermal and subcutaneous injection technique:* the site of application must be aseptic; insert the needle at 1-3 mm depth and microinject 0.2-0.3 ml into the affected tissue.
- *Periarticular injection technique:* the site of application must be aseptic; insert the needle near the joint at different depths.

Preparation for injection
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G, 4 mm.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
There is no history of hypersensitivity to MD-MATRIX. It contains animal-derived collagen from porcine source. However, patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

Warnings and precautions
A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-MATRIX may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
Concerning its use for the treatment of localized adiposity, and for firming the subcutaneous connective tissue layer, MD-MATRIX should preferably be associated with MD-TISSUE (e.g. MD-MATRIX 2 vials, MD-TISSUE 1 vial/treatment).
It may be used in patients who need a collagen supplementation or a topical antiaging treatment.

Instructions in case of damage to the sterile vials
Do not use if the seal is broken or if the vial is not perfectly sealed. Once open, the content of the vial must be immediately injected. Do not use if the package is damaged.

7EX099

CE 0373

Information reserved for healthcare professionals

GUNA medical device

Guna S.p.a. • Milan - Italy
collagenmd.guna.com

MD-MUSCLE

Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Hypericum, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-MUSCLE is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-MUSCLE is a medical device designed to help muscle and joint movement. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-MUSCLE is a medical device intended to be used by a qualified staff in private or public health Facilities to:
- ⇨ Help muscle stretching and function.
- ⇨ Help to support the muscle tissue in bad posture disorders.
- ⇨ Improve joint movement.
- ⇨ Soothe local pain, or pain caused by movement and bad posture.

Directions for use
Therapeutic protocol:
1-2 treatments weekly for 10 consecutive weeks.

Intramuscular injection technique (the site of application must be aseptic; insert the needle into the muscle to be treated at 2-4 mm depth)
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Intraarticular injection technique
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.

The application of a topical anaesthetic to the skin is recommended.
- Needles: sterile 22 G.
- Syringes: 2 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
There is no history of hypersensitivity to MD-MUSCLE. It contains animal-derived collagen from porcine source. However, patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be carefully monitored for 1 hour.

Warnings and precautions
Muscle pain requires differential diagnosis for metameric nerve pain, tendonitis, and deep blood accumulation.
A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-MUSCLE may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for the connective tissue matrix or when an antiaging action is necessary, MD-MUSCLE can be associated with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:

- Pain management: acute, subacute, and chronic.
- Referred somatic pain area management (in association with MD-NEURAL).
- Trigger points management (in association with MD-NEURAL).
- Fibromyalgia syndrome (in association with MD-NEURAL).
- Dermatomyositis.

Administration may vary according to individual needs.

Instructions in case of damage to the sterile vials
Do not use if the seal is broken or if the vial is not perfectly sealed. Once open, the content of the vial must be immediately injected. Do not use if the package is damaged.

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MD-MUSCLE

Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Hypericum, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-MUSCLE is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-MUSCLE is a medical device designed to help muscle and joint movement. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-MUSCLE is a medical device intended to be used by a qualified staff in private or public health Facilities to:
- ⇨ Help muscle stretching and function.
- ⇨ Help to support the muscle tissue in bad posture disorders.
- ⇨ Improve joint movement.
- ⇨ Soothe local pain, or pain caused by movement and bad posture.

Directions for use
Therapeutic protocol:
1-2 treatments weekly for 10 consecutive weeks.

Intramuscular injection technique (the site of application must be aseptic; insert the needle into the muscle to be treated at 2-4 mm depth)
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Intraarticular injection technique
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.

The application of a topical anaesthetic to the skin is recommended.
- Needles: sterile 22 G.
- Syringes: 2 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
There is no history of hypersensitivity to MD-MUSCLE. It contains animal-derived collagen from porcine source. However, patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be carefully monitored for 1 hour.

Warnings and precautions
Muscle pain requires differential diagnosis for metameric nerve pain, tendonitis, and deep blood accumulation.
A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-MUSCLE may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for the connective tissue matrix or when an antiaging action is necessary, MD-MUSCLE can be associated with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:

- Pain management: acute, subacute, and chronic.
- Referred somatic pain area management (in association with MD-NEURAL).
- Trigger points management (in association with MD-NEURAL).
- Fibromyalgia syndrome (in association with MD-NEURAL).
- Dermatomyositis.

Administration may vary according to individual needs.

Instructions in case of damage to the sterile vials
Do not use if the seal is broken or if the vial is not perfectly sealed. Once open, the content of the vial must be immediately injected. Do not use if the package is damaged.

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MD-MUSCLE

Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Hypericum, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-MUSCLE is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-MUSCLE is a medical device designed to help muscle and joint movement. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-MUSCLE is a medical device intended to be used by a qualified staff in private or public health Facilities to:
- ⇨ Help muscle stretching and function.
- ⇨ Help to support the muscle tissue in bad posture disorders.
- ⇨ Improve joint movement.
- ⇨ Soothe local pain, or pain caused by movement and bad posture.

Directions for use
Therapeutic protocol:
1-2 treatments weekly for 10 consecutive weeks.

Intramuscular injection technique (the site of application must be aseptic; insert the needle into the muscle to be treated at 2-4 mm depth)
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Intraarticular injection technique
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.

The application of a topical anaesthetic to the skin is recommended.
- Needles: sterile 22 G.
- Syringes: 2 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
There is no history of hypersensitivity to MD-MUSCLE. It contains animal-derived collagen from porcine source. However, patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be carefully monitored for 1 hour.

Warnings and precautions
Muscle pain requires differential diagnosis for metameric nerve pain, tendonitis, and deep blood accumulation.
A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-MUSCLE may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for the connective tissue matrix or when an antiaging action is necessary, MD-MUSCLE can be associated with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:

- Pain management: acute, subacute, and chronic.
- Referred somatic pain area management (in association with MD-NEURAL).
- Trigger points management (in association with MD-NEURAL).
- Fibromyalgia syndrome (in association with MD-NEURAL).
- Dermatomyositis.

Administration may vary according to individual needs.

Instructions in case of damage to the sterile vials
Do not use if the seal is broken or if the vial is not perfectly sealed. Once open, the content of the vial must be immediately injected. Do not use if the package is damaged.

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MD-MUSCLE

Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Hypericum, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-MUSCLE is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-MUSCLE is a medical device designed to help muscle and joint movement. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-MUSCLE is a medical device intended to be used by a qualified staff in private or public health Facilities to:
- ⇨ Help muscle stretching and function.
- ⇨ Help to support the muscle tissue in bad posture disorders.
- ⇨ Improve joint movement.
- ⇨ Soothe local pain, or pain caused by movement and bad posture.

Directions for use
Therapeutic protocol:
1-2 treatments weekly for 10 consecutive weeks.

Intramuscular injection technique (the site of application must be aseptic; insert the needle into the muscle to be treated at 2-4 mm depth)
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Intraarticular injection technique
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.

The application of a topical anaesthetic to the skin is recommended.
- Needles: sterile 22 G.
- Syringes: 2 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
There is no history of hypersensitivity to MD-MUSCLE. It contains animal-derived collagen from porcine source. However, patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be carefully monitored for 1 hour.

Warnings and precautions
Muscle pain requires differential diagnosis for metameric nerve pain, tendonitis, and deep blood accumulation.
A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-MUSCLE may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for the connective tissue matrix or when an antiaging action is necessary, MD-MUSCLE can be associated with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:

- Pain management: acute, subacute, and chronic.
- Referred somatic pain area management (in association with MD-NEURAL).
- Trigger points management (in association with MD-NEURAL).
- Fibromyalgia syndrome (in association with MD-NEURAL).
- Dermatomyositis.

Administration may vary according to individual needs.

Instructions in case of damage to the sterile vials
Do not use if the seal is broken or if the vial is not perfectly sealed. Once open, the content of the vial must be immediately injected. Do not use if the package is damaged.

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MD-MUSCLE

Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Hypericum, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-MUSCLE is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-MUSCLE is a medical device designed to help muscle and joint movement. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-MUSCLE is a medical device intended to be used by a qualified staff in private or public health Facilities to:
- ⇨ Help muscle stretching and function.
- ⇨ Help to support the muscle tissue in bad posture disorders.
- ⇨ Improve joint movement.
- ⇨ Soothe local pain, or pain caused by movement and bad posture.

Directions for use
Therapeutic protocol:
1-2 treatments weekly for 10 consecutive weeks.

Intramuscular injection technique (the site of application must be aseptic; insert the needle into the muscle to be treated at 2-4 mm depth)
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Intraarticular injection technique
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.

The application of a topical anaesthetic to the skin is recommended.
- Needles: sterile 22 G.
- Syringes: 2 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
There is no history of hypersensitivity to MD-MUSCLE. It contains animal-derived collagen from porcine source. However, patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be carefully monitored for 1 hour.

Warnings and precautions
Muscle pain requires differential diagnosis for metameric nerve pain, tendonitis, and deep blood accumulation.
A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-MUSCLE may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for the connective tissue matrix or when an antiaging action is necessary, MD-MUSCLE can be associated with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:

- Pain management: acute, subacute, and chronic.
- Referred somatic pain area management (in association with MD-NEURAL).
- Trigger points management (in association with MD-NEURAL).
- Fibromyalgia syndrome (in association with MD-NEURAL).
- Dermatomyositis.

Administration may vary according to individual needs.

Instructions in case of damage to the sterile vials
Do not use if the seal is broken or if the vial is not perfectly sealed. Once open, the content of the vial must be immediately injected. Do not use if the package is damaged.

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MD-NECK

Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Silica, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-NECK is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-NECK is a medical device designed to help neck movement, specifically the cervical area of the vertebral spine. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-NECK is a medical device intended to be used by a qualified staff in private or public health Facilities to:
⇨ Improve the movement of the cervical tract of the spine.
⇨ Help cervical muscle stretching.
⇨ Help to support cervical muscle tissue.
⇨ Help to support cervical muscle tissue in bad posture disorders.
⇨ Soothe pain in cervical column movements.

Directions for use
Therapeutic protocol:
1-2 treatments weekly for 10 consecutive weeks.

Periarticular injection technique (the site of application must be aseptic; insert the needle at 2-4 mm depth)
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
Patients treated with anticoagulants or with recognized vessel fragility or affected by coagulation diseases should be carefully monitored during the therapy.
There is no history of hypersensitivity to MD-NECK. It contains animal-derived collagen from porcine source. However, patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

Warnings and precautions
Cervical spine pain requires differential diagnosis for cervical discopathies, primary or secondary cancer pain, spondylolisthesis.
A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-NECK may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for acute pain, MD-NECK can be associated with MD-NEURAL, MD-POLY and MD-MUSCLE (together with one or more than one of these).
Moreover, when a supportive treatment is needed for the connective tissue matrix or when the physiological aging process should be slowed down, MD-NECK can be associated with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:
- Neck pain due to cartilage degenerative cervical spine disorders (cervical osteoarthritis, in association with MD-POLY).
- Neck pain due to cervical muscular trigger points (in association with MD-MUSCLE).
- Stiff neck syndrome (in association with MD-NEURAL).
- Simple neck pain (in association with MD-NEURAL and MD-MUSCLE).
- Whiplash (in association with MD-NEURAL and MD-MUSCLE).
- Postural neck ache (in association with MD-NEURAL and MD-MUSCLE).
- Mechanical imbalance (facet joint syndrome) (in association with MD-NEURAL).
- Cervical spinal ligament syndrome (in association with MD-NEURAL).
- Cervical spinal nerve root pain (in association with MD-NEURAL).

Administration may vary according to individual needs.

Instructions in case of damage to the sterile vials
Do not use if the seal is broken or if the vial is not perfectly sealed. Once open, the content of the vial must be immediately injected. Do not use if the package is damaged.

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MD-NECK

Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Silica, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-NECK is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-NECK is a medical device designed to help neck movement, specifically the cervical area of the vertebral spine. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-NECK is a medical device intended to be used by a qualified staff in private or public health Facilities to:
⇨ Improve the movement of the cervical tract of the spine.
⇨ Help cervical muscle stretching.
⇨ Help to support cervical muscle tissue.
⇨ Help to support cervical muscle tissue in bad posture disorders.
⇨ Soothe pain in cervical column movements.

Directions for use
Therapeutic protocol:
1-2 treatments weekly for 10 consecutive weeks.

Periarticular injection technique (the site of application must be aseptic; insert the needle at 2-4 mm depth)
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
Patients treated with anticoagulants or with recognized vessel fragility or affected by coagulation diseases should be carefully monitored during the therapy.
There is no history of hypersensitivity to MD-NECK. It contains animal-derived collagen from porcine source. However, patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

Warnings and precautions
Cervical spine pain requires differential diagnosis for cervical discopathies, primary or secondary cancer pain, spondylolisthesis.
A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-NECK may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for acute pain, MD-NECK can be associated with MD-NEURAL, MD-POLY and MD-MUSCLE (together with one or more than one of these).
Moreover, when a supportive treatment is needed for the connective tissue matrix or when the physiological aging process should be slowed down, MD-NECK can be associated with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:
- Neck pain due to cartilage degenerative cervical spine disorders (cervical osteoarthritis, in association with MD-POLY).
- Neck pain due to cervical muscular trigger points (in association with MD-MUSCLE).
- Stiff neck syndrome (in association with MD-NEURAL).
- Simple neck pain (in association with MD-NEURAL and MD-MUSCLE).
- Whiplash (in association with MD-NEURAL and MD-MUSCLE).
- Postural neck ache (in association with MD-NEURAL and MD-MUSCLE).
- Mechanical imbalance (facet joint syndrome) (in association with MD-NEURAL).
- Cervical spinal ligament syndrome (in association with MD-NEURAL).
- Cervical spinal nerve root pain (in association with MD-NEURAL).

Administration may vary according to individual needs.

Instructions in case of damage to the sterile vials
Do not use if the seal is broken or if the vial is not perfectly sealed. Once open, the content of the vial must be immediately injected. Do not use if the package is damaged.

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MD-NEURAL

Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Colocynthis, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-NEURAL is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-NEURAL is a medical device designed to help joint movement, specifically in bad posture disorders. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-NEURAL is a medical device intended to be used by a qualified staff in private or public health Facilities.

Directions for use
Therapeutic protocol:
1-2 treatments weekly for 10 consecutive weeks.

Periarticular injection technique (the site of application must be aseptic; insert the needle at 2-4 mm depth)
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Intraarticular injection technique
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.

The application of a topical anaesthetic on the skin area to be treated is recommended.
- Needles: sterile 22 G.
- Syringes: 2 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
There is no history of hypersensitivity to MD-NEURAL. It contains animal-derived collagen from porcine source. However, patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

Warnings and precautions
Nerve pain requires differential diagnosis for visceral pain, primary or metastatic cancer pain. A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-NEURAL may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for the connective tissue matrix or when an antiaging action is necessary, MD-NEURAL can be associated with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:

- Brachial pain (in association with MD-NECK).
- Brachial nerve pain due to cervical entrapment (in association with MD-NECK).
- Persistent intercostal neuralgia (in association with MD-THORACIC).
- Postherpetic neuralgia (in association with MD-THORACIC or MD-LUMBAR).
- Atypical facial neuritis (in association with MD-NECK).
- Trigeminal neuralgia (in association with MD-NECK).
- Temporomandibular joint pain (in association with MD-NECK).
- Cervical, thoracic, lumbar and sacrolumbar nerve root pain (respectively in association with MD-NECK, MD-THORACIC, MD-LUMBAR and MD-ISCHIAL).

Instructions in case of damage to the sterile vials
Do not use if the seal is broken or if the vial is not perfectly sealed. Once open, the content of the vial must be immediately injected. Do not use if the package is damaged.

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Information reserved for healthcare professionals

GUNA medical device
Guna S.p.a. • Milan - Italy
collagenmd.guna.com

MD-NEURAL

Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Colocynthis, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-NEURAL is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-NEURAL is a medical device designed to help joint movement, specifically in bad posture disorders. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-NEURAL is a medical device intended to be used by a qualified staff in private or public health Facilities.

Directions for use
Therapeutic protocol:
1-2 treatments weekly for 10 consecutive weeks.

Periarticular injection technique (the site of application must be aseptic; insert the needle at 2-4 mm depth)
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Intraarticular injection technique
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.

The application of a topical anaesthetic on the skin area to be treated is recommended.
- Needles: sterile 22 G.
- Syringes: 2 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
There is no history of hypersensitivity to MD-NEURAL. It contains animal-derived collagen from porcine source. However, patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

Warnings and precautions
Nerve pain requires differential diagnosis for visceral pain, primary or metastatic cancer pain. A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-NEURAL may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for the connective tissue matrix or when an antiaging action is necessary, MD-NEURAL can be associated with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:

- Brachial pain (in association with MD-NECK).
- Brachial nerve pain due to cervical entrapment (in association with MD-NECK).
- Persistent intercostal neuralgia (in association with MD-THORACIC).
- Postherpetic neuralgia (in association with MD-THORACIC or MD-LUMBAR).
- Atypical facial neuritis (in association with MD-NECK).
- Trigeminal neuralgia (in association with MD-NECK).
- Temporomandibular joint pain (in association with MD-NECK).
- Cervical, thoracic, lumbar and sacrolumbar nerve root pain (respectively in association with MD-NECK, MD-THORACIC, MD-LUMBAR and MD-ISCHIAL).

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MD-NEURAL

Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Colocynthis, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-NEURAL is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-NEURAL is a medical device designed to help joint movement, specifically in bad posture disorders. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-NEURAL is a medical device intended to be used by a qualified staff in private or public health Facilities.

Directions for use
Therapeutic protocol:
1-2 treatments weekly for 10 consecutive weeks.

Periarticular injection technique (the site of application must be aseptic; insert the needle at 2-4 mm depth)
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Intraarticular injection technique
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.

The application of a topical anaesthetic on the skin area to be treated is recommended.
- Needles: sterile 22 G.
- Syringes: 2 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
There is no history of hypersensitivity to MD-NEURAL. It contains animal-derived collagen from porcine source. However, patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

Warnings and precautions
Nerve pain requires differential diagnosis for visceral pain, primary or metastatic cancer pain. A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-NEURAL may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for the connective tissue matrix or when an antiaging action is necessary, MD-NEURAL can be associated with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:

- Brachial pain (in association with MD-NECK).
- Brachial nerve pain due to cervical entrapment (in association with MD-NECK).
- Persistent intercostal neuralgia (in association with MD-THORACIC).
- Postherpetic neuralgia (in association with MD-THORACIC or MD-LUMBAR).
- Atypical facial neuritis (in association with MD-NECK).
- Trigeminal neuralgia (in association with MD-NECK).
- Temporomandibular joint pain (in association with MD-NECK).
- Cervical, thoracic, lumbar and sacrolumbar nerve root pain (respectively in association with MD-NECK, MD-THORACIC, MD-LUMBAR and MD-ISCHIAL).

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Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Colocynthis, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-NEURAL is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-NEURAL is a medical device designed to help joint movement, specifically in bad posture disorders. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-NEURAL is a medical device intended to be used by a qualified staff in private or public health Facilities.

Directions for use
Therapeutic protocol:
1-2 treatments weekly for 10 consecutive weeks.

Periarticular injection technique (the site of application must be aseptic; insert the needle at 2-4 mm depth)
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
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Intraarticular injection technique
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The application of a topical anaesthetic on the skin area to be treated is recommended.
- Needles: sterile 22 G.
- Syringes: 2 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
There is no history of hypersensitivity to MD-NEURAL. It contains animal-derived collagen from porcine source. However, patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

Warnings and precautions
Nerve pain requires differential diagnosis for visceral pain, primary or metastatic cancer pain. A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
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Instructions on use
MD-NEURAL may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for the connective tissue matrix or when an antiaging action is necessary, MD-NEURAL can be associated with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:

- Brachial pain (in association with MD-NECK).
- Brachial nerve pain due to cervical entrapment (in association with MD-NECK).
- Persistent intercostal neuralgia (in association with MD-THORACIC).
- Postherpetic neuralgia (in association with MD-THORACIC or MD-LUMBAR).
- Atypical facial neuritis (in association with MD-NECK).
- Trigeminal neuralgia (in association with MD-NECK).
- Temporomandibular joint pain (in association with MD-NECK).
- Cervical, thoracic, lumbar and sacrolumbar nerve root pain (respectively in association with MD-NECK, MD-THORACIC, MD-LUMBAR and MD-ISCHIAL).

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Composition: Collagen of porcine origin.

Excipients: Colocynthis, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-NEURAL is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-NEURAL is a medical device designed to help joint movement, specifically in bad posture disorders. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-NEURAL is a medical device intended to be used by a qualified staff in private or public health Facilities.

Directions for use
Therapeutic protocol:
1-2 treatments weekly for 10 consecutive weeks.

Periarticular injection technique (the site of application must be aseptic; insert the needle at 2-4 mm depth)
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Intraarticular injection technique
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.

The application of a topical anaesthetic on the skin area to be treated is recommended.
- Needles: sterile 22 G.
- Syringes: 2 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
There is no history of hypersensitivity to MD-NEURAL. It contains animal-derived collagen from porcine source. However, patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

Warnings and precautions
Nerve pain requires differential diagnosis for visceral pain, primary or metastatic cancer pain. A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

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Instructions on use
MD-NEURAL may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for the connective tissue matrix or when an antiaging action is necessary, MD-NEURAL can be associated with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:

- Brachial pain (in association with MD-NECK).
- Brachial nerve pain due to cervical entrapment (in association with MD-NECK).
- Persistent intercostal neuralgia (in association with MD-THORACIC).
- Postherpetic neuralgia (in association with MD-THORACIC or MD-LUMBAR).
- Atypical facial neuritis (in association with MD-NECK).
- Trigeminal neuralgia (in association with MD-NECK).
- Temporomandibular joint pain (in association with MD-NECK).
- Cervical, thoracic, lumbar and sacrolumbar nerve root pain (respectively in association with MD-NECK, MD-THORACIC, MD-LUMBAR and MD-ISCHIAL).

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MD-NEURAL

Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Colocynthis, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-NEURAL is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-NEURAL is a medical device designed to help joint movement, specifically in bad posture disorders. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-NEURAL is a medical device intended to be used by a qualified staff in private or public health Facilities.

Directions for use
Therapeutic protocol:
1-2 treatments weekly for 10 consecutive weeks.

Periarticular injection technique (the site of application must be aseptic; insert the needle at 2-4 mm depth)
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Intraarticular injection technique
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.

The application of a topical anaesthetic on the skin area to be treated is recommended.
- Needles: sterile 22 G.
- Syringes: 2 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
There is no history of hypersensitivity to MD-NEURAL. It contains animal-derived collagen from porcine source. However, patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

Warnings and precautions
Nerve pain requires differential diagnosis for visceral pain, primary or metastatic cancer pain. A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-NEURAL may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for the connective tissue matrix or when an antiaging action is necessary, MD-NEURAL can be associated with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:

- Brachial pain (in association with MD-NECK).
- Brachial nerve pain due to cervical entrapment (in association with MD-NECK).
- Persistent intercostal neuralgia (in association with MD-THORACIC).
- Postherpetic neuralgia (in association with MD-THORACIC or MD-LUMBAR).
- Atypical facial neuritis (in association with MD-NECK).
- Trigeminal neuralgia (in association with MD-NECK).
- Temporomandibular joint pain (in association with MD-NECK).
- Cervical, thoracic, lumbar and sacrolumbar nerve root pain (respectively in association with MD-NECK, MD-THORACIC, MD-LUMBAR and MD-ISCHIAL).

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MD-NEURAL

Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Colocynthis, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-NEURAL is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-NEURAL is a medical device designed to help joint movement, specifically in bad posture disorders. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-NEURAL is a medical device intended to be used by a qualified staff in private or public health Facilities.

Directions for use
Therapeutic protocol:
1-2 treatments weekly for 10 consecutive weeks.

Periarticular injection technique (the site of application must be aseptic; insert the needle at 2-4 mm depth)
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Intraarticular injection technique
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.

The application of a topical anaesthetic on the skin area to be treated is recommended.
- Needles: sterile 22 G.
- Syringes: 2 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
There is no history of hypersensitivity to MD-NEURAL. It contains animal-derived collagen from porcine source. However, patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

Warnings and precautions
Nerve pain requires differential diagnosis for visceral pain, primary or metastatic cancer pain. A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-NEURAL may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for the connective tissue matrix or when an antiaging action is necessary, MD-NEURAL can be associated with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:

- Brachial pain (in association with MD-NECK).
- Brachial nerve pain due to cervical entrapment (in association with MD-NECK).
- Persistent intercostal neuralgia (in association with MD-THORACIC).
- Postherpetic neuralgia (in association with MD-THORACIC or MD-LUMBAR).
- Atypical facial neuritis (in association with MD-NECK).
- Trigeminal neuralgia (in association with MD-NECK).
- Temporomandibular joint pain (in association with MD-NECK).
- Cervical, thoracic, lumbar and sacrolumbar nerve root pain (respectively in association with MD-NECK, MD-THORACIC, MD-LUMBAR and MD-ISCHIAL).

Instructions in case of damage to the sterile vials
Do not use if the seal is broken or if the vial is not perfectly sealed. Once open, the content of the vial must be immediately injected. Do not use if the package is damaged.

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GUNA medical device
Guna S.p.a. • Milan - Italy
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MD-POLY

Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Drosera, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-POLY is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-POLY is a medical device designed to help movement, specifically the vertebral spine. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-POLY is a medical device intended to be used by a qualified staff in private or public health Facilities to:
⇨ Improve movement of the joints.
⇨ Help muscle stretching.
⇨ Help to support the muscle tissue in bad posture disorders.
⇨ Soothe local pain, or pain caused by movement and bad posture.

Directions for use
Therapeutic protocol:
1-2 treatments weekly for 10 consecutive weeks.

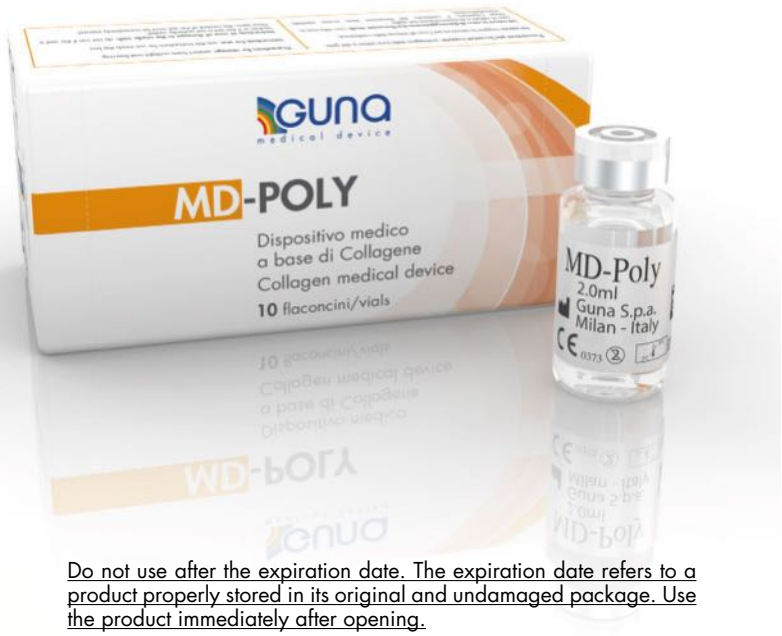
Periarticular injection technique (the site of application must be aseptic; insert the needle at a 3-6 mm depth)
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Intraarticular injection technique
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.

The application of a topical anaesthetic to the skin is recommended.
- Needles: sterile 22 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
There is no history of hypersensitivity to MD-POLY. It contains animal-derived collagen from porcine source. However, patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

Warnings and precautions
Joint pain requires differential diagnosis for acute or subacute joint viral diseases, pain due to overweight (leg joints), hyperuricemia, gout.
A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.



Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-POLY may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for the connective tissue matrix or when an antiaging action is necessary, MD-POLY can be used together with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:
- Small joints rheumatoid arthritis of hand and foot (in association with MD-SMALL JOINTS).
- Non-specific diffuse pain (in association with MD-NECK and MD-NEURAL).
- Costo-sternal syndrome (in association with MD-NEURAL).
- Chronic polyarthritis due to auto-immune diseases (e.g. *Lupus erithematosus sistemicus*) (in association with MD-NEURAL when nerve pain is dominant; in association with MD-MUSCLE when muscle pain is dominant).
- Breakbone fever (when nerve pain is dominant in association with MD-NEURAL; when muscle pain is dominant in association with MD-MUSCLE).
- Joint pain due to viral or protozoic disease (in association with another Guna medical device containing the same type of collagen contained in the joint to be treated).
- Joint pain due to cancer (chronic leukaemia, multiple myeloma) (in association with another Guna medical device containing the same type of collagen contained in the joint to be treated).

Instructions in case of damage to the sterile vials
Do not use if the seal is broken or if the vial is not perfectly sealed. Once open, the content of the vial must be immediately injected. Do not use if the package is damaged.

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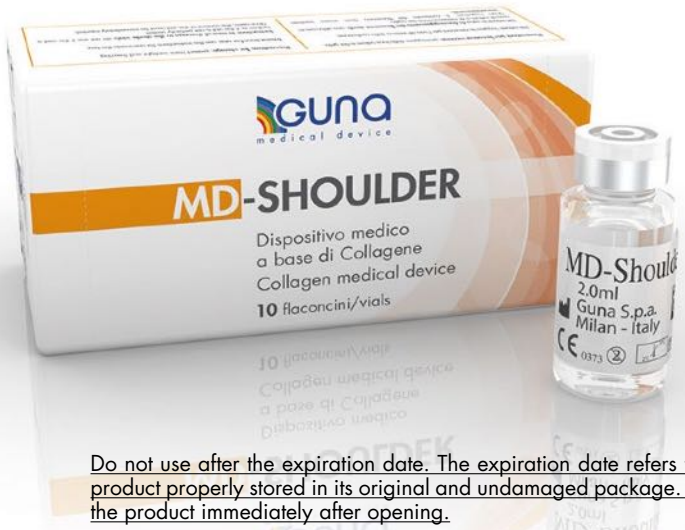
MD-SHOULDER

Collagen medical device



Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Iris, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-SHOULDER is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-SHOULDER is a medical device designed to help joint movement of the shoulder and the arm. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-SHOULDER is a medical device intended to be used by a qualified staff in private or public health Facilities to:
⇨ Improve movement of the shoulder joint and the arm.
⇨ Help muscle stretching.
⇨ Help to support the muscle tissue.
⇨ Soothe local pain and pain caused by movement.

Directions for use
Therapeutic protocol:
1-2 treatments weekly for 10 consecutive weeks.

Periarticular injection technique (the site of application must be aseptic; insert the needle at a 2-4 mm depth)
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Intraarticular injection technique
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.

The application of a topical anaesthetic on the skin area to be treated is recommended.
- Needles: sterile 22 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
There is no history of hypersensitivity to MD-SHOULDER. It contains animal-derived collagen from porcine source. However, patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

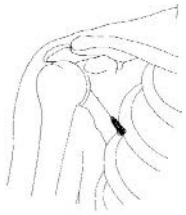
Warnings and precautions
Shoulder pain requires differential diagnosis for chronic cervical syndrome, ischemic heart disease (acute/chronic, only on the left side), gallbladder disease (only on the right side), cervical-brachial nerve pain, muscle trigger in the trapezium muscle. A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-SHOULDER may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for acute pain, MD-SHOULDER can be associated with MD-NEURAL, MD-POLY and MD-MUSCLE (together with one or more than one of these). Moreover, when a supportive treatment is needed for the connective tissue matrix or when the physio-logical aging process should be slowed down, MD-SHOULDER can be associated with MD-MA-TRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:
- Shoulder-arm polyarthritis (in association with MD-POLY).
- Rotator cuff syndrome (in association with MD-MUSCLE).
- Shoulder-arm syndrome (in association with MD-NEURAL and MD-MUSCLE).
- Frozen shoulder (in association with MD-MUS-CLE).
- Shoulder pain due to dislocation (therapeutic rest, in association with MD-NEURAL).
- Epicondylitis (in association with MD-NEURAL and MD-POLY).

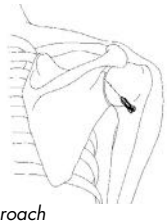
Instructions in case of damage to the sterile vials
Do not use if the seal is broken or if the vial is not perfectly sealed. Once open, the content of the vial must be immediately injected. Do not use if the package is damaged.



Anterior approach. With the patient's hand on the thigh and the shoulder muscles relaxed, the glenohumeral joint can be palpated by placing the fingers between the coracoid process and the humeral head. As the shoulder is internally rotated, the humeral head can be felt turning inward and the joint space can be felt as a groove just lateral to the coracoid process. A 22 G needle can be inserted lateral to the coracoid. Insert the needle into the joint space.

Shoulder – Intraarticular injection, anterior approach

Posterior approach. The posterior aspect of the shoulder joint can be identified by making the patient's arm rotate. This position is achieved by placing the patient's ipsilateral hand on the opposite shoulder. The humeral head can be palpated by placing a finger posteriorly along the acromion while the shoulder is rotated. A 22 G needle is inserted about 1 cm inferior to the posterior tip of the acromion and directed anteriorly and medially.



Shoulder – Intraarticular injection, posterior approach

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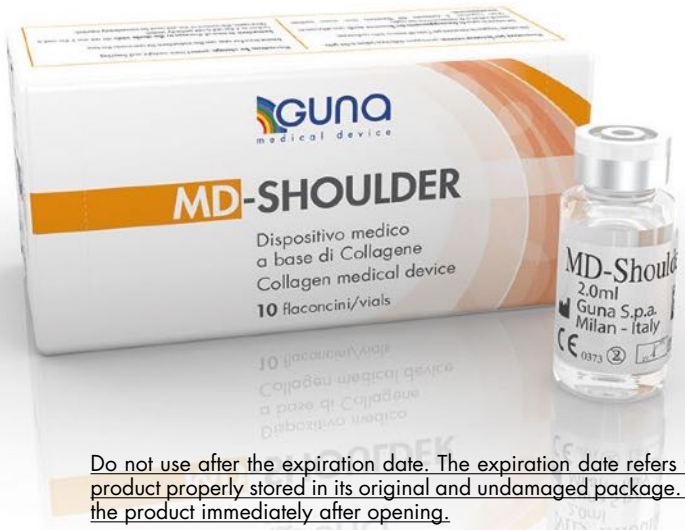
MD-SHOULDER

Collagen medical device



Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Iris, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-SHOULDER is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-SHOULDER is a medical device designed to help joint movement of the shoulder and the arm. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-SHOULDER is a medical device intended to be used by a qualified staff in private or public health Facilities to:
⇨ Improve movement of the shoulder joint and the arm.
⇨ Help muscle stretching.
⇨ Help to support the muscle tissue.
⇨ Soothe local pain and pain caused by movement.

Directions for use
Therapeutic protocol:
1-2 treatments weekly for 10 consecutive weeks.

Periarticular injection technique (the site of application must be aseptic; insert the needle at a 2-4 mm depth)
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Intraarticular injection technique
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.

The application of a topical anaesthetic on the skin area to be treated is recommended.
- Needles: sterile 22 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
There is no history of hypersensitivity to MD-SHOULDER. It contains animal-derived collagen from porcine source. However, patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

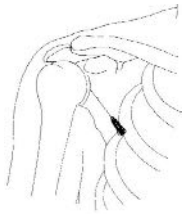
Warnings and precautions
Shoulder pain requires differential diagnosis for chronic cervical syndrome, ischemic heart disease (acute/chronic, only on the left side), gallbladder disease (only on the right side), cervical-brachial nerve pain, muscle trigger in the trapezium muscle. A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-SHOULDER may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for acute pain, MD-SHOULDER can be associated with MD-NEURAL, MD-POLY and MD-MUSCLE (together with one or more than one of these). Moreover, when a supportive treatment is needed for the connective tissue matrix or when the physio-logical aging process should be slowed down, MD-SHOULDER can be associated with MD-MA-TRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:
- Shoulder-arm polyarthritis (in association with MD-POLY).
- Rotator cuff syndrome (in association with MD-MUSCLE).
- Shoulder-arm syndrome (in association with MD-NEURAL and MD-MUSCLE).
- Frozen shoulder (in association with MD-MUS-CLE).
- Shoulder pain due to dislocation (therapeutic rest, in association with MD-NEURAL).
- Epicondylitis (in association with MD-NEURAL and MD-POLY).

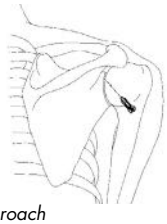
Instructions in case of damage to the sterile vials
Do not use if the seal is broken or if the vial is not perfectly sealed. Once open, the content of the vial must be immediately injected. Do not use if the package is damaged.



Anterior approach. With the patient's hand on the thigh and the shoulder muscles relaxed, the glenohumeral joint can be palpated by placing the fingers between the coracoid process and the humeral head. As the shoulder is internally rotated, the humeral head can be felt turning inward and the joint space can be felt as a groove just lateral to the coracoid process. A 22 G needle can be inserted lateral to the coracoid. Insert the needle into the joint space.

Shoulder – Intraarticular injection, anterior approach

Posterior approach. The posterior aspect of the shoulder joint can be identified by making the patient's arm rotate. This position is achieved by placing the patient's ipsilateral hand on the opposite shoulder. The humeral head can be palpated by placing a finger posteriorly along the acromion while the shoulder is rotated. A 22 G needle is inserted about 1 cm inferior to the posterior tip of the acromion and directed anteriorly and medially.



Shoulder – Intraarticular injection, posterior approach

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GUNA medical device

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MD-SMALL JOINTS

Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Viola, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-SMALL JOINTS is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-SMALL JOINTS is a medical device designed to help movement of small joints (such as those of foot, hand and ankle). Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-SMALL JOINTS is a medical device intended to be used by a qualified staff in private or public health Facilities to:
- ⇨ Improve movement of the small joints of hand, foot and ankle.
- ⇨ Help muscle stretching.
- ⇨ Help to support the muscle tissue.
- ⇨ Soothe local pain and pain caused by joint movement.

Directions for use
Therapeutic protocol:
1 treatment weekly for 10 consecutive weeks.

Periarticular injection technique (the site of application must be aseptic; insert the needle at a 2-4 mm depth)
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Intraarticular injection technique
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.

The application of a topical anaesthetic on the skin area to be treated is recommended.
- Needles: sterile 22 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Ankle intraarticular application
Foot joints can be treated with intraarticular injections in the ankle. This treatment can be also applied to the ankle joint.
For medial and lateral approach, the foot is first placed at about a 45-degree angle of plantar flexion.

Contraindications / Side effects
There is no history of hypersensitivity to MD-SMALL JOINTS. It contains animal-derived collagen from porcine source. However, patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

Warnings and precautions
Hand/foot and small joints pain requires differential diagnosis for primary nerve pain, post-traumatic pain, secondary pain due to recent or past bone fractures.

A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-SMALL JOINTS may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for acute pain, MD-SMALL JOINTS can be associated with MD-NEURAL, MD-POLY and MD-MUSCLE (together with one or more than one of these).
Moreover, when a supportive treatment is needed for the connective tissue matrix or when the physiological aging process should be slowed down, MD-SMALL JOINTS can be associated with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:
- Osteoarthritis of the fingers.
- Rhizoarthrosis of the thumb (Forestier disease).
- Arthrosis pain due to hammer toe.
- Carpal-tunnel syndrome (in association with MD-NEURAL).
- De Quervain disease (in association with MD-NEURAL).
- Metatarsal pain.
- Metatarsal pain accompanied by Morton's neuroma (in association with MD-NEURAL).
- Rheumatoid arthritis of the hand/foot (in association with MD-POLY).
- Hand/foot tendon pain due to prolonged immobilization.

Instructions in case of damage to the sterile vials
Do not use if the seal is broken or if the vial is not perfectly sealed. Once open, the content of the vial must be immediately injected. Do not use if the package is damaged.

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MD-SMALL JOINTS

Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Viola, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-SMALL JOINTS is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-SMALL JOINTS is a medical device designed to help movement of small joints (such as those of foot, hand and ankle). Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-SMALL JOINTS is a medical device intended to be used by a qualified staff in private or public health Facilities to:
- ⇨ Improve movement of the small joints of hand, foot and ankle.
- ⇨ Help muscle stretching.
- ⇨ Help to support the muscle tissue.
- ⇨ Soothe local pain and pain caused by joint movement.

Directions for use
Therapeutic protocol:
1 treatment weekly for 10 consecutive weeks.

Periarticular injection technique (the site of application must be aseptic; insert the needle at a 2-4 mm depth)
For this purpose the use of the following materials and accessories is recommended:
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Intraarticular injection technique
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The application of a topical anaesthetic on the skin area to be treated is recommended.
- Needles: sterile 22 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Ankle intraarticular application
Foot joints can be treated with intraarticular injections in the ankle. This treatment can be also applied to the ankle joint.
For medial and lateral approach, the foot is first placed at about a 45-degree angle of plantar flexion.

Contraindications / Side effects
There is no history of hypersensitivity to MD-SMALL JOINTS. It contains animal-derived collagen from porcine source. However, patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

Warnings and precautions
Hand/foot and small joints pain requires differential diagnosis for primary nerve pain, post-traumatic pain, secondary pain due to recent or past bone fractures.

A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
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Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

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Instructions on use
MD-SMALL JOINTS may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for acute pain, MD-SMALL JOINTS can be associated with MD-NEURAL, MD-POLY and MD-MUSCLE (together with one or more than one of these).
Moreover, when a supportive treatment is needed for the connective tissue matrix or when the physiological aging process should be slowed down, MD-SMALL JOINTS can be associated with MD-MATRIX and MD-TISSUE.

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- Osteoarthritis of the fingers.
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- Arthrosis pain due to hammer toe.
- Carpal-tunnel syndrome (in association with MD-NEURAL).
- De Quervain disease (in association with MD-NEURAL).
- Metatarsal pain.
- Metatarsal pain accompanied by Morton's neuroma (in association with MD-NEURAL).
- Rheumatoid arthritis of the hand/foot (in association with MD-POLY).
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Instructions in case of damage to the sterile vials
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Collagen medical device

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Composition: Collagen of porcine origin.

Excipients: Viola, NaCl, Water for injection.

For this medical device the following packages are available:
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Intended use
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- ⇨ Improve movement of the small joints of hand, foot and ankle.
- ⇨ Help muscle stretching.
- ⇨ Help to support the muscle tissue.
- ⇨ Soothe local pain and pain caused by joint movement.

Directions for use
Therapeutic protocol:
1 treatment weekly for 10 consecutive weeks.

Periarticular injection technique (the site of application must be aseptic; insert the needle at a 2-4 mm depth)
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Intraarticular injection technique
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.

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Ankle intraarticular application
Foot joints can be treated with intraarticular injections in the ankle. This treatment can be also applied to the ankle joint.
For medial and lateral approach, the foot is first placed at about a 45-degree angle of plantar flexion.

Contraindications / Side effects
There is no history of hypersensitivity to MD-SMALL JOINTS. It contains animal-derived collagen from porcine source. However, patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

Warnings and precautions
Hand/foot and small joints pain requires differential diagnosis for primary nerve pain, post-traumatic pain, secondary pain due to recent or past bone fractures.

A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-SMALL JOINTS may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for acute pain, MD-SMALL JOINTS can be associated with MD-NEURAL, MD-POLY and MD-MUSCLE (together with one or more than one of these).
Moreover, when a supportive treatment is needed for the connective tissue matrix or when the physiological aging process should be slowed down, MD-SMALL JOINTS can be associated with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:
- Osteoarthritis of the fingers.
- Rhizoarthrosis of the thumb (Forestier disease).
- Arthrosis pain due to hammer toe.
- Carpal-tunnel syndrome (in association with MD-NEURAL).
- De Quervain disease (in association with MD-NEURAL).
- Metatarsal pain.
- Metatarsal pain accompanied by Morton's neuroma (in association with MD-NEURAL).
- Rheumatoid arthritis of the hand/foot (in association with MD-POLY).
- Hand/foot tendon pain due to prolonged immobilization.

Instructions in case of damage to the sterile vials
Do not use if the seal is broken or if the vial is not perfectly sealed. Once open, the content of the vial must be immediately injected. Do not use if the package is damaged.

7EX104

CE 0373

Information reserved for healthcare professionals

Guna S.p.a. • Milan - Italy
collagenmd.guna.com

MD-THORACIC

Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Cimicifuga, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-THORACIC is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

MD-THORACIC is a medical device designed to help movement, specifically the thoracic area of the vertebral spine. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-THORACIC is a medical device intended to be used by a qualified staff in private or public health Facilities to:
- ⇨ Improve movement of the thoracic tract of the spine.
- ⇨ Help muscle stretching.
- ⇨ Help to support the muscle tissue in bad posture disorders.
- ⇨ Soothe local pain, pain caused by movement and bad posture.

Directions for use
Periarticular injection technique:
2 treatments weekly for the first 2 weeks, 1 treatment weekly until improvement of symptoms (average 8-10 sessions). For chronic pathologies: go on with 1 treatment weekly for 1 month until improvement of symptoms, then 1 treatment monthly.

The site of application must be aseptic; insert the needle at a 2-4 mm depth.

For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
There is no history of hypersensitivity to MD-THORACIC. It contains animal-derived collagen from porcine source. However, patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

Warnings and precautions
Spinal pain requires differential diagnosis for primary or secondary cancer pain, reflex and referred pain from internal organs.
A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-THORACIC may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
When a supportive treatment is needed for acute pain, MD-THORACIC can be associated with MD-NEURAL, MD-POLY and MD-MUSCLE (together with one or more than one of these).
Moreover, when a supportive treatment is needed for the connective tissue matrix or when the physiological aging process should be slowed down, MD-THORACIC can be associated with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:
- Thoracic pain due to cartilage degenerative thoracic spine disorders (thoracic osteoarthrosis) (in association with MD-POLY).
- Thoracic pain due to scoliosis (in association with MD-MUSCLE and MD-NEURAL).
- Thoracic pain due to thoracic long muscle trigger points (in association with MD-MUSCLE).
- Pain due to thoracic spine osteophytosis (in association with MD-NEURAL).
- Pain from spinal osteoporosis (in association with MD-NEURAL and MD-MUSCLE).
- Mechanical imbalance (costo-vertebral facet joint syndrome) (in association with MD-NEURAL).
- Thoracic spinal ligament syndrome (in association with MD-NEURAL).
- Thoracic spinal nerve root pain (in association with MD-NEURAL).

Instructions in case of damage to the sterile vials
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- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
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- Needles: sterile 27 G.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
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Warnings and precautions
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Instructions on use
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Moreover, when a supportive treatment is needed for the connective tissue matrix or when the physiological aging process should be slowed down, MD-THORACIC can be associated with MD-MATRIX and MD-TISSUE.

It may also be used as mechanical support while treating the following diseases:
- Thoracic pain due to cartilage degenerative thoracic spine disorders (thoracic osteoarthrosis) (in association with MD-POLY).
- Thoracic pain due to scoliosis (in association with MD-MUSCLE and MD-NEURAL).
- Thoracic pain due to thoracic long muscle trigger points (in association with MD-MUSCLE).
- Pain due to thoracic spine osteophytosis (in association with MD-NEURAL).
- Pain from spinal osteoporosis (in association with MD-NEURAL and MD-MUSCLE).
- Mechanical imbalance (costo-vertebral facet joint syndrome) (in association with MD-NEURAL).
- Thoracic spinal ligament syndrome (in association with MD-NEURAL).
- Thoracic spinal nerve root pain (in association with MD-NEURAL).

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MD-TISSUE

Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Ascorbic acid, Magnesium gluconate, Pyridoxine hydrochloride, Riboflavin, Thiamine hydrochloride, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-TISSUE is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

Due to its special function, MD-TISSUE is also intended to limit the physiological deterioration of the skin and subcutaneous connective tissue, and counterbalance the effects of chrono-ageing and photo-ageing, such as:
- local anti-ageing treatment
- face and neck wrinkles
- firming of the subcutaneous and perivascular connective *layer* of the face and neck
- alteration of the trophicity of the connective tissue of face and neck induced by airborne pollutants / metabolic disorders.

MD-TISSUE is a medical device designed to help movement by counteracting the physiological aging of the connective tissue. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-TISSUE is a medical device intended to be used by a qualified staff in private or public health Facilities to:
⇨ Act as a defensive barrier against free radicals.
⇨ Counteract the physiological aging of the connective tissue.
⇨ Soothe local pain caused by movement.

Directions for use
Therapeutic protocol:
2 treatments weekly for the first 2 weeks, 1 treatment weekly until improvement of symptoms (average 8-10 sessions). It is possible to go on with 1 treatment every other week for 10 weeks at most. For chronic pathologies: go on with 1 treatment weekly for 1 month until improvement of symptoms, then 1 treatment monthly.

- *Intradermal injection technique:* the site of application must be aseptic;
  Microinjections: insert the needle at 1-3 mm depth, and inject 0.2-0.3 ml into the affected tissue.
  Tunnelling injection technique: inject 0.3 ml per wrinkle. Insert the needle beneath the skin the full length of the needle, cannula-te the wrinkle by moving the needle gently to left and right, while injecting the content of the syringe as the needle is withdrawn.
- *Periarticular injection technique:* the site of applica-tion must be aseptic; insert the needle perpendicu-lar to the skin surface at 2-4 mm depth, and perform microinjections of 0.3-0.5 ml.

Preparation for injection
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles for microinjections: sterile 27 G, 4 mm.
- Needles for tunnelling injection technique: sterile 30 G, 13 mm.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
There is no history of hypersensitivity to MD-TISSUE. It contains animal-derived collagen from porcine source. However, patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

Warnings and precautions
A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
Skin cleansing/disinfection is required before and after application.
Pyogenic bacteria may produce injection site abscesses.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.

Do not use after the expiration date. The expiration date refers to a product properly stored in its original and undamaged package. Use the product immediately after opening.

Instructions on use
MD-TISSUE may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
Concerning its use for the treatment of face and neck wrinkles, and for firming the subcutaneous connective tissue *layer*, MD-TISSUE should preferably be associated with MD-MATRIX (e.g. MD-TISSUE 2 vials, MD-MATRIX 1 vial/treatment).
It may be used in patients who need a collagen supplementation or a topical antiaging treatment.

Instructions in case of damage to the sterile vials
Do not use if the seal is broken or if the vial is not perfectly sealed. Once open, the content of the vial must be immediately injected. Do not use if the package is damaged.

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GUNA medical device

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MD-TISSUE

Collagen medical device

Manufacturer: GUNA S.p.a., Via Palmanova 71, 20132 Milano, Italy

Composition: Collagen of porcine origin.

Excipients: Ascorbic acid, Magnesium gluconate, Pyridoxine hydrochloride, Riboflavin, Thiamine hydrochloride, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-TISSUE is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

Due to its special function, MD-TISSUE is also intended to limit the physiological deterioration of the skin and subcutaneous connective tissue, and counterbalance the effects of chrono-ageing and photo-ageing, such as:
- local anti-ageing treatment
- face and neck wrinkles
- firming of the subcutaneous and perivascular connective *layer* of the face and neck
- alteration of the trophicity of the connective tissue of face and neck induced by airborne pollutants / metabolic disorders.

MD-TISSUE is a medical device designed to help movement by counteracting the physiological aging of the connective tissue. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-TISSUE is a medical device intended to be used by a qualified staff in private or public health Facilities to:
⇨ Act as a defensive barrier against free radicals.
⇨ Counteract the physiological aging of the connective tissue.
⇨ Soothe local pain caused by movement.

Directions for use
Therapeutic protocol:
2 treatments weekly for the first 2 weeks, 1 treatment weekly until improvement of symptoms (average 8-10 sessions). It is possible to go on with 1 treatment every other week for 10 weeks at most. For chronic pathologies: go on with 1 treatment weekly for 1 month until improvement of symptoms, then 1 treatment monthly.

- *Intradermal injection technique:* the site of application must be aseptic;
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- *Periarticular injection technique:* the site of applica-tion must be aseptic; insert the needle perpendicu-lar to the skin surface at 2-4 mm depth, and perform microinjections of 0.3-0.5 ml.

Preparation for injection
For this purpose the use of the following materials and accessories is recommended:
- Materials for aseptic skin preparation: single-use gloves, iodine solution, alcohol solution, sterile gauze pads, ethyl chloride spray for the skin.
- Needles for microinjections: sterile 27 G, 4 mm.
- Needles for tunnelling injection technique: sterile 30 G, 13 mm.
- Syringes: 5 or 10 cc size, according to the volume of the solution to inject.

Contraindications / Side effects
There is no history of hypersensitivity to MD-TISSUE. It contains animal-derived collagen from porcine source. However, patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

Warnings and precautions
A slight reddening at the injection site may be due to a mechanical effect of the needle or to a skin reaction. The application might cause symptoms of burning/pain at the injection site, that usually solve spontaneously within 5-10 minutes after the treatment.
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Pyogenic bacteria may produce injection site abscesses.
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Instructions on use
MD-TISSUE may be used as a single treatment or mixed with other medical devices of the same range, in order to make a customised treatment according to clinical evolution.
Concerning its use for the treatment of face and neck wrinkles, and for firming the subcutaneous connective tissue *layer*, MD-TISSUE should preferably be associated with MD-MATRIX (e.g. MD-TISSUE 2 vials, MD-MATRIX 1 vial/treatment).
It may be used in patients who need a collagen supplementation or a topical antiaging treatment.

Instructions in case of damage to the sterile vials
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Composition: Collagen of porcine origin.

Excipients: Ascorbic acid, Magnesium gluconate, Pyridoxine hydrochloride, Riboflavin, Thiamine hydrochloride, NaCl, Water for injection.

For this medical device the following packages are available:
- Box: 5 vials (single vial 2 ml – extraction volume)
- Box: 10 vials (single vial 2 ml – extraction volume)
- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-TISSUE is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

Due to its special function, MD-TISSUE is also intended to limit the physiological deterioration of the skin and subcutaneous connective tissue, and counterbalance the effects of chrono-ageing and photo-ageing, such as:
- local anti-ageing treatment
- face and neck wrinkles
- firming of the subcutaneous and perivascular connective *layer* of the face and neck
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⇨ Act as a defensive barrier against free radicals.
⇨ Counteract the physiological aging of the connective tissue.
⇨ Soothe local pain caused by movement.

Directions for use
Therapeutic protocol:
2 treatments weekly for the first 2 weeks, 1 treatment weekly until improvement of symptoms (average 8-10 sessions). It is possible to go on with 1 treatment every other week for 10 weeks at most. For chronic pathologies: go on with 1 treatment weekly for 1 month until improvement of symptoms, then 1 treatment monthly.

- *Intradermal injection technique:* the site of application must be aseptic;
  Microinjections: insert the needle at 1-3 mm depth, and inject 0.2-0.3 ml into the affected tissue.
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Contraindications / Side effects
There is no history of hypersensitivity to MD-TISSUE. It contains animal-derived collagen from porcine source. However, patients with known hypersensitivity to any ingredient or excipient should be tested before use, making a spot injection into one arm and be monitored for 1 hour.

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Instructions on use
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Intended use
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Contraindications / Side effects
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- Box: 50 vials (single vial 2 ml – extraction volume)

Intended use
MD-TISSUE is a medical device designed to help movement by limiting a physiological degeneration of joints and tissues as well as by counterbalancing any damage caused by:
- aging
- bad posture
- concomitant chronic diseases
- blows and injuries
- pollutants.

Due to its special function, MD-TISSUE is also intended to limit the physiological deterioration of the skin and subcutaneous connective tissue, and counterbalance the effects of chrono-ageing and photo-ageing, such as:
- local anti-ageing treatment
- face and neck wrinkles
- firming of the subcutaneous and perivascular connective *layer* of the face and neck
- alteration of the trophicity of the connective tissue of face and neck induced by airborne pollutants / metabolic disorders.

MD-TISSUE is a medical device designed to help movement by counteracting the physiological aging of the connective tissue. Its main therapeutic functions include:
1. A barrier effect.
2. A lubricating action.
3. Mechanical support while administering other pharmacological treatments.

MD-TISSUE is a medical device intended to be used by a qualified staff in private or public health Facilities to:
⇨ Act as a defensive barrier against free radicals.
⇨ Counteract the physiological aging of the connective tissue.
⇨ Soothe local pain caused by movement.

Directions for use
Therapeutic protocol:
2 treatments weekly for the first 2 weeks, 1 treatment weekly until improvement of symptoms (average 8-10 sessions). It is possible to go on with 1 treatment every other week for 10 weeks at most. For chronic pathologies: go on with 1 treatment weekly for 1 month until improvement of symptoms, then 1 treatment monthly.

- *Intradermal injection technique:* the site of application must be aseptic;
  Microinjections: insert the needle at 1-3 mm depth, and inject 0.2-0.3 ml into the affected tissue.
  Tunnelling injection technique: inject 0.3 ml per wrinkle. Insert the needle beneath the skin the full length of the needle, cannula-te the wrinkle by moving the needle gently to left and right, while injecting the content of the syringe as the needle is withdrawn.
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GUNA medical device

Guna S.p.a. • Milan - Italy
collagenmd.guna.com

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CLINICAL

M. Ottaviani

TREATMENT OF JOINT CONDITIONS WITH GUNA COLLAGEN MEDICAL DEVICES

– CLINICAL STUDY ON 257 PATIENTS

SUMMARY

Collagen is the main extracellular structural protein to be found in the connective tissue and bone tissue of most animals. In humans aged about 50 years its synthesis begins to reduce, with consequent cartilage and tendon degeneration and inevitable development of osteoarthritis and tendonitis. Since these degenerative conditions are very common and evolve towards pain and joint stiffness, there is an urgent need for tools that allow practitioners not only to limit this degenerative evolution, but also, in certain cases, to induce its regression.

This clinical study was conducted on 257 patients with joint and tendon disorders (impingement syndrome, shoulder tendinopathy, hip arthritis, knee arthritis, trapeziometacarpal osteoarthritis, Achilles' tendinopathy) frequently reflected in clinical evidence, such as pain and joint stiffness; they were all treated exclusively with local injections of Guna Collagen Medical Devices.

The data were collected through self-assessment scales, validated by the WHO and the results showed that Guna Collagen MD can give a useful contribution to containing the problems associated with joint degeneration.

PAROLE CHIAVE

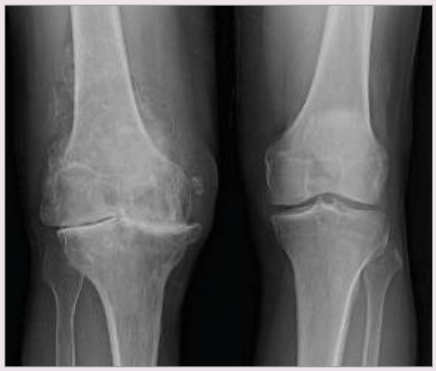
GUNA COLLAGEN MEDICAL DEVICES, COLLAGEN, OSTEOARTRHITIS, TENDINOPATHY, PAIN

INTRODUCTION

Collagen is a glycoprotein characterised by a structure in which a simple **basic module** is repeated: collagen molecules join together to form a collagen fibril; a union in which each molecule overlaps with that above by one quarter of its length.

This creates a kind of *wall*, in which the individual bricks that make it up are staggered in order to achieve considerable resistance to both incident tangential and perpendicular forces (FIG. 1).

– This characteristic arrangement gives the collagen significant sturdiness in terms of **resistance**, **extensibility** and **incompressibility**, whilst guaranteeing **plasticity**, **flexibility**, allowing **torsion**



http://www.georgeackermanmd.com/knee-osteoarthritis.html

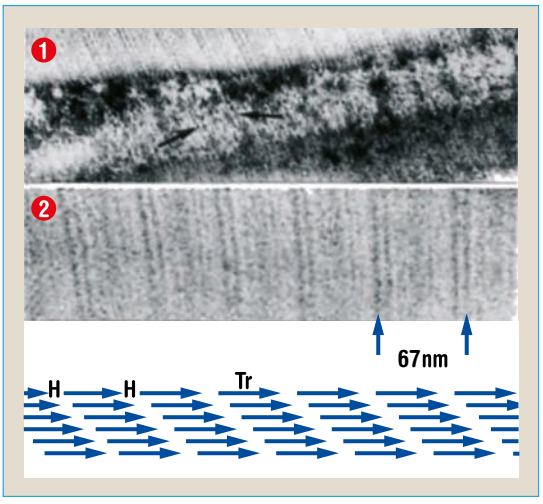
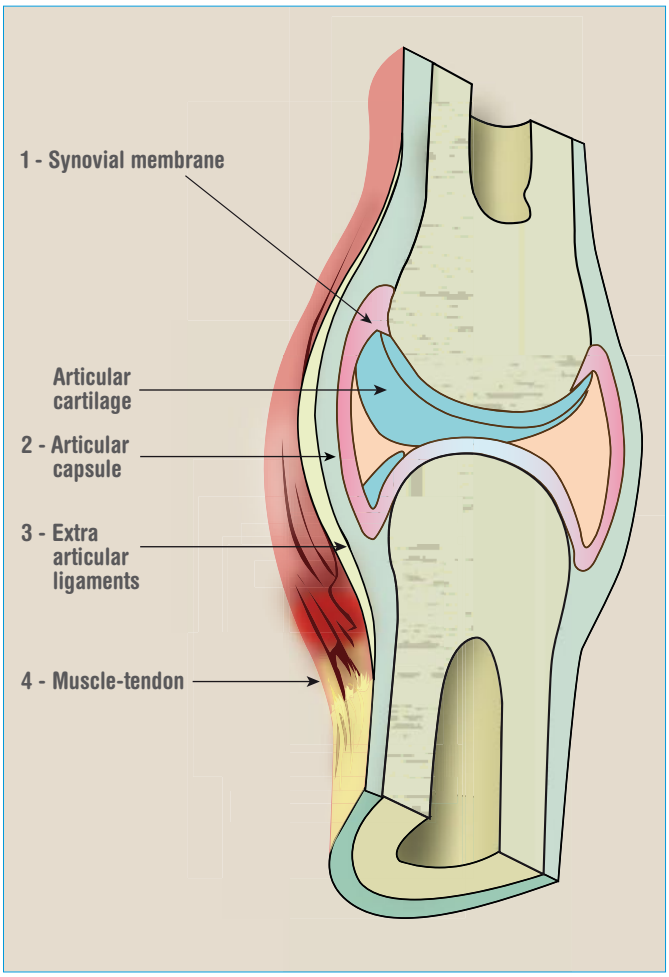


FIG. 1

Structure of collagen.
1: Sugars bound to collagen. Relationship between sugar (black precipitations) **and the density of collagen fibrils** (ME 112.000X)**;**
2: Section of a collagen fibril (ME 240.000X)**.**
A cycle of 67 nm (670 A) **forms on the base of collagen molecules, each of which is staggered by ¼ of their length.**

FIG. 2
Extra-articular containment system.



and **great resistance** to load.
In order to be functional, almost all joints must possess two, apparently contradictory, characteristics: stability and mobility.
The **articular stabilisation** systems consist of the structures pertaining to both the **extra-articular component** and the **intra-articular component**; collagen is present in abundance in both of these structures.

– The extra-articular component consists of ligaments, the articular capsule, tendons and muscles; the intra-articular component is formed of ligaments (for the knee and hip joints only) and of joint cartilage (FIG. 2).

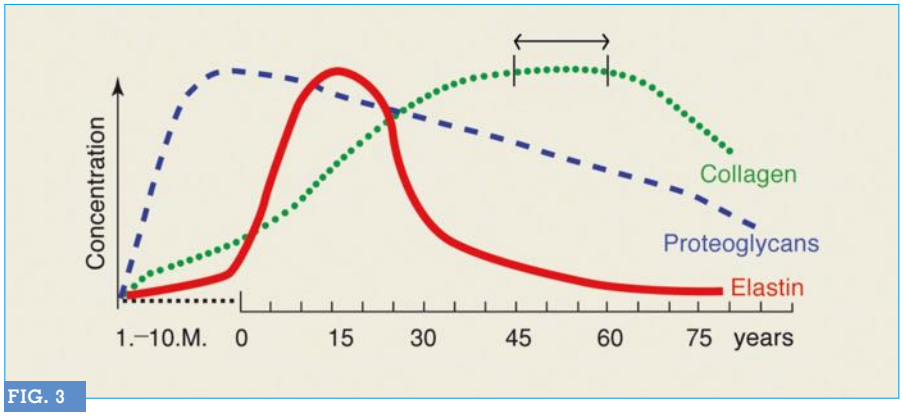


FIG. 3
Age-related biosynthesis of collagen, proteoglycans, and elastin.

One of the most important causes of joint pain is the **laxity** of the intra- and extra-articular stabilisation structures; lax containment systems result in **articular hypermobility**, especially in non-physiological directions and at non-physiological angles that, on the one hand, lead to greater, early wear of the containment systems themselves and, on the other, cause progressive cartilage degeneration.

The mechanical support provided by collagen represents an effective natural scaffolding.

– In humans, the biosynthesis of collagen starts to decrease at 55-60 years of age (FIG. 3);
From this age onwards, there is a quantitative and qualitative deterioration in the joint structures. More specifically, in the musculoskeletal system, the cartilage surfaces become thinner and degenerate to osteoarthritis, whereas the tendinous and ligamentous structures become less elastic and progress to tendinoses and tendinopathies of varying severities. Often in musculoskeletal conditions, the instrumental diagnostic evidence (x-ray, ultrasound, etc.) is not consistent with the clinical findings.

The term **Osteoarthritis state** is used to indicate physiological age-related articular ageing; it is a paraphysiological condition that does not cause any clinical situation and is often incidentally observed during imaging studies performed for other reasons (e.g. injury).
However, when osteoarthritis makes itself felt by causing the characteristic onset symptoms, such as *stiffness* and joint pain, we talk about osteoarthritis disease. Osteophytes are irregular beak- or crest-shaped proliferations of bone tissue that form in the vicinity of joints affected by a number of pathological processes, but above all in the presence of osteoarthritis. Their presence can involve disorders of various types, with restrictions to joint movement or the compression and irritation of nearby structures, in particular, nerve branches and tendon insertions. Osteophytes are the

bone tissue's attempt to increase the surface area of the heads of the articular bones damaged by osteoarthritis, in an attempt to stabilize the joint (FIG. 4).

In addition, it is common for ultrasound scans and MRI studies to show complete or multiple tendon damage, despite the presence of little or no signs and symptoms; conversely, in other cases, the tendon is intact but the patient experiences very severe pain and functional impairment.
As regards the tendinous-ligamentous sub-system, an anatomopathological distinction can be made between tendinites or tenosynovitis, tendinoses and tendon injuries of various degrees.

– Tendinites or tenosynovites are inflammatory states of the tendon and possibly also of its sheath, with or without peritendinous effusion; they may be a consequence of either a traumatic event or a functional overload.

When the repair process of the affected element starts in the presence of inflammation, the scar tissue that forms is a connective tissue that is devoid of the characteristics of elasticity and resistance that are typical of native tendons; this makes the structure more prone to partial or complete tears.

– For this reason, an inflammatory process affecting a tendinous or ligamentous structure should not be underestimated, rather it should be kept under close observation and resolved as soon as possible.

Also on the basis of our experience we can undoubtedly state that clinical and diagnostic evidence are not always consistent. In Italy, osteoarthritis accounts for **72.6%** of all rheumatic diseases and is responsible for **70%** of cases of chronic pain. The potential therapeutic approach to osteoarthritis, and tendinopathy, can be of different types:
– educational
– pharmacological
– rehabilitative
– surgical.

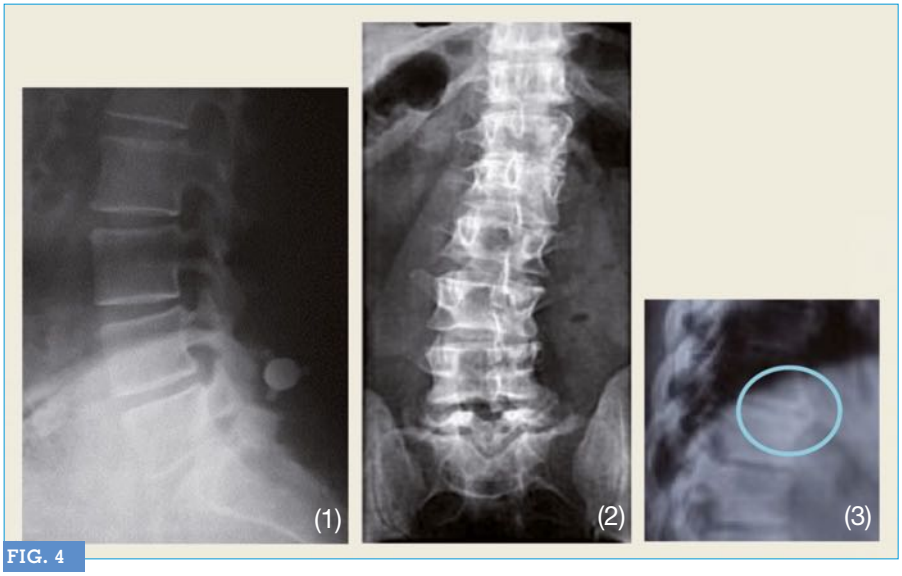


FIG. 4

X-ray of the L-S spine of an individual with severe low back pain without osteoarthritic skeletal alterations (1); of a L-S spine with significant radiological signs of osteoarthritic degeneration (2) in an asymptomatic patient; osteophytes (3).

The educational approach is represented by an improvement in quality of life including health education intervention, the use of braces, where necessary, and weight loss, when appropriate.
The conventional medicinal products used to treat osteoarthritis and tendinopathies (NSAIDs, Coxibs, Paracetamol, Steroids, and Opioids) have a symptomatic action and are used on both systemic and local levels (e.g. intra-articular steroid injections).
There are other medicinal products, whose real efficacy is not recognised by all Authors, which are thought to exert a slow chondroprotective action, these are: glucosamine sulphate, chondroitin sulphate, and hyaluronic acid.

The local use – and therefore – the intra-articular injection of hyaluronic acid boosts its efficacy; this kind of treatment is referred to as "visco-supplementation" and it has **only** a lubricating and shock-absorbing action.

Until just a few years ago, osteoarthritis was considered a progressive degenerative disease; subsequently, a prevention campaign against the progression of osteoarthritis with the use of "Cartilage integrators", was started.

– For some years now, it possible to state that osteoarthritis is a process that is, at least in part, reversible.
Given the ongoing rise in the population's average age, it goes without saying that having access to tools able to maintain high quality of life standards despite *chrono-aging* is an important breakthrough.

Guna Collagen Medical Devices are products for local injection constituted by **collagen** of porcine origin (porcine tissues have a very high collagen content) and a substance known as an *ancillary* or vehicle, of plant or mineral origin, characterised by a particular tropism for the specific articular segments.
A tangential filtration process, combined with sterilisation and control of the molecular weight, makes it possible to obtain a pure product with standard chemical and physical characteristics.
The availability of Guna Collagen Medical Devices for local injection is a determining factor in the repair process that follows anti-inflammatory intervention.
Lax joint support elements cause local nociceptor stimulation and excessive tension and stress: which explains why the reinforcement of these structures is **analgesic** as well as **regenerative**.

AREA	M	F	Total N.	Age - average	Age - range
SHOULDER, UPPER LIMB	30%	70%	**147**	53,5	34-78
KNEE	66%	34%	**53**	67,5	55-82
HIP	30%	70%	**30**	67	53-78
ACHILLES	20%	80%	**27**	43,3	32-63

TAB. 1

General caseload. Patient distribution according to gender and age.

– These characteristics translate directly into organoleptic properties: collagen is a **tissue structurer** (structural protein) and also possesses lubricating qualities.

– These bases form the significant difference between the properties of collagen and those of hyaluronic acid.

The latter is a lubricant (high viscosity) only of the articular cavity, that acts on the intra-articular component **only**, primarily in the large joints.
Collagen **also** and **primarily**, acts on the structures of the extra-articular component (capsule, ligaments, tendons) of small, medium, and large joints.
In addition, hyaluronic acid is efficacious in cases of modest and intermediate clinical severity, whereas collagen is also efficacious in those cases in which the patient's mobility is more severely impaired: it replaces the *bricks* where the *wall* had crumbled.

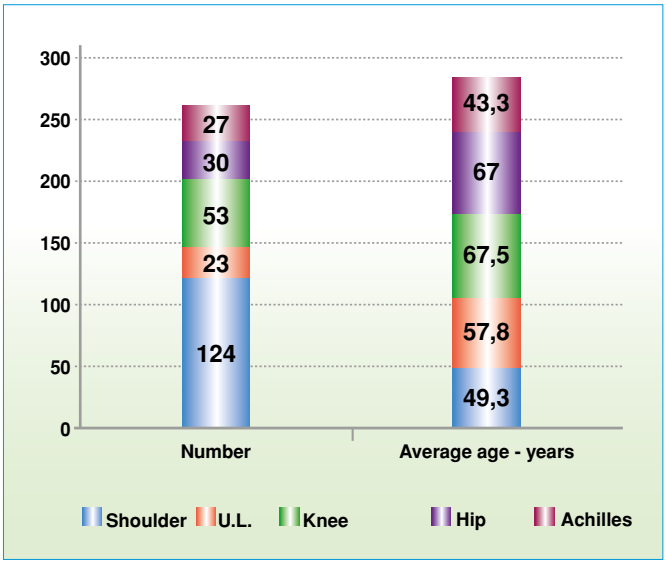
– Guna Collagen Medical Devices can be used alone or in home combinations with conventional or Physiological Regulating Medicine (PRM) products as **Guna-Arthro, Guna-Flam, Guna-Anti IL 1, Guna-Interleukin 10**; the treatment programme may also include other systemic pharmacological and rehabilitation treatments.

MATERIALS AND METHODS

A total of **257 patients** (36.5% M; 63.5% F) were enrolled in this clinical study. The mean age was 58.7 years, with a range of 32-82 years.
TAB. 1 shows the joint segments considered and treated and the corresponding epidemiological characteristics of the caseload.

FIG. 5

General caseload. – Number and mean age of patients included in the study per individual condition considered.



More specifically, because of the type of assessment scale used, the "Shoulder and upper limb (SUL)" Group included **124** patients with problems relating to the shoulder alone (rotator cuff syndrome, with possible tendon lesions); the remaining **23** had a number of other conditions, such as trapeziometacarpal osteoarthritis, epicondylitis and ganglion cysts of the wrist (U.L.).
It was consequently decided to analyse the results of these two sub-Groups independently (FIG. 5).

As far as the "Knee" Group was concerned, all **53** treated cases were classified as stage I, II and III osteoarthritis of the knee using the Kellgren-Lawrence radiological scale.
In the "Hip" Group, the treated hip joint (s) were affected by mild and moderate primary hip osteoarthritis (stage I and II); in this Group (**30** patients), patients were considered holistically, and only patients with a normal physique were included, so that the needle used was able to reach the pericapsular area.
In the "Achilles" Group, all the cases treated were mono- or bilateral Achilles' tendinopathies; **11** cases of tendonitis in the same area with ultrasound-documented exudate were also treated.
All patients were told about the type of treatment that they were being offered and the main differences that it would have compared to a similar injection therapy with hyaluronic acid or Guna Collagen MDs. They all signed the informed consent form.
The clinical and symptomatic findings of the patients enrolled were collected using assessment questionnaires validated by the WHO, more specifically:

- the Pain symptom was measured using a five-point visual-analogue scale (VAS), in which "0" = no pain and "5" = unbearable pain;
- D.A.S.H. (Disability for Arm, Shoulder and Hand) for the shoulder, elbow, hand, and wrist (range 0-100, in which 0 = no disability) (TAB. 2);
- O.K.S. (Oxford Knee Score) for the knee (range 48-0, in which 48 = no disability) (TAB. 3);
- O.H.S. (Oxford Hip Score) for the

hip (range 48-0, in which 48 = no disability) (TAB. 4);
- V.I.S.A.-A (Victorian Institute of Sport Assessment – Achilleus) for the Achilles' tendon (range 68-0, in which 68 = no disability) (TAB. 5).

The questionnaires were filled out by patients; the dedicated questionnaire was administered at the **first visit** and at the **end of treatment**.
Patients were administered **intra-articular** (shoulder, elbow, wrist, hand and knee), **pericapsular** (hip) and **local** (tendons) injections **with the appropriate** and **specific MDs**; 5 cc disposable syringes were used, with 23G x 1-1/2 - mm 0.60 x 40 needles for the hip, knee, and shoulder injections and 26G x 1/2 - mm 0.40 x 16 needles for hand, wrist, elbow, and foot injections.
Before administration, the skin was disinfected using a liquid product containing quaternary ammonium salt.

– In those segments in which administration was intra-articular, sterile surgical gloves were used and the injection area was disinfected thoroughly using sterile gauze soaked in surgical Betadine. In certain segments that are particularly rich in pain-sensitive nerve terminations, spray "ice" was used for analgesic purposes. The injections were administered **twice-weekly** for **5 consecutive weeks** (total = 10 injections).

– The patients treated for chronic degenerative diseases (knee osteoarthritis, hip osteoarthritis, trapeziometacarpal osteoarthritis and one case of severe Achilles' tendinopathy in a semi-professional dancer) continued with **maintenance therapy** (1 session a month for 6 consecutive months, then every 3 months). In no case was it suggested for the pharmacological therapy to be suspended or varied; patients taking NSAIDs or Paracetamol were asked to use this therapy only when absolutely necessary.
The evolution of the pain symptom in particular was monitored in the 8 patients who were taking opioid analgesics, in order to gradually reduce the posology of these drugs.

RESULTS

All the patients included in this study completed the treatment. None of them reported any side effect after the administration of the Guna Collagen Medical Devices. In those patients on antiplatelet or dicoumarol therapy, small areas of ecchymosis were observed at the injection site, but it reabsorbed rapidly without requiring any particular intervention.
All patients considerably **reduced** their use of conventional medicinal products and in **75%** ≈ of all cases their administration was not considered necessary.

– Of the 8 patients on treatment with opioid analgesics, 3 continued taking these medicinal products, albeit at considerably lower doses, whereas the remaining 5 gradually discontinued their use.

Generally speaking, the pain symptoms started to subside from the **4th** or **5th administration**; however, in cases of subacromial impingement and Achilles' or elbow tendinopathy the positive effects on pain were observed later.
In the osteoarthritic forms, affecting both the knee and the hip joint, the first effect reported by patients was a sensation of a **greater range of joint motion**; this sensation was perceived by patients after the first 2 - 3 sessions.

One particularly complex case was that of a male patient with polycythaemia, with concomitant severe osteoarthritis of the knee, hip and shoulder joint and significant functional impairment.
This was the case in which the improvement assessed by the questionnaires used in the study was poor; however, considering the initial clinical situation, it can be said that this was the patient who was most satisfied with the treatment received.

– We initially treated the shoulder alone and only subsequently, at the patient's insistence, also treated the knees. At a later date, we will decide if and when to treat the hips.

▶ Pain

The pain assessment scale showed a reduction from **3.06** (initial mean value including all the cases analysed) to a final value of **1.34**.
– The variation in the pain experienced in the various segments is shown in FIG. 6.

Shoulder and upper limb Group
(FIG. 7)

D.A.S.H. is an assessment questionnaire that considers a number of everyday situations facing the patient (disability concerning movements of the shoulder, hand, and elbow). The worst score is 100 and describes an extremely invalidating situation; a normal situation coincides with a score of 0.

In the caseload managed in this study regarding conditions of the **Shoulder**, the score dropped from an initial average of **78.7** to a final score of **17.3**.
As far as the **Upper limb** Group is concerned, from the initial mean of **66.8** the score dropped to **18.2**.

– In this case, the use of the D.A.S.H. questionnaire proved to be a disputable choice, as it pooled the results for a number of different segments. In the future, we intend to use a dedicated score, such as the *Oxford Shoulder Score* to assess shoulder function.

Knee Group

O.K.S. (The Oxford Knee Score) is an assessment scale including different common situations of everyday life.
The patient is invited to reply with regard to the 4 months prior to completion of the questionnaire; for obvious time reasons, post-treatment completion refers to the time at which it is filled out.
A score of 0 coincides with the most impaired situation, whereas a score of 48 coincides with a condition of full function. Of the 53 patients included (FIG. 8), the average initial score was **13.6**, whereas a score of **35.8** was achieved at the end of treatment.

D.A.S.H.

This questionnaire asks about your symptoms as well as your ability to perform certain activities. Please answer every question , based on your condition in the last week. If you did not have the opportunity to perform an activity in the past week, please make your best estimate on which response would be the most accurate. It doesn't matter which hand or arm you use to perform the activity; please answer based on you ability regardless of how you perform the task.

Please rate your ability to do the following activities in the last week

		NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1	Open a tight or new jar	1	2	3	4	5
2	Write	1	2	3	4	5
3	Turn a key	1	2	3	4	5
4	Prepare a meal	1	2	3	4	5
5	Push open a heavy door	1	2	3	4	5
6	Place an object on a shelf above your head	1	2	3	4	5
7	Do heavy household chores (e.g., wash walls, wash floors)	1	2	3	4	5
8	Garden or do yard work	1	2	3	4	5
9	Make a bed	1	2	3	4	5
10	Carry a shopping bag or briefcase	1	2	3	4	5
11	Carry a heavy object (over 10 lbs).	1	2	3	4	5
12	Change a lightbulb overhead	1	2	3	4	5
13	Wash or blow dry your hair	1	2	3	4	5
14	Wash your back	1	2	3	4	5
15	Put on pullover sweater	1	2	3	4	5
16	Use a knife to cut food	1	2	3	4	5
17	Recreational activities which require little effort (e.g., cardplaying, knitting, etc…)	1	2	3	4	5
18	Recreational activities in which you take some force or impact through your arm, shoulder or hand (e.g golf, hammering, tennis, etc…)	1	2	3	4	5
19	Recreational activities in which you move your arm freely (e.g., playing freesby, badminton, etc…)	1	2	3	4	5
20	Manage transportation needs (getting from one place to another)	1	2	3	4	5
21	Recreational activities which require considerable effort (e.g. push-ups, shaking a spray can, etc…)	1	2	3	4	5

22.During the past week, to what extend has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbours or groups? (circle number)

NOT AT ALL	SLIGHTLY	MODERATELY	QUITE A BIT	EXTREMELY
1	2	3	4	5

23.During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem? (circle number)

NO LIMITED AT ALL	SLIGHTLY LIMITED	MODERATELY LIMITED	VERY LIMITED	UNABLE
1	2	3	4	5

		NONE	MILD	MODERATE	SEVERE	EXTREME
24	Arm, Shoulder or hand pain	1	2	3	4	5
25	Arm, Shoulder or hand pain when you performed any specific activity	1	2	3	4	5
26	Tingling (pins and needles) in your arm, shoulder or hand	1	2	3	4	5
27	Weakness in your arm, shoulder or hand	1	2	3	4	5
28	Stiffness in your arm, shoulder or hand	1	2	3	4	5

29. During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand? (circle number)

NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	SO MUCH DIFFICULTY THAT I CAN'T SLEEP
1	2	3	4	5

30. I feel less capable, less confident or less useful because of my arm, shoulder or hand problem (circle number)

NONE	MILD	MODERATE	SEVERE	EXTREME
1	2	3	4	5

The following questions ask about the impact of your arms, shoulder or hand problem on your ability to work. Please circle the number that best describes your physical ability in the past week.

	Did you have difficulty:	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	EXTREME DIFFICULTY	UNABLE
31	Using your usual technique for your work?	1	2	3	4	5
32	Doing your usual work because of arm, shoulder or hand pain?					
33	Doing your work as well as you would like?					
34	Spending your usual amount of time doing your work?					

The following questions relate to the impact of your arms, shoulder or hand problem on playing your musical instrument or sport or both. If you play more than one sport or instrument (or play both), please answer with respect to that activity which is most important to you. Please circle the number that best describes your physical ability in the past week.

	Did you have difficulty:	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	EXTREME DIFFICULTY	UNABLE
35	Using your usual for playing your instrument or sport?	1	2	3	4	5
36	Playing your musical instrument or sport because of arm, shoulder or hand pain?	1	2	3	4	5
37	Playing your musical instrument or sport as well as you would like?	1	2	3	4	5
38	Spending your usual amount of time practicing or playing your instrument or sport?	1	2	3	4	5

Thank you for filling in this form.

TAB. 2

– D.A.S.H. (Disability for Arm, Shoulder and Hand) Questionnaire.

O.K.S. - OXFORD KNEE SCORE

NEW OXFORD KNEE SCORE QUESTIONNAIRE

Please answer the following 12 questions. Please only consider how you have been getting on during the past four weeks

1. How would you describe the pain you have usually from your knee? Score
None – 4
Very mild – 3
Mild – 2
Mild moderate – 1
Severe – 0

2. Have you had any trouble with washing and drying yourself all over because of your knee?
No trouble at all – 4
Very little trouble – 3
Moderate trouble – 2
Extreme difficulty – 1
Impossible to do – 0

3. Have you had any trouble getting in and out of a car or using public transport because of your knee?
No trouble at all – 4
Very little trouble – 3
Moderate trouble – 2
Extreme difficulty – 1
Impossible to do – 0

4. If you were to kneel down could you stand up afterwards?
Yes, easily – 4
With little difficulty – 3
With moderate difficulty – 2
With extreme difficulty – 1
No, impossible – 0

5. Have you been limping when walking because of your knee?
Rarely/never – 4
Sometimes or just at first – 3
Often, not just at first – 2
Most of the time – 1
All of the time – 0

6. Have you felt that your knee might suddenly give way or let you down?
Rarely/never – 4
Sometimes or just at first – 3
Often, not just at first – 2
Most of the time – 1
All of the time – 0

7. Could you kneel down and get up afterwards?
Rarely/never – 4
Sometimes or just at first – 3
Often, not just at first – 2
Most of the time – 1
All of the time – 0

8. Have you been able to do your own household shopping on your own? Score
Yes, easily – 4
With little difficulty – 3
With moderate difficulty – 2
With extreme difficulty – 1
No, impossible – 0

9. For how long have you been able to walk before the pain from your knee became severe (with or without a stick)?
No pain, even after more than 30 minutes – 4
16-30 minutes – 3
5-15 minutes – 2
Around the house only – 1
Unable to walk at all – 0

10. Have you been able to walk down a flight of stairs
Yes, easily – 4
With little difficulty – 3
With moderate difficulty – 2
With extreme difficulty – 1
No, impossible – 0

11. After a meal (sat at a table) how painful has it been for you to stand up from a chair because of your knee?
Not at all painful – 4
Slightly painful – 3
Moderately painful – 2
Very painful – 1
Unbearable – 0

12. How much pain from your knee interfered with your usual work (including housework)?
Not at all – 4
A little bit – 3
Moderately – 2
Greatly – 1
Totally – 0

13. Have you been troubled by pain from your knee in bed at night?
No nights – 4
Only 1 or 2 nights – 3
Some nights – 2
Most nights – 1
Every night – 0

TAB. 3
– O.K.S. (Oxford Knee Score) Questionnaire.

O.H.S. - OXFORD HIP SCORE

OXFORD HIP SCORE

Please answer the following 12 questions.

During the past 4 weeks...

1. How would you describe the pain you usually have in your hip?
4) None
3) Very mild
2) Mild
1) Moderate
0) Severe

2. Have you been troubled by pain from your hip in bed at night?
4) No nights
3) Only 1 or 2 nights
2) Some nights
1) Most nights
0) Every night

3. Have you had any sudden, severe pain-' shooting ', 'stabbing', or 'spasms' from your affected hip?
4) No days
3) Only 1 or 2 days
2) Some days
1)Most days
0) Every day

4. Have you been limping when walking because of your hip?
4) Rarely/never
3) Sometimes or just at first
2) Often, not just at first
1) Most of the time
0) All of the time

5. For how long have you been able to walk before the pain in your hip becomes severe (with or without a walking aid)?
4) No pain for 30 minutes or more.
3) 16 to 30 minutes
2) 5 to 15 minutes
1) Around the house only
0) Not at all

6. Have you been able to climb a flight of stairs?
4) Yes, easily
3) With little difficulty
2) With moderate difficulty
1) With extreme difficulty

7. Have you been able to put on a pair of socks, stockings or tights?
4) Yes, easily
3) With little difficulty
2) With moderate difficulty
1) With extreme difficulty
0) No, impossible

8. After a meal (sat at a table), how painful has it been for you to stand up from a chair because of your hip?
4) Not at all painful
3) Slightly painful
2) Moderately painful
1) Very painful
0) Unbearable

9. Have you had any trouble getting in and out of a car or using public transportation because of your hip?
4) No trouble at all
3) Very little trouble
2) Moderate trouble
1) Extreme difficulty
0) Impossible to do

10. Have you had any trouble with washing and drying yourself (all over) because of your hip?
4) No trouble at all
3) Very little trouble
2) Moderate trouble
1) Extreme difficulty
0) Impossible to do

11. Could you do the household shopping on your own?
4) Yes, easily
3) With little difficulty
2) With moderate difficulty
1) With extreme difficulty
0) No, impossible

12. How much has pain from your hip interfered with your usual work, including housework?
4)Not at all
3) A little bit
2) Moderately
1) Greatly
0) Totally

TAB. 4
– O.H.S. (Oxford Hip Score) Questionnaire.

TAB. 5
– V.I.S.A.-A (Victorian Institute of Sport Assesment- Achilles tendon) Questionnaire.

V.I.S.A.-A

IN THIS QUESTIONNAIRE, THE TERM PAIN REFERS SPECIFICALLY TO PAIN IN THE ACHILLES TENDON REGION

1. For how many minutes do you have stiffness in the Achilles region on first getting up?

100 mins ☐☐☐☐☐☐☐☐☐☐ 0 mins — POINTS ☐

0 1 2 3 4 5 6 7 8 9 10

2. Once you are warmed up for the day, do you have pain when stretching the Achilles tendon fully over the edge of a step? (keeping knee straight)

strong severe pain ☐☐☐☐☐☐☐☐☐☐ no pain — POINTS ☐

3. After walking on flat ground for 30 minutes, do you have pain within the next 2 hours?

strong severe pain ☐☐☐☐☐☐☐☐☐☐ no pain — POINTS ☐

4. Do you have pain walking downstairs with a normal gait cycle?

strong severe pain ☐☐☐☐☐☐☐☐☐☐ no pain — POINTS ☐

5. Do you have pain during or immediately after doing 10 (single leg) heel raises from a flat surface?

strong severe pain ☐☐☐☐☐☐☐☐☐☐ no pain — POINTS ☐

6. How many single leg hops can you do without pain?

0 ☐☐☐☐☐☐☐☐☐☐ 10 — POINTS ☐

7. Are you currently undertaking sport or other physical activity?

0 ☐ Not at all — POINTS

4 ☐ Modified training ± modified competition ☐

7 ☐ Full training ± competition but not at same level as when symptoms began

10 ☐ Competing at the same or higher level as when symptoms began

At the end of the treatment, patients were offered the chance to continue with maintenance therapy: all the patients agreed to continue the treatment, saying that they were satisfied and confident. The improvements achieved were maintained in the following months. In some cases, further improvements were seen; however, in order to quantify these data, the situation must be evaluated on a case-by-case basis.

Hip Group

O.H.S. (The Oxford Hip Score) is an assessment scale for hip joint function.
The patient must answer regarding his/her every day motor performance.
Once again, patients were invited to answer the end-of-treatment questionnaire, by entering their replies at the time of assessment. Full joint integrity coincides with a score of 48 points, whereas a clinical situation of maximum impairment coincides with a score of 0.
It is important to remember that the patients in this Group presented radiographic evidence of a stage I or II condition, the phases of the disease in which pain and functional impairment emerge.
In this Group, the mean score decreased from an initial value of **10.2** (indicating somewhat severe general impairment) to a final score of **37.2** (FIG. 9).

Achilles' Group

This Group of patients, suffering from an inflammation of the Achilles' tendon, answered the Victorian Institute of Sport Assessment (V.I.S.A.-A) questionnaire, which refers to the Achilles' tendon alone and provides a score of between 0 and 68 points; the latter value refers to a condition of complete and perfect function.
In this case, as shown by the data in FIG. 10, the score increased from an initial value of **21.0**, to a final value of **54.0** points.
The patients in this Group had an ultrasound study, with a finding of effusion between the tendon folds.
– As ultrasound is a non-invasive imaging technique, at the end of treatment the patients had a follow-up ultrasound scan, to show the reabsorption of the signs of inflammation (FIG.11).

CONCLUSIONS

All the treated patients declared that they were satisfied with the result achieved.
– There were no drop outs, despite the fact that the treatment lasted 5 - 6 weeks.
As far as all of the assessment questionnaires as a whole are concerned, there was a considerable, statistically significant, subjective improvement.
To this we must add the objective improvement, confirmed by imaging studies (follow-up ultrasound) for those patients with Achilles' tendon conditions, and clinically by range of joint motion tests.
After the first 3 - 4 administrations, almost all patients in the Shoulder, Hip and Knee Groups, expressed their surprise at the feeling of greater joint freedom.
The Hip Group was the Group that expressed the greatest and earliest satisfaction with the treatment. From a percentage standpoint, the best result was achieved in the Achilles' Group: this can be attributed to the fact that this Group was constituted by patients with the lowest average age and that in which the condition was not secondary to an overload or degenerative process.
The members of this Group and the Shoulder Group were not offered any maintenance therapy. A single addition-

al administration was required in just two cases, both in the Shoulder Group. For the patients in the Hip, Knee and Upper Limb Groups (in the latter, for cases of trapeziometacarpal osteoarthritis only) the treatment is still on-going. Administration is once-monthly for the first six months.

Subsequently, if stable remission is achieved, the treatment is administered once every two months and, later, once every three months.
Having been thoroughly informed of the role played by locally-administered collagen (Guna Collagen MDs), the patients readily understood that their attention to symptoms is fundamental to a successful outcome of treatment, in order to achieve long-lasting results.

– Another positive aspect of treatment with Guna Collagen MDs is the rapid effect on pain, even and above all in patients on dicoumarol anti-coagulant therapy, who cannot take NSAIDs or steroids.

A positive and somewhat rapid response was also observed in those patients with heavy pharmacological regimens due to comorbidities.
It is important to note that, in most of the cases observed in this study (as is the case for the majority of patients referred to a physiatrist), the patient was referred after at least two months of attempts using conventional pharmacological therapy (NSAIDs, Steroids, Paracetamol) without achieving any stable result. Their body was therefore intoxicated.

– The toxins from conventional anti-inflammatory drugs accumulate above all in the structures comprising the musculoskeletal system.

– Even subjects on heavy chronic pharmacological treatment (steroids, oral hypoglycaemic agents, insulin, anticoagulants), the positive response to therapy was achieved without any interference with their ongoing chronic therapies. ■

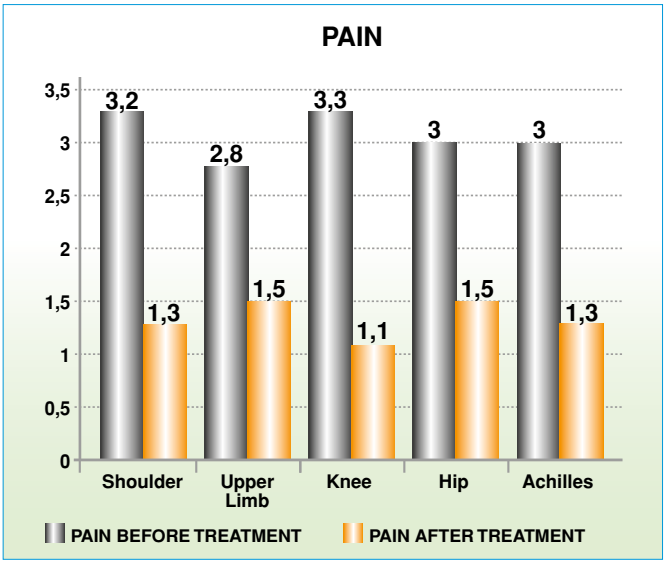
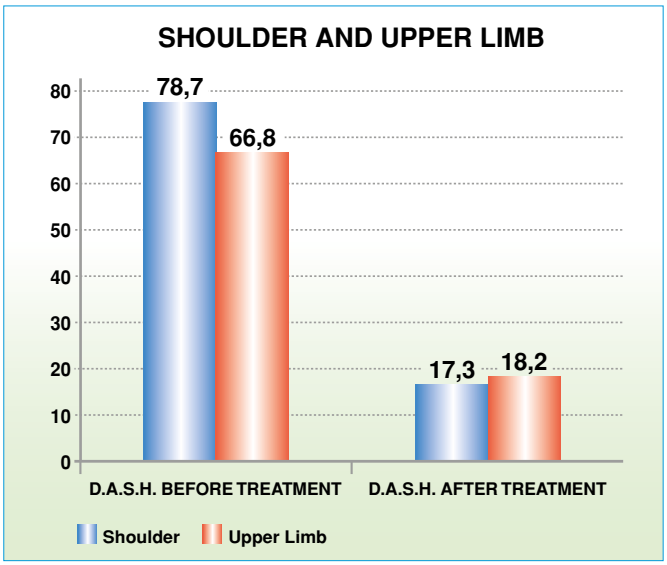


FIG. 6

Variation in the pain symptoms pre- and post-treatment in the different Groups treated with Guna Collagen MDs.

FIG. 7

Results of the analysis of the data collected using the D.A.S.H. questionnaire for conditions affecting the shoulder and upper limb (elbow, wrist, and hand).



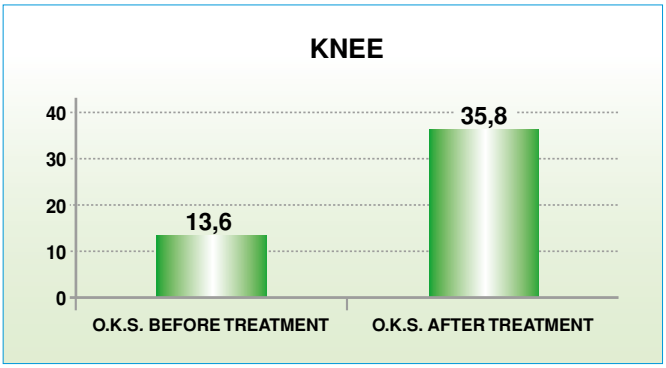


FIG. 8

Results of the analysis of the data collected using the O.K.S., for knee conditions.

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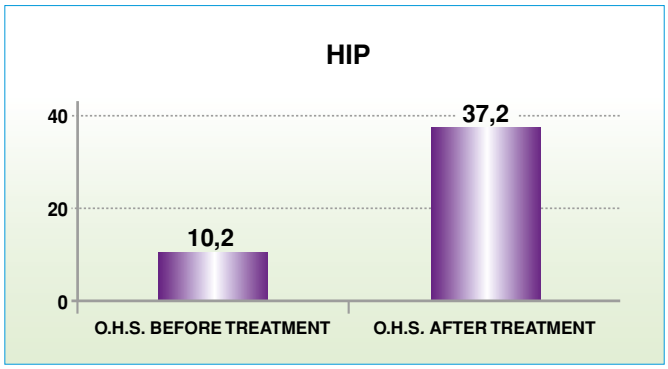
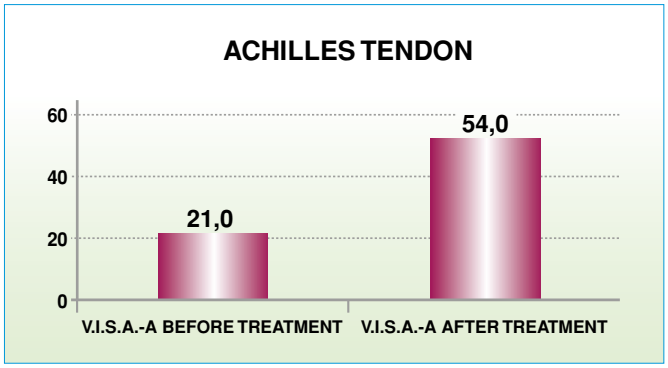


FIG. 9

Results of the analysis of the data collected using the O.H.S., for hip conditions.

FIG. 10

Results of the analysis of the data collected using the V.I.S.A.-A, for Achilles' tendon conditions.



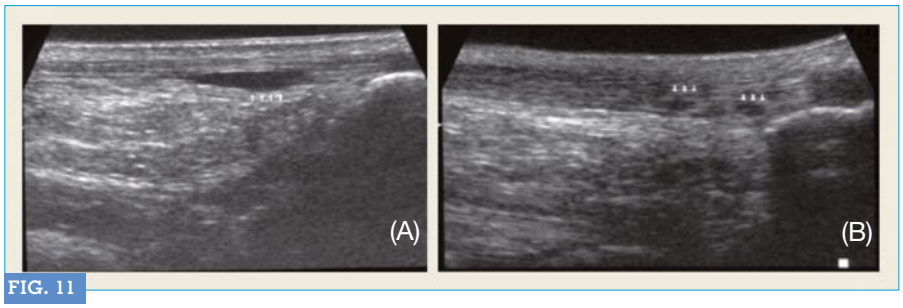


FIG. 11

(A) Achilles' tendon in the presence of effusion in the peritendineum; (B) The effusion is no longer visible. A situation of chronic tendinosis persists, with microcalcifications.

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COLLAGEN MEDICAL DEVICE INFILTRATIONS IN SHOULDER PATHOLOGIES. CALCIFIC SUPRASPINATUS TENDINITIS

SUMMARY

The Calcific supraspinatus tendinitis is an excellent type of lesion to be treated with a collagen device.
This kind of injury consists of a metaplasia by conversion of collagen fibers into calcium crystals.

– This is the reason why we believe that this collagen device in indicated for the treatment of Calcific supraspinatus tendinitis.

In our study, we used a sample of 10 patients with a macroscopic Calcific supraspinatus tendinitis, easily diagnosable by a simple radiography.

We established a protocol of one weekly injection for 4 consecutive weeks, because we believe this is the minimum dose necessary to have a therapeutic effect.

With respect to the clinical results, when applying the EVA Scale, we could verify an improvement of the pain in 6.2 points on average.

In terms of the Constant Scale we found an improvement of 64.8 points on average, which indicates a very important functional improvement.

One weekly injection for 4 consecutive weeks in the affected area under ultrasound control, obtaining good results based on our experience in terms of pain relief, functional improvement, and in 3 cases decrease of the calcification size.

KEY WORDS

CALCIFIC SUPRASPINATUS TENDINITIS, COLLAGEN MEDICAL DEVICE, GUNA COLLAGEN MD-SHOULDER

INTRODUCTION

Anisotropy is a mechanical property of collagen.
– It is the *ability* of its fibers to spread tensile forces towards one single specific direction.

An optimal formation and distribution of collagen fibers is fundamental not only for the integrity and the structural function of the tissue, but it also plays a central role in the transmission of tensile forces to fibroblasts dispersed in the matrix, and it is responsible for the deposition of collagen itself.

A good example of all this is the tendon, which fulfills all the characteristics explained above.

During a tendinous healing, there is an alteration of the normal structure and disposition of the collagen fibers.
These changes in the tendinous structure produce an alteration of anisotropy and therefore of the mechanisms of tendon repair (1, 2).

In this respect, the treatment with injectable collagen reactivates the *ability* of the fibroblasts to synthesize new collagen to restore the anisotropy properties and it reactivates the mechanisms of repair and the remodelling of the injured Connective Tissue.

Calcific supraspinatus tendinitis is probably the best expression of the alteration of the collagen structure in a tendon and possibly one of the main fields of application of a collagen medical device.
– Therefore, we aimed to evaluate the therapeutic effect of the collagen injectable medical devices in calcific supraspinatus tendinitis.

MATERIALS AND METHODS

We analyzed a Group of **10 patients** suffering from **Calcific supraspinatus tendinitis**.

The age ranged between 35 and 45 years, including both F and M.
We used 2 measuring scales to evaluate our results:

– EVA (VAS), a subjective pain scale;
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tion of the shoulder with respect to 4 parameters:

- Pain
- Functional capacity
- Mobility
- Strength.

Assessment was made before the treatment and 2 weeks after the end of the last injections.
We also used image tests before and 2 weeks after the last injection. In particular, patients underwent:

- X-ray
- Ultrasound
- MRI (Magnetic Resonance Imaging) scan.

In the present study we used **Guna Collagen MD-Shoulder** with the following protocol: 1 weekly injection for 4 consecutive weeks.
All the injections were made under ultrasound control.

RESULTS

We planned our study based on 3 types of results:

- Clinical results
- Functional results
- Mechanical results.

Before Treatment	8.9
After Treatment	2.7
Differential	6.2

TAB. 1
EVA Scale.

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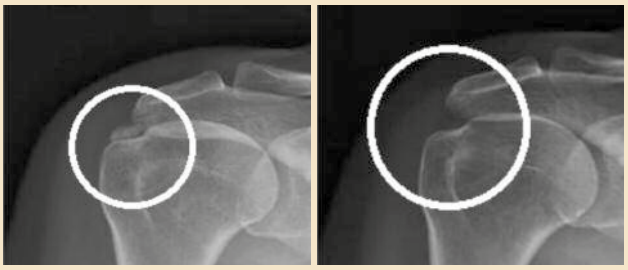
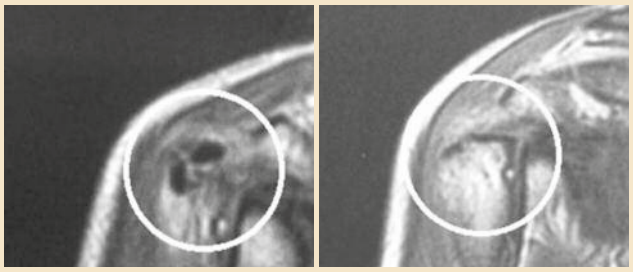


FIG. 1
X-ray study before and after treatment with injectable Collagen MD-Shoulder.



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On this basis, the NSAIDs are not effective in chronic tendinopathies because the inflammatory factor barely exists.

They may cause damage during recovery phase, because they inhibit the collagen synthesis (3).

The corticosteroid injections reduce pain in the short term compared to other treatments, but this effect is reversed in the medium and the long term. Moreover, the response to injection should not be generalized because of the variable effects in different sites affected by tendinopathy (4).

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The collagen device, for istance, is effective on knee ostheoartritis symptoms over 6 months after a 5-weekly injection treatment, and it is as much effective as the reference sodium hyaluronate (6).

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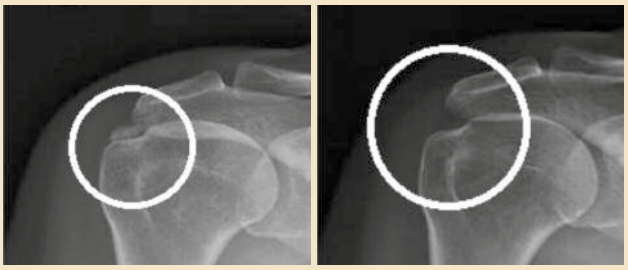

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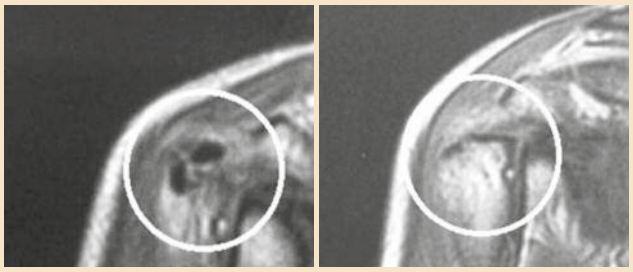

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Paper presented in the 1st International Congress - Collagen in musculoskeletal System disorders. A journey through pain relief, tissue repair, and functional recovery. Milan, 19th November 2016.

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Case Report

CASE REPORT

Use of injectable collagen in partial-thickness tears of the supraspinatus tendon: a case report

Bruno Corrado[1,*,†], Ilenia Bonini[1], Vincenzo Alessio Chirico[1], Nicola Rosano[2] and Pietro Gisonni[2]

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Abstract

Management of partial-thickness rotator cuff tears is actually controversial. We treated a patient with a partial-thickness tear of the supraspinatus tendon by a series of four type I porcine collagen ultrasound-guided injections, at weekly intervals. At the same time the patient underwent physical therapy, consisting of motor re-education and proprioceptive exercises. The patient was assessed before the treatment and up to 18 months after the last injection by the Constant–Murley score, the Disability of Arm, Shoulder and Hand questionnaire and ultrasonography. Shoulder pain and functional limitation progressively improved and they almost completely disappeared at the last follow-up. Ultrasonography showed a gradual healing of the partial-thickness tear and a regeneration of the tendon structure. This is the first study on ultrasound-guided injections of type I porcine collagen for the treatment of partial-thickness rotator cuff tears. Future research should confirm the excellent result achieved in this case report.

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Based on physical examination we suspected left SSP tendon involvement. We excluded glenohumeral osteoarthritis by X-rays. Shoulder ultrasonography, performed by a radiologist with >20 years of experience in skeletal muscle US, revealed a partial-thickness tear of the articular surface of the SSP tendon (Grade II according to Ellman classification). We decided to treat the patient with a series of four US-guided intratendineous injections of 2-ml porcine type I collagen at weekly intervals in combination with physical therapy. After a full and clear description of the study, the patient was invited to sign the informed consent.

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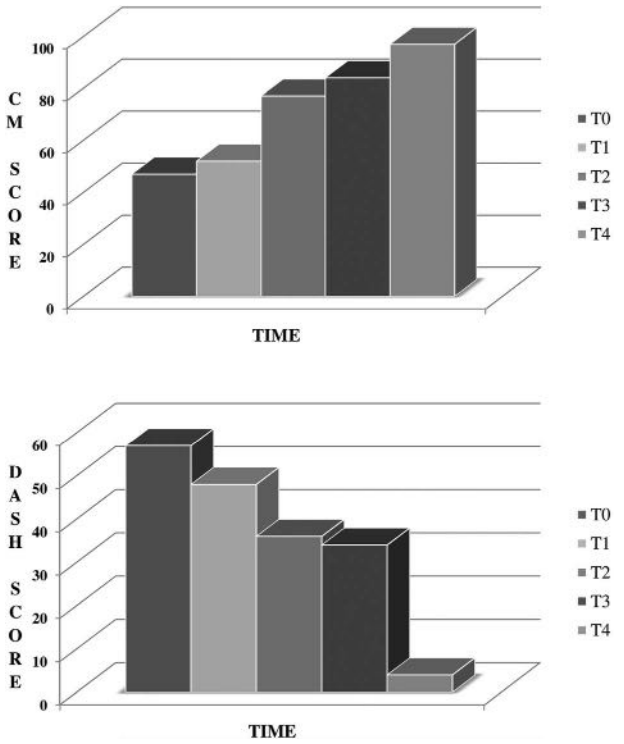

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US assessment was performed at T0, T3 and T4 by the same expert radiologist. As shown in Fig. 2, longitudinal US of the SSP tendon at T0 showed a well-defined hypoechoic area, indicating partial-thickness tear of the articular surface of the tendon, without retraction (Grade II according to Ellman classification). Three months following the last injection, the partial-thickness tear became smaller and less defined (Grade I according to Ellman classification). Eventually, the T4 US assessment no longer showed tear within the tendon, which in addition appeared quite regular and isoechoic.

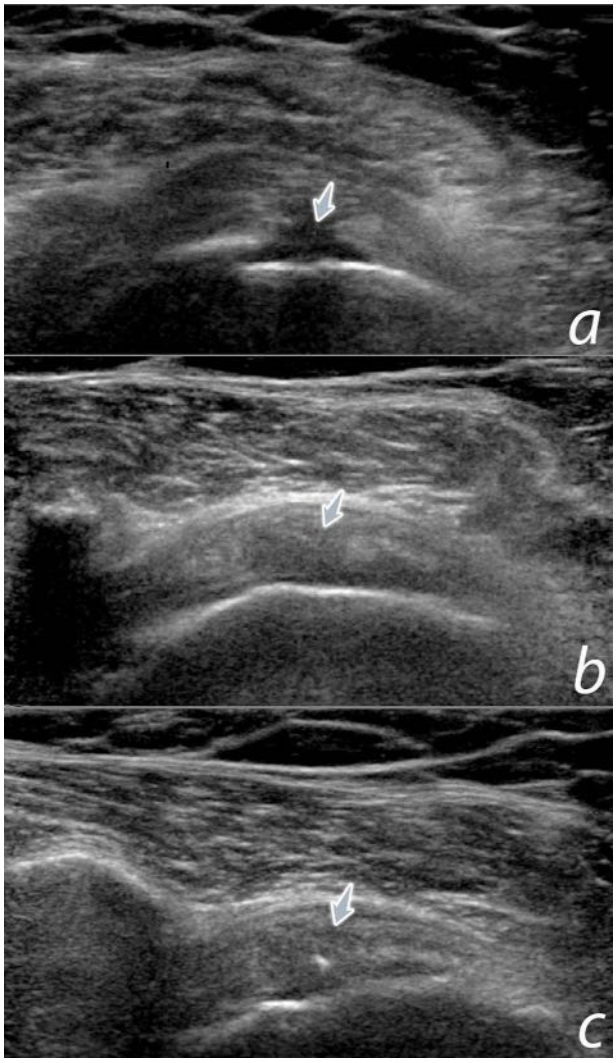

Figure 2: US assessment of the SSP tendon across multiple follow-up intervals. (**a**) Longitudinal US of the SSP tendon at T0 showed a well-defined partial-thickness tear of the articular surface of the tendon, without retraction (arrow). (**b**) Three months following the last injection, the partial-thickness tear became smaller and less defined (arrow). (**c**) At 18-month follow-up, the tendon looked quite regular and isoechoic, without any sign of tear (arrow).

The patient was totally compliant, following all the appointments given. No adverse events have been described after collagen injections.

DISCUSSION

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Different injectable therapies have been proposed in the past years for the treatment of PRTCTs (e.g. hyaluronic acid, platelet-rich plasma, prolotherapy), but they have achieved controversial effectiveness according to literature [3].

We have decided to treat the PTRCT of our patient with type I collagen injections on the base of (i) the positive effect proved by injectable collagen on the tendon structure of cultured tenocytes [6]; (ii) the good results achieved by collagen patches implanted arthroscopically in the treatment of large and massive RC tears [7] and (iii) the promising outcomes of collagen injections in the treatment of epicondylitis and SSP tendinopathy without tears [8, 9]. Studies of degenerative tendons have found a small but significant decrease in the total collagen content and an increased proportion of collagen type III relative to collagen type I. The increase in the collagen type III to collagen type I ratio was consistent with smaller, less organized and weaker tendons.

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In conclusion, the tear healing, the improvement in the tendon structure, the clinical and functional positive outcomes and the absence of side effects allow us to propose collagen injections as a valid option for the treatment of PTRCTs. A regenerative effect of collagen injections on tendon structure may be assumed to account the results achieved. More studies are needed to confirm these findings.

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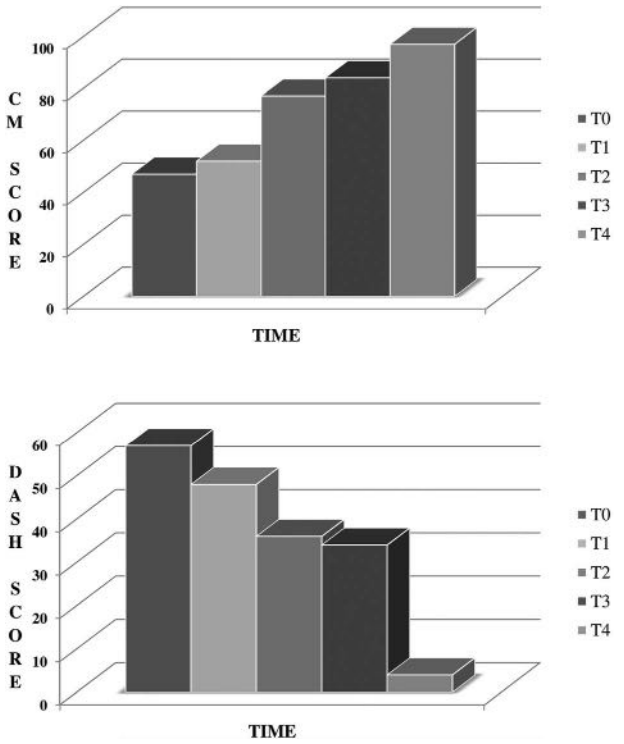

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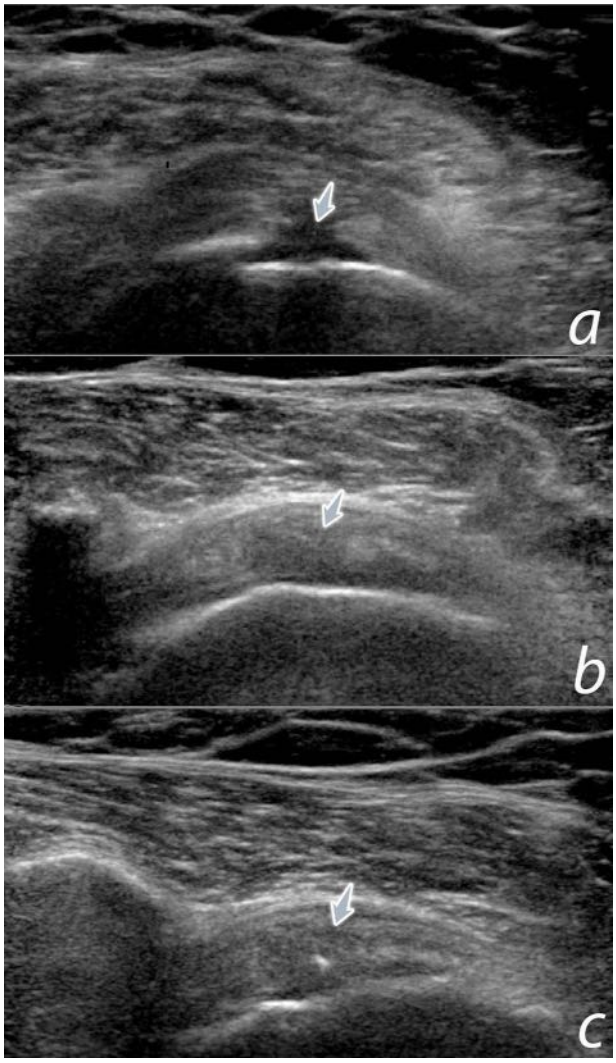

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COLLAGEN MEDICAL DEVICES AND CHELT IN SHOULDER AND KNEE OSTEOARTICULAR PAIN

D. Feninno, A. Bonacina

ABSTRACT: This observational study proposes an innovative method for treating osteoarticular pain, by combining Mesotherapy using Collagen MD-Shoulder or Collagen MD-Knee and CHELT (Cryo High Energy Laser Therapy) in rapid succession.
Individually, both techniques have a defined rationale with documented biological effects; this study describes the results of their close application in 40 patients studied over a 4-month period and divided into 2 groups: shoulder conditions (20) and knee conditions (20).
Observation was carried out at 3 timepoints - T0, T1 (at 1 month) and T2 (at 4 months) - with the administration of 3 tests: Visual Analogue Scale (VAS) for pain, and the Simple Shoulder Test (SST) or Oxford Knee Score (OKS) for shoulder and knee function, respectively.
The analysis of the data showed a significant improvement in all parameters: perceived pain, as rated using the VAS, improved by 50% after the first month of therapy (shoulder: 8.5 at T0; 4.55 at T1; 1.2 at T2; knee: 8.4 at T0, 4.65 at T1; 0.8 at T2);
joint functional in the first month improved by 48% in the shoulder group and by 22% in the knee group, as rated using the functional scales SST (6.55 at T0; 3.65 at T1; 1.15 at T2) and OKS (32.6 at T0; 39.8 at T1; 46.05 at T2).
The results suggest further studies should be conducted to evaluate the interactions between Collagen MDs injected using classical mesotherapy and photo-stimulation with laser and cryotherapy (CHELT).

INTRODUCTION

Osteoarticular pain accounts for a significant portion of requests for general medicine consultations and the various types of pain involving shoulder function alone account for 20% of such requests (1).
The purpose of this study conducted on a sample of **40 patients** was to establish to whether **MD-Shoulder** or **MD-Knee** administered using the conventional mesotherapy technique, in combination with an innovative physical energy technique (Cryo High Energy Laser Therapy, **CHELT**) is able to rapidly reduce acute and chronic pain symptoms, as well as to establish the improvement in shoulder and knee joint function.

This method could be an innovative alternative to conventional medical therapy with NSAIDs and pain killers in various formulations.

According to Karu (2), laser technology for therapeutic purposes can "be considered a true medicine, through the photobiostimulation of pathological tissues."
This provides the rationale for verifying the effectiveness of these physical energies in combination with mesotherapy (3) using Collagen MDs in order to achieve recovery through the adverse effect-free stimulation of repair processes.

- It is interesting to consider the better biological and curative effect produced with the combined application.

The patients were objectively assessed by administering a patient-reported functional test (Oxford Knee Score - OKS or Simple Shoulder Test - SST) (4, 5) and a Visual Analogue Scale **(VAS)** (6), at Time 0 (start of therapy), Time 1 (at 1 month) and time 2 (at 4 months).

The study showed that the perception of pain, rated using the VAS, improved in all cases from the first month of treatment, and that combining the two methods significantly reduces joint pain, and maintains and implements this outcome without recurrence, even 4 months after the start of treatment.

The results suggest that further studies should be conducted to evaluate the interactions between Collagen MDs and CHELT photostimulation.

MATERIALS AND METHODS

The patients were enrolled over a 6-month period: following careful assessment, **20 cases** with **shoulder** pain (average age 60 years, *range* 42-78, 9 M and 11 F) and **20 cases** with **knee** pain (average age 52 years, *range* 20-75, 13 M and 7 F) were enrolled amongst patients with acute and chronic single-joint pain, without recent injury sequelae.

The treatments were administered for most of the osteoarticular conditions affecting the shoulder and knee.
The sample was intentionally non-homogeneous in terms of age and the conditions considered, since the purpose of the study was to describe the effects of the therapy administered on pain and joint function.

The patients were first informed regarding the treatment they would be administered, as well as the need to pay great attention to the evolution of their symptoms, an aspect of fundamental importance to the success of both the treatment and the clinical trial

Patients were also reassured that the treatment was painless and free of adverse effects.

All patients were administered a self-reported functional test (Oxford Knee Scale - OKS or Simple Shoulder Test - SST) and the VAS at T0 (start of therapy), T1 (at 1 month) and T2 (at 4 months).

During each mesotherapy session, subjects were administered **MD-Shoulder** or **MD-Knee** by means of a 2.5 cc syringe with a 13-mm 30 G needle, using the classic access routes for the shoulder and knee, as described by Pistor Each Collagen MD application was followed by an administration of CHELT, in accordance with the regimens recommended for conditions in the subacute phase: Cryotherapy for 2 minutes, High-Energy Yag Laser in super-pulsed analgesia mode, cryotherapy for 2 minutes, High-Energy Laser in continuous biostimulation mode, cryotherapy for 2 minutes.

The full course of treatment consisted of 6-10 once- or twice-weekly sessions over a period of 4-6 weeks.

The results are provided in **TAB. 1** for patients with shoulder conditions and in **TAB. 2** for patients with knee conditions. (see below).

TAB. I
Shoulder patients: VAS and SST *(Simple Shoulder Test)* at T0 - T1 - T2.

	Patient	Age	Gender	VAS			SST		
				T0	T1	T2	T0	T1	T2
1	D.M.	52	F	8	4	0	4	2	1
2	Z.F.	62	M	8	3	0	4	1	0
3	C.G.	42	F	8	4	1	2	1	0
4	E.S.	64	M	10	5	2	6	5	1
5	L.M.	51	F	9	6	3	8	6	4
6	P.D.	70	F	10	8	7	8	5	3
7	V.A.	61	F	9	6	1	10	5	1
8	S.P.F.	78	M	10	5	2	10	6	2
9	C.A.	57	F	8	5	1	7	4	1
10	T.I.	71	F	8	3	0	8	3	0
11	B.S.	68	M	7	3	0	7	3	0
12	V.L.	45	M	7	5	1	6	3	1
13	B.F.	67	M	10	5	0	5	3	0
14	P.C.	78	F	10	5	2	10	5	3
15	P.C.	76	F	9	2	0	6	3	1
16	C.L.	42	M	7	4	0	6	4	0
17	C.R.	63	F	8	5	2	5	3	2
18	F.P.	44	M	7	3	0	5	3	0
19	R.G.B.	58	M	9	6	0	8	5	1
20	L.P.	54	F	8	4	2	6	3	2
	SIMPLE MEAN	**60.15**	***RATIO*** **M:F = 9:11**	**8.5**	**4.55**	**1.2**	**6.55**	**3.65**	**1.15**

MESOTHERAPY

Mesotherapy is a technique for administering medicinal products via an intraepidermal, superficial and deep intradermal, subcutaneous or hypodermic route (7).

The method was standardised and disseminated by the French physician Michel Pistor starting in 1952 (8). Mesotherapy is “a method for bringing the therapy closer to the disease site” (8).

Although its underlying concept is simple, mesotherapy requires adequate training in order to be carried out effectively (9).

The advantage of this technique consists in using minute doses of the active substance, which diffuse within the tissue surrounding the inoculation site and persist for longer than with intramuscular administration, bringing advantages that include:
1) long-lasting effect;
2) limited involvement of other organs;
3) lower risk of adverse events and side effects (10).
- It is used primarily for the treatment of osteoarticular and degenerative diseases

Mesotherapy has an adjuvant role; for example, in cases of moderate pain it helps to reduce the intake of systemic medicinal products.

For some of the above-mentioned indications there are significant clinical data supporting the efficacy of certain treatment protocols, for others the data are less significant

TAB. 2
Knee patients: VAS and OKS (*Oxford Knee Score*) at T0 - T1 - T2.

	Patient	Age	Gender	VAS			OKS		
				T0	T1	T2	T0	T1	T2
1	L.L.	68	M	10	6	2	31	40	46
2	L.M.	68	F	8	5	2	38	42	46
3	T.I.	71	F	10	5	0	21	38	47
4	C.F.	30	M	8	4	0	35	42	48
5	G.T.	48	F	7	4	0	39	43	48
6	C.M.	43	F	8	4	1	33	40	45
7	G.M.	75	F	8	6	2	40	43	45
8	V.L.	65	M	9	6	2	26	31	41
9	A.G.	30	M	7	5	1	38	42	46
10	B.P.	20	M	9	4	0	29	39	46
11	M.F.	32	M	9	4	0	30	40	48
12	B.S.	70	M	9	7	3	32	34	40
13	P.G.	66	M	10	5	0	28	35	48
14	P.P.	57	M	8	5	0	34	40	47
15	O.F.	58	F	9	4	1	32	40	45
16	F.P.	44	M	7	3	0	35	43	48
17	S.R.	51	F	10	5	1	31	41	46
18	T.C.	60	M	8	6	1	33	38	45
19	M.C.	51	M	7	3	0	34	42	48
20	C.F.	32	M	7	2	0	33	43	48
	SIMPLE MEAN	**51.95**	***RATIO*** **M:F = 13:7**	**8.4**	**4.65**	**0.8**	**32.6**	**39.8**	**46.05**

The Società Italiana di Mesoterapia [Italian Mesotherapy Society], which was founded in 1975, is therefore currently reviewing the criteria for the use of the technique in order to issue up-to-date guidelines on the various application settings. The Society recommends administering this therapy only once patients have been given adequate clinical information and have given informed consent to the treatment (11). In Italy, mesotherapy is considered a medical procedure.

In 1987, the Académie Française de Médicine acknowledged Mesotherapy part of traditional medicine and in many European countries, the USA and South America this technique has become practically routine practice.

CHELT

CHELT is the acronym of Cryo High Energy Laser Therapy, a treatment method that was developed starting in the 1990s and recently used in trials at Policlinico di Bari (12).

The rationale behind the method is the biostimulation of pathological tissue by applying high-energy laser and cryotherapy with cold dry air flows with a temperature of -30°C, following standardised sequences whose timings and powers depend on the depth of the tissue to be treated and the acute or chronic stage of the condition.
Combining laser therapy with cryotherapy led to the advent of CHELT, which is currently administered using the technology developed by Mectronic Medicale - Bergamo, Italy (13).

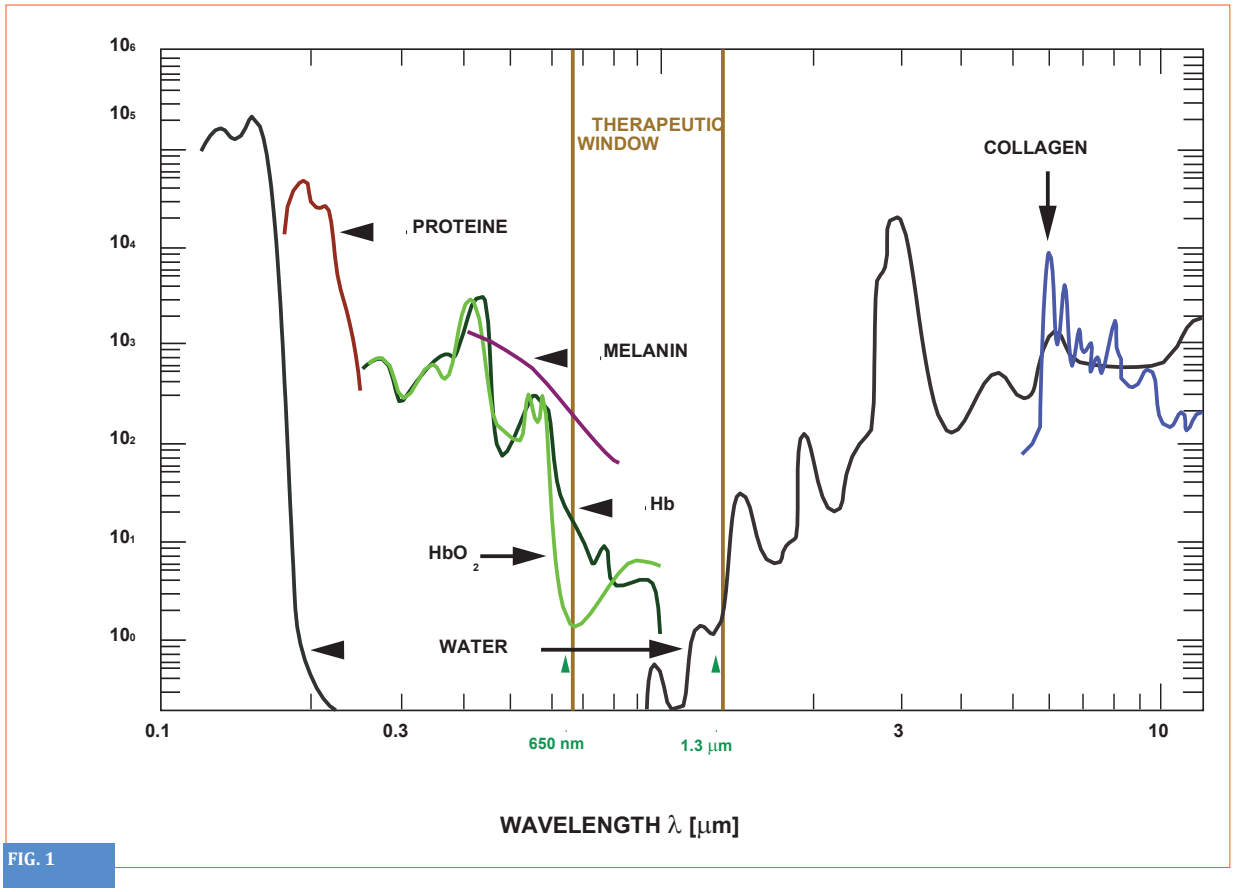


FIG. 1

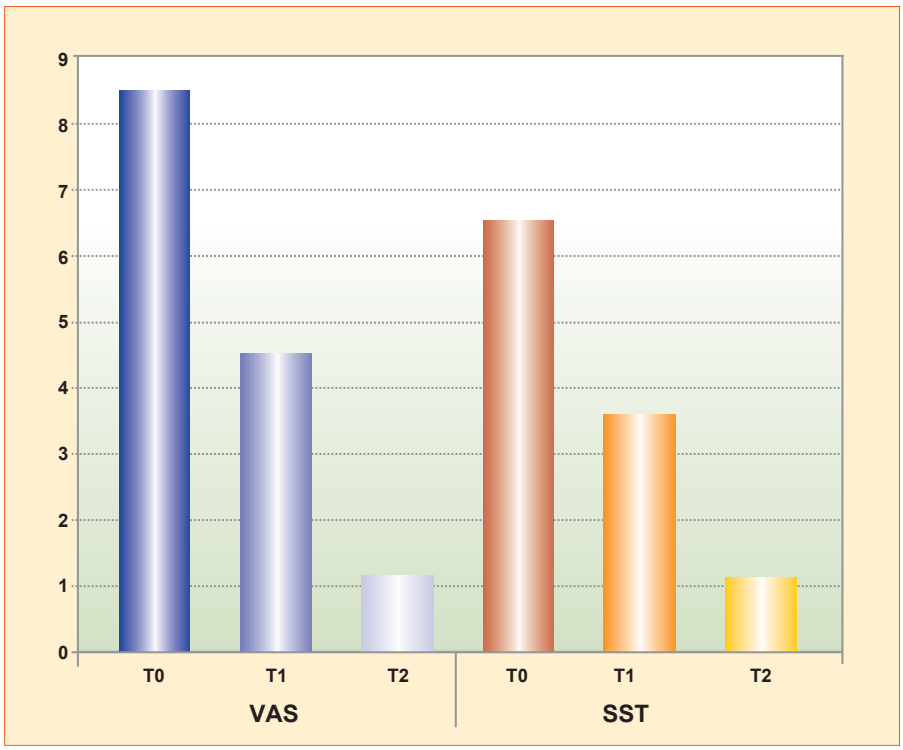
FIG.1 Optical absorption spectrum of various tissue components within the ultraviolet-infrared frequency range. From: The Warren Research Group, Duke University, Trinity College of Arts & Sciences-USA.

The laser energy produced by the deep interaction between the radiation and the damaged tissue has several therapeutic actions:
1) analgesic effect with the inhibition of the peripheral nociceptors (15,16); 2) modulation of inflammation and increase in cellular metabolic activity (17,18); 3) biostimulating effect with remodelling of the tissues due to the increase in cellular energy processes (19).

The power and wavelength of the laser are the technical characteristics that define the penetration of the quantity of energy required to activate biological responses in the target area (often located a few centimetres below the skin), due to the presence of cellular chromophore receptors that are sensitive to the radiation and photostimulation (20, 21, 22).

We conducted our trial using a 1064 nm single-frequency, high-energy laser, a source with a greater delivered energy density due to its limited scattering, as is shown in the Figure comparing the various therapeutic frequencies and their penetration into the tissues (FIG. 1). The greater output power is directly correlated with the amount of energy irradiated to the tissues by the biostimulating high intensity laser beam (23).

The term “cryotherapy” refers to a targeted exogenous cooling treatment. The superficial skin temperatures achieved during the transfer of negative energy (cooling) are between 2 °C and 15 ° C.



TAB. 3

The cold dry air flow used in cryotherapy has a rapid effect on oedema and pain: strong air flows with short action times produce immediate analgesia due to the thermal shock generated; weak flows with long application times have an effect on oedema and tissue inflammation due to their effect on the local microcirculation (24).
The cold air delivered during cryotherapy acts as a vector for the laser, as the vasoconstriction reduces the oedema and allows better energy absorption.

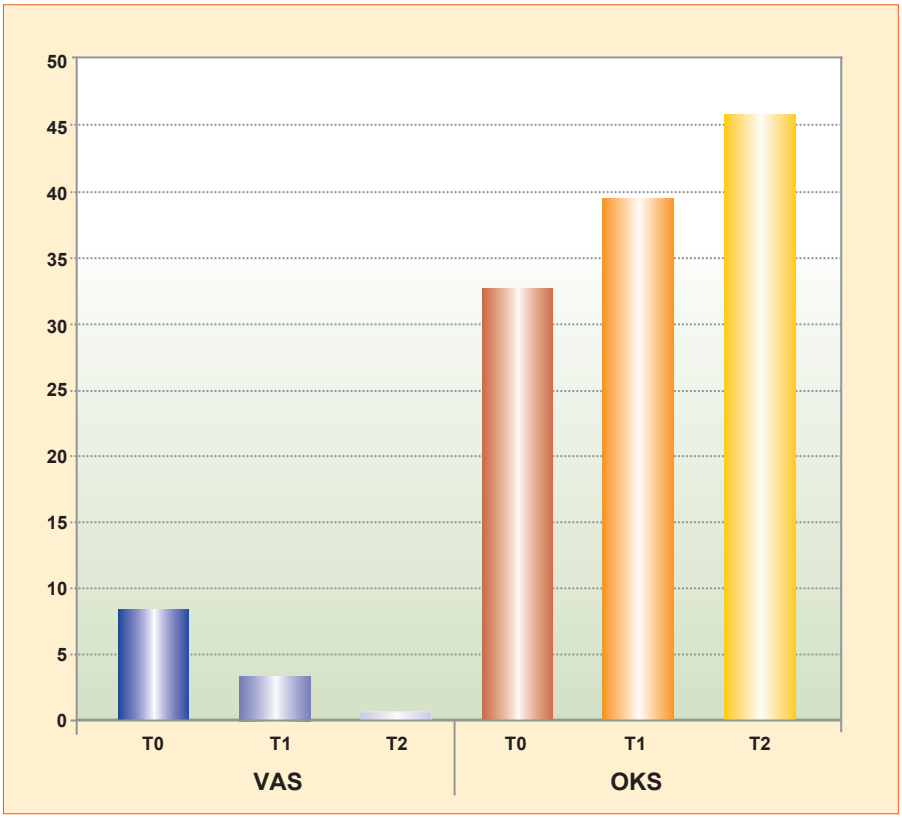
Cryotherapy was used with intermediate flows and application times before, during and after the laser applications, in order to favour tissue drainage and further activate cell metabolism (25, 26).

This is the methodological rationale that justifies the application of CHELT after each session of Mesotherapy with the Collagen Medical Devices (Guna S.p.A, Milan, Italy): activation of cellular metabolic processes and of the microcirculation with the delivery of physical energy (frequencies - photons – thermal) in order to accelerate the action of the collagen and optimise its absorption.

We calculated the simple mean of the data obtained, which were used to create the histograms for shoulder (TAB. 3) and knee (TAB. 4), which show the time trends of the values.

The study showed that the subjective perception of the pain, rated using the VAS, significantly improves in all cases from the first month of treatment, and that joint function (SST or OKS) also improves in line with the reduction in perceived pain.

The result in terms of improved joint function was significant even in the first month.



TAB. 4

CONCLUSIONS

The results achieved are positive and encourage further research.
The therapy administered, Collagen MD-Shoulder and Collagen MD-Knee injected using a conventional mesotherapy technique in combination with CHELT, undoubtedly brings a number of advantages:
1) rapid analgesic effectiveness;
2) functional recovery;
3) absence of adverse effects;
4) good patient compliance .

RESULTS AND DISCUSSION

The results are provided in the Table containing the data for each patient and subsequently in the two Tables containing the findings for patients with shoulder conditions (TAB. 1) and knee conditions (TAB. 2), showing the VAS scores and SST or OKS functional rating scale scores at T0 (time of the initial assessment), at T1 (after 1 month) and at T2 (4 months after the start of treatment).

It can be seen that the combination of the two methods results in a 50% average reduction in pain in the first month of treatment, as defined by the self-reported VAS (shoulder: 8.5 at T0; 4.55 at T1; 1.2 at T2; knee: 8.4 at T0; 4.65 at T1; 0.8 at T2) and maintains and implements this result without recurrence even 4 months after the first treatment (on average 2.5 months after the first treatment).

The therapeutic results obtained, without administering corticosteroids and/or local or systemic analgesics, suggest further research should be undertaken in order to adequately analyse the interactions between Collagen Medical Devices and photostimulation with cryotherapy and Yag laser (CHELT).

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CLINICAL

E. Milano

MD-SHOULDER IN THE INTEGRATED REHABILITATION TREATMENT OF SHOULDER PAIN IN POST-STROKE HEMIPLEGIC PATIENTS

SUMMARY

Shoulder pain (SP) is the most frequent complication in patients with post-stroke hemiplegia.
– SP can occur either in the first few weeks after the stroke (most frequently in the first 3 months), or 6-8 months after the acute cerebrovascular event (chronic shoulder pain).
– We recruited 40 patients undergoing ordinary hospitalisation in a Level II rehabilitation hospital for ischaemic stroke (transferred from acute hospital Stroke Units). All patients complained of shoulder pain on the hemiplegic side that presented in the first 3 months after the ischaemic event. The diagnosis of adhesive capsulitis was based on clinical findings and symptoms, as well as standard X-ray and musculoskeletal ultrasound.
– Patients were randomised to 2 treatment groups (Group A and Group B), stratified by age, gender and pain intensity. Outcomes were assessed at 1, 6 and 10 months. Group A was treated with intra-articular injection of Triamcinolone 40 mg 1 vial and Ropivacaine 2% 3 mL (total volume 4 mL) weekly for the first 2 weeks; the third treatment was administered 15 days after the second.
Group B was treated with injection of Guna MD-Shoulder 3 vials (for a total volume of 6 mL) intra-articularly (4 mL) and in the pericapsular area (the remaining 2 mL).
Use of Guna MD-Shoulder made it possible to obtain a biological effect of organic reconditioning of the compromised anatomical structures, and thus obtaining a positive result on the stabilisation of the glenohumeral joint, its range of motion and, therefore, on the pain symptom, not only in the early stage, but especially in the weeks following the treatment, with a continuous improvement of the outcomes recorded at the follow-up time-points.

KEY WORDS

SHOULDER PAIN, POST-STROKE HEMIPLEGIA, MD-SHOULDER

https://www.homeceuconnection.com/blog/proper-positioning-for-stroke-patients/

INTRODUCTION

Shoulder pain (SP) is the most commonly observed complication in patients with post-stroke hemiplegia.
Its incidence varies greatly according to the different clinical studies published in literature, with estimated rates ranging from **16%** to **72%** of cases.

– SP may present either in the first few weeks after the stroke (usually within the first 3 months), or later, 6-8 months after the acute cerebrovascular event (chronic shoulder pain).
For precisely this reason, SP is a complication that can condition the patient's neuromotor rehabilitation treatment and can have even significant repercussions on the functional recovery required for the activities of daily living.
According to the studies consulted, SP is most common **1)** in subjects with right brain injury, **2)** in subjects with spasticity scoring > 1 on the Ashworth scale, **3)** in ischaemic stroke, **4)** among females and **5)** in elderly patients.

– The aetiopathogenesis of shoulder pain in hemiplegic patients is still unclear.
In the late 1950s, Basmajian & Bazant attributed hemiplegic shoulder pain to the **dislocation** of the **glenohumeral joint (GHJD)**.
– This hypothesis, better known as the "Basmajian Theorem", resulted in many

FIG. 1

PROM (Passive Range of motion)

– Absolute values.

PROM – *PASSIVE RANGE OF MOTION*

		GROUP A	GROUP B
T0	ABD	120	122
	ER	94	93
	FLEX	35	34
T1	ABD	130	125
	ER	110	98
	FLEX	50	40
T2	ABD	131	135
	ER	100	100
	FLEX	54	55
T3	ABD	125	140
	ER	100	120
	FLEX	45	60

ABD = Abduction
ER = External rotation
FLEX = Anterior flexion

rehabilitation practitioners using orthoses to prevent dislocation. However, in the 1990s, some authors expressed certain doubts regarding the "responsibility" of GHJD in hemiplegic shoulder pain, claiming that the albeit common association does not necessarily mean there is a cause-effect relationship.

– Nowadays, the Literature is concordant in identifying three possible causes:

1) Conditions affecting the periarticular soft tissues of the GHJ: rotator cuff injury, rotator cuff tendinopathy (most commonly affecting the tendons of the *supraspinatus*, *subscapularis* and *biceps brachii* muscles), glenohumeral dislocation and, most commonly, **adhesive capsulitis**.

– The causes are undoubtedly the consequences of a functional imbalance of the agonist and antagonist muscles of the scapulohumeral girdle and consequently of the overload the shoulder joint is subject to in the course of post-stroke clinical evolution, as muscle flaccidity transitions to hypertonus;

2) CRPS (Complex Regional Pain Syndrome);

3) Central Hypersensitivity: in this case, the brain damage often has a precise location that can be seen on the MRI (thalamus, basal ganglia, cerebellopontine angle, bulb).

Pinpointing the cause of the SP is often rather challenging as, depending on the brain damage, the patient may have an even very complex neurological situation, with cognitive, motor and verbal impairment with aphasia. Furthermore, the clinical signs and symptoms are often rather generic and difficult to correlate with a single aetiology.

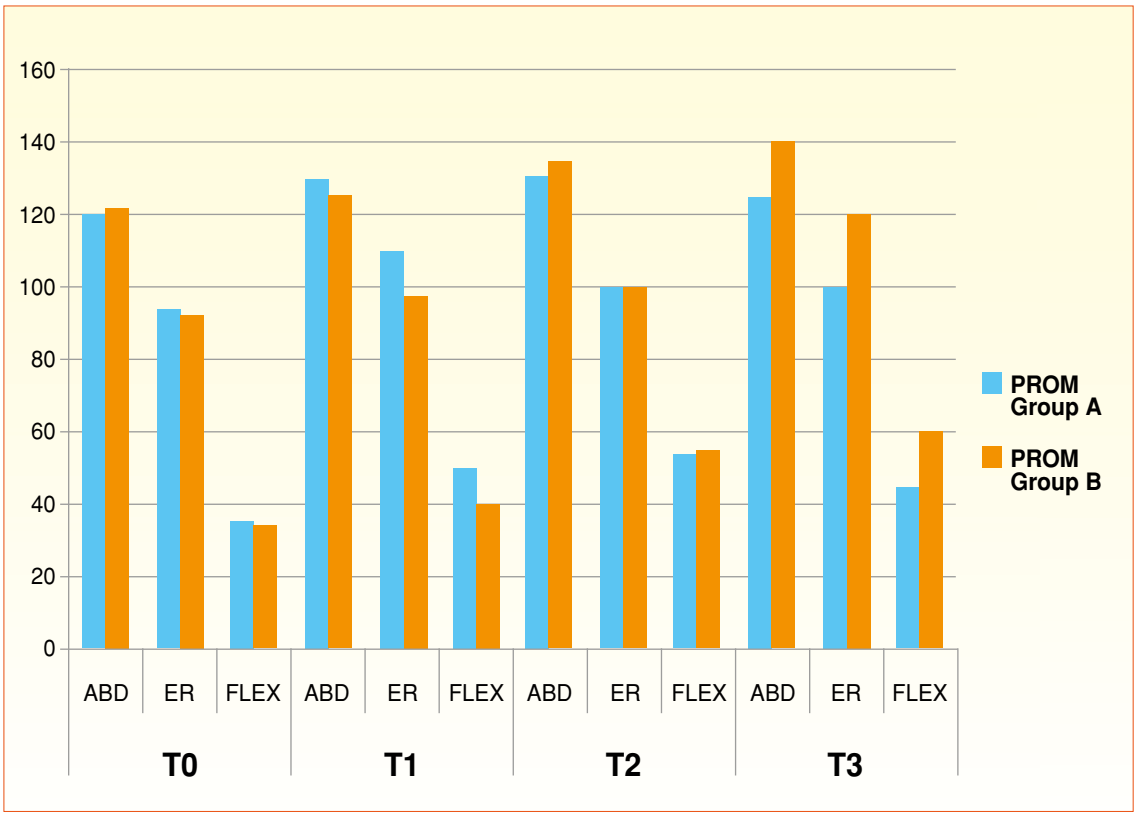
It is also necessary to remember that the clinical complexity of cases of SP may be due to the existence of multiple concurrent causes.

– In literature, the factors that may have an impact on the onset and evolution of SP are indicated as being the presence

FIG. 2

PROM (Passive Range of motion)

– Histograms representing the values presented in Fig. 1.



of severe motor damage (according to the Daniels Scale), significant changes in muscle tone in both the flaccidity and the hypertonic stages, and speech disorders (consistent with cognitive impairment).

Conventional treatment, which is not always satisfactory in clinical practice and is often conditioned by the fact that these patients are extremely frail, involves the prescription and use of **1)** upper limb orthoses, **2)** pharmacological therapy with analgesics, anti-inflammatories and a central muscle relaxant, **3)** peri/intra-articular injections with cortisone derivatives, and **4)** an adequate neuromotor rehabilitation protocol, with or without **5)** a combination of analgesic physiotherapy and functional electrical stimulation (FES).

Research conducted to optimise conservative rehabilitation treatment in post-stroke SP with an essentially musculoskeletal aetiopathogenesis (adhesive capsulitis) taking into consideration all the anatomical structures involved, has made it possible to formulate a number of considerations.

The use of medical devices for injection containing porcine collagen (Medical Device) allows a more effective and specific *in situ* positioning of the collagen, which serves a carrier and stabilisation function.

– This makes it possible to replace, strengthen, structure and protect (barrier against adhesion) cartilage, tendons, ligaments and joint capsules, consequently improving the status of the collagen fibres and all the other anatomical structures it contains and therefore to provide mechanical support to the affected anatomical segment.

MATERIALS AND METHODS

Therefore, the hypothesis on which our study was based was that injection treatment with **Guna MD-Shoulder** would recondition the compromised anatomical structure and improve the stability of the shoulder; a "combined" treatment can improve the functional outcomes of rehabilitation and/or produce better pain control in the subacute phase, as well as having a positive impact on the progression of the disease (less frequent exacerbations).

– We recruited **40 patients** undergoing ordinary hospitalisation in a Level II rehabilitation hospital for ischaemic stroke (transferred from acute hospital Stroke Units).
All patients complained of shoulder pain on the hemiplegic side that appeared in the first 3 months after the ischaemic event (SP appearing after 3 months is more often due to central hypersensitivity or CRPS).
The diagnosis of adhesive capsulitis was based on clinical findings and symp-

WBS – DAYTIME AND NIGHT-TIME PAIN

		GROUP A	GROUP B
T0	N	4,2	3,5
	D	7,1	6
T1	N	3,5	3
	D	4,2	5,2
T2	N	2,1	2,1
	D	4	4
T3	N	2,3	2,1
	D	6	3,2

FIG. 3

WBS (Wong-Baker Scale)
– Absolute values.

N – Night-time
D – Daytime

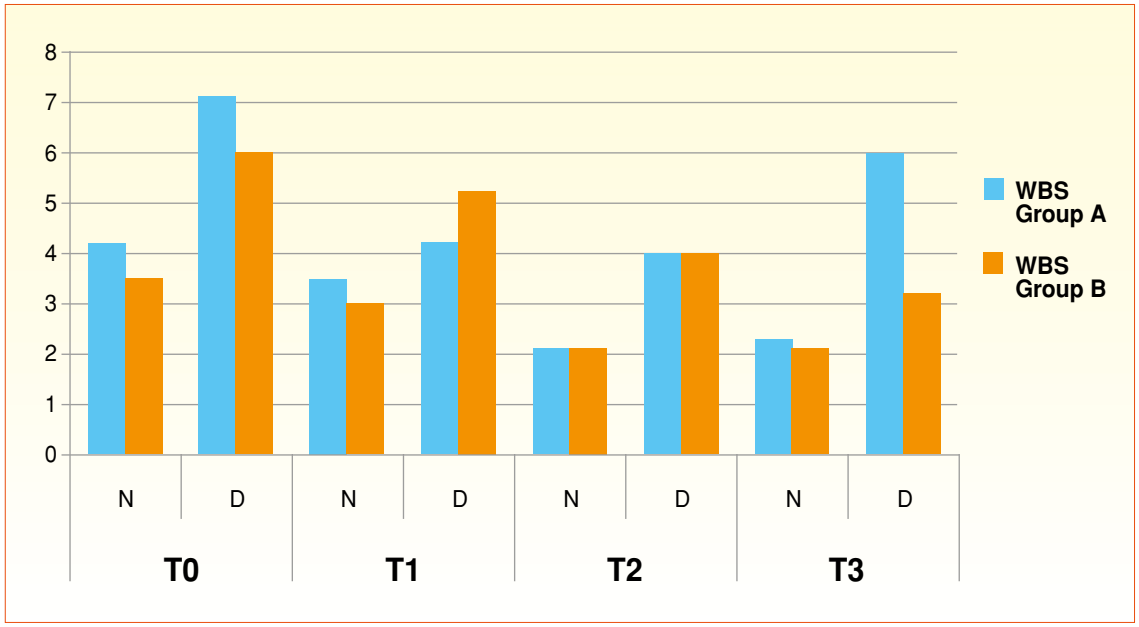


FIG. 4

WBS (Wong-Baker Scale)

– Histograms representing the values presented in Fig. 3.

N – Night-time
D – Daytime

toms, as well as standard X-ray and musculoskeletal ultrasound.

– Patients were randomised to **2** treatment groups (**Group A** and **Group B**), stratified by age, gender and pain intensity (Wong-Baker Scale). The outcomes were assessed at 1, 6, and 10 months.

– Inclusion criteria: F and M patients aged between 55 and 75 years who recently had a stroke; clinical and instrumental diagnosis of SP on the hemiplegic side due to adhesive capsulitis, from less than 3 months after the cerebral ischaemic event; WBS (Wong-Baker Scale) > 5, not using NSAIDs, cortisones or opiates.

– Exclusion criteria: past history of SP secondary to musculoskeletal conditions; prior shoulder and elbow fracture; rheumatoid arthritis; current diagnosis of rotator cuff tear and calcified tendinopathy; episodes of shoulder dislocation during the muscle flaccidity stage; serious comorbidity (CIRS 4); Parkinson's disease; dementia (evaluated using the Mini-Mental State Examination); severe neurological damage (emineglect*, speech disorders, Ashworth > 3 muscle hypertonus, severe residual motor damage according to the *Daniels Scale*); use of anticoagulants (warfarin or new oral anticoagulants); use of opiates or cortisone derivatives during the previous month; intra/peri-articular injections to the shoulder in the previous 3 months.

Both groups (A and B) received treatment with the same multidisciplinary rehabilitation protocol (inter-hospital therapeutic and diagnostic pathway) focussing on neuromotor treatment (mobilisation of the paralysed limb, facilitation of active neuromuscular unit recruitment, inhibition of muscle hypertonus and coordination of the inhibitory and excitatory activities of the agonist and antagonist muscles during the performance of the different motor tasks), neuropsychiatric treatment to stimulate the cognitive-motor afferences, ergonomic education and occupational therapy to recover activities of daily living and occupational activities.

The multidisciplinary rehabilitation treatment during the 60 days of ordinary hospitalisation was administered for 3 hours every day.
The patient then switched rehabilitation setting to a daily outpatient treatment with approximately one-hour sessions, for a total of 10 sessions.

• Both treatment groups (A and B) also received ultrasound-guided (Clarius Ultrasound portable linear probe) injection therapy.

Group A was treated with intra-articular injection of **Triamcinolone** 40 mg 1 vial and **Ropivacaine 2%** 3 mL (for a total volume of 4 mL) weekly for the first 2 weeks; the third treatment was administered 15 days after the second.

Group B was treated with injection of **Guna MD-Shoulder** 3 vials (for a total volume of 6 mL) intra-articularly (4 mL) and in the peri-capsular area (the remaining 2 mL).

The following were then analysed as clinical and functional outcomes **1)** daytime and night-time pain **(WBS)**; **2)** passive ROM **(PROM)** of the hemiplegic shoulder in anterior flexion **(FLEX)**, abduction **(ABD)** and external rotation **(ER)** (using a protractor), in addition to records of NSAID use during the follow-up period (FIGS. 1-4).

▶ The results obtained make it possible to conclude that in the multidisciplinary neuromotor rehabilitation protocol for ischaemic stroke patients, ultrasound-guided injection treatment with MD-Shoulder plays a decisive role when the complication known as SD, with a prevalent musculoskeletal aetiology (adhesive capsulitis), presents at an early stage.

Evidently the greater the residual neurological damage and the later the complication presents, the less effective the ultrasound-guided treatment will be, because other non-musculoskeletal causes (CRPS and central hypersensitivity) will sustain the pain symptoms.

CONSIDERATIONS

In the early stage, the injection treatment with cortisone derivative was undeniably effective on both the pain and the passive range of motion of the shoulder, before losing its beneficial effect over time.

On the other hand, in literature, the cortisone derivative is extensively reported as having a "toxic" effect on biological tissues with a prevalent collagen component.
Furthermore, the use of these medicinal products is potentially hazardous when they are used on a frail population such as that considered in this study.
In approximately half of all cases, patients experienced adverse effects such as blood pressure increases, onset of headache and facial rash. It goes without say that this treatment was not offered to diabetic subjects or those with poor glycaemia control.

– The injection treatment with Guna MD-Shoulder, on the other hand, did not give rise to any adverse reaction, confirming that it is absolutely safe.

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MD-SHOULDER IN THE INTEGRATED REHABILITATION TREATMENT OF SHOULDER PAIN IN POST-STROKE HEMIPLEGIC PATIENTS

SUMMARY

Shoulder pain (SP) is the most frequent complication in patients with post-stroke hemiplegia.
– SP can occur either in the first few weeks after the stroke (most frequently in the first 3 months), or 6-8 months after the acute cerebrovascular event (chronic shoulder pain).
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– Patients were randomised to 2 treatment groups (Group A and Group B), stratified by age, gender and pain intensity. Outcomes were assessed at 1, 6 and 10 months. Group A was treated with intra-articular injection of Triamcinolone 40 mg 1 vial and Ropivacaine 2% 3 mL (total volume 4 mL) weekly for the first 2 weeks; the third treatment was administered 15 days after the second.
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Use of Guna MD-Shoulder made it possible to obtain a biological effect of organic reconditioning of the compromised anatomical structures, and thus obtaining a positive result on the stabilisation of the glenohumeral joint, its range of motion and, therefore, on the pain symptom, not only in the early stage, but especially in the weeks following the treatment, with a continuous improvement of the outcomes recorded at the follow-up time-points.

KEY WORDS

SHOULDER PAIN, POST-STROKE HEMIPLEGIA, MD-SHOULDER

https://www.homeceuconnection.com/blog/proper-positioning-for-stroke-patients/

INTRODUCTION

Shoulder pain (SP) is the most commonly observed complication in patients with post-stroke hemiplegia.
Its incidence varies greatly according to the different clinical studies published in literature, with estimated rates ranging from **16%** to **72%** of cases.

– SP may present either in the first few weeks after the stroke (usually within the first 3 months), or later, 6-8 months after the acute cerebrovascular event (chronic shoulder pain).
For precisely this reason, SP is a complication that can condition the patient's neuromotor rehabilitation treatment and can have even significant repercussions on the functional recovery required for the activities of daily living.
According to the studies consulted, SP is most common **1)** in subjects with right brain injury, **2)** in subjects with spasticity scoring > 1 on the Ashworth scale, **3)** in ischaemic stroke, **4)** among females and **5)** in elderly patients.

– The aetiopathogenesis of shoulder pain in hemiplegic patients is still unclear.
In the late 1950s, Basmajian & Bazant attributed hemiplegic shoulder pain to the **dislocation** of the **glenohumeral joint (GHJD)**.
– This hypothesis, better known as the "Basmajian Theorem", resulted in many

FIG. 1

PROM (Passive Range of motion)

– Absolute values.

PROM – *PASSIVE RANGE OF MOTION*

		GROUP A	GROUP B
T0	ABD	120	122
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	FLEX	35	34
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	ER	110	98
	FLEX	50	40
T2	ABD	131	135
	ER	100	100
	FLEX	54	55
T3	ABD	125	140
	ER	100	120
	FLEX	45	60

ABD = Abduction
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rehabilitation practitioners using orthoses to prevent dislocation. However, in the 1990s, some authors expressed certain doubts regarding the "responsibility" of GHJD in hemiplegic shoulder pain, claiming that the albeit common association does not necessarily mean there is a cause-effect relationship.

– Nowadays, the Literature is concordant in identifying three possible causes:

1) Conditions affecting the periarticular soft tissues of the GHJ: rotator cuff injury, rotator cuff tendinopathy (most commonly affecting the tendons of the *supraspinatus*, *subscapularis* and *biceps brachii* muscles), glenohumeral dislocation and, most commonly, **adhesive capsulitis**.

– The causes are undoubtedly the consequences of a functional imbalance of the agonist and antagonist muscles of the scapulohumeral girdle and consequently of the overload the shoulder joint is subject to in the course of post-stroke clinical evolution, as muscle flaccidity transitions to hypertonus;

2) CRPS (Complex Regional Pain Syndrome);

3) Central Hypersensitivity: in this case, the brain damage often has a precise location that can be seen on the MRI (thalamus, basal ganglia, cerebellopontine angle, bulb).

Pinpointing the cause of the SP is often rather challenging as, depending on the brain damage, the patient may have an even very complex neurological situation, with cognitive, motor and verbal impairment with aphasia. Furthermore, the clinical signs and symptoms are often rather generic and difficult to correlate with a single aetiology.

It is also necessary to remember that the clinical complexity of cases of SP may be due to the existence of multiple concurrent causes.

– In literature, the factors that may have an impact on the onset and evolution of SP are indicated as being the presence

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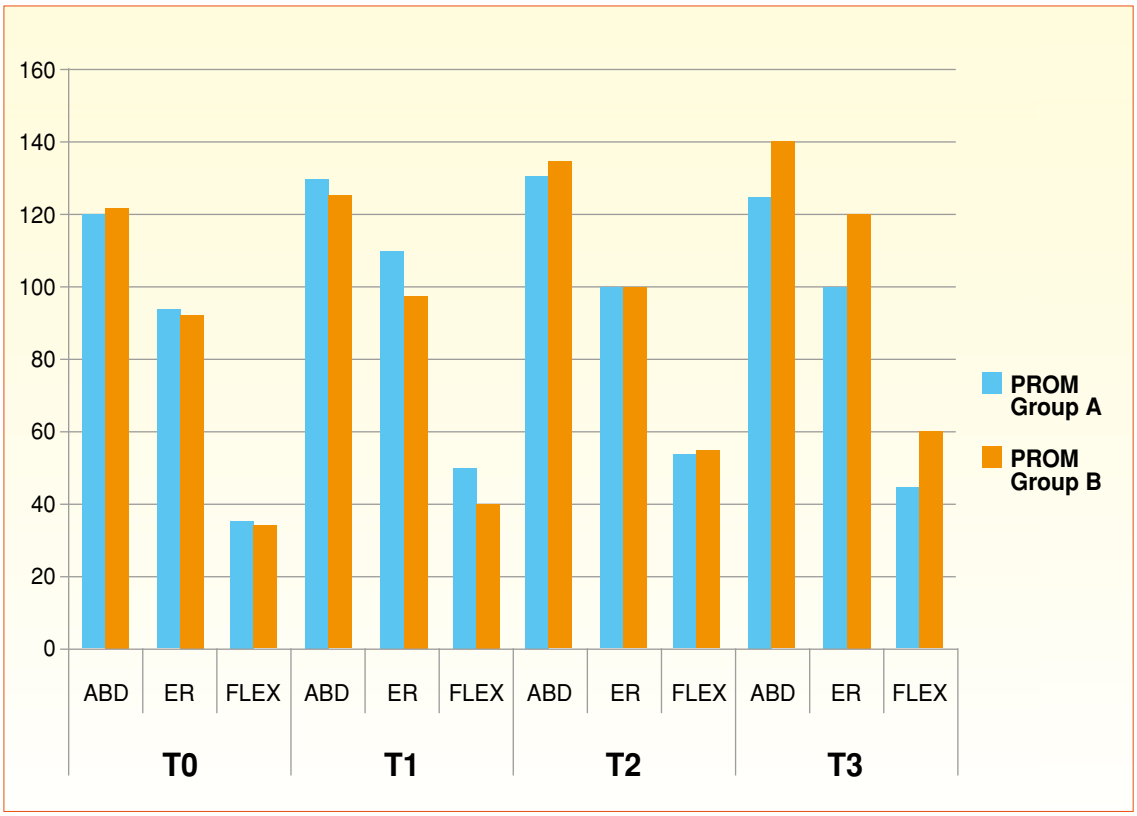

of severe motor damage (according to the Daniels Scale), significant changes in muscle tone in both the flaccidity and the hypertonic stages, and speech disorders (consistent with cognitive impairment).

Conventional treatment, which is not always satisfactory in clinical practice and is often conditioned by the fact that these patients are extremely frail, involves the prescription and use of **1)** upper limb orthoses, **2)** pharmacological therapy with analgesics, anti-inflammatories and a central muscle relaxant, **3)** peri/intra-articular injections with cortisone derivatives, and **4)** an adequate neuromotor rehabilitation protocol, with or without **5)** a combination of analgesic physiotherapy and functional electrical stimulation (FES).

Research conducted to optimise conservative rehabilitation treatment in post-stroke SP with an essentially musculoskeletal aetiopathogenesis (adhesive capsulitis) taking into consideration all the anatomical structures involved, has made it possible to formulate a number of considerations.

The use of medical devices for injection containing porcine collagen (Medical Device) allows a more effective and specific *in situ* positioning of the collagen, which serves a carrier and stabilisation function.

– This makes it possible to replace, strengthen, structure and protect (barrier against adhesion) cartilage, tendons, ligaments and joint capsules, consequently improving the status of the collagen fibres and all the other anatomical structures it contains and therefore to provide mechanical support to the affected anatomical segment.

MATERIALS AND METHODS

Therefore, the hypothesis on which our study was based was that injection treatment with **Guna MD-Shoulder** would recondition the compromised anatomical structure and improve the stability of the shoulder; a "combined" treatment can improve the functional outcomes of rehabilitation and/or produce better pain control in the subacute phase, as well as having a positive impact on the progression of the disease (less frequent exacerbations).

– We recruited **40 patients** undergoing ordinary hospitalisation in a Level II rehabilitation hospital for ischaemic stroke (transferred from acute hospital Stroke Units).
All patients complained of shoulder pain on the hemiplegic side that appeared in the first 3 months after the ischaemic event (SP appearing after 3 months is more often due to central hypersensitivity or CRPS).
The diagnosis of adhesive capsulitis was based on clinical findings and symp-

WBS – DAYTIME AND NIGHT-TIME PAIN

		GROUP A	GROUP B
T0	N	4,2	3,5
	D	7,1	6
T1	N	3,5	3
	D	4,2	5,2
T2	N	2,1	2,1
	D	4	4
T3	N	2,3	2,1
	D	6	3,2

FIG. 3

WBS (Wong-Baker Scale)
– Absolute values.

N – Night-time
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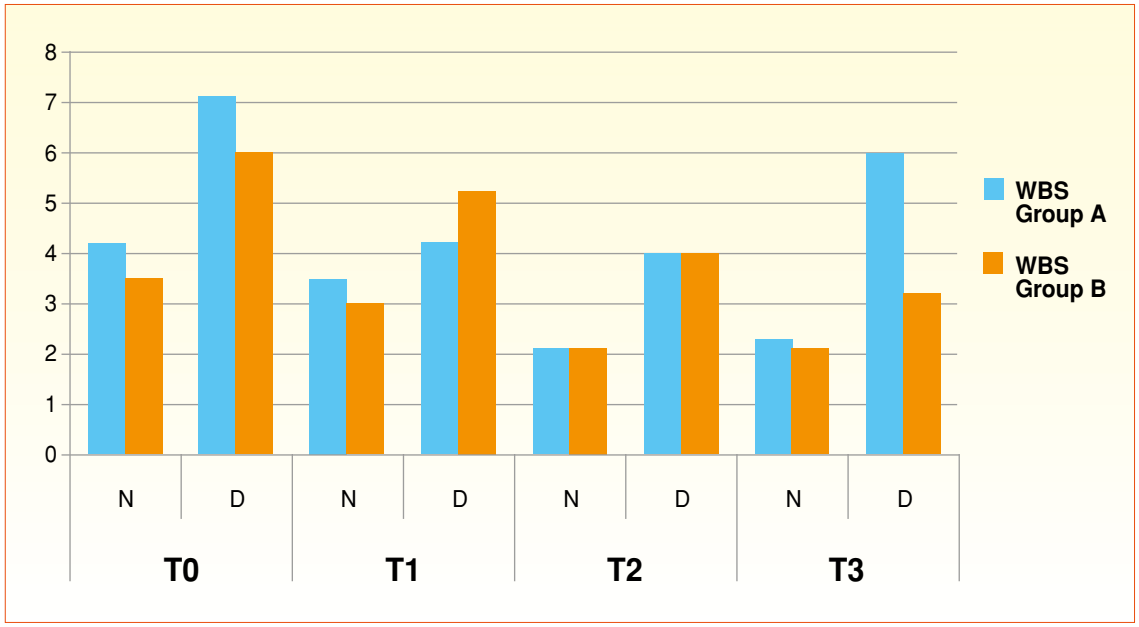

FIG. 4

WBS (Wong-Baker Scale)

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N – Night-time
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toms, as well as standard X-ray and musculoskeletal ultrasound.

– Patients were randomised to **2** treatment groups (**Group A** and **Group B**), stratified by age, gender and pain intensity (Wong-Baker Scale). The outcomes were assessed at 1, 6, and 10 months.

– Inclusion criteria: F and M patients aged between 55 and 75 years who recently had a stroke; clinical and instrumental diagnosis of SP on the hemiplegic side due to adhesive capsulitis, from less than 3 months after the cerebral ischaemic event; WBS (Wong-Baker Scale) > 5, not using NSAIDs, cortisones or opiates.

– Exclusion criteria: past history of SP secondary to musculoskeletal conditions; prior shoulder and elbow fracture; rheumatoid arthritis; current diagnosis of rotator cuff tear and calcified tendinopathy; episodes of shoulder dislocation during the muscle flaccidity stage; serious comorbidity (CIRS 4); Parkinson's disease; dementia (evaluated using the Mini-Mental State Examination); severe neurological damage (emineglect*, speech disorders, Ashworth > 3 muscle hypertonus, severe residual motor damage according to the *Daniels Scale*); use of anticoagulants (warfarin or new oral anticoagulants); use of opiates or cortisone derivatives during the previous month; intra/peri-articular injections to the shoulder in the previous 3 months.

Both groups (A and B) received treatment with the same multidisciplinary rehabilitation protocol (inter-hospital therapeutic and diagnostic pathway) focussing on neuromotor treatment (mobilisation of the paralysed limb, facilitation of active neuromuscular unit recruitment, inhibition of muscle hypertonus and coordination of the inhibitory and excitatory activities of the agonist and antagonist muscles during the performance of the different motor tasks), neuropsychiatric treatment to stimulate the cognitive-motor afferences, ergonomic education and occupational therapy to recover activities of daily living and occupational activities.

The multidisciplinary rehabilitation treatment during the 60 days of ordinary hospitalisation was administered for 3 hours every day.
The patient then switched rehabilitation setting to a daily outpatient treatment with approximately one-hour sessions, for a total of 10 sessions.

• Both treatment groups (A and B) also received ultrasound-guided (Clarius Ultrasound portable linear probe) injection therapy.

Group A was treated with intra-articular injection of **Triamcinolone** 40 mg 1 vial and **Ropivacaine 2%** 3 mL (for a total volume of 4 mL) weekly for the first 2 weeks; the third treatment was administered 15 days after the second.

Group B was treated with injection of **Guna MD-Shoulder** 3 vials (for a total volume of 6 mL) intra-articularly (4 mL) and in the peri-capsular area (the remaining 2 mL).

The following were then analysed as clinical and functional outcomes **1)** daytime and night-time pain **(WBS)**; **2)** passive ROM **(PROM)** of the hemiplegic shoulder in anterior flexion **(FLEX)**, abduction **(ABD)** and external rotation **(ER)** (using a protractor), in addition to records of NSAID use during the follow-up period (FIGS. 1-4).

▶ The results obtained make it possible to conclude that in the multidisciplinary neuromotor rehabilitation protocol for ischaemic stroke patients, ultrasound-guided injection treatment with MD-Shoulder plays a decisive role when the complication known as SD, with a prevalent musculoskeletal aetiology (adhesive capsulitis), presents at an early stage.

Evidently the greater the residual neurological damage and the later the complication presents, the less effective the ultrasound-guided treatment will be, because other non-musculoskeletal causes (CRPS and central hypersensitivity) will sustain the pain symptoms.

CONSIDERATIONS

In the early stage, the injection treatment with cortisone derivative was undeniably effective on both the pain and the passive range of motion of the shoulder, before losing its beneficial effect over time.

On the other hand, in literature, the cortisone derivative is extensively reported as having a "toxic" effect on biological tissues with a prevalent collagen component.
Furthermore, the use of these medicinal products is potentially hazardous when they are used on a frail population such as that considered in this study.
In approximately half of all cases, patients experienced adverse effects such as blood pressure increases, onset of headache and facial rash. It goes without say that this treatment was not offered to diabetic subjects or those with poor glycaemia control.

– The injection treatment with Guna MD-Shoulder, on the other hand, did not give rise to any adverse reaction, confirming that it is absolutely safe.

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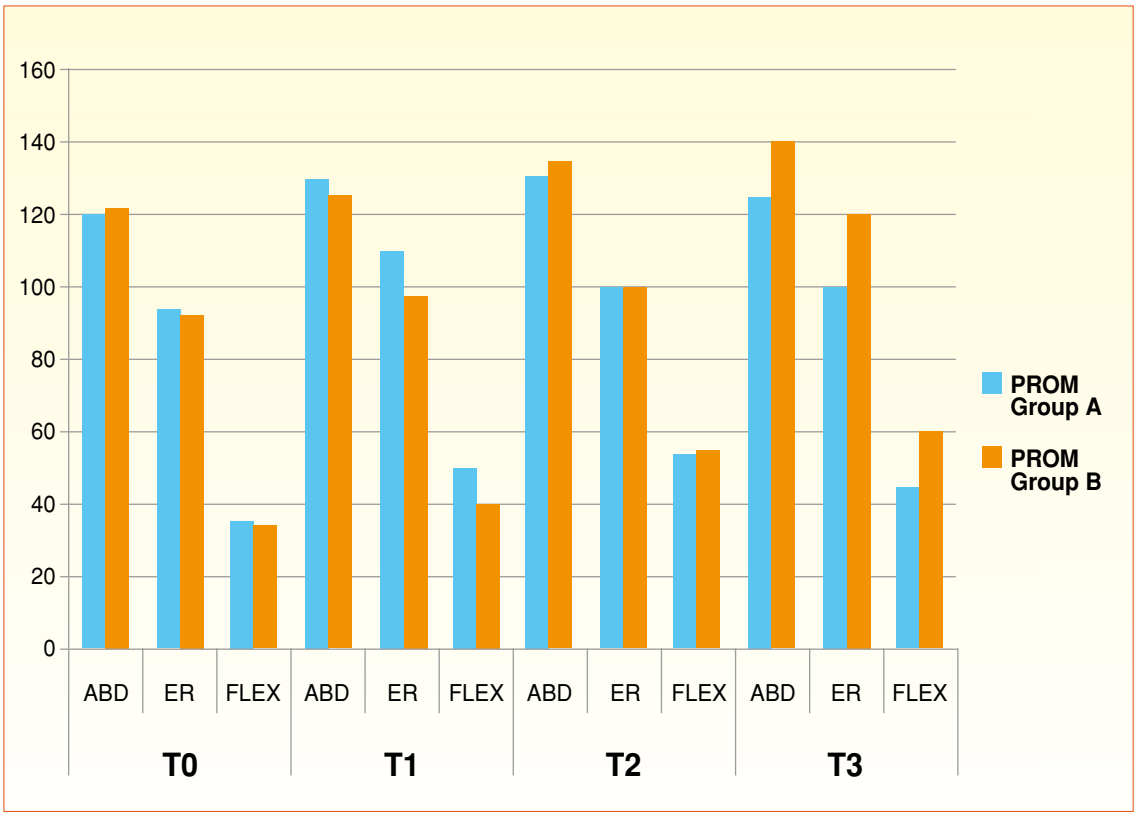

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T2	N	2,1	2,1
	D	4	4
T3	N	2,3	2,1
	D	6	3,2

FIG. 3

WBS (Wong-Baker Scale)
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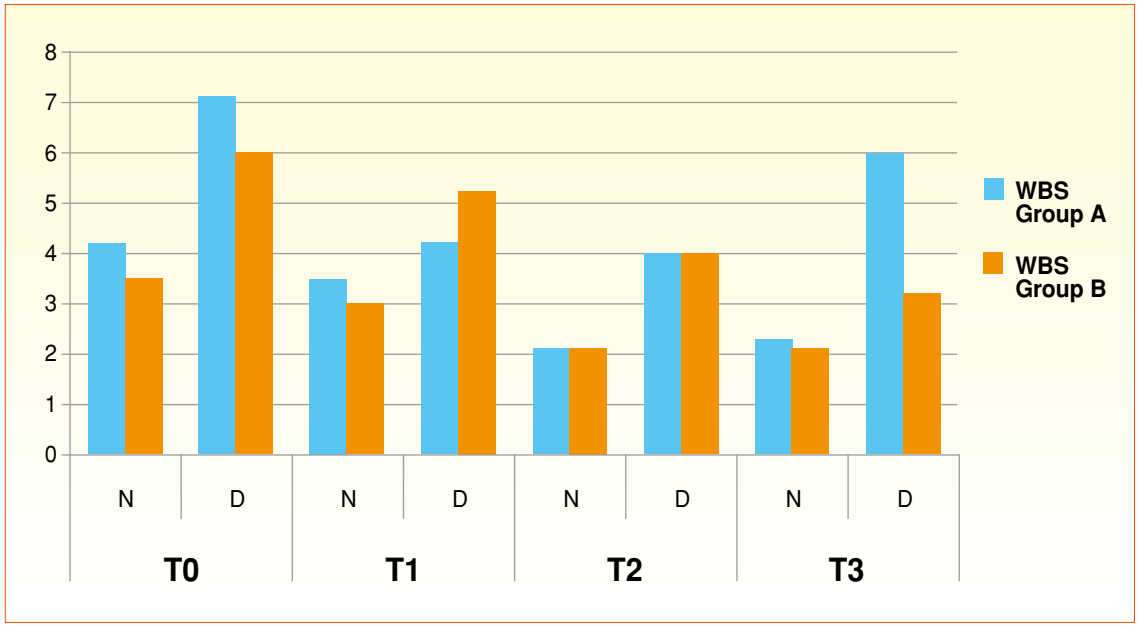

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D – Daytime

toms, as well as standard X-ray and musculoskeletal ultrasound.

– Patients were randomised to **2** treatment groups (**Group A** and **Group B**), stratified by age, gender and pain intensity (Wong-Baker Scale). The outcomes were assessed at 1, 6, and 10 months.

– Inclusion criteria: F and M patients aged between 55 and 75 years who recently had a stroke; clinical and instrumental diagnosis of SP on the hemiplegic side due to adhesive capsulitis, from less than 3 months after the cerebral ischaemic event; WBS (Wong-Baker Scale) > 5, not using NSAIDs, cortisones or opiates.

– Exclusion criteria: past history of SP secondary to musculoskeletal conditions; prior shoulder and elbow fracture; rheumatoid arthritis; current diagnosis of rotator cuff tear and calcified tendinopathy; episodes of shoulder dislocation during the muscle flaccidity stage; serious comorbidity (CIRS 4); Parkinson's disease; dementia (evaluated using the Mini-Mental State Examination); severe neurological damage (emineglect*, speech disorders, Ashworth > 3 muscle hypertonus, severe residual motor damage according to the *Daniels Scale*); use of anticoagulants (warfarin or new oral anticoagulants); use of opiates or cortisone derivatives during the previous month; intra/peri-articular injections to the shoulder in the previous 3 months.

Both groups (A and B) received treatment with the same multidisciplinary rehabilitation protocol (inter-hospital therapeutic and diagnostic pathway) focussing on neuromotor treatment (mobilisation of the paralysed limb, facilitation of active neuromuscular unit recruitment, inhibition of muscle hypertonus and coordination of the inhibitory and excitatory activities of the agonist and antagonist muscles during the performance of the different motor tasks), neuropsychiatric treatment to stimulate the cognitive-motor afferences, ergonomic education and occupational therapy to recover activities of daily living and occupational activities.

The multidisciplinary rehabilitation treatment during the 60 days of ordinary hospitalisation was administered for 3 hours every day.
The patient then switched rehabilitation setting to a daily outpatient treatment with approximately one-hour sessions, for a total of 10 sessions.

• Both treatment groups (A and B) also received ultrasound-guided (Clarius Ultrasound portable linear probe) injection therapy.

Group A was treated with intra-articular injection of **Triamcinolone** 40 mg 1 vial and **Ropivacaine 2%** 3 mL (for a total volume of 4 mL) weekly for the first 2 weeks; the third treatment was administered 15 days after the second.

Group B was treated with injection of **Guna MD-Shoulder** 3 vials (for a total volume of 6 mL) intra-articularly (4 mL) and in the peri-capsular area (the remaining 2 mL).

The following were then analysed as clinical and functional outcomes **1)** daytime and night-time pain **(WBS)**; **2)** passive ROM **(PROM)** of the hemiplegic shoulder in anterior flexion **(FLEX)**, abduction **(ABD)** and external rotation **(ER)** (using a protractor), in addition to records of NSAID use during the follow-up period (FIGS. 1-4).

▶ The results obtained make it possible to conclude that in the multidisciplinary neuromotor rehabilitation protocol for ischaemic stroke patients, ultrasound-guided injection treatment with MD-Shoulder plays a decisive role when the complication known as SD, with a prevalent musculoskeletal aetiology (adhesive capsulitis), presents at an early stage.

Evidently the greater the residual neurological damage and the later the complication presents, the less effective the ultrasound-guided treatment will be, because other non-musculoskeletal causes (CRPS and central hypersensitivity) will sustain the pain symptoms.

CONSIDERATIONS

In the early stage, the injection treatment with cortisone derivative was undeniably effective on both the pain and the passive range of motion of the shoulder, before losing its beneficial effect over time.

On the other hand, in literature, the cortisone derivative is extensively reported as having a "toxic" effect on biological tissues with a prevalent collagen component.
Furthermore, the use of these medicinal products is potentially hazardous when they are used on a frail population such as that considered in this study.
In approximately half of all cases, patients experienced adverse effects such as blood pressure increases, onset of headache and facial rash. It goes without say that this treatment was not offered to diabetic subjects or those with poor glycaemia control.

– The injection treatment with Guna MD-Shoulder, on the other hand, did not give rise to any adverse reaction, confirming that it is absolutely safe.

The use of Guna MD-Shoulder made it possible to obtain a biological effect of organic reconditioning of the impaired anatomical structures, together with a hydraulic distension associated with the volume of product injected, making it possible to achieve a positive result on the stabilisation of the gleno-humeral joint, its range of motion and, consequently, on the daytime and night-time pain symptoms, not only in the early stage, but especially in the weeks after the treatment, with a continuous improvement in the outcomes recorded at the follow-up time-points.

* **Ed. Emineglect**: Clinical deficits such as poor left visual exploration, inaccurate identification of the mid-point on a line, left limb hypokinesia and anosognosia. This kind of deficit is usually caused by right brain injury.

These results obviously allowed the patient to obtain greater benefit from the neuromotor rehabilitation treatment provided.

The injection treatment with MD-Shoulder would also appear to better control the progression of the shoulder condition, by reducing the frequency of exacerbations over time (control of the pro-inflammatory cytokine network).

– In coming months, it will be necessary to confirm the results achieved by expanding the study case load and, in particular, attempting to identify the correct timing for subsequent injection treatments as part of a personalised rehabilitation project (maintenance treatment). ■

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ORIGINAL ARTICLE

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Treatment of Lateral Epicondylitis with Collagen Injections: a Pilot Study

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SUMMARY

Background. Lateral epicondylitis, or tennis elbow, is the prevalent cause of elbow pain among adults. Collagen injections are used to treat different musculoskeletal disorders. Type I porcine collagen has proved to enhance tendon repair in vitro. Aims of the present pilot study were to verify the effects of type I porcine collagen injections on pain and disability in patients with tennis elbow and therefore to check if there are grounds for carry out a randomized controlled trial.

Methods. Fifty patients, who have been suffering lateral epicondylitis for at least 6 months, were treated with a series of 5 type I porcine collagen injections, at weekly intervals. The Patient-Rated Tennis Elbow Evaluation questionnaire was employed to verify the effects of collagen injections at 1-month and 3-month follow-up.

Results. As regards the baseline, the total score showed an average reduction of 57% (55% in terms of pain and 58% in terms of function) at 1-month follow-up and an average reduction of 66.1% (68.9% in terms of pain and 63.2% in terms of function) at 3-month follow-up. The results were statistically significant ($p<0.05$) according to the Kruskal-Wallis test.

Conclusions. Up until now there were no studies about treatment of tennis elbow with collagen injections. Compared to other regenerative injection therapies, collagen injections seemed to be one of the most effective and fast-acting. The positive findings of this pilot study can be the bases for conducting clinical trials with higher level of evidence.

KEY WORDS

collagen; injections; lateral epicondylitis; tendinopathy; tennis elbow

BACKGROUND

Lateral epicondylitis (LE), also known as tennis elbow, is a frequent painful syndrome of the elbow, due to tendinopathy of the common extensor tendon at the lateral epicondyle of the humerus (1). The prevalence of LE in adults is between 1% and 3%; it occurs most frequently in the fourth and fifth decades of life, with no gender-related predisposition. As regards etiopathogenesis, causes are not always clearly identified (2). However, the main risk factors are well known: old age, high Body Mass Index (BMI), high total cholesterol levels, previous rotator cuff disease, De Quervain's disease, carpal tunnel syndrome, smoking, and low social status (3). LE is often associated with activities involving repetitive movements, such as grabbing objects, wrist extension, forearm supination or pronation. The most involved muscles in the pathogenesis of LE are the extensor carpi radialis brevis (ECRB), then the supinator and other extensor muscles such as the extensor carpi radialis longus (ECRL), extensor digitorum (ED), extensor digiti minimi (EDM) and extensor carpi ulnaris (ECU). Despite the name with which this pathology is known, only 5-10% of patients with lateral epicondylitis actually play tennis (4).

Considering the absence of any inflammatory process in the LE histology findings, the inflammation theory of the disease has been fully rejected (5). At this stage, the majority of the authors consider LE as a degenerative process triggered by a single trauma or several repetitive microtrauma (6). Nirschl first described the LE pathogenesis as angiofibroblas-

tic proliferation, in which tendons exhibit hyperactivity of fibroblasts, vascular hyperplasia and unstructured collagen fibers (with loss of the physiological compactness and orientation) (7). More recently, it has been shown that LE tendinosis is characterized by the variability in tendon cell density, the extracellular matrix alteration, the presence of chondroid-like proteins, and the increase of water in the tendon structure. Moreover, an increase in matrix metalloproteinases has been described together with anarchic neovascularization and sprouting of small nerve fibers with receptors for substance P in areas that are physiologically almost entirely deprived of them (8). Another histological feature of LE is the reduction of type I collagen within the tendon structure. Type I collagen is gradually replaced by type III collagen, which shows reduced fiber cross-linking and consequent change of the structure of collagen fibrils (chaotic and not linear anymore). Therefore, the tendon will have less resistance to stresses and will be more susceptible to injuries (9).
The above-mentioned histological findings are progressive and lead slowly to clinical symptoms, which are, by the way, quite heterogeneous. Mostly patients refer a pain anteriorly or above the lateral epicondyle of the elbow. The pain typically radiates towards the bellies of forearm extensor muscles. Pain may be intermittent, persistent but mild, or severe with functional disability. Often the pain's trigger is the contraction of carpal and digital extensor muscles.
There are several clinical tests for the diagnosis of LE: Maudley's test, Thomson's manoeuvre, the chair lift test and the hand-grip strength evaluation. Imaging can be of use for the diagnosis of LE, above all ultrasounds and Magnetic Resonance (10). The electrodiagnostic evaluation of the posterior interosseous nerve and the elbow X-ray can play an important role in the differential diagnosis (5).
Despite the high prevalence of LE, there is still no agreement about treatment. Following limitation of physical activities and analgesic drugs use, a spontaneous remission of the disease may occur. In the event of symptoms persistence, several treatments are available, both conservative and surgical. The aim of the surgical treatment is the debridement of the angiofibrotic tissue produced during the tendon degenerative process and, eventually, the injured tendons reconstruction. LE conservative treatment includes: rest, physical therapy, braces, medicated plaster (11), Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Extracorporeal Shock-Wave Therapy (ESWT), percutaneous radiofrequency lesioning, laser therapy, acupuncture, and injection therapy (12). Several injection therapy options are available and described in the medical literature, including injection of: corticosteroids, hyaluronic acid (HA), botulinum toxin, platelet-rich plasma (PRP), tenocyte-like cells derived from cutaneous fibroblasts, and stem cells derived from autologous adipose tissue (12). These injection treatments have shown variable effectiveness and have some criticalities. For example, corticosteroids are useful in the short term, but useless in the long term; PRP or autologous stem cells are expensive and not easy to use.
Collagen injections are used to treat different musculoskeletal disorders (13-15). However, to date no studies on the effectiveness of collagen injections in treating tennis elbow have been published. Biological rationale for the use of type I porcine collagen injections in the treatment of LE was based on the results of the 2018 study by Randelli et al. (16), who stated that type I porcine collagen could induce in tenocytes an anabolic phenotype by stimulating tenocyte proliferation and migration and type I collagen synthesis, maturation, and secretion, thus favoring tendon repair.
The aims of this pilot study were (a) to evaluate the effects of a series of 5 collagen injections (once a week) on pain and disability in a group of patients who have been affected by LE for at least 6 months, and consequently, (b) to investigate whether crucial components of a randomized controlled trial (RCT) will be feasible.

MATERIALS AND METHODS

This is a prospective observational pilot study and was carried out at Federico II University Hospital in Naples, Italy, Department of Rehabilitation and Orthopedics. The subjects were all outpatients and we enrolled them from January 2017 to October 2018. All the patients who referred symptoms of LE was evaluated to verify the criteria for the enrollment. The inclusion criteria were: (a) age >18 years, (b) clinical symptoms of LE for at least 6 months, (c) lack of therapy in the last 6 months, (d) pain triggered by pression on lateral epicondyle (on proximal insertion of the common extensor tendon), (e) positive Maudley's test and Thomson's manoeuvre, (f) absence of bone lesions on plain X-ray. The exclusion criteria are listed in **table I**. After a full and clear description of the study protocol, all patients enrolled were invited to sign the informed consent. The study was carried out in accordance with the principles of the Declaration of Helsinki and meets the ethical standards of the journal (17) and of the local ethics committee as well.
We enrolled 50 patients, of which 33 males and 17 females, with an average age of 52.25 ± 13.25 years. For the treatment we planned five injections of 2 ml porcine type I collagen, once a week. Injections were performed using the palpatory technique at the level of the proximal insertion of the wrist and fingers extensor tendons on the lateral epicondyle. The palpatory technique has proved to be accurate (18) and with the same effectiveness of the echo-guided method (19). No other treatment has been associated with collagen injections.

Table I. Exclusion criteria.

Traumatic elbow injuries in the previous 6 weeks
Elbow instability
Previous surgery of the elbow
Any other pathology affecting the same arm
Cervicobrachial pain syndrome
Contraindications to injection therapy
Any other therapy for epicondylitis in the last 6 months
Hemorrhagic diathesis or anticoagulant therapy
Local or systemic infections
Diabetes or autoimmune diseases
Obesity (Body Mass Index ≥ 30)
Definite chronic hyperglicemia (HbA1c ≥ 6.5%)
Hypercholesterolemia (total cholesterol levels ≥ 240 mg/dL)
Definite hypertension (SBP ≥ 140 mmHg or DBP ≥ 85 mmHg)
Pregnancy or feeding time
Psychiatric disorders

Patients were evaluated at the time of enrollment (T0), and one month (T1) and three months (T2) after the last injection by means of the Patient-Rated Tennis Elbow Evaluation (PRTEE) questionnaire. The PRTEE was introduced in clinical practice by MacDermid in 2005 (20). It is a self-compiled 15-item questionnaire that assesses pain and disability in patients with tennis elbow. The PRTEE consists of 2 subscales: pain (5 items) and function (10 items). The function subscale, in its turn, includes usual activities (4 items) and specific activities (6 items). Each item has a score between 0 (no pain or disability) and 10 (the worst possible pain or complete disability). The total score goes from 0 to 100, with the highest scores indicating the worse situation in terms of pain and disability. Pain and function are equally represented in the score. The PRTEE questionnaire is highly reliable, reproducible and sensitive (21). In the present study we used the 2012 Italian version of the PRTEE questionnaire (22).

RESULTS

The Kruskal-Wallis test and the Dunn's post-hoc analysis were employed for the statistical analysis. The confidence interval was established at 95% ($p < 0.05$). Both the average total score on the PRTEE questionnaire and the average scores of the pain and function subscales have been taken into consideration. At the time of enrollment (T0) the average scores of the PRTEE questionnaire were: (a) total score 68.42 ± 16.50, (b) pain score 35.6 ± 7.57, and (c) function score 32.82 ± 9.96. At T1 follow-up (1 month after last injection) the scores were: (a) total score 29.74 ± 16.95, (b) pain score 15.9 ± 8.9, function score 13.84 ± 9.33. At T2 follow-up (3 months after last injection) the scores were: (a) total score 23.17 ± 13.68, (b) pain score 11.08 ± 6.08, function score 12.09 ± 8.9. The Kruskal-Wallis test provided very strong evidence ($p = 0.000$) for all the three variables analysed (pain score, function score and total score). The Dunn's post-hoc tests were carried out in order to analyse the differences between the three pairs of groups (T0-T1, T0-T2, and T1-T2) for each variable. There was always very strong evidence ($p = 0.000$) of a difference between the group T0 and the group T1 and between the group T0 and the group T2. By contrast, there was never evidence of a difference between the group T1 and the group T2 ($p > 0.05$). As regards the score's variations between T0 and T1, we observed a 55% reduction in the pain score, a 58% reduction in the function score, and a 57% reduction in the total score. Finally, with reference to the score's variations between T0 and T2, a 68.9% reduction in the pain score, a 63.2% reduction in the function score and a 66.1% reduction in the total score were registered. No adverse event has been described after collagen injections, except for some cases of burning sensation at the injection site which resolved spontaneously in a few hours.
All the results are summarized in **figures 1**, ***2*** and **3**.

DISCUSSION

LE is the most frequent cause of elbow pain in adults and, from the etiological point of view, it can be defined as an angiofibroblastic tendinosis. Currently there isn't a consensus regarding the treatment of LE. Many conservative therapeutic approaches have been proposed, both systemic and local, but until now, few of them have valid clinical evidence. Injection therapy is one of the most studied therapeutic approach. This treatment allows the drug to reach the tendon directly, increasing drug effectiveness and reducing systemic side effects. In the recent literature some drugs have proved to be particularly effective in treating LE if administered by infiltration: HA, PRP, dextrose (prolotherapy), high volume 0,9% saline solution and botulinum toxin.
At this stage there aren't in literature studies about collagen injection in the treatment of LE. Therefore, in this pilot study we wanted to evaluate the collagen injection therapy in a cohort of 50 subjects affected by tennis elbow (5 injections, once a week, of type I porcine collagen). The results were evaluated by administering the PRTEE questionnaire, before the first injection, and one month and three months after the last injection. We observed a 57% reduction in the PRTEE total score at T1 follow-up (55% in the PRTEE

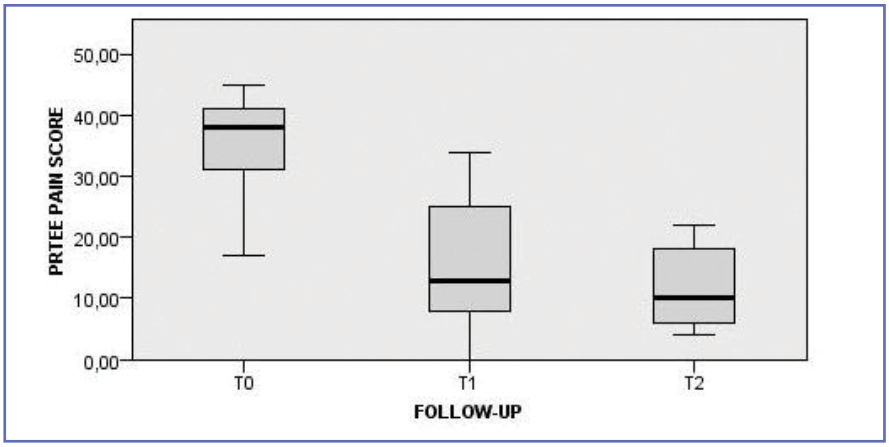

Figure 1. PRTEE function subscale score at baseline (T0), and 1 month (T1) and 3 months (T2) after the last injection.

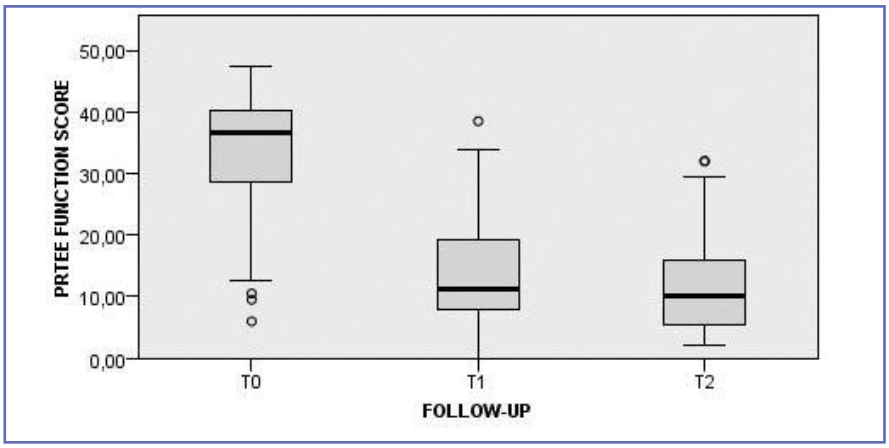

Figure 2. PRTEE pain subscale score at baseline (T0), and 1 month (T1) and 3 months (T2) after the last injection.

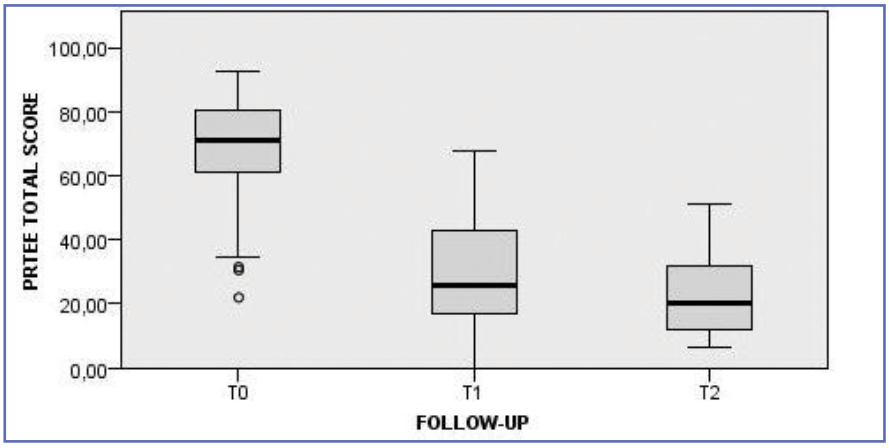

Figure 3. PRTEE total score at baseline (T0), and 1 month (T1) and 3 months (T2) after the last injection.

pain score and 58% in the PRTEE function score, respectively). Finally, three months after the last injection, the PRTEE total score achieved a 66.1% reduction (68.9% as regards the pain score and 63.2% as regards the function score).

Since there are no studies on this topic in the literature, we cannot make a direct comparison.

However, it seemed appropriate to compare our results with other studies in which the effectiveness of regenerative injection therapies has been evaluated, such as the injection of hypertonic dextrose and sodium morruate (prolotherapy), the injection of HA and chondroitin sulfate (CS), and finally the injection of PRP associated with a scaffold of human collagen. All the considered studies used the PRTEE questionnaire for the evaluation of results. Therefore, we could make the comparison.

Rabago et al. in 2013 carried out a randomized controlled trial in order to test the effectiveness of injection of hypertonic dextrose and sodium morruate (prolotherapy) in the treatment of tennis elbow (23). Nine patients were treated with prolotherapy and the results were compared with those obtained in a homogeneous control group treated with the "wait-and-see" approach. The average total score of the PRTEE questionnaire in the treated group was reduced by 5.2% after 4 weeks, by 23.8% after 6 weeks, by 53.5% after 16 weeks and by 74.9% after 32 weeks. The differences with the results obtained in the control group were statistically significant at 6 and at 12 weeks, while no statistically significant differences were found at 4 weeks. The control group did not carry out the follow-up evaluation at 32 weeks.

In their 2015 prospective randomized controlled trial, Tosun et al. evaluated the effects of a single HA + CS injection in 25 patients with LE and compared the results with a single cortisone +

anesthetic injection (control group)(24). In the treated group the authors reported a 51.35% of mean total score reduction after 3 months and a 61.72% after 6 months. The difference between the two groups was statistically significant only at the third month follow-up evaluation.
In a recent paper (2019), Farkash et al. showed good results in LE treatment with a single PRP injection plus a scaffold of human collagen (25). Forty patients were enrolled and the results showed a 34% reduction in the average score at 1 month and a 59% at 6 months, compared to baseline values. We can compare our results at 1-month follow-up with those achieved in the studies by Rabago and Farkash. In the aforementioned trials we can see an average total score reduction of 5.2% and 34%, respectively, while in our cohort study we obtained a reduction of 57%. In his study, Tosun described a 51.35% reduction after a 3-month follow up. This result is lower than the one obtained in our sample after the same time of follow-up (66.1%). We underline that the 5 collagen injections, proposed in our therapeutic approach, have obtained better results at 1 month than the single injection of dextrose + morruate and PRP + collagen scaffold (higher difference in the first and less in the second case) and at the same time our protocol showed greater effectiveness than a single HA + CS injection after a 3-month follow-up.
The present study has several limitations: (a) a relatively small sample, (b) the lack of a control group, (c) the LE diagnosis based solely on history, physical examination and X-ray, and (d) the use of a subjective evaluation tool. However, it should be emphasized that this is a pilot study, and its objective was to evaluate the feasibility of a subsequent randomized controlled clinical trial. To date indeed, this is the first study in the literature on the effectiveness of collagen injection therapy in tennis elbow.
In conclusion, this pilot study has shown that a series of 5 collagen injections, at weekly intervals, is able to reduce significantly pain symptoms and improve the function in a very short time (1 month), in a group of 50 patients with LE. Moreover, we stated that the good results further increase two months later. Therefore, we can conclude that there are grounds for carrying out a RCT to confirm our preliminary data.

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest.

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CLINICAL

F. Brunato

THE TREATMENT OF RHIZOARTHROSIS WITH COLLAGEN MEDICAL DEVICE SMALL JOINTS

SUMMARY

Rhizoarthrosis is a very widespread disease; it affects 20% of the adult population and represents about 10% of all osteoarthritic locations; it is more frequent in females than in males (4:1 ratio). The initial symptom is TM pain followed by difficulty in performing daily activities such as turning a key or opening a bottle. The treatment is initially conservative with the application of immobilization braces and the simultaneous use of chondroprotectors. If this treatment is not effective, before undertaking the definitive surgical treatment, infiltrative therapy with Collagen may be considered. Collagen MDs improve the mechanical qualities of the joint capsule by restoring the anisotropic characteristics of the tissue with an evident positive effect on the "joint hypermobility stabilisation", movement, pain and quality of life.

– The purpose of this trial is to evaluate the efficacy of the endo- and peri-articular injection of MD-Small Joints in patients suffering from rhizoarthrosis before undergoing definitive surgical therapy.

In this clinical study, 22 patients (3 M; 19 F) were included and assessed for 10 weeks with the DASH, VAS scales and Grind Test.

The treatment was well tolerated, and no side effects were observed. The improvement obtained was approximately 60-80% of all rating scales. This trial shows that clinical improvement is directly proportional to the reduction in joint laxity and is therefore a function of the effectiveness of MD-Small Joints on joint collagen.

KEY WORDS **RHIZOARTHOSIS, COLLAGEN MEDICAL DEVICE, MD-SMALL JOINTS, HAND PAIN, DASH, VAS, GRIND TEST, COLLAGEN**

RHIZOARTHROSIS

Rhizoarthrosis (RA) is a type of arthritis that affects the **trapeziometacarpal (TM) joint**. The etymology of the term 'rhizoarthrosis' is Greek: *rizos* means "root"; this joint, in fact, is located at the root of the thumb.

– RA is a widespread condition; it affects **20%** of the adult population (Barra *et* Al., 2003) and represents approximately **10%** of all osteoarthritic localisations in the human body (Sollazzo *et* Al., 2006). RA is more frequent in females than males (4:1 ratio) and generally occurs between the fifth and sixth decades of life.

In women, it frequently begins at menopause, while in men it is more related to overuse phenomena (Bonola *et* Al., 1981).

The TM joint plays a key role in normal thumb function: all gripping actions overload the TM joint because the axis of the thumb exerts force and acts as a fulcrum on this joint.

This force transmits a radial stress at the base of the metacarpal, which, over time, causes a reduction in the tension of the capsuloligamentous system (Bernardini, 2018), resulting in joint hyperlaxity and subluxation of the first metacarpal.

• The preternatural movement of the bone heads alters the joint surface; there is a progressive thinning of the cartilage and subsequent onset of pain and arthritis. Symptomatology is bilateral in 50% of cases.

FUNCTIONAL ANATOMY

The TM joint can be considered the most complex joint of the human body as it allows the thumb to perform volo-volar pincer grips with the long fingers; in other words, it allows the hand to perform its most distinctive function: opposition, that is, prehension (Caroli, 1996).

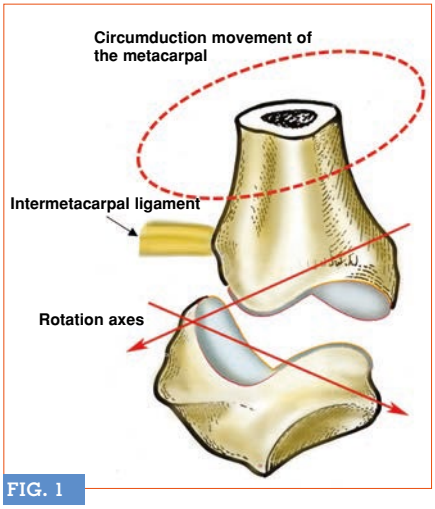


FIG. 1

Trapeziometacarpal joint.

Kapandji (1971) defined the TM joint as a reciprocal interlocking or saddle-shaped joint and compared it to a rider in the saddle with perfectly matching torus-shaped contact surfaces (Bonola *et* Al., 1981).

The movements take place on two perpendicular axes and their combination allows for a true circumduction, conditioned by the intermetacarpal ligament, which acts as a pivot (FIG. 1,2).

The structures that support and stabilize this joint are the capsule, the extracapsular ligaments and the intrinsic and extrinsic muscles.

The capsuloligamentous structures of the TM joint are extremely important, both in providing stability and in guiding the complex movements of the thumb.

The joint capsule is very lax and fits along the contour of the articular surfaces of the trapezium and the base of the metacarpal. This laxity is determined by the fact that the first metacarpal must allow for ample movement and rotation of the metacarpal along its own longitudinal axis (Caroli, 1996).

▶ Ligaments of the capsule

The ligamentous system is equally important because, in addition to ensuring the stability of the TM joint, its maximum tension allows stopping the various movements of the first metacarpal bone, assisted by the fascial and muscular structures in this function.

It should also be noted that the TM ligaments, through their insertion, help to guide the movements of the thumb and mainly those of axial rotation.

A number of thickenings depart from the joint capsule, giving rise to the following ligaments:

- the dorsoradial ligament (DRL) or Arnold's external trapeziometacarpal ligament stops abduction and favours rotation in pronation of the metacarpal joint;
- the dorsoulnar ligament (DUL) or Arnold's internal trapeziometacarpal ligament, which is very thick and wide, stops the retroposition movement and favours rotation in supination of the metacarpal;
- the anterior oblique ligament (AOL). Some authors describe two portions of this ligament: a superficial one and a deep one (beak ligament), which is particularly important in stabilising the TM joint in the degrees of maximum abduction and retroposition movement of the thumb;
- the fibrous, thick and short intermetacarpal ligament (IML): it stretches between the base of the first and second metacarpals; this ligament stops the abduction movement of the first metacarpal.

  The IML is crucial because its loosening causes external subluxation of the base of the first metacarpal, which, as explained below, is one of the most important causes of **joint instability** (Caroli, 1996) (FIG. 2).

- **DRL = Dorsoradial Ligament**
- **DUL = Dorsoulnar Ligament**
- **AOL = Anterior Oblique Ligament *(beak ligament)***
- **IML = Intermetacarpal Ligament**

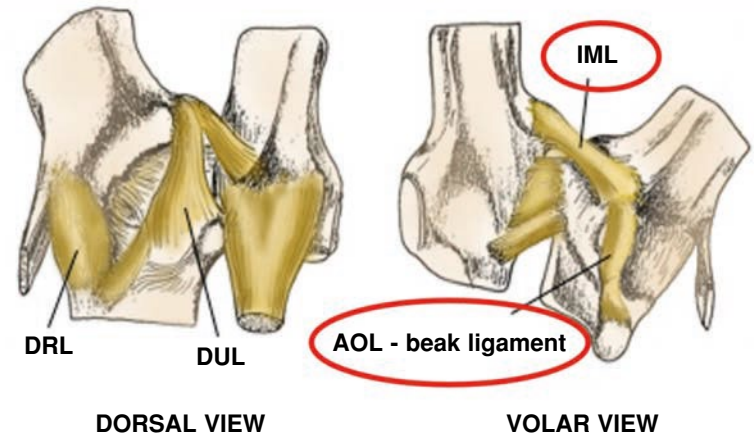


FIG. 2

Ligaments of the trapeziometacarpal joint.

▶ Motor muscles of the thumb

As indicated by Kapandji (1971), the TM joint works in compression as a joint. The intrinsic thenar muscles allow the first metacarpal to orient in all directions of space, as if it were a pile whose orientation can be changed by changing the tension of the cables. According to the author, the muscular components provide support to joint coaptation in all positions, resulting from the synergistic activation of agonist and antagonist muscles (Brunelli *and* Brunelli, 1996).

Mobility is the essential opposition function of the thumb; it is enabled by nine motor muscles:

- Four extrinsic or long muscles located in the forearm. Three are for grip opening movements: The *extensor pollicis longus, extensor pollicis brevis,* and *abductor pollicis longus;* and one for power grip: *flexor pollicis longus.* As a reminder, the extrinsic muscles are the motor muscles for power gripa;

- Intrinsic muscles located in the thenar eminence and first interosseous space; they provide for precision and coordination during different grips and opposition.
  – The external group is composed of three muscles (*opponens pollicis*, *abductor pollicis brevis*, and *flexor pollicis brevis*) that have a synergistic function of thumb opposition.
  – The internal group consists of the adductor and first palmar interosseous muscles.
  These are crucial for gripping/holding objects, because they also perform their action on the **MP (metacarpophalangeal)** and **IP (interphalangeal) joints** (flexion of the former and extension of the latter), making the opposition grip with the index finger more effective.

Opposition is not a fixed movement: indeed, there is a range of oppositions that execute a great variety of grips and actions according to the number of fingers involved and their mode of association (Kapandji, 1971).

- Bi-digital grips give the classic pincer grips between the thumb and index finger; there are 3 types: terminal, subterminal, and subterminolateral.

– The terminal opposition grip is the finest and most precise because it makes it possible to firmly grasp a small object or pick up a very thin object.
The thumb opposes the nail surface of the index finger with the fingertip.
In this grip, as the metacarpal wedges into the trapezius, it protects the joint capsule from any tensional forces and avoids degenerative effects on the joint (FIG. 3).

– The subterminal grip is the most recurrent and instinctive one: the thumb and the index finger oppose each other with the palmar face of the fingertip and this way can grip objects of different calibre, even thin ones, such as a sheet of paper or a pencil.
In this grip, a significant tensive force is created radially at the base of the metacarpal that stretches the joint capsule and the intermetacarpal ligament, making them increasingly lax over time.

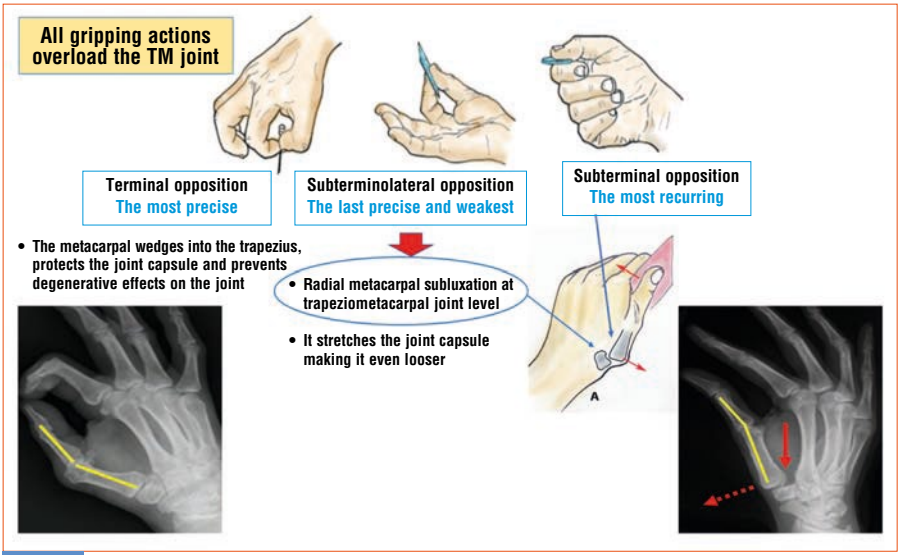


FIG. 3

Effects of grip on the trapeziometacarpal joint.

This laxity produces joint instability, the cause of radial subluxation of the metacarpal and joint degenerative processes.

– The subterminolateral grip is the least fine and weakest compared to the previous ones.
The palmar aspect of the pulp of the thumb rests on the external aspect of the first phalanx of the index finger, creating, in this case too, great radial tension at the base of the metacarpal resulting in the tendency of the TM joint to develop subluxation (Kapandji, 1971).

- The cause of RA always lies in TM joint **instability**.

It can be primary or secondary (TAB. 1).

In ligamentous hyperlaxity, instability is due to an excessive range of motion.
In this case, the palmar ligament (beak ligament) is of great importance, as it limits the hyperextension of the metacarpal and, above all, the intermetacarpal ligament between the base of the first and second metacarpals, which counters the subluxation of the first metacarpal radially, without limiting other movements (FIG. 2).
Laxity and/or degeneration of this ligament produce abnormal TM joint movements, with incongruity of the articular surfaces rapidly triggering degeneration.

– Another known cause that Brunelli (2007) considers to be the most frequent is instability due to the absence of ab-

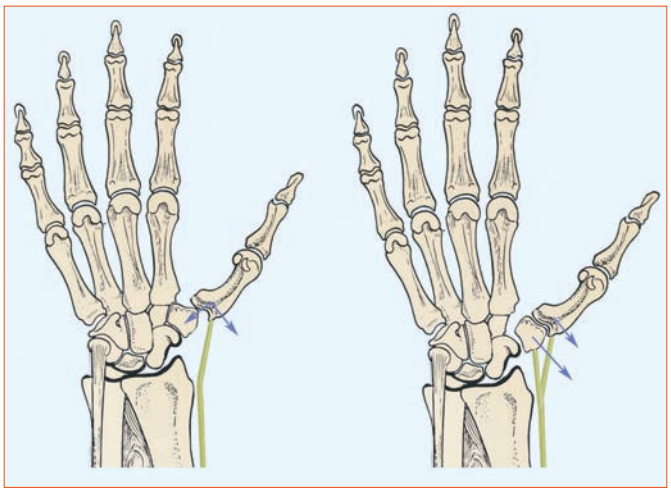
PRIMARY INSTABILITY	SECONDARY INSTABILITY
Hypoplasia of the trapezium, abnormal obliquity of its saddle	Traumatic capsular ligament lesion
Congenital capsular ligament laxity	Outcome of fracture of the trapezium or the base of the first metacarpal
Muscle imbalance due to the absence of insertion of one of the APL tendons on the trapezium	Operational stress due to repetitive work with strong thumb adduction
Muscle hypotonia of the non-dominant hand in elderly people	

TAB. 1

Causes of the trapeziometacarpal joint instability.

FIG. 4

Instability due to the absence of intersection of *abductor pollicis longus* in the trapezium. – Tensive forces.



ductor pollicis longus **(APL)** insertion on the trapezium. In cases where the APL has distal double insertion on the trapezium and on the base of the first metacarpal, with each contraction of the APL the entire thumb-metacarpal-trapezium column shifts in abduction, maintaining normal trapeziometacarpal joint relationships.
Conversely, if there is no insertion on the trapezium, all abductor force is exerted on the base of the first metacarpal, causing significant subluxation tension with a deleterious shear effect on, and cartilage damage, of the TM joint (FIG. 4).
– Repeated stress (overuse) is another frequent cause of TM joint arthritis; the TM joint is subjected to a considerable workload, as it is involved in approximately 50% of all actions of the hand.

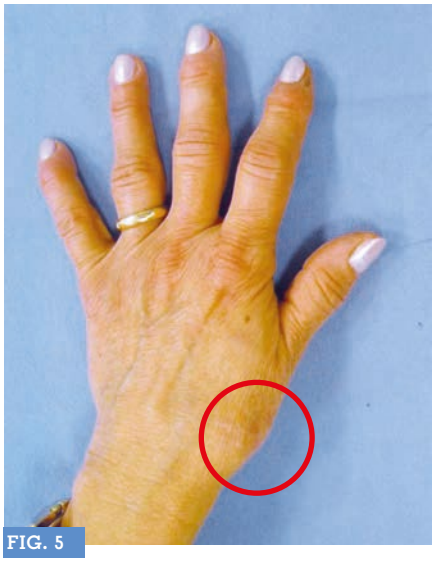


FIG. 5

Subluxation of the first metacarpus.

It is possible to distinguish some activities and habitual gestures that favour the deterioration of the articular surfaces: the repeated prehension of small objects exerts radial stress on the TM joint that does not allow the base of the metacarpal to stay in contact with the articular surface of the trapezium (FIG. 3).
The luxation force transmitted on the metacarpal can be multiplied up to 12-120 times (Cooney *and* Chao, 1977).

SYMPTOMATOLOGY

TM joint instability is often asymptomatic; over time, pain develops, leading the patient to consult a physician.
– The most frequent clinical picture is initially represented by an annoying pain localised at the base of the thumb that appears when active movements in radial abduction such as grips or pincer movements are performed, and/or passive movements in rotation-opposition such as turning a key, unscrewing a cap, turning a handle, writing with a thin pen or even just buttoning a shirt (Dias *et* Al., 2006).
The patient complains of decreased hand strength and mobility.
Later, the pain appears even at rest, at night, and may radiate to the wrist and forearm. In more advanced stages, pain is spontaneous and is associated with bone crepitus due to joint laxity.

– The patient does not "use" the thumb well to avoid pain: over time, this causes muscle weakness in the stabilisation structures of the TM joint; the metacarpal loses the ability to slide on the trapezium along the adduction-abduction axis, in addition to which there is a radial shift of the base of the metacarpal.

The loss of congruence between the bone heads affects the mechanical stability of the joint: it results in dislocation, consequently decreasing movement amplitude (Pomerance, 1995).
During abduction movements, the joint capsule is stretched.
Some capsular fibres are weakened, leading to the dorsal subluxation of the base of the metacarpal; therefore, when the *adductor pollicis* and *flexor pollicis brevis* muscles contract, they pull the distal part of the metacarpal toward the palm.
The result is a "tilt" of the articular surface at the base of the metacarpal on the saddle of the trapezium.

- This tilt, though imperceptible, is the cause of the pain.

That is why, in cases of RA, holding and turning a key, lifting a cup or writing are actions that cause pain: in fact, these actions, although with movements that require little articulation, stress the TM joint and its means of containment (Dias *et* Al., 2006).

– The prevalent clinical signs are:
- deformation and swelling at the base of the first metacarpal (FIG. 5), caused by a combination of dislocation, joint inflammation, and osteophyte formations;
- 1st ray in adduction, more common in advanced stages;
- pain on palpation;
- positive axial compression test or Grind test: the axial load on the trapezium, together with the rotation of the metacarpal, trigger pain at the base of the thumb;
- TM joint dislocation, with or without rotation, which causes stretching of the capsule, which, if inflamed, is painful.

As the disease progresses, TM joint subluxation produces a radial deviation of the MP of the thumb due to the contracture in adduction of the first metacarpal, which is followed by a flexion of the IP, generating a picture of "Z-thumb". This is an expression of one of the most compromised pictures of RA in which, in addition to the TM joint, the MP in hyperextension and IP in flexion are involved.

RADIOGRAPHIC PICTURE – THE EATON-LITTER CLASSIFICATION

RA can be diagnosed through a careful physical examination.
X-rays of the thumb in 3 planes and the particular stress view of the basal joint are necessary to confirm the diagnosis.
The view for the basal joint under stress, when performed correctly, provides an excellent image for assessing the degree of TM joint subluxation.
In this 30° oblique view, the patient is asked to press the tips of the thumbs against each other while the X-ray is being performed (FIG. 6).

X-rays should always be interpreted in relation to the patient's clinical situation. Often, patients with very compromised radiographic pictures report very little or no pain; others with negative or insignificant X-rays may present severe functional deficits with significant impact on daily and/or work activities. There is no indication for MRI and/or ultrasound; only CT may be useful as an additional preoperative investigation.

– Eaton and Glickel (Glickel, 2001) described a method for classifying pathological changes in RA based on the appearance in standard radiographic views and those under stress.
This method has also proven to be useful in medical planning and, if needed, surgery.
– At present, the most widely used classification is the Eaton-Littler classification modified by Brunelli (Barra *et* Al., 2003) which includes both the radiographic picture and clinical picture (TAB. 2).

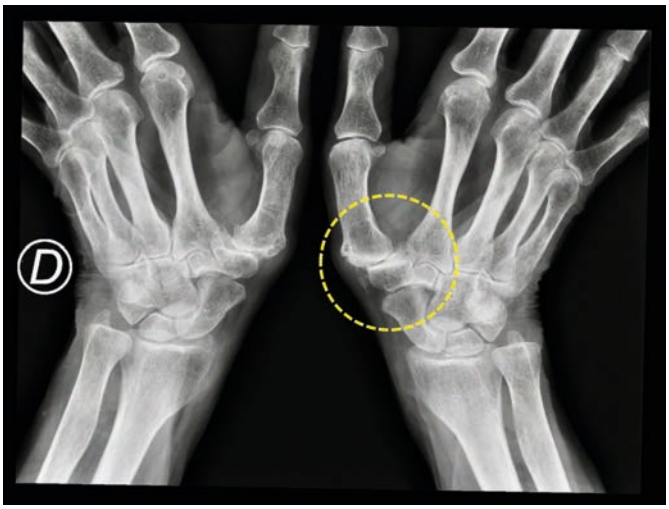


FIG. 6
Stress view.

RHIZOARTHROSIS – CONSERVATIVE TREATMENT

Treatment in all stages of the disease is initially conservative.
– The first step is the application of an immobiliser at night and possibly during the day for 2-3 weeks (Swigart *et* Al., 1999); the reduction in joint head movement and friction leads to decreased pain and stiffening of the capsuloligamentous structures with reduced subluxation (Pomerance, 1995). This can be associated to chondroprotectors that achieve their maximum therapeutic effectiveness if the joint is immobilised; in fact, since there is no wear effect, the cartilage can regenerate (Towheed *et* Al., 2005).
The synergy of these two measures can ensure a good outcome.
Conservative treatment requires early diagnosis of the degenerative process (Towheed *et* Al., 2005) because it is more effective, especially in the early stages (1st and 2nd).
The goals of conservative treatment are:

- to reduce pain at the base of the thumb, both at rest and while performing routine daily activities;
- avoid TM joint overload by teaching the patient correct prehension modes and favouring gripping with terminal opposition (FIG. 3);
- provide TM joint stability with the immobiliser while simultaneously reducing radial metacarpal subluxation.

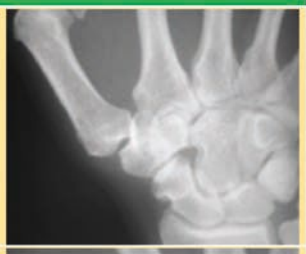
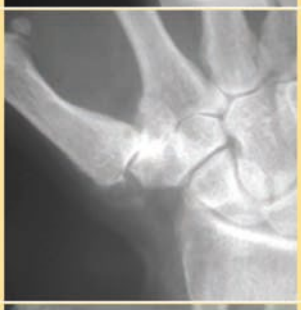
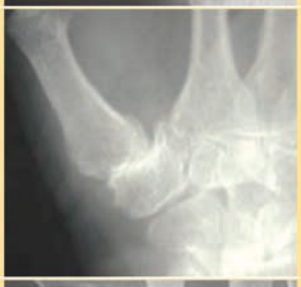
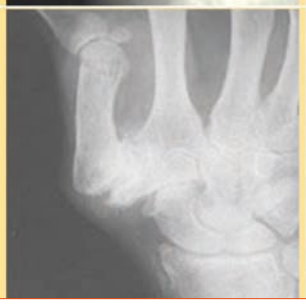
– Corticosteroid injections act on pain; they are sometimes used when the pain is unbearable (Pellegrini, 1992; Swigart *et* Al., 1999). These injections, if repeated, are less and less effective and irreparably damage the articular cartilage (Burton *and* Pellegrini, 1986; Swigart *et* Al., 1999).

RHIZOARTHROSIS – TREATMENT WITH MD-SMALL JOINTS

If initial conservative treatment does not produce positive effects, endo- and periarticular injection therapy may be considered before resorting to definitive surgical treatment.
The anatomical structures forming the containment/stabilisation system are: the joint capsule, ligaments and fibrous membranes that provide "direct seal", while the tendons and muscles provide "indirect seal".

- The extra-articular structures are made of Type I collagen (COL1): the quantity and quality of this triple helix macroprotein ensure optimal and repeated physiological articular movement over time.

– With ageing, all the COL1 forming the peri- and intra-articular structures undergoes important qualitative/quantitative changes (discrepancy between neofibrillogenesis and fibrillolysis) with progressive depletion and/or damage of adequate COL1, so that the articular bone heads are more mobile along the

STAGE	X-RAY	CLINICAL SIGNS	ACCESSORY ELEMENTS
1		TM joint subluxation is less than 1/3 Subchondral sclerosis begins to develop along with initial diastasis of the articular heads Instability, initial pain	Subluxation of the base of the first metacarpal under stress in abduction or in semeiologic manoeuvres (dynamic) Possible hypoplasia of the trapezium on X-ray examination
2		Subluxation is greater than 1/3 The capsule begins to be quite loose The first osteophytes of more than 2 mm in size appear Frequent pain on exertion Modest functional limitation	Instability Joint space narrowing, modest arthritic signs Osteophytes
3		The joint space is greatly reduced and sclerosis is increasingly evident Constant and stronger pain, stiffness Functional limitation Crepitus on palpation of the base of the thumb associated with more or less obvious deformities	Continuous pain Severe limitation
4		Severe anatomical and radiographic alterations resulting in functional impotence TM joint rigidity Severe functional limitation	Decreased pain related to stiffness, sometimes absent

TAB. 2

Eaton-Litter classification modified by Brunelli.

physiological excursion planes and are no longer firmly held in place. Hypermobility of the joints leads to abnormal support with consequent inflammation, first, and then degeneration of articular cartilage, the prime mover towards arthritic degeneration (Milani, 2019).

• In short: according to physiological biomechanics, the incorrect positioning of two contiguous joint heads forming a joint causes wear, pain and difficult movement. The tenocyte, a very specialised fibrocyte, is the cell that produces COL1; it also synthesizes matrix **Proteoglycans (PGs)** and Metalloproteinases (MMPs) (Bernardini, 2018) involved in the degradation of old or damaged fibres by the inflammatory/traumatic process.

– The primary event in the arthritic process is to be found in the reduction and alteration of PGs: mechanical, chemical or cytological factors lead to the depolymerization of the chains of Glycosaminoglycan (GAGs), which, by breaking, cause the decreased resistance of the articular cartilage matrix.

– As a consequence of these events, the collagen fibres that are not adequately protected by the matrix also break into fragments; the cartilage thus loses its elasticity and wears out (Scagliati, 1995).

All extra- and intra-articular structures are fundamentally made of collagen, hence the usefulness of deriving therapeutic means that allow the physician to counter osteo-arthro-myofascial pathologies (Stone *et* Al., 1997; Milani, 2010; 2013; 2019).

▶ MD-Small Joints

Guna Collagen Medical Devices are injectable products (p.a., i.a., s.c., i.d., i.m.) consisting of collagen of porcine origin (porcine collagen is the most similar and akin to human collagen) and one or more ancillary substances characterised by a particular tropism for the various and specific anatomical districts to which the collagen can be conveyed with greater effectiveness and specificity (Milani, 2013; 2019).

Guna Collagen Medical Devices provide collagen in the form of tropocollagen, which is assembled to collagen in the presence of the enzyme lysine hydroxylase, at the level of the extracellular matrix (ECM); it therefore acts as a bioscaffold (Milani, 2010).

– The deposition of neosynthesized collagen fibres in the damaged area secondary to loco-regional injection of the MDs produces a significant improvement in the mechanical qualities of the injured tissue; in particular, the anisotropic characteristics are restored.

Anisotropy is a mechanical property of collagen: it describes the ability of its fibres to propagate tensile forces in a single preferential direction.

Due to the orientation of the collagen fibres in a single direction, proper mechanical support is achieved for optimal function (Milani, 2019).

– Guna Collagen Medical Devices improve the histological make-up of anatomical structures in which collagen is present and provide a mechanical support (bioscaffold) with a clear positive effect on the stabilisation of joint hypermobility, movement, pain, and quality of life; they have a restructuring, repairing and remodelling action and contribute to the containment of the physiological deterioration of joints and tissues to counterbalance the effects due to various

causes including ageing, postural defects, chronic concomitant diseases, traumas and injuries (Various Authors, 2011).

– In addition to collagen, **MD-Small Joints** contains *Viola odorata*, an ancillary substance that is indicated – inter alia – in rheumatic pain of the wrist joints radiating to the forearm (Various Authors, 2011).

MATERIALS AND METHODS

Twenty-two patients (3 M; 19 F) suffering from RA were included in this clinical trial.
In 4 patients the pathology was bilateral; in this study, the most compromised side was considered.

– All patients were tested with the **DASH** questionnaire to assess loss of function (values 0 to 100; 100 = maximum disability), the VAS Scale (values 1 to 10), and the **Grind test** to assess capsuloligamentous laxity (G0 = no joint laxity; G1 = scarce laxity; G2 = lax; G3 = very lax).

– The mean age of the patients was 61.2 years (min. 44, max. 78): 12 patients in stage 2 and 10 patients in stage 3; 10 patients had maximum laxity G3, 5 had minor laxity G2, 7 had minimal laxity G1, and none G0.
All patients at the time of inclusion had decreased strength and functional limitation of the first ray. As regards laterality, 7 patients (33%) had RA in the nondominant hand.
This high percentage is explained by the fact that the nondominant hand, in many activities, must maintain a static grip for a long time thus resulting in severe overuse phenomena.
For example, suffice it to think of a patient who holds a sheet of metal or other material with strength in order to work it with the dominant hand.
In elderly patients, however, it is often due to muscular hypotonia of the nondominant hand: this explains how important the tendons and muscles, namely the structures involved in "indirect gripping", are.

	Age (years)	DASH	VAS	Grind test
Mean	**61.22**	**50.72**	**7.14**	**2.25**
Minimum	44	16.5	5	1
Maximum	78	75.25	9	3

TAB. 3
Patient assessment at inclusion.

The mean **DASH** was **50.72** at the first visit with a minimum of 16.5 and a maximum of 75.25; the mean **VAS** was **7.14** at the first visit with a minimum of 5 and a maximum of 9; the mean Grind test was **2.25** with a minimum of 1 and a maximum of 3 (TAB. 3).

– After one week of home therapy (low dose medicaments), patients began outpatient treatment with **MD-Small Joints** (1 vial = 2 mL), to which 0.5 mL of lidocaine 2% was added. Intra-articular injection was performed with 0.7-0.8 mL (i.e., the average capacity of the TM joint); the remaining amount (approx. 1.0 mL) in the periarticular site (FIG. 7).
In addition, approx. 0.5 mL were used for a second periarticular injection at the level of the 1st commissure in order to attack the deep part of the capsule between the first and second metacarpals, but above all to inject the intermetacarpal ligament in order to stabilise it and reduce the conflict due to its laxity (FIG. 2,8).
Injections were administered 3 or 4 times a week; the 4th or 5th were administered after 2 weeks.
In 8 patients, further treatment was required after another 2 weeks.

– Some patients experienced an exacerbation of symptoms after the 1st or 2nd administration; in 6 cases, therapy had to be temporarily suspended, but at the follow-up of the following week the worsening had completely regressed; in some cases, there was a clinical and

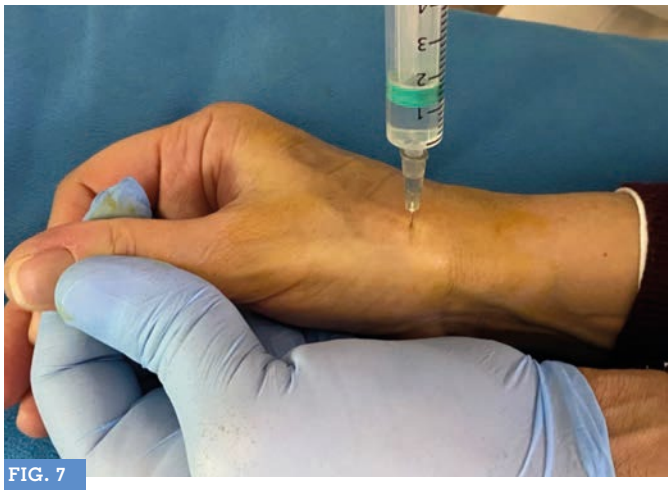


FIG. 7
Intra- and periarticular infiltration.


FIG. 8
Infiltration of the 1st commissure.

Weeks	0	1	Δ Week 1	2	3	4	5	6	7	8	9	10	Δ	%
DASH	50.72	39.87	21.39%	29.71	24.54	18.00	18.25	20.18	16.50	18.75	14.75	8.13	42.59	83.97
VAS	7.14	6.60	7.56%	5.06	4.44	3.85	3.60	4.20	4.29	2.80	3.33	3	4.14	57.98
Grind test	2.25	2	11.11%	1.367	1.233	0.923	1.111	0.714	0.8	0.667	0.5	0.5	1.75	77.7

TAB. 4

DASH, VAS, and Grind test values before and after treatment (10 follow-ups).

psychological improvement, so that treatment was resumed in all patients (no drop-out).

No patients required NSAIDs.
Only one patient, who was very anxious, was given anaesthesia in the superficial branch of the radial nerve, prior to the procedure described, to eliminate the pain of the i.a. and p.a. injections.
The addition of a minimal amount of lidocaine 2% resulted in significant patient compliance.
Case series confirmed the higher incidence of RA in the female gender.

RESULTS

This study enrolled: **1)** patients who had pain at stages that were too early to consider surgical treatment; **2)** non-responders to previous therapies, such as steroid therapy; **3)** patients who, despite having a surgical indication, refused surger.
In any case, it is believed that the earlier this treatment is initiated, the better the chance of an effective clinical response.

– Analysis of the DASH, VAS, and Grind test values showed that after the first week of treatment with low dose medicaments, there was a **21.39%** improvement in the DASH value, **7.56%** improvement in the VAS value, and **11.11%** improvement in the Grind test value. These data demonstrate the effectiveness of this preliminary therapeutic time (TAB. 4).

• Evaluating then the difference from the beginning to the end of the therapy, it can be seen that the DASH value decreased by **42.59 points** (**83.97%** increase in function); pain, according to the VAS Scale, decreased from **7.14** to **3** with a delta of **4.14** and consequently a **57.98%** decrease, while laxity went from a Grind test of **2.25** to a Grind test of **0.5** (**1.75**- point improvement), i.e., an increase in capsuloligamentous tension of **77.7%** (TAB. 4).

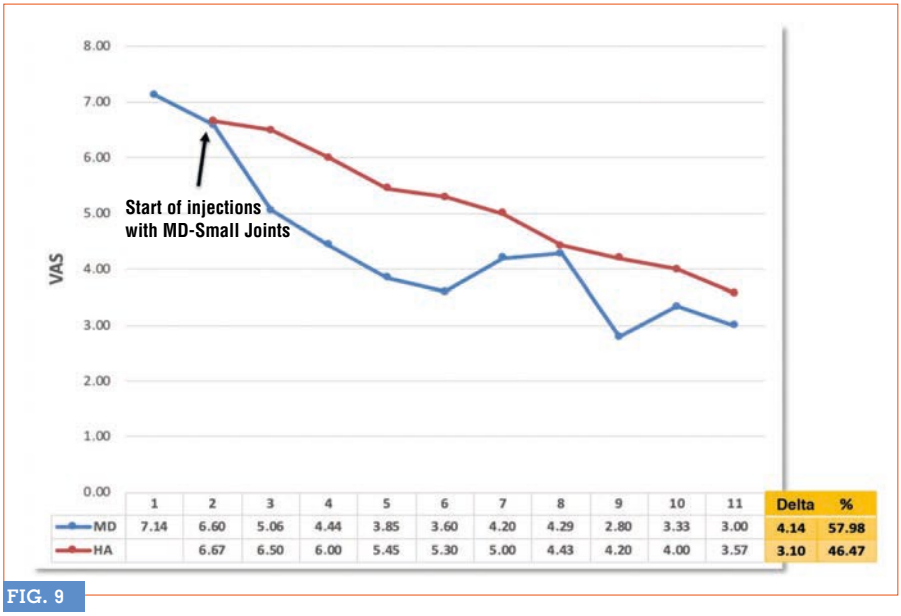


FIG. 9

VAS comparison: MD-Small Joints *vs* Hyaluronic Acid.

MD-SMALL-JOINTS VS HYALURONIC ACID

Intra-articular injection treatment with hyaluronic acid **(HA)** has been and still is another cornerstone of RA therapy, used by physiatrists and hand surgeons (Strass *et* Al., 2009; Volpi *et* Al., 2009; Iannitti *et* Al., 2011).
– Comparing the values obtained with MD-Small Joints with those obtained in a similar study carried out by the author (Brunato, 2012) on 51 patients treated with 3 intra-articular injections of HA administered 3 weeks apart, the following differences were recorded: at 10 weeks the VAS dropped from 6.67 to 3.57.
The difference was **3.10** points versus **4.14** points for MD-Small Joints, demonstrating a greater efficacy in pain control of **1.4 points** for MD-Small Joints (**+ 11,51%**) vs HA.
What is most striking is the early and marked decrease in pain from the first weeks of treatment with MD-Small Joints compared to HA (FIG. 9).
– Comparing the DASH values, the reduction was 42.59 points with MD-Small Joints compared to 27.51 points with HA, an improvement in hand function of **+ 25.7%**.
With MD-Small Joints, daily work activity, as verified with the DASH question-

naire, was maintained with significantly less pain (FIG. 10).

Converting all the values measured by DASH, VAS, and Grind test **to a scale of 10** shows that the improvement in DASH and VAS values is directly proportional to the decrease in Grind test, i.e., the reduction in joint laxity.
The recovery of joint tension is the result of the direct effect of injections with MD-Small Joints on the capsuloligamentous structures and in particular on the intermetacarpal ligament.

This is the clinical observational demonstration that local injection of MD-Small Joints restores the anisotropy of collagen and produces a significant and immediate improvement in the mechanical qualities of the damaged tissue, whence the clinical improvement of RA (FIG. 11).

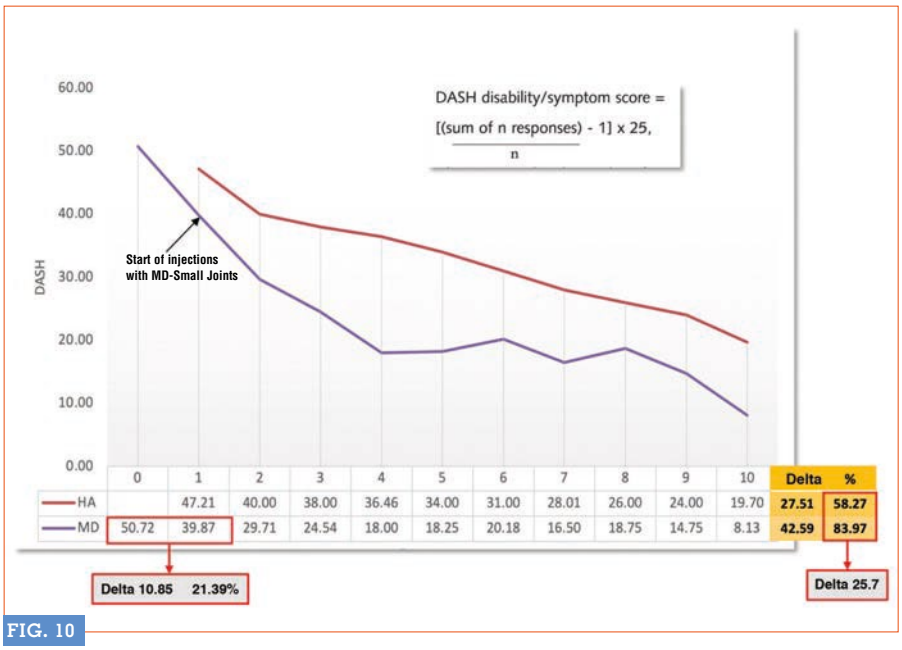


FIG. 10

DASH comparison: MD-Small Joints *vs* Hyaluronic Acid.

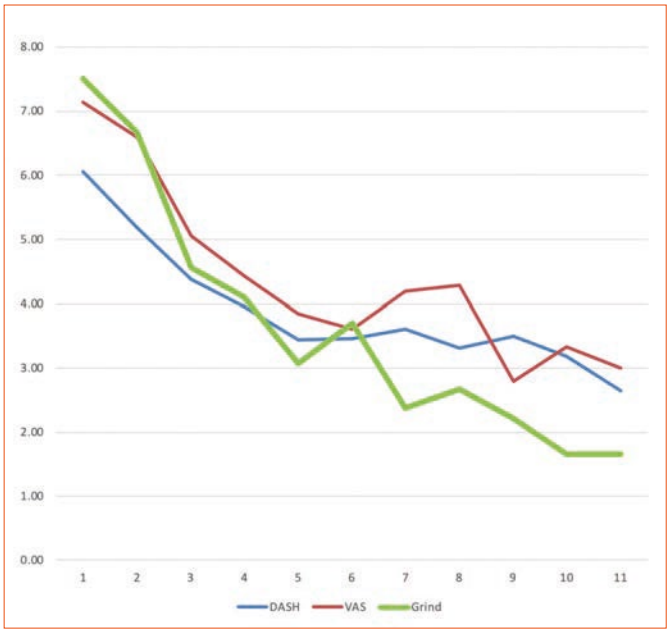


FIG. 11

Comparison of DASH and VAS values as a function of Grind test values.

DISCUSSION

Injection treatment of RA with Collagen Medical Device Small Joints significantly improved patients' symptoms in very few weeks; most importantly, pain clearly decreased, from the outset, as a result of the rapid reduction in joint laxity, proving to be more effective than HA therapy.

Most authors (Dias *et* Al., 2006) consider treating RA with immobilisation and taking NSAIDs for 2-3 months; if symptoms do not regress, surgery should be considered.
Corticosteroid injections act on pain and may be indicated when conservative therapy has not been effective (Pellegrini, 1992; Swigart *et* Al., 1999), but repeated injections have been found to have decreasing efficacy, in addition to irreparably damaging the capsule and articular cartilage (Burton *and* Pellegrini, 1986; Swigart *et* Al., 1999).
HA treatment has been shown to be less effective.

▶ MD-Small Joints has proven to be effective in delaying surgery, providing patients with rapid clinical improvement and an expectation of slowing down the pathology; all this in the absence of side effects and with excellent tolerability. ■

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CLINICAL

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THE TREATMENT OF RHIZOARTHROSIS WITH COLLAGEN MEDICAL DEVICE SMALL JOINTS

SUMMARY

Rhizoarthrosis is a very widespread disease; it affects 20% of the adult population and represents about 10% of all osteoarthritic locations; it is more frequent in females than in males (4:1 ratio). The initial symptom is TM pain followed by difficulty in performing daily activities such as turning a key or opening a bottle. The treatment is initially conservative with the application of immobilization braces and the simultaneous use of chondroprotectors. If this treatment is not effective, before undertaking the definitive surgical treatment, infiltrative therapy with Collagen may be considered. Collagen MDs improve the mechanical qualities of the joint capsule by restoring the anisotropic characteristics of the tissue with an evident positive effect on the "joint hypermobility stabilisation", movement, pain and quality of life.

– The purpose of this trial is to evaluate the efficacy of the endo- and peri-articular injection of MD-Small Joints in patients suffering from rhizoarthrosis before undergoing definitive surgical therapy.

In this clinical study, 22 patients (3 M; 19 F) were included and assessed for 10 weeks with the DASH, VAS scales and Grind Test.

The treatment was well tolerated, and no side effects were observed. The improvement obtained was approximately 60-80% of all rating scales. This trial shows that clinical improvement is directly proportional to the reduction in joint laxity and is therefore a function of the effectiveness of MD-Small Joints on joint collagen.

KEY WORDS **RHIZOARTHOSIS, COLLAGEN MEDICAL DEVICE, MD-SMALL JOINTS, HAND PAIN, DASH, VAS, GRIND TEST, COLLAGEN**

RHIZOARTHROSIS

Rhizoarthrosis (RA) is a type of arthritis that affects the **trapeziometacarpal (TM) joint**. The etymology of the term 'rhizoarthrosis' is Greek: *rizos* means "root"; this joint, in fact, is located at the root of the thumb.

– RA is a widespread condition; it affects **20%** of the adult population (Barra *et* Al., 2003) and represents approximately **10%** of all osteoarthritic localisations in the human body (Sollazzo *et* Al., 2006). RA is more frequent in females than males (4:1 ratio) and generally occurs between the fifth and sixth decades of life.

In women, it frequently begins at menopause, while in men it is more related to overuse phenomena (Bonola *et* Al., 1981).

The TM joint plays a key role in normal thumb function: all gripping actions overload the TM joint because the axis of the thumb exerts force and acts as a fulcrum on this joint.

This force transmits a radial stress at the base of the metacarpal, which, over time, causes a reduction in the tension of the capsuloligamentous system (Bernardini, 2018), resulting in joint hyperlaxity and subluxation of the first metacarpal.

• The preternatural movement of the bone heads alters the joint surface; there is a progressive thinning of the cartilage and subsequent onset of pain and arthritis. Symptomatology is bilateral in 50% of cases.

FUNCTIONAL ANATOMY

The TM joint can be considered the most complex joint of the human body as it allows the thumb to perform volo-volar pincer grips with the long fingers; in other words, it allows the hand to perform its most distinctive function: opposition, that is, prehension (Caroli, 1996).

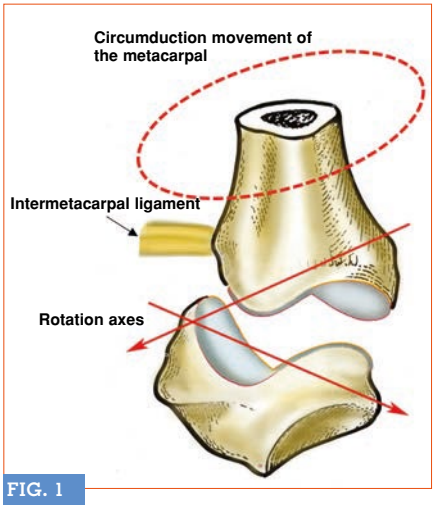


FIG. 1

Trapeziometacarpal joint.

Kapandji (1971) defined the TM joint as a reciprocal interlocking or saddle-shaped joint and compared it to a rider in the saddle with perfectly matching torus-shaped contact surfaces (Bonola *et* Al., 1981).

The movements take place on two perpendicular axes and their combination allows for a true circumduction, conditioned by the intermetacarpal ligament, which acts as a pivot (FIG. 1,2).

The structures that support and stabilize this joint are the capsule, the extracapsular ligaments and the intrinsic and extrinsic muscles.

The capsuloligamentous structures of the TM joint are extremely important, both in providing stability and in guiding the complex movements of the thumb.

The joint capsule is very lax and fits along the contour of the articular surfaces of the trapezium and the base of the metacarpal. This laxity is determined by the fact that the first metacarpal must allow for ample movement and rotation of the metacarpal along its own longitudinal axis (Caroli, 1996).

▶ Ligaments of the capsule

The ligamentous system is equally important because, in addition to ensuring the stability of the TM joint, its maximum tension allows stopping the various movements of the first metacarpal bone, assisted by the fascial and muscular structures in this function.

It should also be noted that the TM ligaments, through their insertion, help to guide the movements of the thumb and mainly those of axial rotation.

A number of thickenings depart from the joint capsule, giving rise to the following ligaments:

- the dorsoradial ligament (DRL) or Arnold's external trapeziometacarpal ligament stops abduction and favours rotation in pronation of the metacarpal joint;
- the dorsoulnar ligament (DUL) or Arnold's internal trapeziometacarpal ligament, which is very thick and wide, stops the retroposition movement and favours rotation in supination of the metacarpal;
- the anterior oblique ligament (AOL). Some authors describe two portions of this ligament: a superficial one and a deep one (beak ligament), which is particularly important in stabilising the TM joint in the degrees of maximum abduction and retroposition movement of the thumb;
- the fibrous, thick and short intermetacarpal ligament (IML): it stretches between the base of the first and second metacarpals; this ligament stops the abduction movement of the first metacarpal.

  The IML is crucial because its loosening causes external subluxation of the base of the first metacarpal, which, as explained below, is one of the most important causes of **joint instability** (Caroli, 1996) (FIG. 2).

- **DRL = Dorsoradial Ligament**
- **DUL = Dorsoulnar Ligament**
- **AOL = Anterior Oblique Ligament *(beak ligament)***
- **IML = Intermetacarpal Ligament**

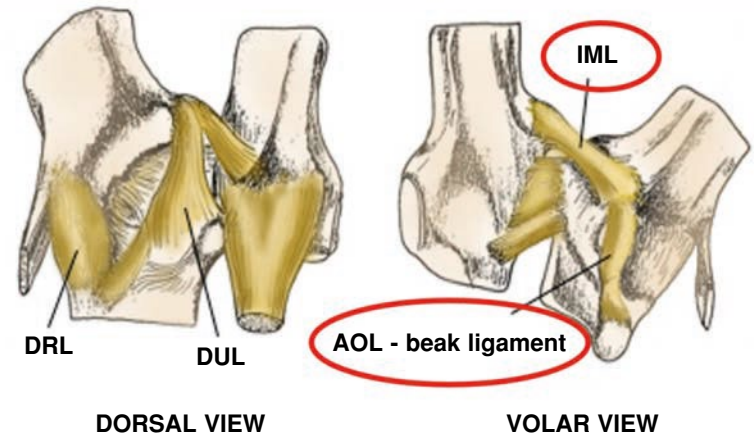


FIG. 2

Ligaments of the trapeziometacarpal joint.

▶ Motor muscles of the thumb

As indicated by Kapandji (1971), the TM joint works in compression as a joint. The intrinsic thenar muscles allow the first metacarpal to orient in all directions of space, as if it were a pile whose orientation can be changed by changing the tension of the cables. According to the author, the muscular components provide support to joint coaptation in all positions, resulting from the synergistic activation of agonist and antagonist muscles (Brunelli *and* Brunelli, 1996).

Mobility is the essential opposition function of the thumb; it is enabled by nine motor muscles:

- Four extrinsic or long muscles located in the forearm. Three are for grip opening movements: The *extensor pollicis longus, extensor pollicis brevis,* and *abductor pollicis longus;* and one for power grip: *flexor pollicis longus.* As a reminder, the extrinsic muscles are the motor muscles for power gripa;

- Intrinsic muscles located in the thenar eminence and first interosseous space; they provide for precision and coordination during different grips and opposition.
  – The external group is composed of three muscles (*opponens pollicis*, *abductor pollicis brevis*, and *flexor pollicis brevis*) that have a synergistic function of thumb opposition.
  – The internal group consists of the adductor and first palmar interosseous muscles.
  These are crucial for gripping/holding objects, because they also perform their action on the **MP (metacarpophalangeal)** and **IP (interphalangeal) joints** (flexion of the former and extension of the latter), making the opposition grip with the index finger more effective.

Opposition is not a fixed movement: indeed, there is a range of oppositions that execute a great variety of grips and actions according to the number of fingers involved and their mode of association (Kapandji, 1971).

- Bi-digital grips give the classic pincer grips between the thumb and index finger; there are 3 types: terminal, subterminal, and subterminolateral.

– The terminal opposition grip is the finest and most precise because it makes it possible to firmly grasp a small object or pick up a very thin object.
The thumb opposes the nail surface of the index finger with the fingertip.
In this grip, as the metacarpal wedges into the trapezius, it protects the joint capsule from any tensional forces and avoids degenerative effects on the joint (FIG. 3).

– The subterminal grip is the most recurrent and instinctive one: the thumb and the index finger oppose each other with the palmar face of the fingertip and this way can grip objects of different calibre, even thin ones, such as a sheet of paper or a pencil.
In this grip, a significant tensive force is created radially at the base of the metacarpal that stretches the joint capsule and the intermetacarpal ligament, making them increasingly lax over time.

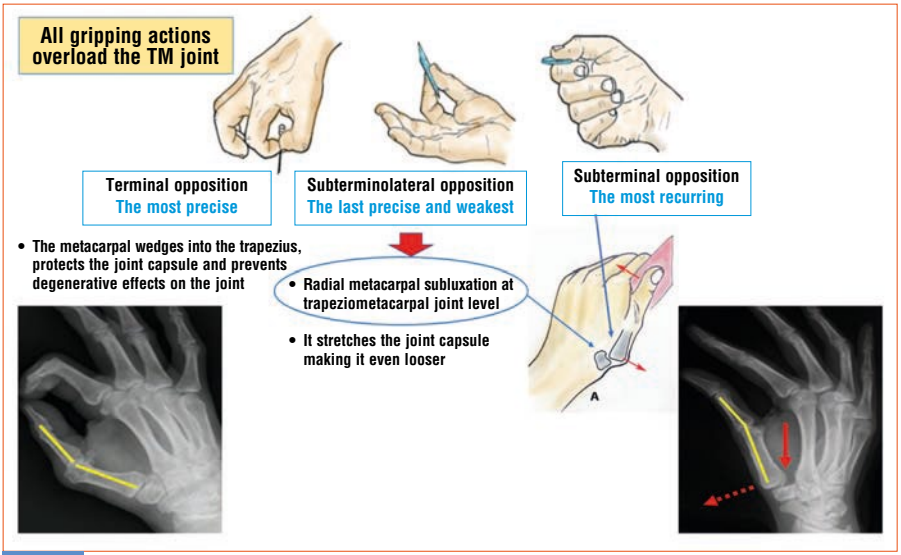


FIG. 3

Effects of grip on the trapeziometacarpal joint.

This laxity produces joint instability, the cause of radial subluxation of the metacarpal and joint degenerative processes.

– The subterminolateral grip is the least fine and weakest compared to the previous ones.
The palmar aspect of the pulp of the thumb rests on the external aspect of the first phalanx of the index finger, creating, in this case too, great radial tension at the base of the metacarpal resulting in the tendency of the TM joint to develop subluxation (Kapandji, 1971).

- The cause of RA always lies in TM joint **instability**.

It can be primary or secondary (TAB. 1).

In ligamentous hyperlaxity, instability is due to an excessive range of motion.
In this case, the palmar ligament (beak ligament) is of great importance, as it limits the hyperextension of the metacarpal and, above all, the intermetacarpal ligament between the base of the first and second metacarpals, which counters the subluxation of the first metacarpal radially, without limiting other movements (FIG. 2).
Laxity and/or degeneration of this ligament produce abnormal TM joint movements, with incongruity of the articular surfaces rapidly triggering degeneration.

– Another known cause that Brunelli (2007) considers to be the most frequent is instability due to the absence of ab-

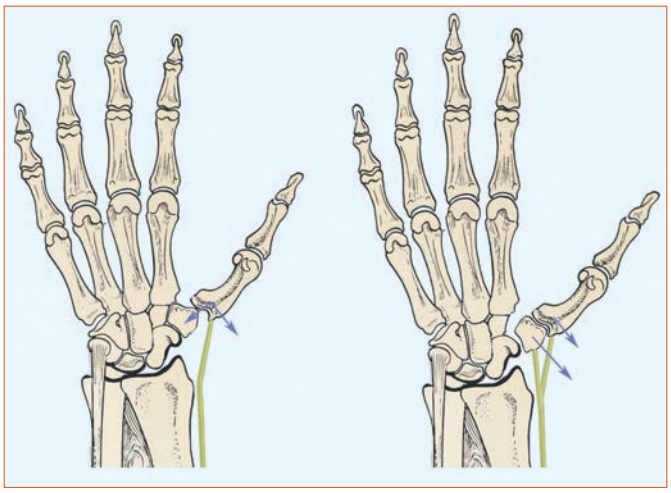
PRIMARY INSTABILITY	SECONDARY INSTABILITY
Hypoplasia of the trapezium, abnormal obliquity of its saddle	Traumatic capsular ligament lesion
Congenital capsular ligament laxity	Outcome of fracture of the trapezium or the base of the first metacarpal
Muscle imbalance due to the absence of insertion of one of the APL tendons on the trapezium	Operational stress due to repetitive work with strong thumb adduction
Muscle hypotonia of the non-dominant hand in elderly people	

TAB. 1

Causes of the trapeziometacarpal joint instability.

FIG. 4

Instability due to the absence of intersection of *abductor pollicis longus* in the trapezium. – Tensive forces.



ductor pollicis longus **(APL)** insertion on the trapezium. In cases where the APL has distal double insertion on the trapezium and on the base of the first metacarpal, with each contraction of the APL the entire thumb-metacarpal-trapezium column shifts in abduction, maintaining normal trapeziometacarpal joint relationships.
Conversely, if there is no insertion on the trapezium, all abductor force is exerted on the base of the first metacarpal, causing significant subluxation tension with a deleterious shear effect on, and cartilage damage, of the TM joint (FIG. 4).
– Repeated stress (overuse) is another frequent cause of TM joint arthritis; the TM joint is subjected to a considerable workload, as it is involved in approximately 50% of all actions of the hand.

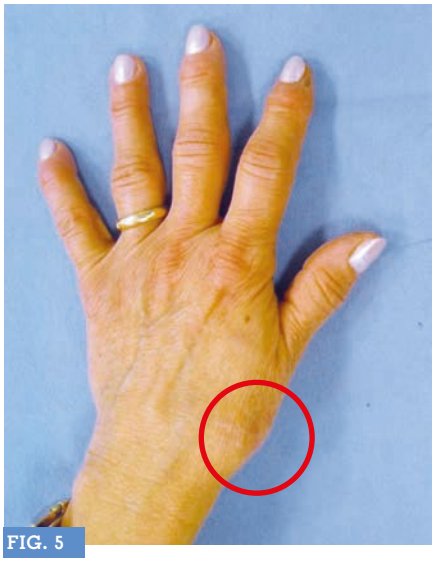


FIG. 5

Subluxation of the first metacarpus.

It is possible to distinguish some activities and habitual gestures that favour the deterioration of the articular surfaces: the repeated prehension of small objects exerts radial stress on the TM joint that does not allow the base of the metacarpal to stay in contact with the articular surface of the trapezium (FIG. 3).
The luxation force transmitted on the metacarpal can be multiplied up to 12-120 times (Cooney *and* Chao, 1977).

SYMPTOMATOLOGY

TM joint instability is often asymptomatic; over time, pain develops, leading the patient to consult a physician.
– The most frequent clinical picture is initially represented by an annoying pain localised at the base of the thumb that appears when active movements in radial abduction such as grips or pincer movements are performed, and/or passive movements in rotation-opposition such as turning a key, unscrewing a cap, turning a handle, writing with a thin pen or even just buttoning a shirt (Dias *et* Al., 2006).
The patient complains of decreased hand strength and mobility.
Later, the pain appears even at rest, at night, and may radiate to the wrist and forearm. In more advanced stages, pain is spontaneous and is associated with bone crepitus due to joint laxity.

– The patient does not "use" the thumb well to avoid pain: over time, this causes muscle weakness in the stabilisation structures of the TM joint; the metacarpal loses the ability to slide on the trapezium along the adduction-abduction axis, in addition to which there is a radial shift of the base of the metacarpal.

The loss of congruence between the bone heads affects the mechanical stability of the joint: it results in dislocation, consequently decreasing movement amplitude (Pomerance, 1995).
During abduction movements, the joint capsule is stretched.
Some capsular fibres are weakened, leading to the dorsal subluxation of the base of the metacarpal; therefore, when the *adductor pollicis* and *flexor pollicis brevis* muscles contract, they pull the distal part of the metacarpal toward the palm.
The result is a "tilt" of the articular surface at the base of the metacarpal on the saddle of the trapezium.

- This tilt, though imperceptible, is the cause of the pain.

That is why, in cases of RA, holding and turning a key, lifting a cup or writing are actions that cause pain: in fact, these actions, although with movements that require little articulation, stress the TM joint and its means of containment (Dias *et* Al., 2006).

– The prevalent clinical signs are:
- deformation and swelling at the base of the first metacarpal (FIG. 5), caused by a combination of dislocation, joint inflammation, and osteophyte formations;
- 1st ray in adduction, more common in advanced stages;
- pain on palpation;
- positive axial compression test or Grind test: the axial load on the trapezium, together with the rotation of the metacarpal, trigger pain at the base of the thumb;
- TM joint dislocation, with or without rotation, which causes stretching of the capsule, which, if inflamed, is painful.

As the disease progresses, TM joint subluxation produces a radial deviation of the MP of the thumb due to the contracture in adduction of the first metacarpal, which is followed by a flexion of the IP, generating a picture of "Z-thumb". This is an expression of one of the most compromised pictures of RA in which, in addition to the TM joint, the MP in hyperextension and IP in flexion are involved.

RADIOGRAPHIC PICTURE – THE EATON-LITTER CLASSIFICATION

RA can be diagnosed through a careful physical examination.
X-rays of the thumb in 3 planes and the particular stress view of the basal joint are necessary to confirm the diagnosis.
The view for the basal joint under stress, when performed correctly, provides an excellent image for assessing the degree of TM joint subluxation.
In this 30° oblique view, the patient is asked to press the tips of the thumbs against each other while the X-ray is being performed (FIG. 6).

X-rays should always be interpreted in relation to the patient's clinical situation. Often, patients with very compromised radiographic pictures report very little or no pain; others with negative or insignificant X-rays may present severe functional deficits with significant impact on daily and/or work activities. There is no indication for MRI and/or ultrasound; only CT may be useful as an additional preoperative investigation.

– Eaton and Glickel (Glickel, 2001) described a method for classifying pathological changes in RA based on the appearance in standard radiographic views and those under stress.
This method has also proven to be useful in medical planning and, if needed, surgery.
– At present, the most widely used classification is the Eaton-Littler classification modified by Brunelli (Barra *et* Al., 2003) which includes both the radiographic picture and clinical picture (TAB. 2).

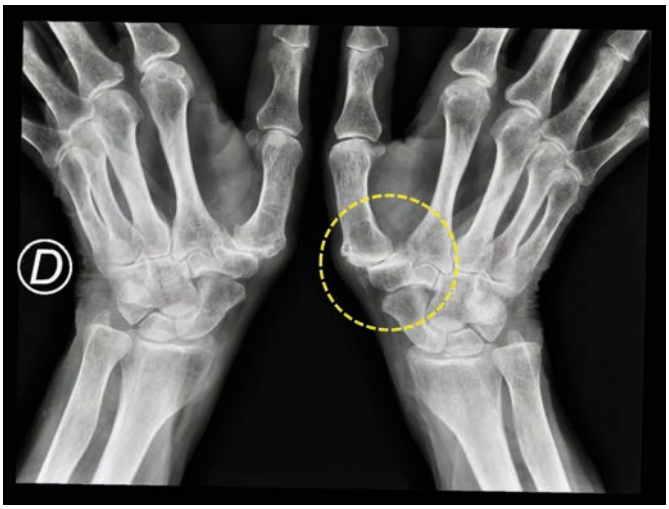


FIG. 6
Stress view.

RHIZOARTHROSIS – CONSERVATIVE TREATMENT

Treatment in all stages of the disease is initially conservative.
– The first step is the application of an immobiliser at night and possibly during the day for 2-3 weeks (Swigart *et* Al., 1999); the reduction in joint head movement and friction leads to decreased pain and stiffening of the capsuloligamentous structures with reduced subluxation (Pomerance, 1995). This can be associated to chondroprotectors that achieve their maximum therapeutic effectiveness if the joint is immobilised; in fact, since there is no wear effect, the cartilage can regenerate (Towheed *et* Al., 2005).
The synergy of these two measures can ensure a good outcome.
Conservative treatment requires early diagnosis of the degenerative process (Towheed *et* Al., 2005) because it is more effective, especially in the early stages (1st and 2nd).
The goals of conservative treatment are:

- to reduce pain at the base of the thumb, both at rest and while performing routine daily activities;
- avoid TM joint overload by teaching the patient correct prehension modes and favouring gripping with terminal opposition (FIG. 3);
- provide TM joint stability with the immobiliser while simultaneously reducing radial metacarpal subluxation.

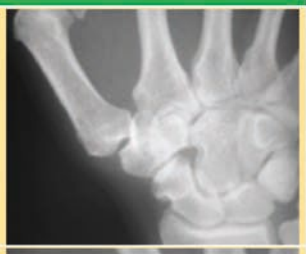
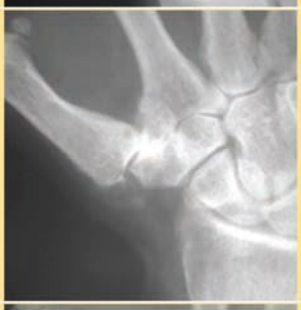
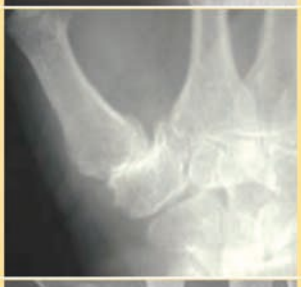
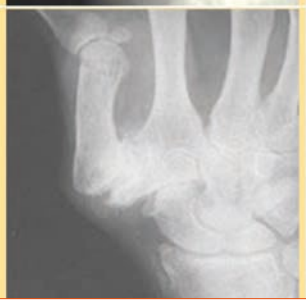
– Corticosteroid injections act on pain; they are sometimes used when the pain is unbearable (Pellegrini, 1992; Swigart *et* Al., 1999). These injections, if repeated, are less and less effective and irreparably damage the articular cartilage (Burton *and* Pellegrini, 1986; Swigart *et* Al., 1999).

RHIZOARTHROSIS – TREATMENT WITH MD-SMALL JOINTS

If initial conservative treatment does not produce positive effects, endo- and periarticular injection therapy may be considered before resorting to definitive surgical treatment.
The anatomical structures forming the containment/stabilisation system are: the joint capsule, ligaments and fibrous membranes that provide "direct seal", while the tendons and muscles provide "indirect seal".

- The extra-articular structures are made of Type I collagen (COL1): the quantity and quality of this triple helix macroprotein ensure optimal and repeated physiological articular movement over time.

– With ageing, all the COL1 forming the peri- and intra-articular structures undergoes important qualitative/quantitative changes (discrepancy between neofibrillogenesis and fibrillolysis) with progressive depletion and/or damage of adequate COL1, so that the articular bone heads are more mobile along the

STAGE	X-RAY	CLINICAL SIGNS	ACCESSORY ELEMENTS
1		TM joint subluxation is less than 1/3 Subchondral sclerosis begins to develop along with initial diastasis of the articular heads Instability, initial pain	Subluxation of the base of the first metacarpal under stress in abduction or in semeiologic manoeuvres (dynamic) Possible hypoplasia of the trapezium on X-ray examination
2		Subluxation is greater than 1/3 The capsule begins to be quite loose The first osteophytes of more than 2 mm in size appear Frequent pain on exertion Modest functional limitation	Instability Joint space narrowing, modest arthritic signs Osteophytes
3		The joint space is greatly reduced and sclerosis is increasingly evident Constant and stronger pain, stiffness Functional limitation Crepitus on palpation of the base of the thumb associated with more or less obvious deformities	Continuous pain Severe limitation
4		Severe anatomical and radiographic alterations resulting in functional impotence TM joint rigidity Severe functional limitation	Decreased pain related to stiffness, sometimes absent

TAB. 2

Eaton-Litter classification modified by Brunelli.

physiological excursion planes and are no longer firmly held in place. Hypermobility of the joints leads to abnormal support with consequent inflammation, first, and then degeneration of articular cartilage, the prime mover towards arthritic degeneration (Milani, 2019).

• In short: according to physiological biomechanics, the incorrect positioning of two contiguous joint heads forming a joint causes wear, pain and difficult movement. The tenocyte, a very specialised fibrocyte, is the cell that produces COL1; it also synthesizes matrix **Proteoglycans (PGs)** and Metalloproteinases (MMPs) (Bernardini, 2018) involved in the degradation of old or damaged fibres by the inflammatory/traumatic process.

– The primary event in the arthritic process is to be found in the reduction and alteration of PGs: mechanical, chemical or cytological factors lead to the depolymerization of the chains of Glycosaminoglycan (GAGs), which, by breaking, cause the decreased resistance of the articular cartilage matrix.

– As a consequence of these events, the collagen fibres that are not adequately protected by the matrix also break into fragments; the cartilage thus loses its elasticity and wears out (Scagliati, 1995).

All extra- and intra-articular structures are fundamentally made of collagen, hence the usefulness of deriving therapeutic means that allow the physician to counter osteo-arthro-myofascial pathologies (Stone *et* Al., 1997; Milani, 2010; 2013; 2019).

▶ MD-Small Joints

Guna Collagen Medical Devices are injectable products (p.a., i.a., s.c., i.d., i.m.) consisting of collagen of porcine origin (porcine collagen is the most similar and akin to human collagen) and one or more ancillary substances characterised by a particular tropism for the various and specific anatomical districts to which the collagen can be conveyed with greater effectiveness and specificity (Milani, 2013; 2019).

Guna Collagen Medical Devices provide collagen in the form of tropocollagen, which is assembled to collagen in the presence of the enzyme lysine hydroxylase, at the level of the extracellular matrix (ECM); it therefore acts as a bioscaffold (Milani, 2010).

– The deposition of neosynthesized collagen fibres in the damaged area secondary to loco-regional injection of the MDs produces a significant improvement in the mechanical qualities of the injured tissue; in particular, the anisotropic characteristics are restored.

Anisotropy is a mechanical property of collagen: it describes the ability of its fibres to propagate tensile forces in a single preferential direction.

Due to the orientation of the collagen fibres in a single direction, proper mechanical support is achieved for optimal function (Milani, 2019).

– Guna Collagen Medical Devices improve the histological make-up of anatomical structures in which collagen is present and provide a mechanical support (bioscaffold) with a clear positive effect on the stabilisation of joint hypermobility, movement, pain, and quality of life; they have a restructuring, repairing and remodelling action and contribute to the containment of the physiological deterioration of joints and tissues to counterbalance the effects due to various

causes including ageing, postural defects, chronic concomitant diseases, traumas and injuries (Various Authors, 2011).

– In addition to collagen, **MD-Small Joints** contains *Viola odorata*, an ancillary substance that is indicated – inter alia – in rheumatic pain of the wrist joints radiating to the forearm (Various Authors, 2011).

MATERIALS AND METHODS

Twenty-two patients (3 M; 19 F) suffering from RA were included in this clinical trial.
In 4 patients the pathology was bilateral; in this study, the most compromised side was considered.

– All patients were tested with the **DASH** questionnaire to assess loss of function (values 0 to 100; 100 = maximum disability), the VAS Scale (values 1 to 10), and the **Grind test** to assess capsuloligamentous laxity (G0 = no joint laxity; G1 = scarce laxity; G2 = lax; G3 = very lax).

– The mean age of the patients was 61.2 years (min. 44, max. 78): 12 patients in stage 2 and 10 patients in stage 3; 10 patients had maximum laxity G3, 5 had minor laxity G2, 7 had minimal laxity G1, and none G0.
All patients at the time of inclusion had decreased strength and functional limitation of the first ray. As regards laterality, 7 patients (33%) had RA in the nondominant hand.
This high percentage is explained by the fact that the nondominant hand, in many activities, must maintain a static grip for a long time thus resulting in severe overuse phenomena.
For example, suffice it to think of a patient who holds a sheet of metal or other material with strength in order to work it with the dominant hand.
In elderly patients, however, it is often due to muscular hypotonia of the nondominant hand: this explains how important the tendons and muscles, namely the structures involved in "indirect gripping", are.

	Age (years)	DASH	VAS	Grind test
Mean	**61.22**	**50.72**	**7.14**	**2.25**
Minimum	44	16.5	5	1
Maximum	78	75.25	9	3

TAB. 3
Patient assessment at inclusion.

The mean **DASH** was **50.72** at the first visit with a minimum of 16.5 and a maximum of 75.25; the mean **VAS** was **7.14** at the first visit with a minimum of 5 and a maximum of 9; the mean Grind test was **2.25** with a minimum of 1 and a maximum of 3 (TAB. 3).

– After one week of home therapy (low dose medicaments), patients began outpatient treatment with **MD-Small Joints** (1 vial = 2 mL), to which 0.5 mL of lidocaine 2% was added. Intra-articular injection was performed with 0.7-0.8 mL (i.e., the average capacity of the TM joint); the remaining amount (approx. 1.0 mL) in the periarticular site (FIG. 7).
In addition, approx. 0.5 mL were used for a second periarticular injection at the level of the 1st commissure in order to attack the deep part of the capsule between the first and second metacarpals, but above all to inject the intermetacarpal ligament in order to stabilise it and reduce the conflict due to its laxity (FIG. 2,8).
Injections were administered 3 or 4 times a week; the 4th or 5th were administered after 2 weeks.
In 8 patients, further treatment was required after another 2 weeks.

– Some patients experienced an exacerbation of symptoms after the 1st or 2nd administration; in 6 cases, therapy had to be temporarily suspended, but at the follow-up of the following week the worsening had completely regressed; in some cases, there was a clinical and

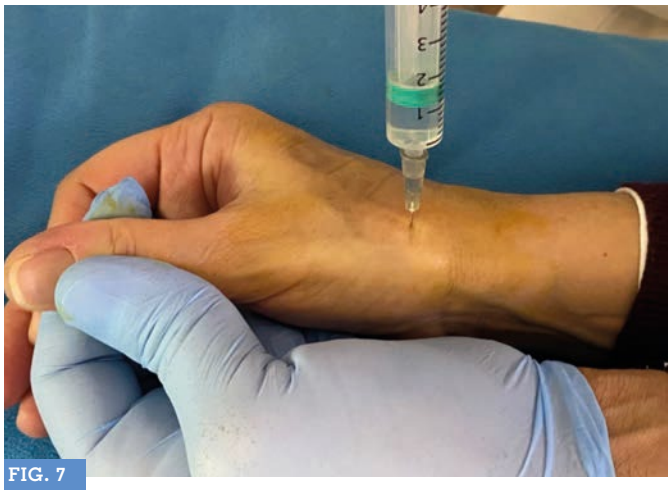


FIG. 7
Intra- and periarticular infiltration.


FIG. 8
Infiltration of the 1st commissure.

Weeks	0	1	Δ Week 1	2	3	4	5	6	7	8	9	10	Δ	%
DASH	50.72	39.87	21.39%	29.71	24.54	18.00	18.25	20.18	16.50	18.75	14.75	8.13	42.59	83.97
VAS	7.14	6.60	7.56%	5.06	4.44	3.85	3.60	4.20	4.29	2.80	3.33	3	4.14	57.98
Grind test	2.25	2	11.11%	1.367	1.233	0.923	1.111	0.714	0.8	0.667	0.5	0.5	1.75	77.7

TAB. 4

DASH, VAS, and Grind test values before and after treatment (10 follow-ups).

psychological improvement, so that treatment was resumed in all patients (no drop-out).

No patients required NSAIDs.
Only one patient, who was very anxious, was given anaesthesia in the superficial branch of the radial nerve, prior to the procedure described, to eliminate the pain of the i.a. and p.a. injections.
The addition of a minimal amount of lidocaine 2% resulted in significant patient compliance.
Case series confirmed the higher incidence of RA in the female gender.

RESULTS

This study enrolled: **1)** patients who had pain at stages that were too early to consider surgical treatment; **2)** non-responders to previous therapies, such as steroid therapy; **3)** patients who, despite having a surgical indication, refused surger.
In any case, it is believed that the earlier this treatment is initiated, the better the chance of an effective clinical response.

– Analysis of the DASH, VAS, and Grind test values showed that after the first week of treatment with low dose medicaments, there was a **21.39%** improvement in the DASH value, **7.56%** improvement in the VAS value, and **11.11%** improvement in the Grind test value. These data demonstrate the effectiveness of this preliminary therapeutic time (TAB. 4).

• Evaluating then the difference from the beginning to the end of the therapy, it can be seen that the DASH value decreased by **42.59 points** (**83.97%** increase in function); pain, according to the VAS Scale, decreased from **7.14** to **3** with a delta of **4.14** and consequently a **57.98%** decrease, while laxity went from a Grind test of **2.25** to a Grind test of **0.5** (**1.75**- point improvement), i.e., an increase in capsuloligamentous tension of **77.7%** (TAB. 4).

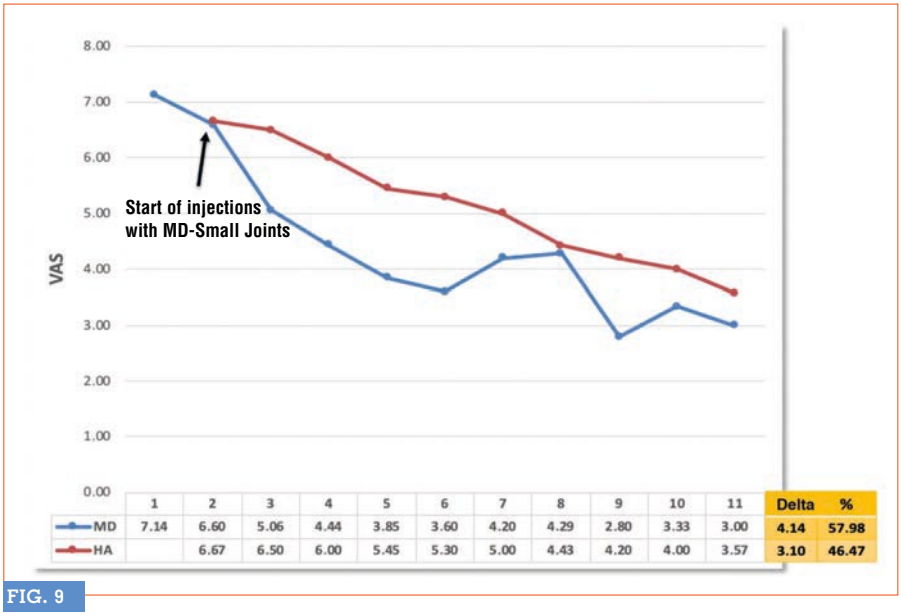


FIG. 9

VAS comparison: MD-Small Joints *vs* Hyaluronic Acid.

MD-SMALL-JOINTS VS HYALURONIC ACID

Intra-articular injection treatment with hyaluronic acid **(HA)** has been and still is another cornerstone of RA therapy, used by physiatrists and hand surgeons (Strass *et* Al., 2009; Volpi *et* Al., 2009; Iannitti *et* Al., 2011).
– Comparing the values obtained with MD-Small Joints with those obtained in a similar study carried out by the author (Brunato, 2012) on 51 patients treated with 3 intra-articular injections of HA administered 3 weeks apart, the following differences were recorded: at 10 weeks the VAS dropped from 6.67 to 3.57.
The difference was **3.10** points versus **4.14** points for MD-Small Joints, demonstrating a greater efficacy in pain control of **1.4 points** for MD-Small Joints (**+ 11,51%**) vs HA.
What is most striking is the early and marked decrease in pain from the first weeks of treatment with MD-Small Joints compared to HA (FIG. 9).
– Comparing the DASH values, the reduction was 42.59 points with MD-Small Joints compared to 27.51 points with HA, an improvement in hand function of **+ 25.7%**.
With MD-Small Joints, daily work activity, as verified with the DASH question-

naire, was maintained with significantly less pain (FIG. 10).

Converting all the values measured by DASH, VAS, and Grind test **to a scale of 10** shows that the improvement in DASH and VAS values is directly proportional to the decrease in Grind test, i.e., the reduction in joint laxity.
The recovery of joint tension is the result of the direct effect of injections with MD-Small Joints on the capsuloligamentous structures and in particular on the intermetacarpal ligament.

This is the clinical observational demonstration that local injection of MD-Small Joints restores the anisotropy of collagen and produces a significant and immediate improvement in the mechanical qualities of the damaged tissue, whence the clinical improvement of RA (FIG. 11).

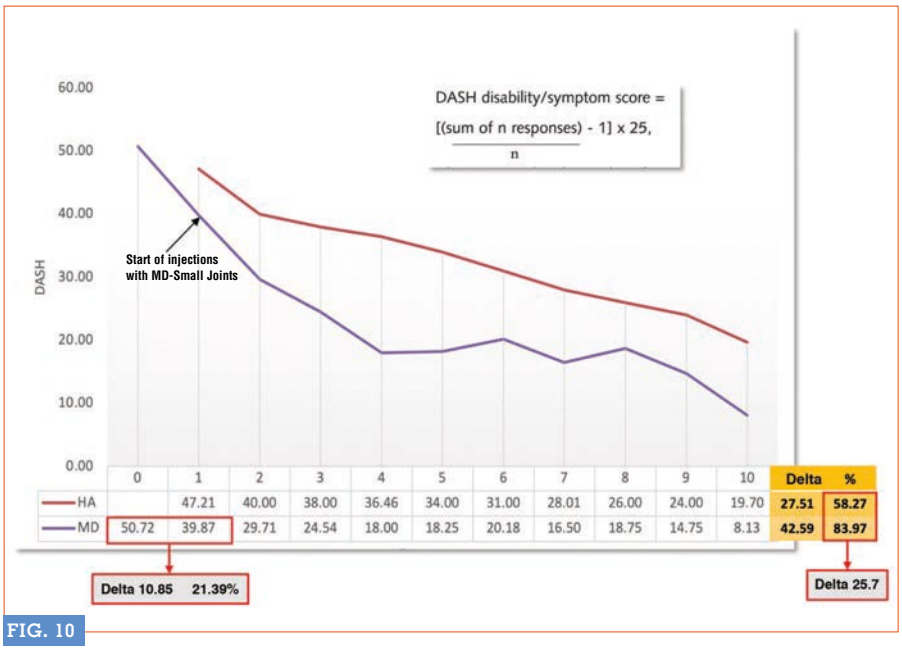


FIG. 10

DASH comparison: MD-Small Joints *vs* Hyaluronic Acid.

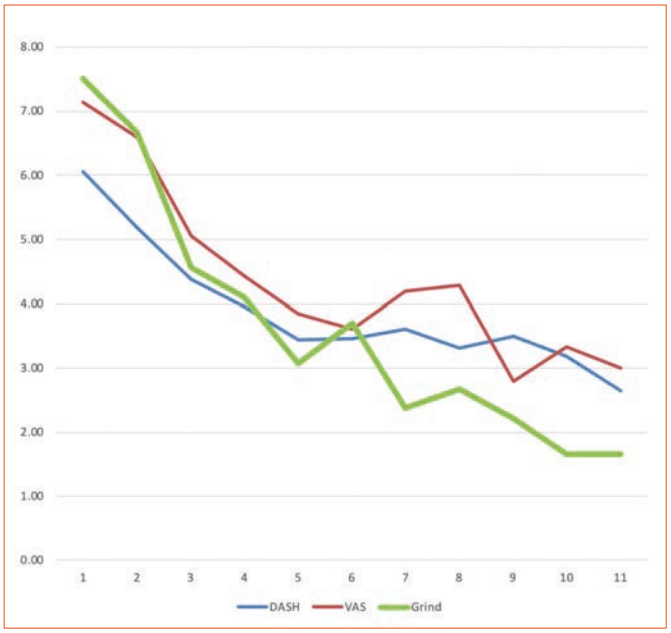


FIG. 11

Comparison of DASH and VAS values as a function of Grind test values.

DISCUSSION

Injection treatment of RA with Collagen Medical Device Small Joints significantly improved patients' symptoms in very few weeks; most importantly, pain clearly decreased, from the outset, as a result of the rapid reduction in joint laxity, proving to be more effective than HA therapy.

Most authors (Dias *et* Al., 2006) consider treating RA with immobilisation and taking NSAIDs for 2-3 months; if symptoms do not regress, surgery should be considered.
Corticosteroid injections act on pain and may be indicated when conservative therapy has not been effective (Pellegrini, 1992; Swigart *et* Al., 1999), but repeated injections have been found to have decreasing efficacy, in addition to irreparably damaging the capsule and articular cartilage (Burton *and* Pellegrini, 1986; Swigart *et* Al., 1999).
HA treatment has been shown to be less effective.

▶ MD-Small Joints has proven to be effective in delaying surgery, providing patients with rapid clinical improvement and an expectation of slowing down the pathology; all this in the absence of side effects and with excellent tolerability. ■

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CLINICAL

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THE TREATMENT OF RHIZOARTHROSIS WITH COLLAGEN MEDICAL DEVICE SMALL JOINTS

SUMMARY

Rhizoarthrosis is a very widespread disease; it affects 20% of the adult population and represents about 10% of all osteoarthritic locations; it is more frequent in females than in males (4:1 ratio). The initial symptom is TM pain followed by difficulty in performing daily activities such as turning a key or opening a bottle. The treatment is initially conservative with the application of immobilization braces and the simultaneous use of chondroprotectors. If this treatment is not effective, before undertaking the definitive surgical treatment, infiltrative therapy with Collagen may be considered. Collagen MDs improve the mechanical qualities of the joint capsule by restoring the anisotropic characteristics of the tissue with an evident positive effect on the "joint hypermobility stabilisation", movement, pain and quality of life.

– The purpose of this trial is to evaluate the efficacy of the endo- and peri-articular injection of MD-Small Joints in patients suffering from rhizoarthrosis before undergoing definitive surgical therapy.

In this clinical study, 22 patients (3 M; 19 F) were included and assessed for 10 weeks with the DASH, VAS scales and Grind Test.

The treatment was well tolerated, and no side effects were observed. The improvement obtained was approximately 60-80% of all rating scales. This trial shows that clinical improvement is directly proportional to the reduction in joint laxity and is therefore a function of the effectiveness of MD-Small Joints on joint collagen.

KEY WORDS **RHIZOARTHOSIS, COLLAGEN MEDICAL DEVICE, MD-SMALL JOINTS, HAND PAIN, DASH, VAS, GRIND TEST, COLLAGEN**

RHIZOARTHROSIS

Rhizoarthrosis (RA) is a type of arthritis that affects the **trapeziometacarpal (TM) joint**. The etymology of the term 'rhizoarthrosis' is Greek: *rizos* means "root"; this joint, in fact, is located at the root of the thumb.

– RA is a widespread condition; it affects **20%** of the adult population (Barra *et* Al., 2003) and represents approximately **10%** of all osteoarthritic localisations in the human body (Sollazzo *et* Al., 2006). RA is more frequent in females than males (4:1 ratio) and generally occurs between the fifth and sixth decades of life.

In women, it frequently begins at menopause, while in men it is more related to overuse phenomena (Bonola *et* Al., 1981).

The TM joint plays a key role in normal thumb function: all gripping actions overload the TM joint because the axis of the thumb exerts force and acts as a fulcrum on this joint.

This force transmits a radial stress at the base of the metacarpal, which, over time, causes a reduction in the tension of the capsuloligamentous system (Bernardini, 2018), resulting in joint hyperlaxity and subluxation of the first metacarpal.

• The preternatural movement of the bone heads alters the joint surface; there is a progressive thinning of the cartilage and subsequent onset of pain and arthritis. Symptomatology is bilateral in 50% of cases.

FUNCTIONAL ANATOMY

The TM joint can be considered the most complex joint of the human body as it allows the thumb to perform volo-volar pincer grips with the long fingers; in other words, it allows the hand to perform its most distinctive function: opposition, that is, prehension (Caroli, 1996).

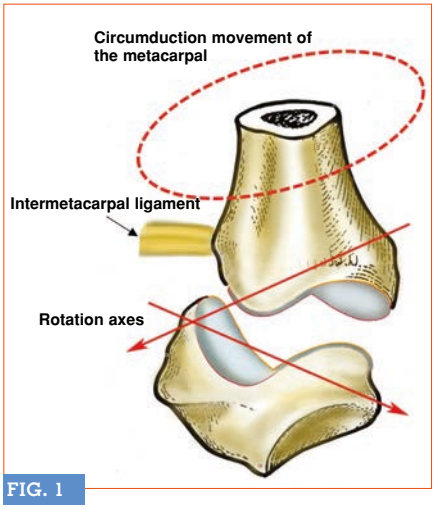


FIG. 1

Trapeziometacarpal joint.

Kapandji (1971) defined the TM joint as a reciprocal interlocking or saddle-shaped joint and compared it to a rider in the saddle with perfectly matching torus-shaped contact surfaces (Bonola *et* Al., 1981).

The movements take place on two perpendicular axes and their combination allows for a true circumduction, conditioned by the intermetacarpal ligament, which acts as a pivot (FIG. 1,2).

The structures that support and stabilize this joint are the capsule, the extracapsular ligaments and the intrinsic and extrinsic muscles.

The capsuloligamentous structures of the TM joint are extremely important, both in providing stability and in guiding the complex movements of the thumb.

The joint capsule is very lax and fits along the contour of the articular surfaces of the trapezium and the base of the metacarpal. This laxity is determined by the fact that the first metacarpal must allow for ample movement and rotation of the metacarpal along its own longitudinal axis (Caroli, 1996).

▶ Ligaments of the capsule

The ligamentous system is equally important because, in addition to ensuring the stability of the TM joint, its maximum tension allows stopping the various movements of the first metacarpal bone, assisted by the fascial and muscular structures in this function.

It should also be noted that the TM ligaments, through their insertion, help to guide the movements of the thumb and mainly those of axial rotation.

A number of thickenings depart from the joint capsule, giving rise to the following ligaments:

- the dorsoradial ligament (DRL) or Arnold's external trapeziometacarpal ligament stops abduction and favours rotation in pronation of the metacarpal joint;
- the dorsoulnar ligament (DUL) or Arnold's internal trapeziometacarpal ligament, which is very thick and wide, stops the retroposition movement and favours rotation in supination of the metacarpal;
- the anterior oblique ligament (AOL). Some authors describe two portions of this ligament: a superficial one and a deep one (beak ligament), which is particularly important in stabilising the TM joint in the degrees of maximum abduction and retroposition movement of the thumb;
- the fibrous, thick and short intermetacarpal ligament (IML): it stretches between the base of the first and second metacarpals; this ligament stops the abduction movement of the first metacarpal.

  The IML is crucial because its loosening causes external subluxation of the base of the first metacarpal, which, as explained below, is one of the most important causes of **joint instability** (Caroli, 1996) (FIG. 2).

- **DRL = Dorsoradial Ligament**
- **DUL = Dorsoulnar Ligament**
- **AOL = Anterior Oblique Ligament *(beak ligament)***
- **IML = Intermetacarpal Ligament**

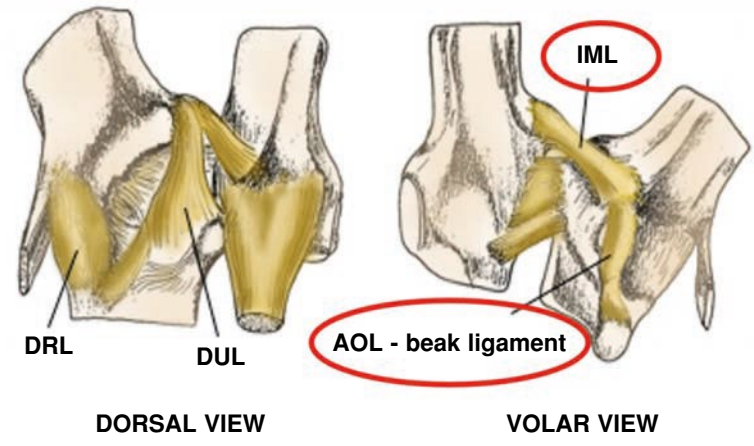


FIG. 2

Ligaments of the trapeziometacarpal joint.

▶ Motor muscles of the thumb

As indicated by Kapandji (1971), the TM joint works in compression as a joint. The intrinsic thenar muscles allow the first metacarpal to orient in all directions of space, as if it were a pile whose orientation can be changed by changing the tension of the cables. According to the author, the muscular components provide support to joint coaptation in all positions, resulting from the synergistic activation of agonist and antagonist muscles (Brunelli *and* Brunelli, 1996).

Mobility is the essential opposition function of the thumb; it is enabled by nine motor muscles:

- Four extrinsic or long muscles located in the forearm. Three are for grip opening movements: The *extensor pollicis longus, extensor pollicis brevis,* and *abductor pollicis longus;* and one for power grip: *flexor pollicis longus.* As a reminder, the extrinsic muscles are the motor muscles for power gripa;

- Intrinsic muscles located in the thenar eminence and first interosseous space; they provide for precision and coordination during different grips and opposition.
  – The external group is composed of three muscles (*opponens pollicis*, *abductor pollicis brevis*, and *flexor pollicis brevis*) that have a synergistic function of thumb opposition.
  – The internal group consists of the adductor and first palmar interosseous muscles.
  These are crucial for gripping/holding objects, because they also perform their action on the **MP (metacarpophalangeal)** and **IP (interphalangeal) joints** (flexion of the former and extension of the latter), making the opposition grip with the index finger more effective.

Opposition is not a fixed movement: indeed, there is a range of oppositions that execute a great variety of grips and actions according to the number of fingers involved and their mode of association (Kapandji, 1971).

- Bi-digital grips give the classic pincer grips between the thumb and index finger; there are 3 types: terminal, subterminal, and subterminolateral.

– The terminal opposition grip is the finest and most precise because it makes it possible to firmly grasp a small object or pick up a very thin object.
The thumb opposes the nail surface of the index finger with the fingertip.
In this grip, as the metacarpal wedges into the trapezius, it protects the joint capsule from any tensional forces and avoids degenerative effects on the joint (FIG. 3).

– The subterminal grip is the most recurrent and instinctive one: the thumb and the index finger oppose each other with the palmar face of the fingertip and this way can grip objects of different calibre, even thin ones, such as a sheet of paper or a pencil.
In this grip, a significant tensive force is created radially at the base of the metacarpal that stretches the joint capsule and the intermetacarpal ligament, making them increasingly lax over time.

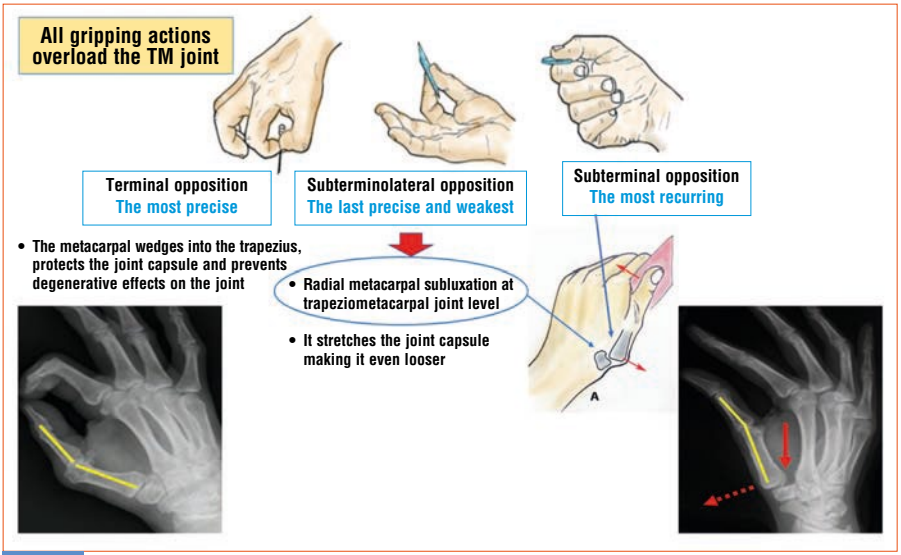


FIG. 3

Effects of grip on the trapeziometacarpal joint.

This laxity produces joint instability, the cause of radial subluxation of the metacarpal and joint degenerative processes.

– The subterminolateral grip is the least fine and weakest compared to the previous ones.
The palmar aspect of the pulp of the thumb rests on the external aspect of the first phalanx of the index finger, creating, in this case too, great radial tension at the base of the metacarpal resulting in the tendency of the TM joint to develop subluxation (Kapandji, 1971).

- The cause of RA always lies in TM joint **instability**.

It can be primary or secondary (TAB. 1).

In ligamentous hyperlaxity, instability is due to an excessive range of motion.
In this case, the palmar ligament (beak ligament) is of great importance, as it limits the hyperextension of the metacarpal and, above all, the intermetacarpal ligament between the base of the first and second metacarpals, which counters the subluxation of the first metacarpal radially, without limiting other movements (FIG. 2).
Laxity and/or degeneration of this ligament produce abnormal TM joint movements, with incongruity of the articular surfaces rapidly triggering degeneration.

– Another known cause that Brunelli (2007) considers to be the most frequent is instability due to the absence of ab-

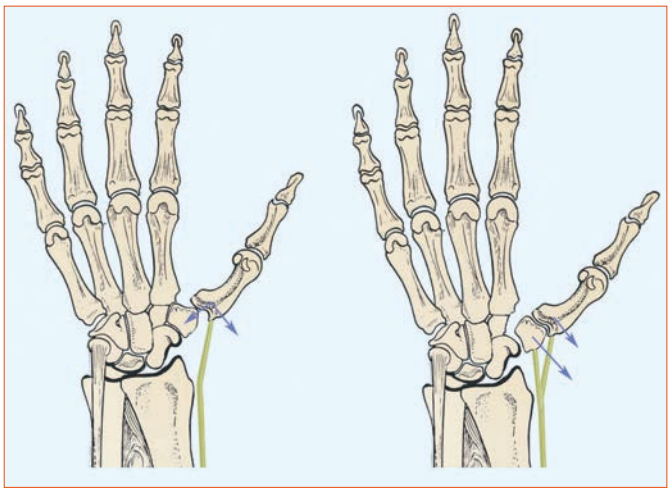
PRIMARY INSTABILITY	SECONDARY INSTABILITY
Hypoplasia of the trapezium, abnormal obliquity of its saddle	Traumatic capsular ligament lesion
Congenital capsular ligament laxity	Outcome of fracture of the trapezium or the base of the first metacarpal
Muscle imbalance due to the absence of insertion of one of the APL tendons on the trapezium	Operational stress due to repetitive work with strong thumb adduction
Muscle hypotonia of the non-dominant hand in elderly people	

TAB. 1

Causes of the trapeziometacarpal joint instability.

FIG. 4

Instability due to the absence of intersection of *abductor pollicis longus* in the trapezium. – Tensive forces.



ductor pollicis longus **(APL)** insertion on the trapezium. In cases where the APL has distal double insertion on the trapezium and on the base of the first metacarpal, with each contraction of the APL the entire thumb-metacarpal-trapezium column shifts in abduction, maintaining normal trapeziometacarpal joint relationships.
Conversely, if there is no insertion on the trapezium, all abductor force is exerted on the base of the first metacarpal, causing significant subluxation tension with a deleterious shear effect on, and cartilage damage, of the TM joint (FIG. 4).
– Repeated stress (overuse) is another frequent cause of TM joint arthritis; the TM joint is subjected to a considerable workload, as it is involved in approximately 50% of all actions of the hand.

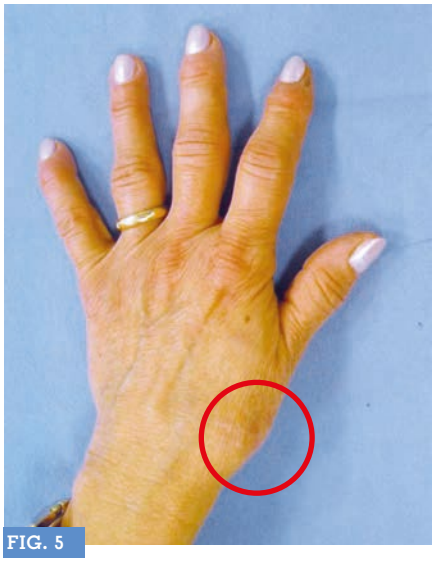


FIG. 5

Subluxation of the first metacarpus.

It is possible to distinguish some activities and habitual gestures that favour the deterioration of the articular surfaces: the repeated prehension of small objects exerts radial stress on the TM joint that does not allow the base of the metacarpal to stay in contact with the articular surface of the trapezium (FIG. 3).
The luxation force transmitted on the metacarpal can be multiplied up to 12-120 times (Cooney *and* Chao, 1977).

SYMPTOMATOLOGY

TM joint instability is often asymptomatic; over time, pain develops, leading the patient to consult a physician.
– The most frequent clinical picture is initially represented by an annoying pain localised at the base of the thumb that appears when active movements in radial abduction such as grips or pincer movements are performed, and/or passive movements in rotation-opposition such as turning a key, unscrewing a cap, turning a handle, writing with a thin pen or even just buttoning a shirt (Dias *et* Al., 2006).
The patient complains of decreased hand strength and mobility.
Later, the pain appears even at rest, at night, and may radiate to the wrist and forearm. In more advanced stages, pain is spontaneous and is associated with bone crepitus due to joint laxity.

– The patient does not "use" the thumb well to avoid pain: over time, this causes muscle weakness in the stabilisation structures of the TM joint; the metacarpal loses the ability to slide on the trapezium along the adduction-abduction axis, in addition to which there is a radial shift of the base of the metacarpal.

The loss of congruence between the bone heads affects the mechanical stability of the joint: it results in dislocation, consequently decreasing movement amplitude (Pomerance, 1995).
During abduction movements, the joint capsule is stretched.
Some capsular fibres are weakened, leading to the dorsal subluxation of the base of the metacarpal; therefore, when the *adductor pollicis* and *flexor pollicis brevis* muscles contract, they pull the distal part of the metacarpal toward the palm.
The result is a "tilt" of the articular surface at the base of the metacarpal on the saddle of the trapezium.

- This tilt, though imperceptible, is the cause of the pain.

That is why, in cases of RA, holding and turning a key, lifting a cup or writing are actions that cause pain: in fact, these actions, although with movements that require little articulation, stress the TM joint and its means of containment (Dias *et* Al., 2006).

– The prevalent clinical signs are:
- deformation and swelling at the base of the first metacarpal (FIG. 5), caused by a combination of dislocation, joint inflammation, and osteophyte formations;
- 1st ray in adduction, more common in advanced stages;
- pain on palpation;
- positive axial compression test or Grind test: the axial load on the trapezium, together with the rotation of the metacarpal, trigger pain at the base of the thumb;
- TM joint dislocation, with or without rotation, which causes stretching of the capsule, which, if inflamed, is painful.

As the disease progresses, TM joint subluxation produces a radial deviation of the MP of the thumb due to the contracture in adduction of the first metacarpal, which is followed by a flexion of the IP, generating a picture of "Z-thumb". This is an expression of one of the most compromised pictures of RA in which, in addition to the TM joint, the MP in hyperextension and IP in flexion are involved.

RADIOGRAPHIC PICTURE – THE EATON-LITTER CLASSIFICATION

RA can be diagnosed through a careful physical examination.
X-rays of the thumb in 3 planes and the particular stress view of the basal joint are necessary to confirm the diagnosis.
The view for the basal joint under stress, when performed correctly, provides an excellent image for assessing the degree of TM joint subluxation.
In this 30° oblique view, the patient is asked to press the tips of the thumbs against each other while the X-ray is being performed (FIG. 6).

X-rays should always be interpreted in relation to the patient's clinical situation. Often, patients with very compromised radiographic pictures report very little or no pain; others with negative or insignificant X-rays may present severe functional deficits with significant impact on daily and/or work activities. There is no indication for MRI and/or ultrasound; only CT may be useful as an additional preoperative investigation.

– Eaton and Glickel (Glickel, 2001) described a method for classifying pathological changes in RA based on the appearance in standard radiographic views and those under stress.
This method has also proven to be useful in medical planning and, if needed, surgery.
– At present, the most widely used classification is the Eaton-Littler classification modified by Brunelli (Barra *et* Al., 2003) which includes both the radiographic picture and clinical picture (TAB. 2).

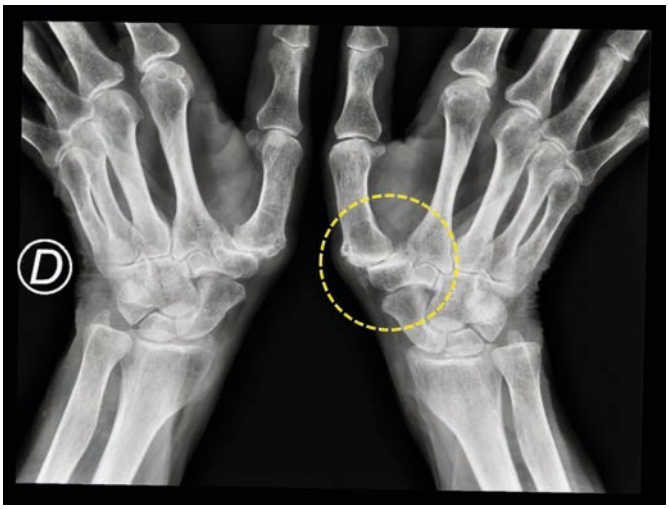


FIG. 6
Stress view.

RHIZOARTHROSIS – CONSERVATIVE TREATMENT

Treatment in all stages of the disease is initially conservative.
– The first step is the application of an immobiliser at night and possibly during the day for 2-3 weeks (Swigart *et* Al., 1999); the reduction in joint head movement and friction leads to decreased pain and stiffening of the capsuloligamentous structures with reduced subluxation (Pomerance, 1995). This can be associated to chondroprotectors that achieve their maximum therapeutic effectiveness if the joint is immobilised; in fact, since there is no wear effect, the cartilage can regenerate (Towheed *et* Al., 2005).
The synergy of these two measures can ensure a good outcome.
Conservative treatment requires early diagnosis of the degenerative process (Towheed *et* Al., 2005) because it is more effective, especially in the early stages (1st and 2nd).
The goals of conservative treatment are:

- to reduce pain at the base of the thumb, both at rest and while performing routine daily activities;
- avoid TM joint overload by teaching the patient correct prehension modes and favouring gripping with terminal opposition (FIG. 3);
- provide TM joint stability with the immobiliser while simultaneously reducing radial metacarpal subluxation.

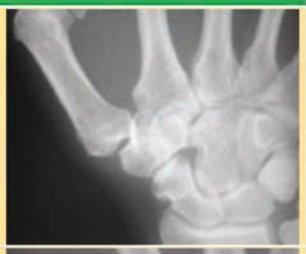
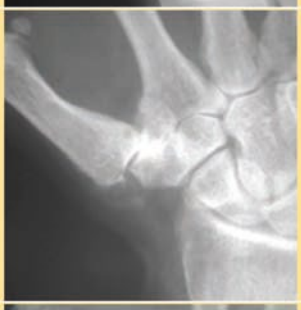
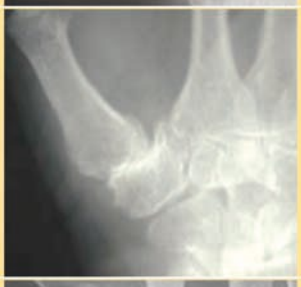
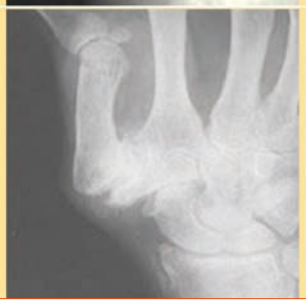
– Corticosteroid injections act on pain; they are sometimes used when the pain is unbearable (Pellegrini, 1992; Swigart *et* Al., 1999). These injections, if repeated, are less and less effective and irreparably damage the articular cartilage (Burton *and* Pellegrini, 1986; Swigart *et* Al., 1999).

RHIZOARTHROSIS – TREATMENT WITH MD-SMALL JOINTS

If initial conservative treatment does not produce positive effects, endo- and periarticular injection therapy may be considered before resorting to definitive surgical treatment.
The anatomical structures forming the containment/stabilisation system are: the joint capsule, ligaments and fibrous membranes that provide "direct seal", while the tendons and muscles provide "indirect seal".

- The extra-articular structures are made of Type I collagen (COL1): the quantity and quality of this triple helix macroprotein ensure optimal and repeated physiological articular movement over time.

– With ageing, all the COL1 forming the peri- and intra-articular structures undergoes important qualitative/quantitative changes (discrepancy between neofibrillogenesis and fibrillolysis) with progressive depletion and/or damage of adequate COL1, so that the articular bone heads are more mobile along the

STAGE	X-RAY	CLINICAL SIGNS	ACCESSORY ELEMENTS
1		TM joint subluxation is less than 1/3 Subchondral sclerosis begins to develop along with initial diastasis of the articular heads Instability, initial pain	Subluxation of the base of the first metacarpal under stress in abduction or in semeiologic manoeuvres (dynamic) Possible hypoplasia of the trapezium on X-ray examination
2		Subluxation is greater than 1/3 The capsule begins to be quite loose The first osteophytes of more than 2 mm in size appear Frequent pain on exertion Modest functional limitation	Instability Joint space narrowing, modest arthritic signs Osteophytes
3		The joint space is greatly reduced and sclerosis is increasingly evident Constant and stronger pain, stiffness Functional limitation Crepitus on palpation of the base of the thumb associated with more or less obvious deformities	Continuous pain Severe limitation
4		Severe anatomical and radiographic alterations resulting in functional impotence TM joint rigidity Severe functional limitation	Decreased pain related to stiffness, sometimes absent

TAB. 2

Eaton-Litter classification modified by Brunelli.

physiological excursion planes and are no longer firmly held in place. Hypermobility of the joints leads to abnormal support with consequent inflammation, first, and then degeneration of articular cartilage, the prime mover towards arthritic degeneration (Milani, 2019).

• In short: according to physiological biomechanics, the incorrect positioning of two contiguous joint heads forming a joint causes wear, pain and difficult movement. The tenocyte, a very specialised fibrocyte, is the cell that produces COL1; it also synthesizes matrix **Proteoglycans (PGs)** and Metalloproteinases (MMPs) (Bernardini, 2018) involved in the degradation of old or damaged fibres by the inflammatory/traumatic process.

– The primary event in the arthritic process is to be found in the reduction and alteration of PGs: mechanical, chemical or cytological factors lead to the depolymerization of the chains of Glycosaminoglycan (GAGs), which, by breaking, cause the decreased resistance of the articular cartilage matrix.

– As a consequence of these events, the collagen fibres that are not adequately protected by the matrix also break into fragments; the cartilage thus loses its elasticity and wears out (Scagliati, 1995).

All extra- and intra-articular structures are fundamentally made of collagen, hence the usefulness of deriving therapeutic means that allow the physician to counter osteo-arthro-myofascial pathologies (Stone *et* Al., 1997; Milani, 2010; 2013; 2019).

▶ MD-Small Joints

Guna Collagen Medical Devices are injectable products (p.a., i.a., s.c., i.d., i.m.) consisting of collagen of porcine origin (porcine collagen is the most similar and akin to human collagen) and one or more ancillary substances characterised by a particular tropism for the various and specific anatomical districts to which the collagen can be conveyed with greater effectiveness and specificity (Milani, 2013; 2019).

Guna Collagen Medical Devices provide collagen in the form of tropocollagen, which is assembled to collagen in the presence of the enzyme lysine hydroxylase, at the level of the extracellular matrix (ECM); it therefore acts as a bioscaffold (Milani, 2010).

– The deposition of neosynthesized collagen fibres in the damaged area secondary to loco-regional injection of the MDs produces a significant improvement in the mechanical qualities of the injured tissue; in particular, the anisotropic characteristics are restored.

Anisotropy is a mechanical property of collagen: it describes the ability of its fibres to propagate tensile forces in a single preferential direction.

Due to the orientation of the collagen fibres in a single direction, proper mechanical support is achieved for optimal function (Milani, 2019).

– Guna Collagen Medical Devices improve the histological make-up of anatomical structures in which collagen is present and provide a mechanical support (bioscaffold) with a clear positive effect on the stabilisation of joint hypermobility, movement, pain, and quality of life; they have a restructuring, repairing and remodelling action and contribute to the containment of the physiological deterioration of joints and tissues to counterbalance the effects due to various

causes including ageing, postural defects, chronic concomitant diseases, traumas and injuries (Various Authors, 2011).

– In addition to collagen, **MD-Small Joints** contains *Viola odorata*, an ancillary substance that is indicated – inter alia – in rheumatic pain of the wrist joints radiating to the forearm (Various Authors, 2011).

MATERIALS AND METHODS

Twenty-two patients (3 M; 19 F) suffering from RA were included in this clinical trial.
In 4 patients the pathology was bilateral; in this study, the most compromised side was considered.

– All patients were tested with the **DASH** questionnaire to assess loss of function (values 0 to 100; 100 = maximum disability), the VAS Scale (values 1 to 10), and the **Grind test** to assess capsuloligamentous laxity (G0 = no joint laxity; G1 = scarce laxity; G2 = lax; G3 = very lax).

– The mean age of the patients was 61.2 years (min. 44, max. 78): 12 patients in stage 2 and 10 patients in stage 3; 10 patients had maximum laxity G3, 5 had minor laxity G2, 7 had minimal laxity G1, and none G0.
All patients at the time of inclusion had decreased strength and functional limitation of the first ray. As regards laterality, 7 patients (33%) had RA in the nondominant hand.
This high percentage is explained by the fact that the nondominant hand, in many activities, must maintain a static grip for a long time thus resulting in severe overuse phenomena.
For example, suffice it to think of a patient who holds a sheet of metal or other material with strength in order to work it with the dominant hand.
In elderly patients, however, it is often due to muscular hypotonia of the nondominant hand: this explains how important the tendons and muscles, namely the structures involved in "indirect gripping", are.

	Age (years)	DASH	VAS	Grind test
Mean	**61.22**	**50.72**	**7.14**	**2.25**
Minimum	44	16.5	5	1
Maximum	78	75.25	9	3

TAB. 3
Patient assessment at inclusion.

The mean **DASH** was **50.72** at the first visit with a minimum of 16.5 and a maximum of 75.25; the mean **VAS** was **7.14** at the first visit with a minimum of 5 and a maximum of 9; the mean Grind test was **2.25** with a minimum of 1 and a maximum of 3 (TAB. 3).

– After one week of home therapy (low dose medicaments), patients began outpatient treatment with **MD-Small Joints** (1 vial = 2 mL), to which 0.5 mL of lidocaine 2% was added. Intra-articular injection was performed with 0.7-0.8 mL (i.e., the average capacity of the TM joint); the remaining amount (approx. 1.0 mL) in the periarticular site (FIG. 7).
In addition, approx. 0.5 mL were used for a second periarticular injection at the level of the 1st commissure in order to attack the deep part of the capsule between the first and second metacarpals, but above all to inject the intermetacarpal ligament in order to stabilise it and reduce the conflict due to its laxity (FIG. 2,8).
Injections were administered 3 or 4 times a week; the 4th or 5th were administered after 2 weeks.
In 8 patients, further treatment was required after another 2 weeks.

– Some patients experienced an exacerbation of symptoms after the 1st or 2nd administration; in 6 cases, therapy had to be temporarily suspended, but at the follow-up of the following week the worsening had completely regressed; in some cases, there was a clinical and

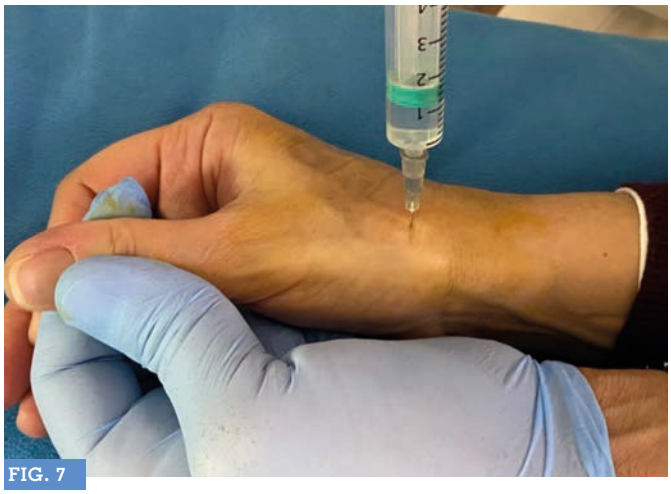


FIG. 7
Intra- and periarticular infiltration.


FIG. 8
Infiltration of the 1st commissure.

Weeks	0	1	Δ Week 1	2	3	4	5	6	7	8	9	10	Δ	%
DASH	50.72	39.87	21.39%	29.71	24.54	18.00	18.25	20.18	16.50	18.75	14.75	8.13	42.59	83.97
VAS	7.14	6.60	7.56%	5.06	4.44	3.85	3.60	4.20	4.29	2.80	3.33	3	4.14	57.98
Grind test	2.25	2	11.11%	1.367	1.233	0.923	1.111	0.714	0.8	0.667	0.5	0.5	1.75	77.7

TAB. 4

DASH, VAS, and Grind test values before and after treatment (10 follow-ups).

psychological improvement, so that treatment was resumed in all patients (no drop-out).

No patients required NSAIDs.
Only one patient, who was very anxious, was given anaesthesia in the superficial branch of the radial nerve, prior to the procedure described, to eliminate the pain of the i.a. and p.a. injections.
The addition of a minimal amount of lidocaine 2% resulted in significant patient compliance.
Case series confirmed the higher incidence of RA in the female gender.

RESULTS

This study enrolled: **1)** patients who had pain at stages that were too early to consider surgical treatment; **2)** non-responders to previous therapies, such as steroid therapy; **3)** patients who, despite having a surgical indication, refused surger.
In any case, it is believed that the earlier this treatment is initiated, the better the chance of an effective clinical response.

– Analysis of the DASH, VAS, and Grind test values showed that after the first week of treatment with low dose medicaments, there was a **21.39%** improvement in the DASH value, **7.56%** improvement in the VAS value, and **11.11%** improvement in the Grind test value. These data demonstrate the effectiveness of this preliminary therapeutic time (TAB. 4).

• Evaluating then the difference from the beginning to the end of the therapy, it can be seen that the DASH value decreased by **42.59 points** (**83.97%** increase in function); pain, according to the VAS Scale, decreased from **7.14** to **3** with a delta of **4.14** and consequently a **57.98%** decrease, while laxity went from a Grind test of **2.25** to a Grind test of **0.5** (**1.75**- point improvement), i.e., an increase in capsuloligamentous tension of **77.7%** (TAB. 4).

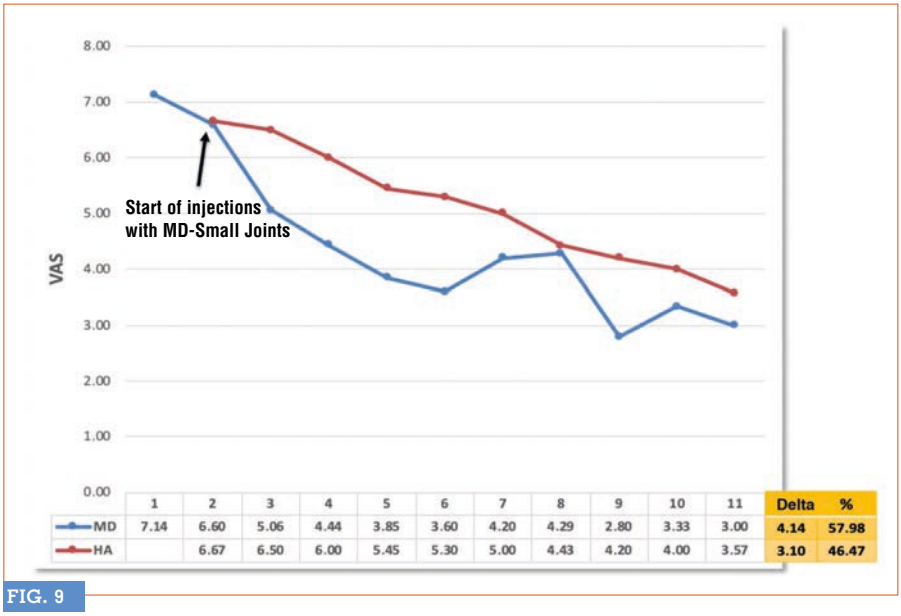


FIG. 9

VAS comparison: MD-Small Joints *vs* Hyaluronic Acid.

MD-SMALL-JOINTS VS HYALURONIC ACID

Intra-articular injection treatment with hyaluronic acid **(HA)** has been and still is another cornerstone of RA therapy, used by physiatrists and hand surgeons (Strass *et* Al., 2009; Volpi *et* Al., 2009; Iannitti *et* Al., 2011).
– Comparing the values obtained with MD-Small Joints with those obtained in a similar study carried out by the author (Brunato, 2012) on 51 patients treated with 3 intra-articular injections of HA administered 3 weeks apart, the following differences were recorded: at 10 weeks the VAS dropped from 6.67 to 3.57.
The difference was **3.10** points versus **4.14** points for MD-Small Joints, demonstrating a greater efficacy in pain control of **1.4 points** for MD-Small Joints (**+ 11,51%**) vs HA.
What is most striking is the early and marked decrease in pain from the first weeks of treatment with MD-Small Joints compared to HA (FIG. 9).
– Comparing the DASH values, the reduction was 42.59 points with MD-Small Joints compared to 27.51 points with HA, an improvement in hand function of **+ 25.7%**.
With MD-Small Joints, daily work activity, as verified with the DASH question-

naire, was maintained with significantly less pain (FIG. 10).

Converting all the values measured by DASH, VAS, and Grind test **to a scale of 10** shows that the improvement in DASH and VAS values is directly proportional to the decrease in Grind test, i.e., the reduction in joint laxity.
The recovery of joint tension is the result of the direct effect of injections with MD-Small Joints on the capsuloligamentous structures and in particular on the intermetacarpal ligament.

This is the clinical observational demonstration that local injection of MD-Small Joints restores the anisotropy of collagen and produces a significant and immediate improvement in the mechanical qualities of the damaged tissue, whence the clinical improvement of RA (FIG. 11).

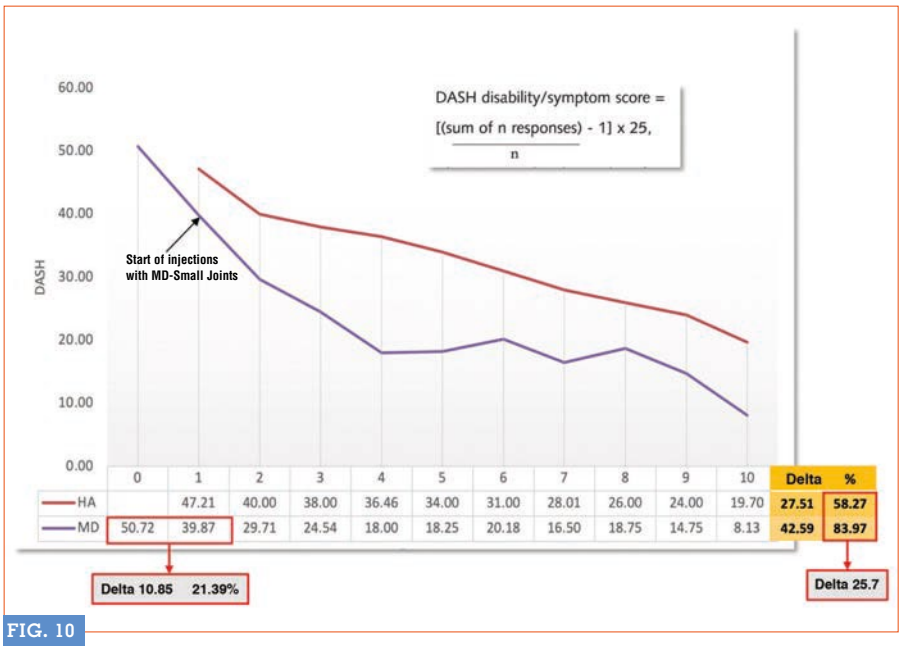


FIG. 10

DASH comparison: MD-Small Joints *vs* Hyaluronic Acid.

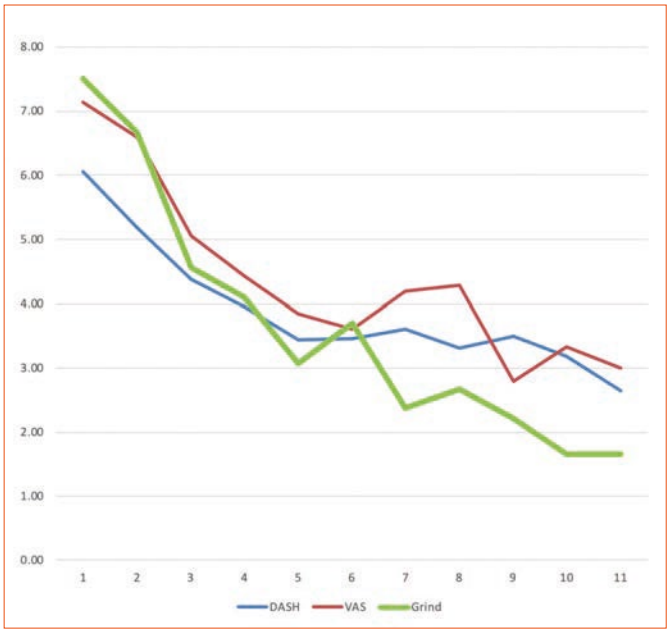


FIG. 11

Comparison of DASH and VAS values as a function of Grind test values.

DISCUSSION

Injection treatment of RA with Collagen Medical Device Small Joints significantly improved patients' symptoms in very few weeks; most importantly, pain clearly decreased, from the outset, as a result of the rapid reduction in joint laxity, proving to be more effective than HA therapy.

Most authors (Dias *et* Al., 2006) consider treating RA with immobilisation and taking NSAIDs for 2-3 months; if symptoms do not regress, surgery should be considered.
Corticosteroid injections act on pain and may be indicated when conservative therapy has not been effective (Pellegrini, 1992; Swigart *et* Al., 1999), but repeated injections have been found to have decreasing efficacy, in addition to irreparably damaging the capsule and articular cartilage (Burton *and* Pellegrini, 1986; Swigart *et* Al., 1999).
HA treatment has been shown to be less effective.

▶ MD-Small Joints has proven to be effective in delaying surgery, providing patients with rapid clinical improvement and an expectation of slowing down the pathology; all this in the absence of side effects and with excellent tolerability. ■

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CLINICAL

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INTRA-ARTICULAR ADMINISTRATION OF MD-HIP IN 24 PATIENTS AFFECTED BY SYMPTOMATIC HIP OSTEOARTHRITIS – A 24-MONTH COHORT STUDY

SUMMARY

The aim of this clinical trial is to report the efficacy and safety profiles of MD-Hip in patients affected by hip OA.

24 patients (10 M; 14 F) were enrolled in the study; none of them suffered from bilateral hip OA.

All parameters improved after the first injection, and improvement kept increasing during the whole 24-month follow-up.
No infectious complications were reported; 1 patient reported a transient discomfort in the treated hip for 1 day after the injection, which regressed spontaneously.

Our data suggest that the beneficial effects obtained by the ultrasound-guided intra-articular injection of the hip joint are present after the very first injection and are maintained over 24 months by the repetition of intra-articular injection every 6 months.

KEY WORDS

HIP OSTEOARTHRITIS, MD-HIP

BACKGROUND

Previous clinical data on cohorts of patients undergoing intra-articular injections with hyaluronic acids or hylans, under ultrasonographic guidance with a 3-48 month follow-up showed good safety and efficacy, with results similar to those already obtained in other studies on knee joint viscosupplementation.
Ultrasound guidance allows a better rate of success in the hip intra-articular injections.
No data are currently available in the scientific literature reporting safety and efficacy profiles of **MD-Hip** in patients affected by hip osteoarthritis undergoing ultrasound-guided intra-articular injections of the hip.

AIM OF THE STUDY

The aim of this study is to report the efficacy and safety profiles of MD-Hip in patients affected by hip OA.

MATERIALS AND METHODS

Adult patients suffering from hip OA grade 1-3 according to Kellgren and Lawrence scale were considered eligible for the study.
Patients were injected with one syringe (2 vials) of Guna Collagen **MD-Hip** under ultrasound guidance.
A 3.5 MHz convex transducer was used with a sterilized biopsy guide attached.
The hip joint was scanned through an anterior parasagittal approach.

The efficacy was assessed by using the Lequesne Index and VAS pain score at baseline and then every 6 months after the first injection of MD-Hip.

NSAIDs consumption was also evaluated during the month before the injection (number of days of NSAIDs use in the last month) and then every 6 months after the first injection of MD-Hip until month 24.

– Safety was assessed by recording any adverse event during the follow-up.

RESULTS

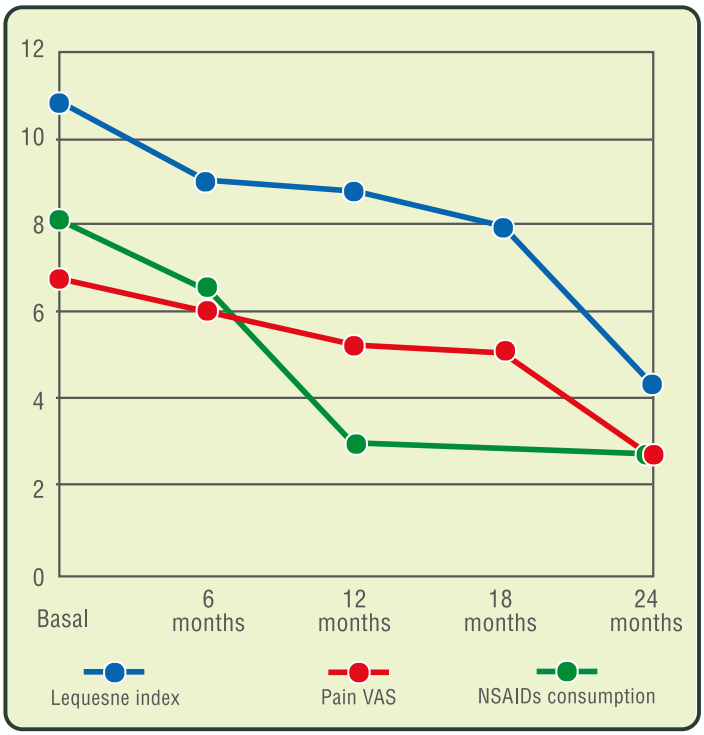
24 patients (10 M; 14 F) were enrolled in the study; none of them suffered from bilateral hip OA.
– All parameters improved after the first injection, and improvement kept increasing during the whole 24-month follow-up. No infectious complications were reported; 1 patient reported a transient discomfort in the treated hip for 1 day after the injection, which regressed spontaneously.

CONCLUSIONS

Our data suggest that the beneficial effects obtained by the ultrasound-guided intra-articular injection of the hip joint are present after the very first injection and are maintained over 24 months by the repetition of intra-articular injection every 6 months (FIGURE 1).

– Guna Collagen MD-Hip proved to be efficacious and safe when used in patients affected by hip OA.
This introduces new investigation aims in the field of intra-articular therapy. ■

FIGURE 1



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CLINICAL

THE ROLE OF MD-HIP IN ULTRASOUND-GUIDED INJECTION THERAPY IN OSTEOARTHRITIS OF THE HIP

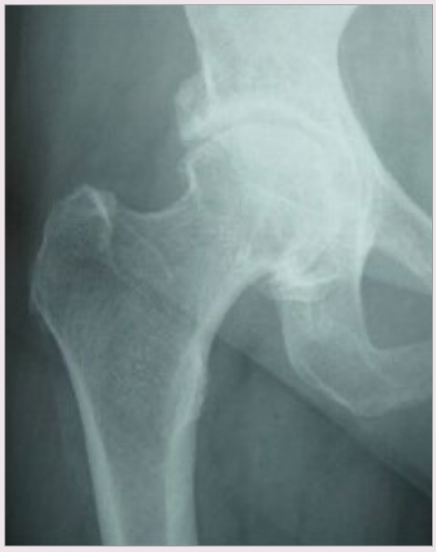
ABSTRACT

Osteoarthritis of the hip is a commonly observed disease in outpatient clinics dedicated to musculoskeletal pain management. The non-surgical therapeutic tools at our disposal are few and not always effective, especially in the advanced stages of the disease, in which joint damage is considerable.
In recent years, joint injection therapy with hyaluronic acid has become common, using an ultrasound-guided technique to improve the safety and appropriateness of the injection.
In literature, data on the efficacy of this treatment are more than encouraging.
– The combined use of hyaluronic acid and Collagen Medical Device MD-HIP via intra-articular and peri-articular injections are a valuable therapeutic tool in the treatment of hip osteoarthritis.

– This study aimed to assess its effectiveness on pain, functionality, tolerability, and safety.

KEY WORDS

COLLAGEN MEDICAL DEVICE, HYALURONIC ACID, MD-HIP, OSTEOARTHRITIS, PAIN, REHABILITATION, INJECTION, ULTRASOUND



https://www.boneclinic.com.sg/orthopaedic-conditions/hip-pain/hip-osteoarthritis/

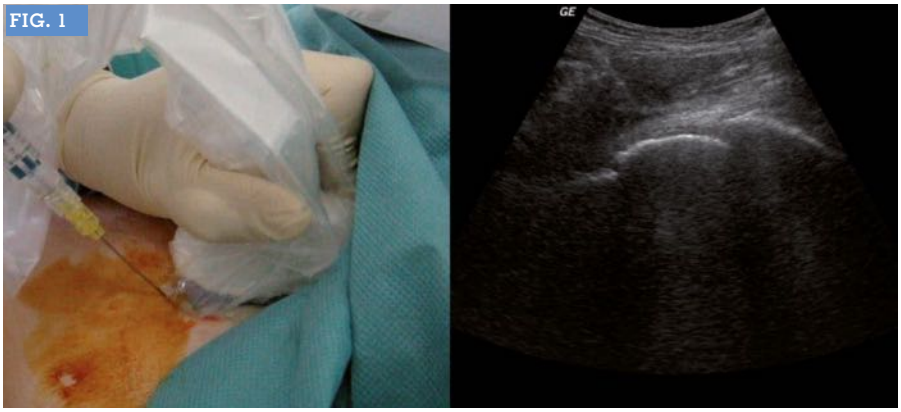
INTRODUCTION

Osteoarthritis (**OA**) is the most common arthritic condition and the main cause of disability amongst the elderly population.

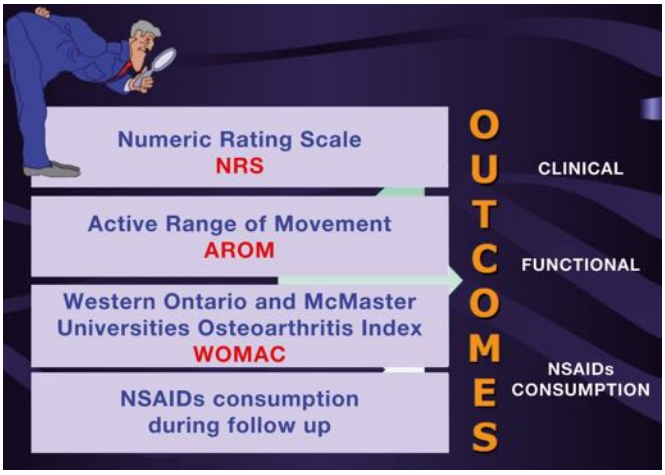
– The hip is the second most commonly affected joint, with a prevalence range between **3%** and **11%** in the population over 35 years of age.

OA of the hip is characterised by the progressive de-structuration of the joint cartilage. Clinically, it presents a progressive increase in pain symptoms associated with joint movement, leading to a loss of segmental function and alteration of motor dynamics.
At the current time, both the pharmacological (NSAIDs, cortisones, low dose medicines and herbal remedies) and non-pharmacological (rehabilitation, physiotherapy, acupuncture) treatment options aim to control pain symptoms, improve the consequent disability and, where possible, restrict the structural damage to the affected joint.

FIG. 1



TAB. 1



– Over the past 15 years, intra-articular injection therapy with hyaluronic acid (HA) has become increasingly extensively used worldwide, supported by the good results obtained in certain investigational clinical studies on the reduction of pain and improvement in joint function, making it possible to postpone the need for hip replacement surgery by several years.
HA is a high-molecular-weight glycosaminoglycan, constituted by a sequential repetition of glucuronic acid and N-acetylglucosamine.

In joints affected by OA, the concentration and molecular weight of physiological HA undergo a 33 - 50% reduction, with an obvious reduction in its effectiveness in protecting the joint.

Intra-articular viscoinduction and viscosupplementation are based on HA's physiological capacity to restore synovial fluid to an optimum viscosity and elasticity and its natural joint-protecting function, overcoming the loss of HA and stimulating its endogenous production, as well as controlling the production and activity of the pro-inflammatory mediators and matrix metalloproteinases.

– **Guna Collagen Medical Devices (MDs)** constitute a significant part of the possible options and therapeutic solutions for the treatment of painful and dysfunctional musculoskeletal conditions, such as OA.

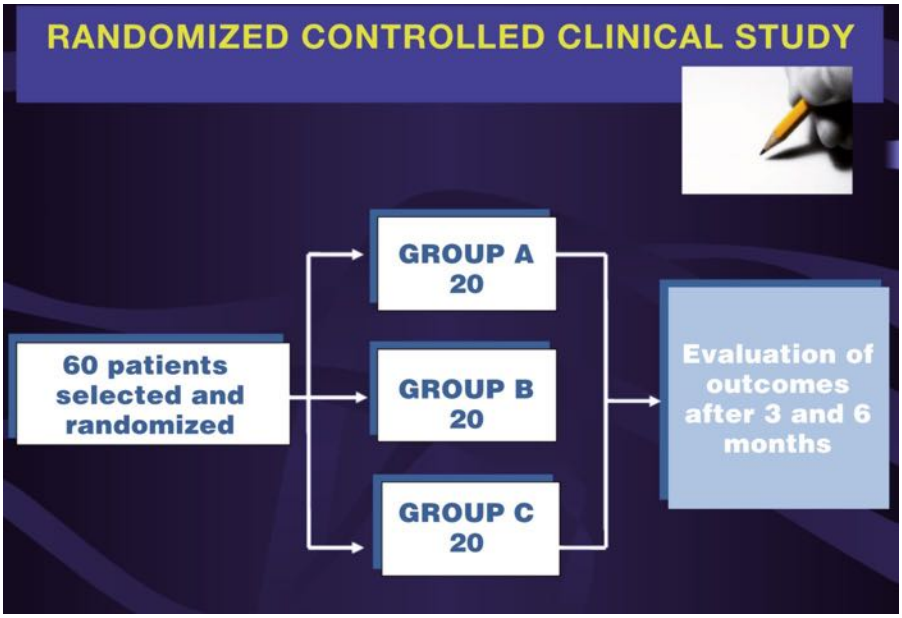
– With their porcine collagen content and ancillary substances of natural origin (vehicular excipients), they allow a **new structuring of the intra-articular tissues** (ligaments and joint cartilage) and **extra-articular tissues** [ligaments, joint capsule, tendons (which are primarily constituted by collagen) and muscles], providing a mechanical scaffold to favour the best arrangement of the damaged collagen fibres and to counter any joint laxity that may cause pain.

– In addition, the Guna Collagen MDs improve the viscoelastic properties of the intra-articular fluid, thanks to the cementing function of the collagen fibres of the proteoglycans of the extracellular matrix.

HA + Guna Collagen MD combination therapy is even more interesting considering the most recent physiopathological hypotheses regarding OA, according to which it is precisely the **extra-articular segment**, which is far more-richly vascularised, that is the *primum movens* of the pathological process.

– The aim of this study was to evaluate the therapeutic efficacy of **HA + MD combination therapy** in **osteoarthritis of the hip**.

TAB. 2



PATIENTS AND METHODS

This clinical study involved patients of both genders (51-77 years of age), who referred to the University Physical Medicine and Rehabilitation Unit - Turin - Italy for hip joint pain.
The following inclusion criteria were used:

- diagnosis of primary OA for more than 12 months, according to *American College of Rheumatology* criteria;
- Kellgren-Lawrence radiological clas-

sification: **grades II-III**;
- moderate-severe pain with Numerical Rating Scale (NRS): score > 5, without taking NSAIDs;
- walking possible for intermediate distances (> 50 m), without aids.

Patients satisfying any of the following criteria were excluded from the study:
- diagnosis of RA, chondrocalcinosis, psoriasis, metabolic bone disease, gout, active phase infections;
- OA with rapid impairment, significant or congenital dysplasia of the acetabulum or head of the femur;
- symptomatic bilateral OA of the hip;
- previous injections of HA and/or intra-articular or oral cortisone therapy taken in the month prior to inclusion;
- mental illness;
- oral anticoagulant therapy, pregnancy, obesity;
- orthopaedic or neurological conditions compromising ability to walk.

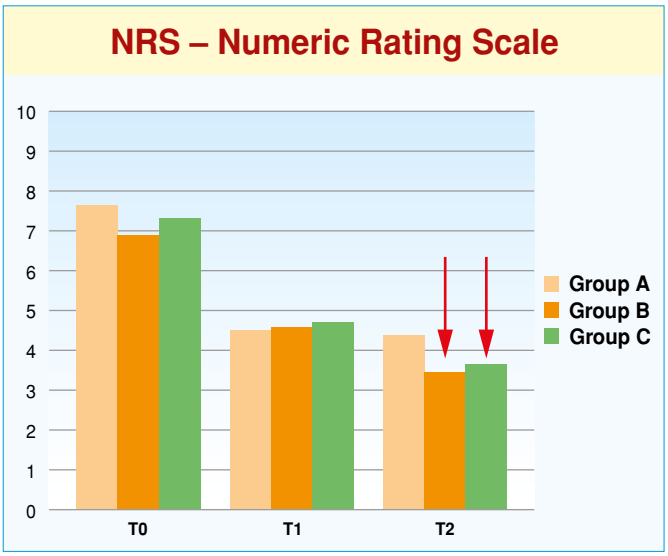
Having received specific information on the potential risks of intra-articular therapy and having given their written informed consent – the enrolled patients were randomised to one of three Groups (**A, B, C**).

– **Group A** received a cycle of 3 intra-articular injections of high-molecular-weight HA (MW 500-700,000, 20 mg/2mL, **Hyalubrix**, Fidia Farmaceutici Spa) at 10-day intervals.

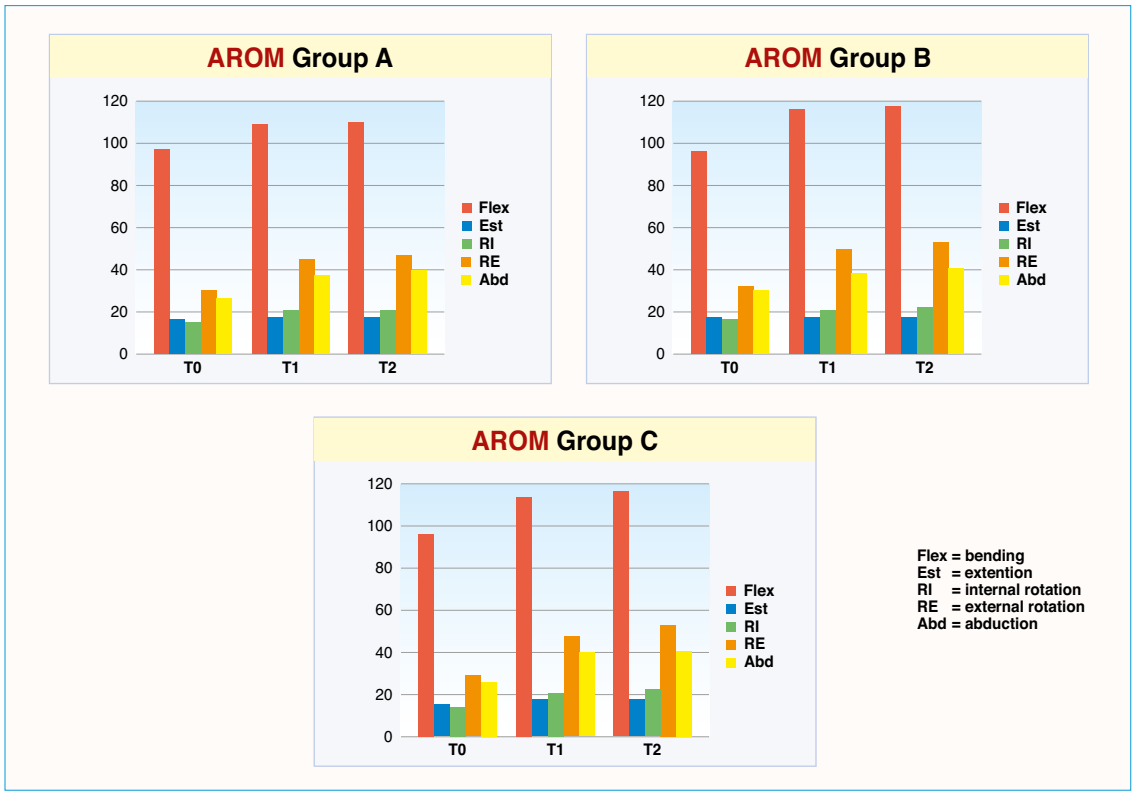
– **Group B** received a cycle of 3 intra-articular injections of high-molecular weight HA (MW 500-700,000, 20 mg/2mL, **Hyalubrix**) and peri-capsular injections of **MD-Hip** (Guna Spa - Milan) (2 ampoules) at T0, T14 and T35, alternated with 2 peri-/intracapsular injections with **MD-Hip** (2 ampoules) at T7 and T21.

– **Group C** received a cycle of 2 intra-articular injections of high-molecular weight HA (MW 500- 700,000, 20 mg/2mL, **Hyalubrix**) and peri-capsular injections of **MD-Hip** (2 ampoules) at T7 and T14, alternated with 2 peri-/intra-

TAB. 3



TAB. 4



capsular injections with **MD-Hip** (2 ampoules) at T0, T14 and T35.

The patients included in the 3 Groups were also trained, by means of a short cycle of specific group rehabilitation sessions (*Hip School*), to correctly perform an exercise protocol to be repeated at home as self-treatment, at least 3 times a week.

The peri- and intra-articular injection treatment was administered under ultrasound guidance, using a Convex 3.5-MHz transducer with a standard technique (FIG. 1).

A number of clinical studies published in literature agree on the fact that multiple articular injection treatment does not present a higher risk of adverse events or post-hip replacement infections than single articular injection.

Clinical and functional outcomes were measured at **3** and **6 months** from the first injection treatment.

The following were quantified:
1) pain using the NRS;
2) active range of movement (AROM) of the hip;
3) functional capacities;
4) pain using the WOMAC Index (*Western Ontario and McMaster Universities Osteoarthritis Index*), a multidimensional tool evaluating 17 functional patient activities, in addition to the 5 influenced by pain and the 2 items regarding joint stiffness.

In addition, any use of NSAIDs by the patients throughout the entire follow-up period and the occurrence of any adverse events was also recorded (TAB. 1).

RESULTS

The study was conducted on **60 patients** who met the inclusion and exclusion criteria and were randomised, stratified by gender and age, in the order of 20 subjects to each treatment Group (Group A, B, and C) (TAB. 2).
No patient abandoned the study before the 6-month follow-up.

– Pain measured using the NRS had dropped in all 3 treatment Groups at the 3-month visit (T1) and to an even greater extent at 6 months (T2) in Groups **B** and **C** (TAB. 3).

– The active range of movement (AROM) progressively improved on all spatial planes in all 3 Groups (TAB. 4).

By plotting a graph of the sum of the articular gain obtained by patients in the single Groups at 3 and 6 months, a higher, progressive increase in *articular gain* is observed for Groups **B** and **C** (TAB. 5).

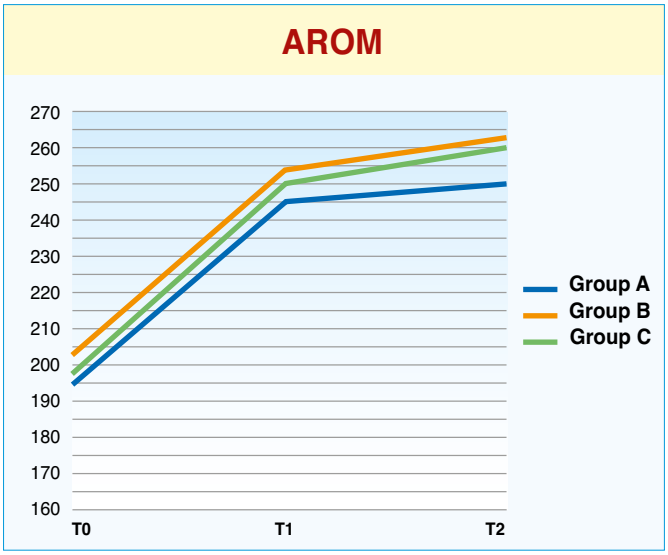
The WOMAC global score showed an improvement in functional activities for all patients, especially amongst Group **B** patients at the 6-month visit (TAB. 6).

By breaking the WOMAC index down into its 3 main items (*pain score, stiffness score, function score*), the function score increased progressively at both 3 and 6 months in Groups **B** and **C** (TAB. 7).

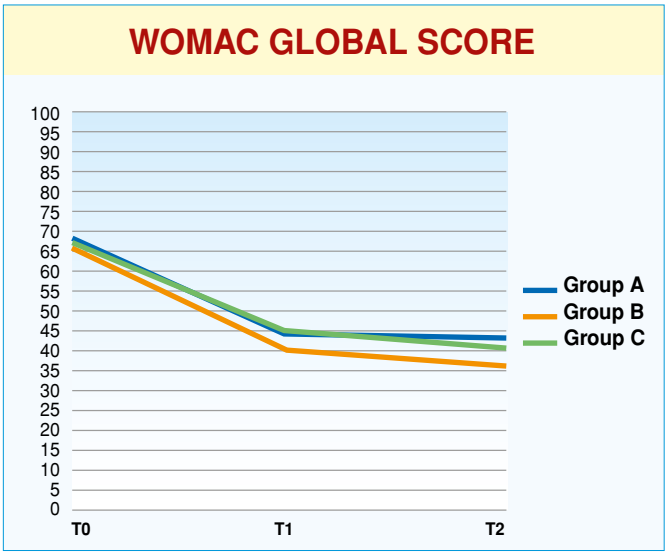
In the 3 Groups, there was a modest and homogeneous increase in the use of NSAIDs over time (TAB. 8).
No adverse events were recorded.

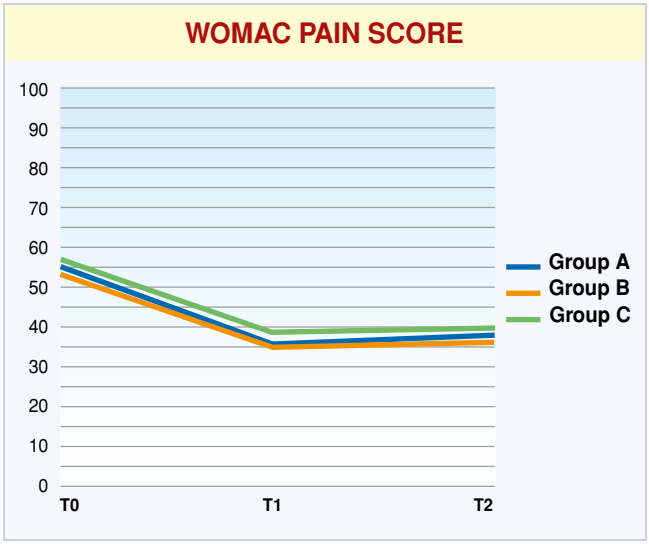
– All patients included in the study showed good compliance as regards performance at least three times a week of the home exercise programme that they had been taught (TAB. 9).

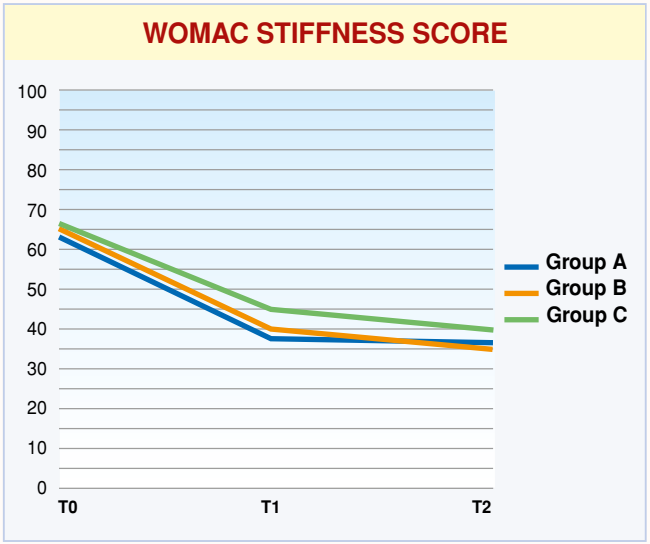
TAB. 5

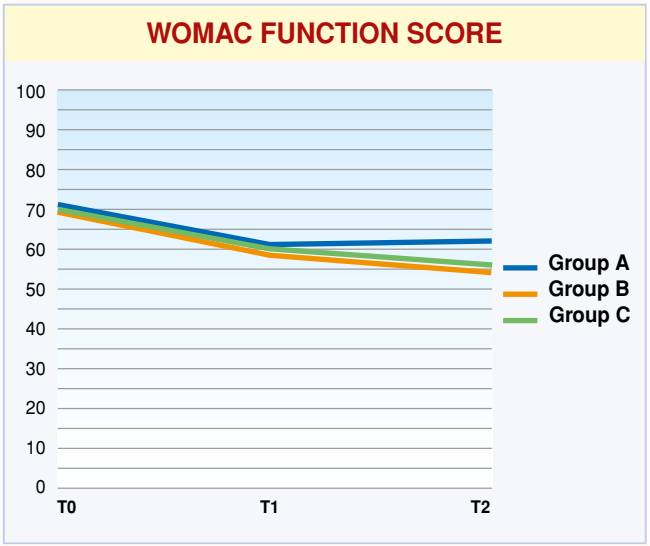


TAB. 6



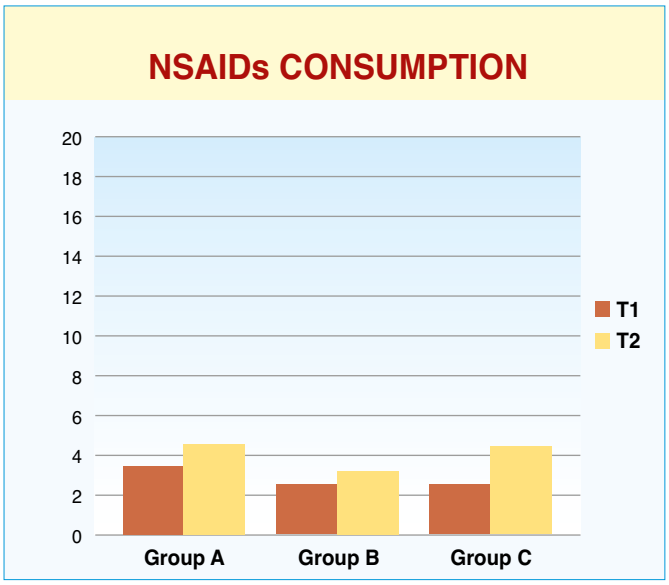






TAB. 7

TAB. 8



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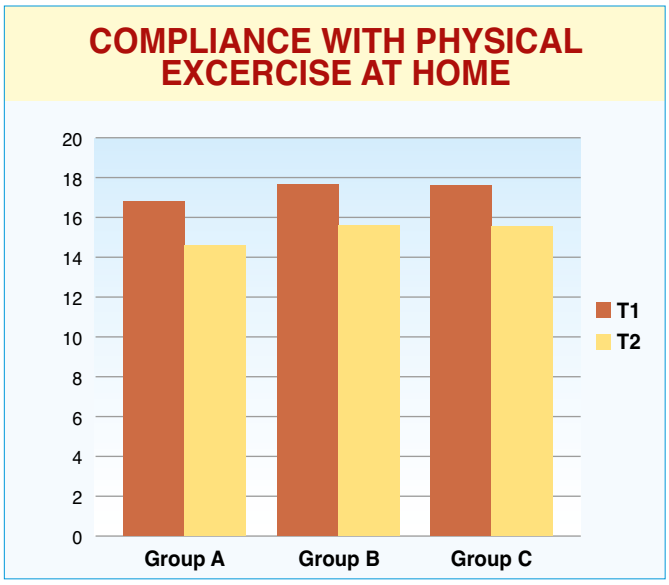

CONCLUSIONS

The results obtained in this controlled, randomised, clinical study conducted on a homogeneous population with symptomatic osteoarthritis of the hip were those hypothesised during the initial study design phase.

– **HA + MD-Hip** combination therapy makes it possible to obtain **a more significant** and **longer-lasting** improvement in terms of **pain**, **overall range of movement** of the hip and, above all, its **function** than with treatment with HA alone.

The use of MD-Hip fills an unmet therapeutic need, making it possible to obtain **better clinical results**, by acting on the **periarticular tissues** that play a crucial role in the pathogenesis of osteoarthritic conditions.

– Moreover, this combination therapy also makes it possible to reduce the number of articular injections of HA, without compromising the therapeutic result, especially with regard to daily activities.

– As has already been highlighted several times in literature, good compliance in performing a specific home exercise programme with a certain constancy affects the final therapeutic result.

– During the clinical study, MD-Hip did not show any negative side effect and was seen to have an excellent safety profile. ■

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CLINICAL

THE ROLE OF MD-HIP IN ULTRASOUND-GUIDED INJECTION THERAPY IN OSTEOARTHRITIS OF THE HIP

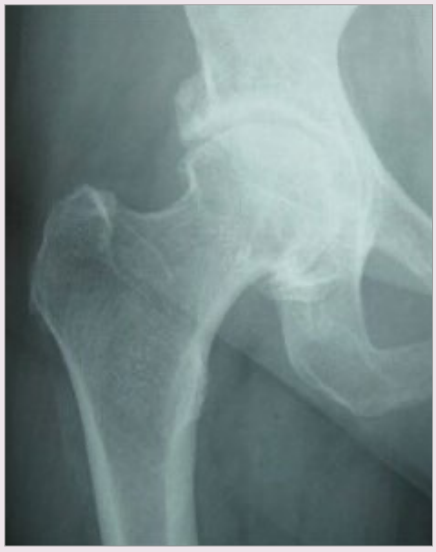
ABSTRACT

Osteoarthritis of the hip is a commonly observed disease in outpatient clinics dedicated to musculoskeletal pain management. The non-surgical therapeutic tools at our disposal are few and not always effective, especially in the advanced stages of the disease, in which joint damage is considerable.
In recent years, joint injection therapy with hyaluronic acid has become common, using an ultrasound-guided technique to improve the safety and appropriateness of the injection.
In literature, data on the efficacy of this treatment are more than encouraging.
– The combined use of hyaluronic acid and Collagen Medical Device MD-HIP via intra-articular and peri-articular injections are a valuable therapeutic tool in the treatment of hip osteoarthritis.

– This study aimed to assess its effectiveness on pain, functionality, tolerability, and safety.

KEY WORDS

COLLAGEN MEDICAL DEVICE, HYALURONIC ACID, MD-HIP, OSTEOARTHRITIS, PAIN, REHABILITATION, INJECTION, ULTRASOUND



https://www.boneclinic.com.sg/orthopaedic-conditions/hip-pain/hip-osteoarthritis/

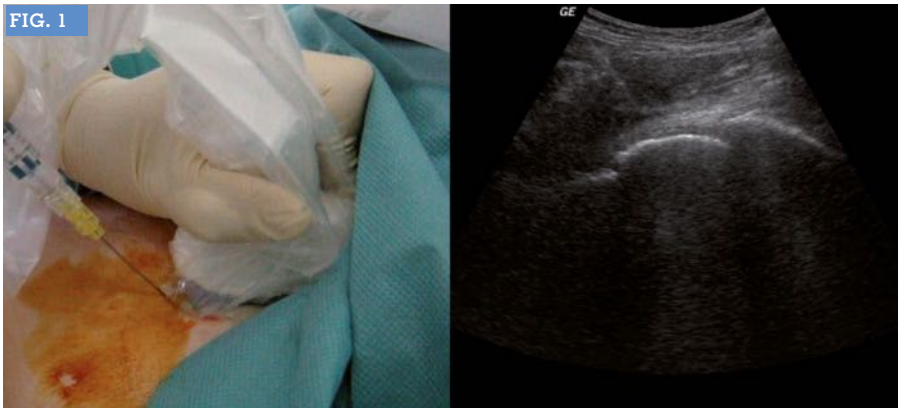
INTRODUCTION

Osteoarthritis (**OA**) is the most common arthritic condition and the main cause of disability amongst the elderly population.

– The hip is the second most commonly affected joint, with a prevalence range between **3%** and **11%** in the population over 35 years of age.

OA of the hip is characterised by the progressive de-structuration of the joint cartilage. Clinically, it presents a progressive increase in pain symptoms associated with joint movement, leading to a loss of segmental function and alteration of motor dynamics.
At the current time, both the pharmacological (NSAIDs, cortisones, low dose medicines and herbal remedies) and non-pharmacological (rehabilitation, physiotherapy, acupuncture) treatment options aim to control pain symptoms, improve the consequent disability and, where possible, restrict the structural damage to the affected joint.

FIG. 1



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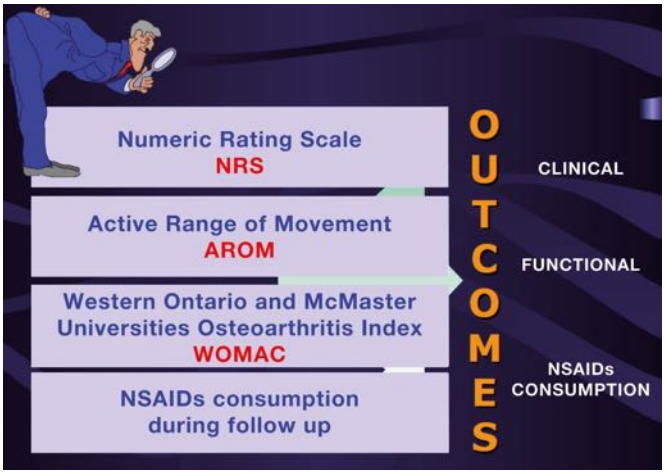


– Over the past 15 years, intra-articular injection therapy with hyaluronic acid (HA) has become increasingly extensively used worldwide, supported by the good results obtained in certain investigational clinical studies on the reduction of pain and improvement in joint function, making it possible to postpone the need for hip replacement surgery by several years.
HA is a high-molecular-weight glycosaminoglycan, constituted by a sequential repetition of glucuronic acid and N-acetylglucosamine.

In joints affected by OA, the concentration and molecular weight of physiological HA undergo a 33 - 50% reduction, with an obvious reduction in its effectiveness in protecting the joint.

Intra-articular viscoinduction and viscosupplementation are based on HA's physiological capacity to restore synovial fluid to an optimum viscosity and elasticity and its natural joint-protecting function, overcoming the loss of HA and stimulating its endogenous production, as well as controlling the production and activity of the pro-inflammatory mediators and matrix metalloproteinases.

– **Guna Collagen Medical Devices (MDs)** constitute a significant part of the possible options and therapeutic solutions for the treatment of painful and dysfunctional musculoskeletal conditions, such as OA.

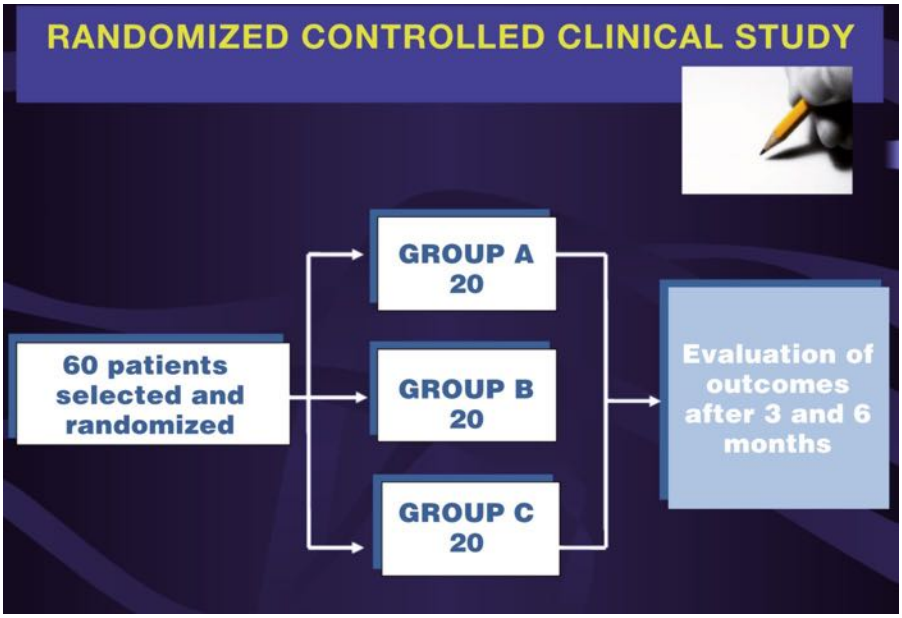
– With their porcine collagen content and ancillary substances of natural origin (vehicular excipients), they allow a **new structuring of the intra-articular tissues** (ligaments and joint cartilage) and **extra-articular tissues** [ligaments, joint capsule, tendons (which are primarily constituted by collagen) and muscles], providing a mechanical scaffold to favour the best arrangement of the damaged collagen fibres and to counter any joint laxity that may cause pain.

– In addition, the Guna Collagen MDs improve the viscoelastic properties of the intra-articular fluid, thanks to the cementing function of the collagen fibres of the proteoglycans of the extracellular matrix.

HA + Guna Collagen MD combination therapy is even more interesting considering the most recent physiopathological hypotheses regarding OA, according to which it is precisely the **extra-articular segment**, which is far more-richly vascularised, that is the *primum movens* of the pathological process.

– The aim of this study was to evaluate the therapeutic efficacy of **HA + MD combination therapy** in **osteoarthritis of the hip**.

TAB. 2



PATIENTS AND METHODS

This clinical study involved patients of both genders (51-77 years of age), who referred to the University Physical Medicine and Rehabilitation Unit - Turin - Italy for hip joint pain.
The following inclusion criteria were used:

- diagnosis of primary OA for more than 12 months, according to *American College of Rheumatology* criteria;
- Kellgren-Lawrence radiological clas-

sification: **grades II-III**;
- moderate-severe pain with Numerical Rating Scale (NRS): score > 5, without taking NSAIDs;
- walking possible for intermediate distances (> 50 m), without aids.

Patients satisfying any of the following criteria were excluded from the study:
- diagnosis of RA, chondrocalcinosis, psoriasis, metabolic bone disease, gout, active phase infections;
- OA with rapid impairment, significant or congenital dysplasia of the acetabulum or head of the femur;
- symptomatic bilateral OA of the hip;
- previous injections of HA and/or intra-articular or oral cortisone therapy taken in the month prior to inclusion;
- mental illness;
- oral anticoagulant therapy, pregnancy, obesity;
- orthopaedic or neurological conditions compromising ability to walk.

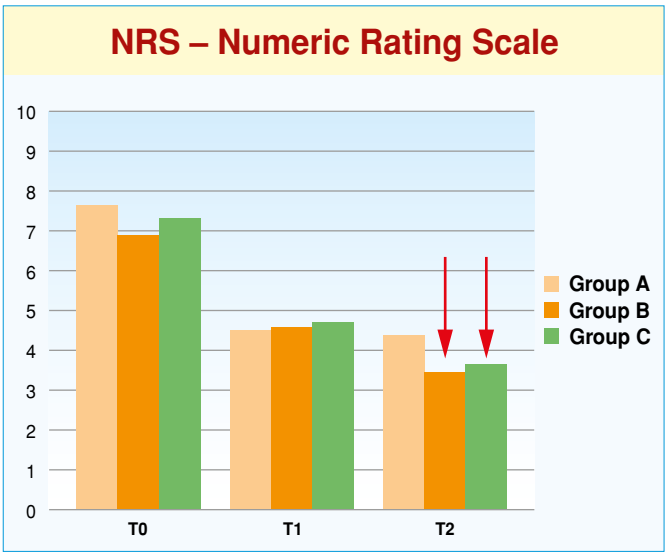
Having received specific information on the potential risks of intra-articular therapy and having given their written informed consent – the enrolled patients were randomised to one of three Groups (**A, B, C**).

– **Group A** received a cycle of 3 intra-articular injections of high-molecular-weight HA (MW 500-700,000, 20 mg/2mL, **Hyalubrix**, Fidia Farmaceutici Spa) at 10-day intervals.

– **Group B** received a cycle of 3 intra-articular injections of high-molecular weight HA (MW 500-700,000, 20 mg/2mL, **Hyalubrix**) and peri-capsular injections of **MD-Hip** (Guna Spa - Milan) (2 ampoules) at T0, T14 and T35, alternated with 2 peri-/intracapsular injections with **MD-Hip** (2 ampoules) at T7 and T21.

– **Group C** received a cycle of 2 intra-articular injections of high-molecular weight HA (MW 500- 700,000, 20 mg/2mL, **Hyalubrix**) and peri-capsular injections of **MD-Hip** (2 ampoules) at T7 and T14, alternated with 2 peri-/intra-

TAB. 3



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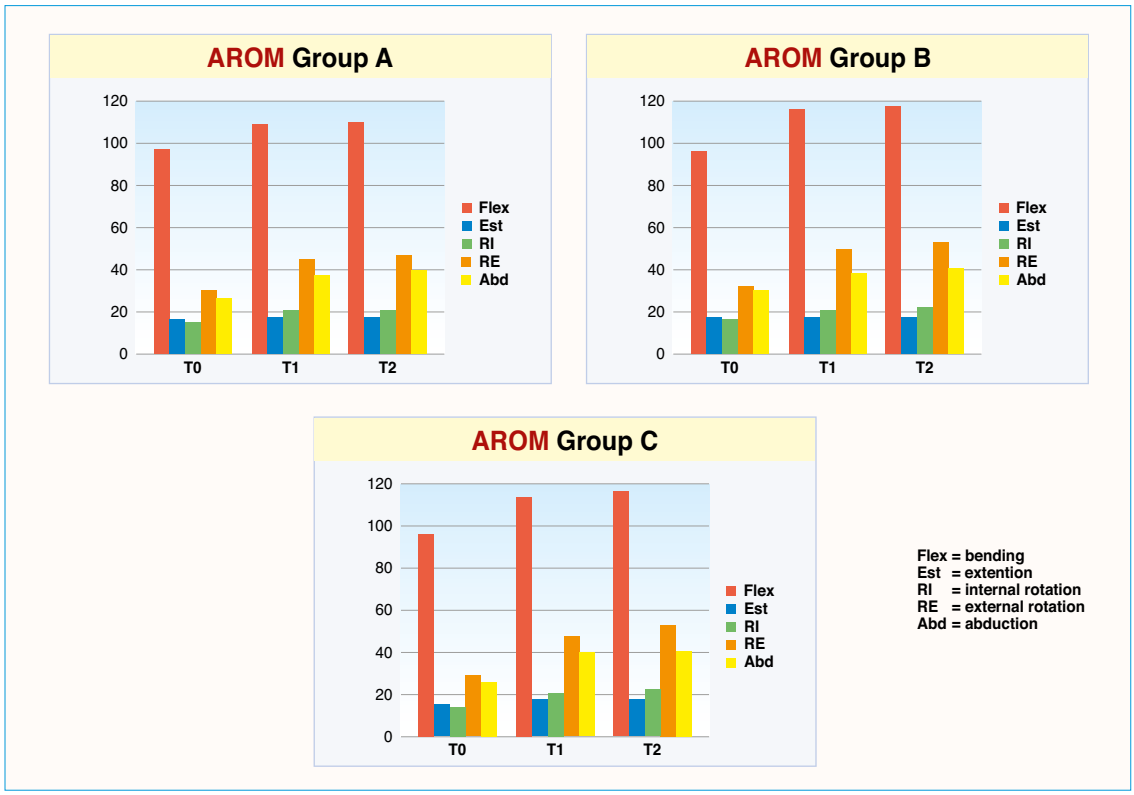


capsular injections with **MD-Hip** (2 ampoules) at T0, T14 and T35.

The patients included in the 3 Groups were also trained, by means of a short cycle of specific group rehabilitation sessions (*Hip School*), to correctly perform an exercise protocol to be repeated at home as self-treatment, at least 3 times a week.

The peri- and intra-articular injection treatment was administered under ultrasound guidance, using a Convex 3.5-MHz transducer with a standard technique (FIG. 1).

A number of clinical studies published in literature agree on the fact that multiple articular injection treatment does not present a higher risk of adverse events or post-hip replacement infections than single articular injection.

Clinical and functional outcomes were measured at **3** and **6 months** from the first injection treatment.

The following were quantified:
1) pain using the NRS;
2) active range of movement (AROM) of the hip;
3) functional capacities;
4) pain using the WOMAC Index (*Western Ontario and McMaster Universities Osteoarthritis Index*), a multidimensional tool evaluating 17 functional patient activities, in addition to the 5 influenced by pain and the 2 items regarding joint stiffness.

In addition, any use of NSAIDs by the patients throughout the entire follow-up period and the occurrence of any adverse events was also recorded (TAB. 1).

RESULTS

The study was conducted on **60 patients** who met the inclusion and exclusion criteria and were randomised, stratified by gender and age, in the order of 20 subjects to each treatment Group (Group A, B, and C) (TAB. 2).
No patient abandoned the study before the 6-month follow-up.

– Pain measured using the NRS had dropped in all 3 treatment Groups at the 3-month visit (T1) and to an even greater extent at 6 months (T2) in Groups **B** and **C** (TAB. 3).

– The active range of movement (AROM) progressively improved on all spatial planes in all 3 Groups (TAB. 4).

By plotting a graph of the sum of the articular gain obtained by patients in the single Groups at 3 and 6 months, a higher, progressive increase in *articular gain* is observed for Groups **B** and **C** (TAB. 5).

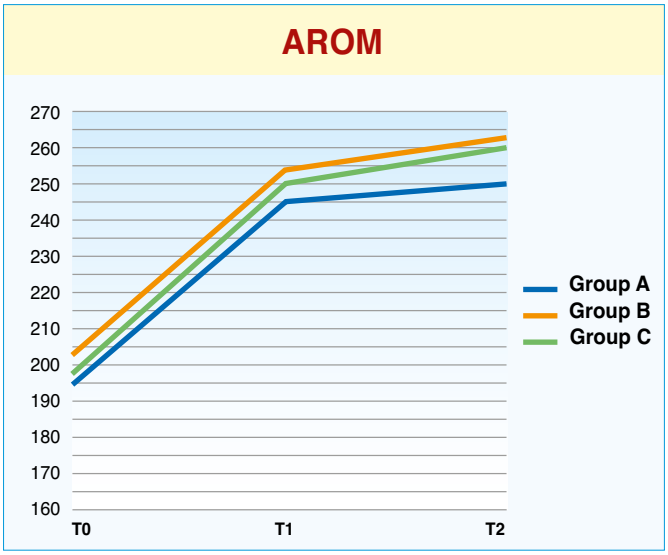
The WOMAC global score showed an improvement in functional activities for all patients, especially amongst Group **B** patients at the 6-month visit (TAB. 6).

By breaking the WOMAC index down into its 3 main items (*pain score, stiffness score, function score*), the function score increased progressively at both 3 and 6 months in Groups **B** and **C** (TAB. 7).

In the 3 Groups, there was a modest and homogeneous increase in the use of NSAIDs over time (TAB. 8).
No adverse events were recorded.

– All patients included in the study showed good compliance as regards performance at least three times a week of the home exercise programme that they had been taught (TAB. 9).

TAB. 5



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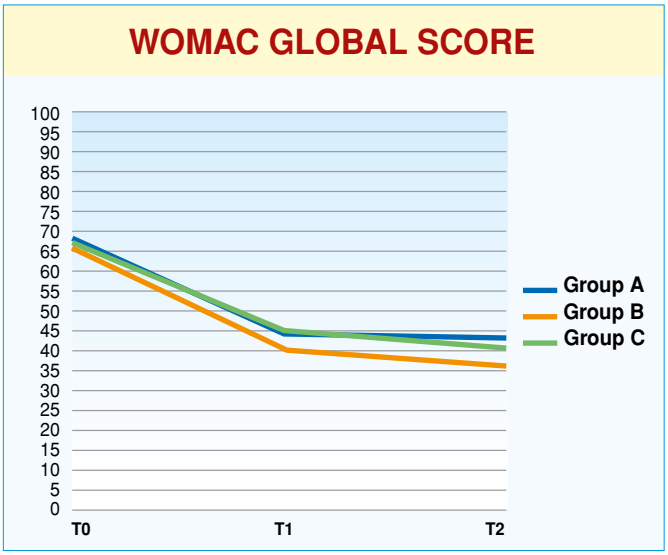

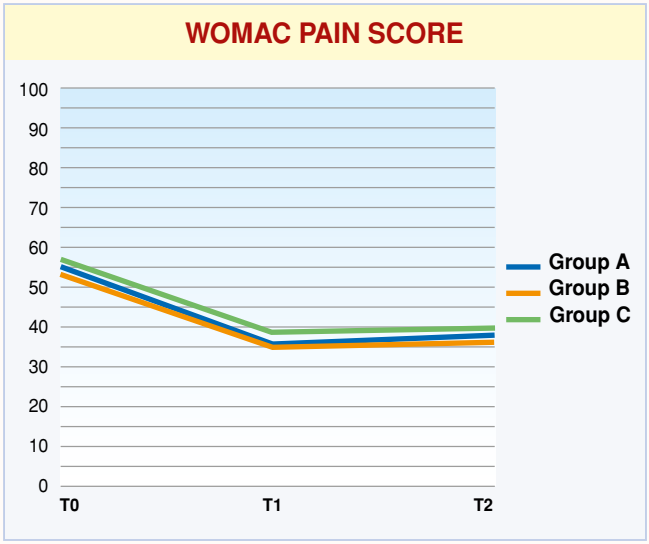

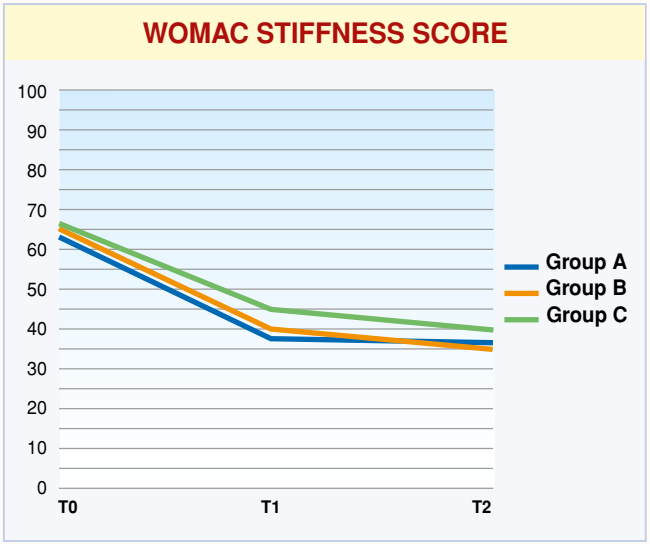

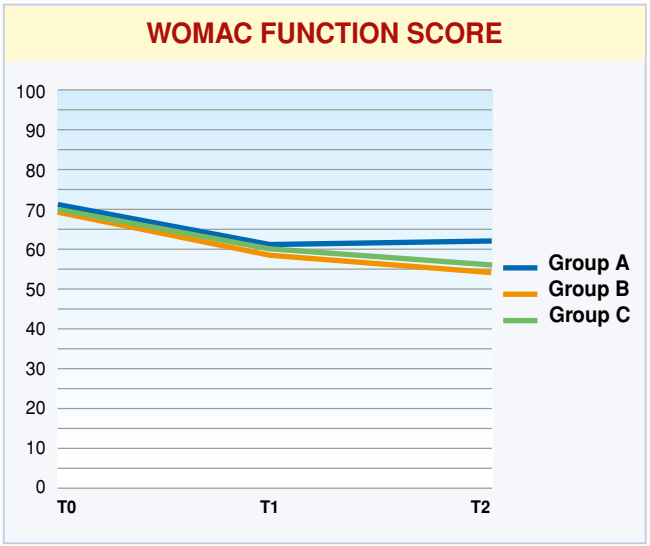

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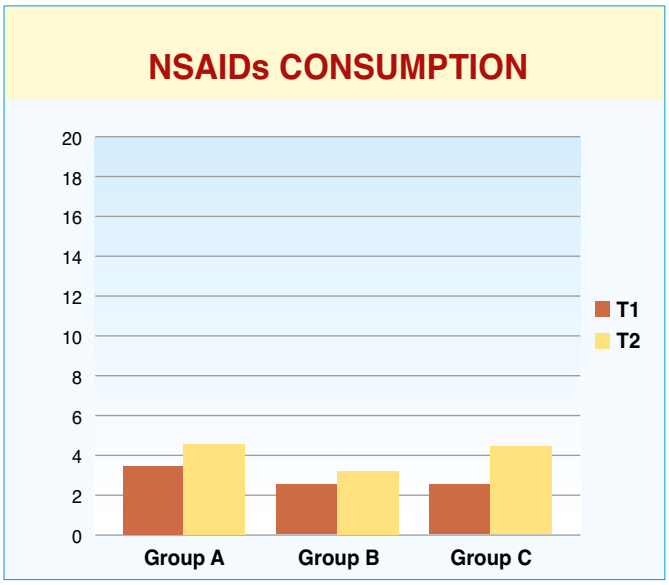

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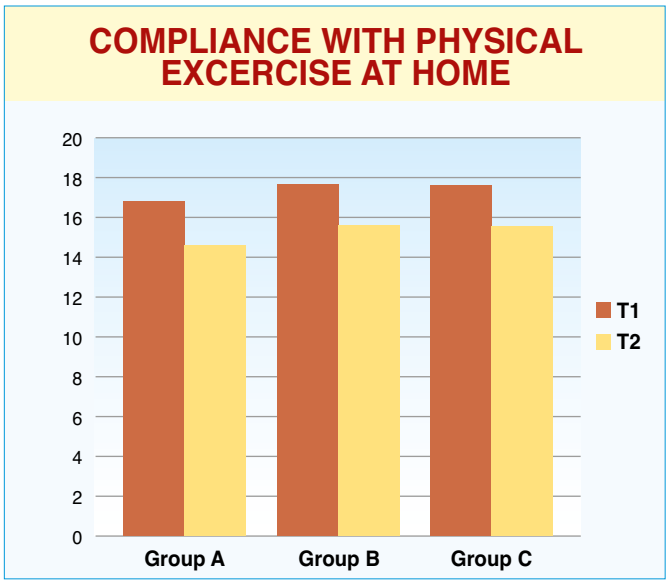

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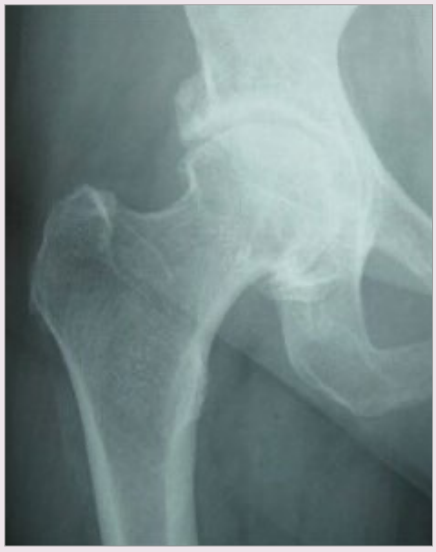

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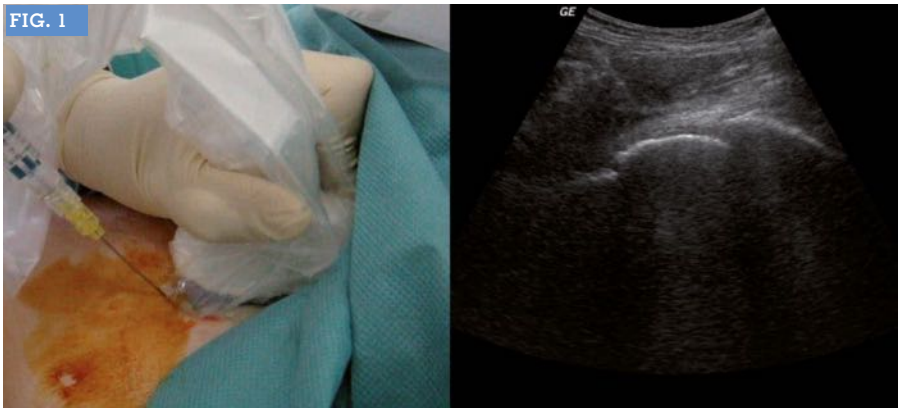

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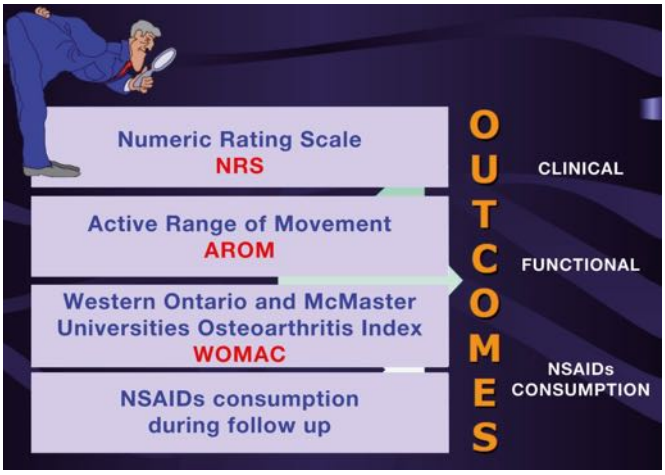

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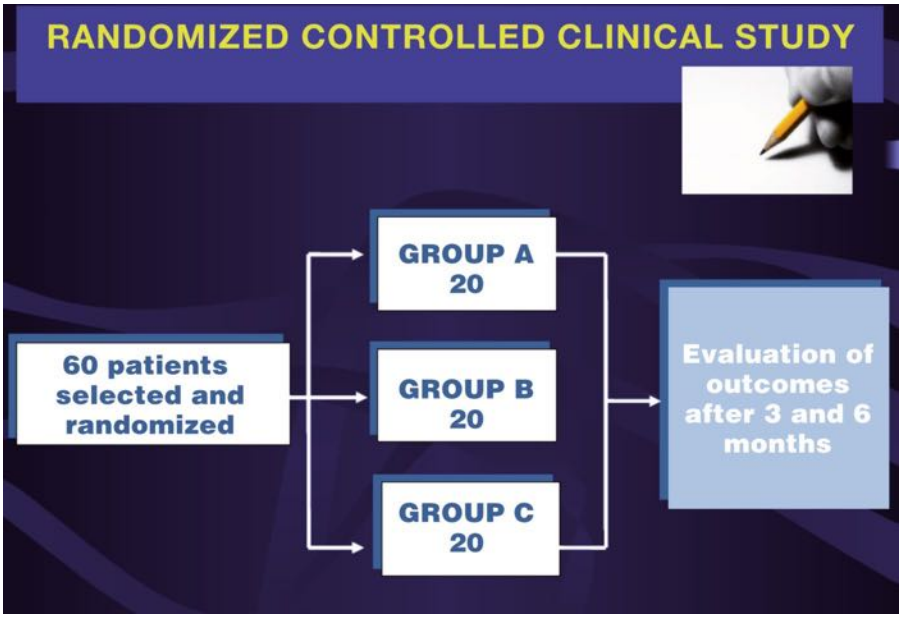

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This clinical study involved patients of both genders (51-77 years of age), who referred to the University Physical Medicine and Rehabilitation Unit - Turin - Italy for hip joint pain.
The following inclusion criteria were used:

- diagnosis of primary OA for more than 12 months, according to *American College of Rheumatology* criteria;
- Kellgren-Lawrence radiological clas-

sification: **grades II-III**;
- moderate-severe pain with Numerical Rating Scale (NRS): score > 5, without taking NSAIDs;
- walking possible for intermediate distances (> 50 m), without aids.

Patients satisfying any of the following criteria were excluded from the study:
- diagnosis of RA, chondrocalcinosis, psoriasis, metabolic bone disease, gout, active phase infections;
- OA with rapid impairment, significant or congenital dysplasia of the acetabulum or head of the femur;
- symptomatic bilateral OA of the hip;
- previous injections of HA and/or intra-articular or oral cortisone therapy taken in the month prior to inclusion;
- mental illness;
- oral anticoagulant therapy, pregnancy, obesity;
- orthopaedic or neurological conditions compromising ability to walk.

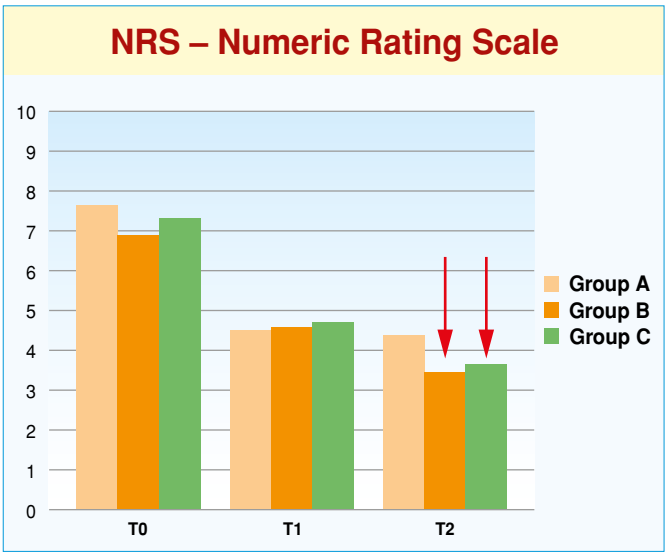
Having received specific information on the potential risks of intra-articular therapy and having given their written informed consent – the enrolled patients were randomised to one of three Groups (**A, B, C**).

– **Group A** received a cycle of 3 intra-articular injections of high-molecular-weight HA (MW 500-700,000, 20 mg/2mL, **Hyalubrix**, Fidia Farmaceutici Spa) at 10-day intervals.

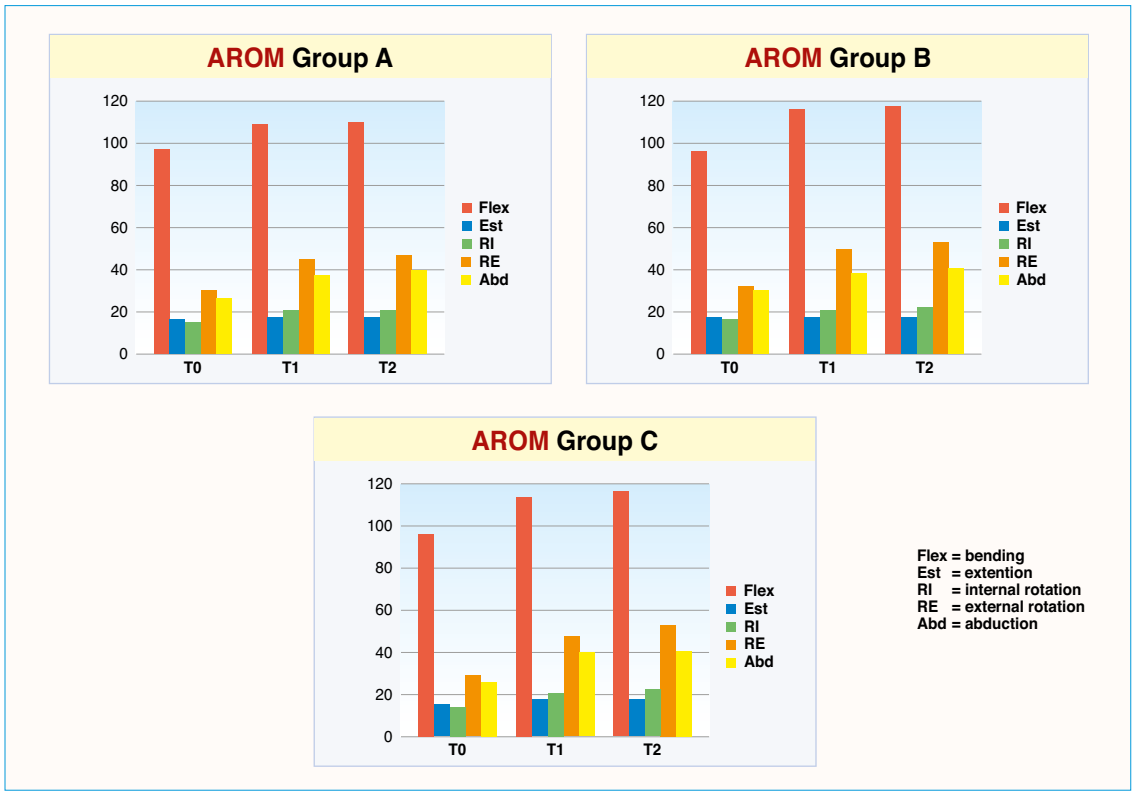
– **Group B** received a cycle of 3 intra-articular injections of high-molecular weight HA (MW 500-700,000, 20 mg/2mL, **Hyalubrix**) and peri-capsular injections of **MD-Hip** (Guna Spa - Milan) (2 ampoules) at T0, T14 and T35, alternated with 2 peri-/intracapsular injections with **MD-Hip** (2 ampoules) at T7 and T21.

– **Group C** received a cycle of 2 intra-articular injections of high-molecular weight HA (MW 500- 700,000, 20 mg/2mL, **Hyalubrix**) and peri-capsular injections of **MD-Hip** (2 ampoules) at T7 and T14, alternated with 2 peri-/intra-

TAB. 3



TAB. 4



capsular injections with **MD-Hip** (2 ampoules) at T0, T14 and T35.

The patients included in the 3 Groups were also trained, by means of a short cycle of specific group rehabilitation sessions (*Hip School*), to correctly perform an exercise protocol to be repeated at home as self-treatment, at least 3 times a week.

The peri- and intra-articular injection treatment was administered under ultrasound guidance, using a Convex 3.5-MHz transducer with a standard technique (FIG. 1).

A number of clinical studies published in literature agree on the fact that multiple articular injection treatment does not present a higher risk of adverse events or post-hip replacement infections than single articular injection.

Clinical and functional outcomes were measured at **3** and **6 months** from the first injection treatment.

The following were quantified:
1) pain using the NRS;
2) active range of movement (AROM) of the hip;
3) functional capacities;
4) pain using the WOMAC Index (*Western Ontario and McMaster Universities Osteoarthritis Index*), a multidimensional tool evaluating 17 functional patient activities, in addition to the 5 influenced by pain and the 2 items regarding joint stiffness.

In addition, any use of NSAIDs by the patients throughout the entire follow-up period and the occurrence of any adverse events was also recorded (TAB. 1).

RESULTS

The study was conducted on **60 patients** who met the inclusion and exclusion criteria and were randomised, stratified by gender and age, in the order of 20 subjects to each treatment Group (Group A, B, and C) (TAB. 2).
No patient abandoned the study before the 6-month follow-up.

– Pain measured using the NRS had dropped in all 3 treatment Groups at the 3-month visit (T1) and to an even greater extent at 6 months (T2) in Groups **B** and **C** (TAB. 3).

– The active range of movement (AROM) progressively improved on all spatial planes in all 3 Groups (TAB. 4).

By plotting a graph of the sum of the articular gain obtained by patients in the single Groups at 3 and 6 months, a higher, progressive increase in *articular gain* is observed for Groups **B** and **C** (TAB. 5).

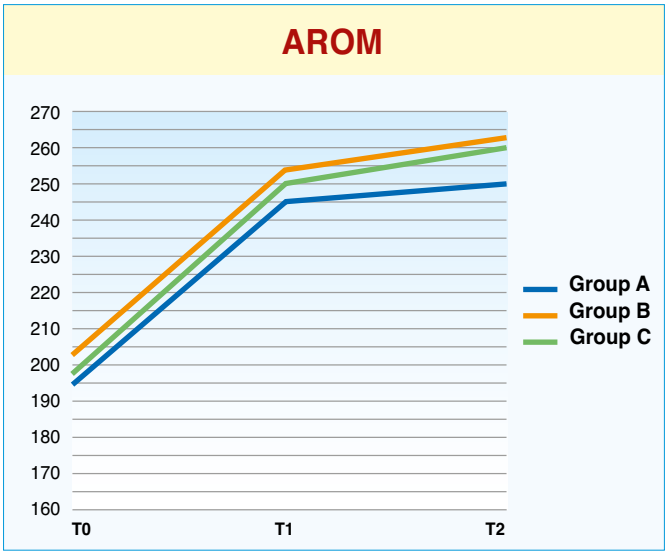
The WOMAC global score showed an improvement in functional activities for all patients, especially amongst Group **B** patients at the 6-month visit (TAB. 6).

By breaking the WOMAC index down into its 3 main items (*pain score, stiffness score, function score*), the function score increased progressively at both 3 and 6 months in Groups **B** and **C** (TAB. 7).

In the 3 Groups, there was a modest and homogeneous increase in the use of NSAIDs over time (TAB. 8).
No adverse events were recorded.

– All patients included in the study showed good compliance as regards performance at least three times a week of the home exercise programme that they had been taught (TAB. 9).

TAB. 5



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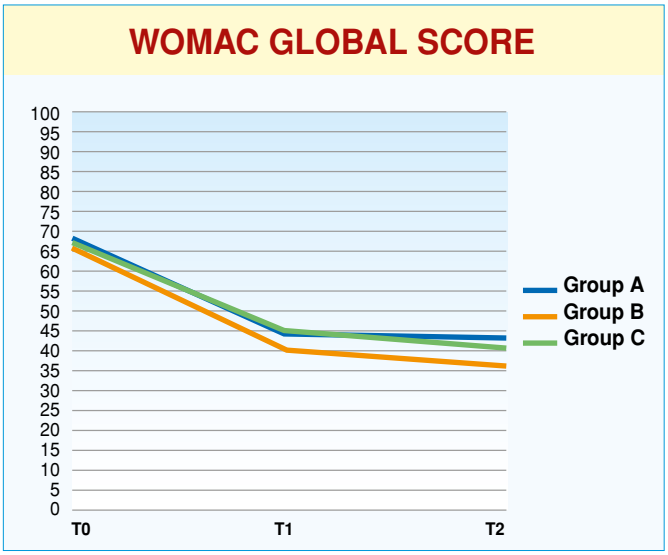
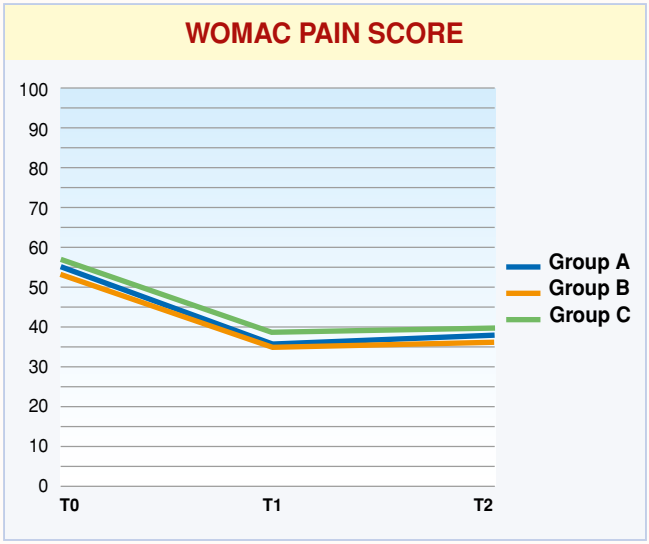
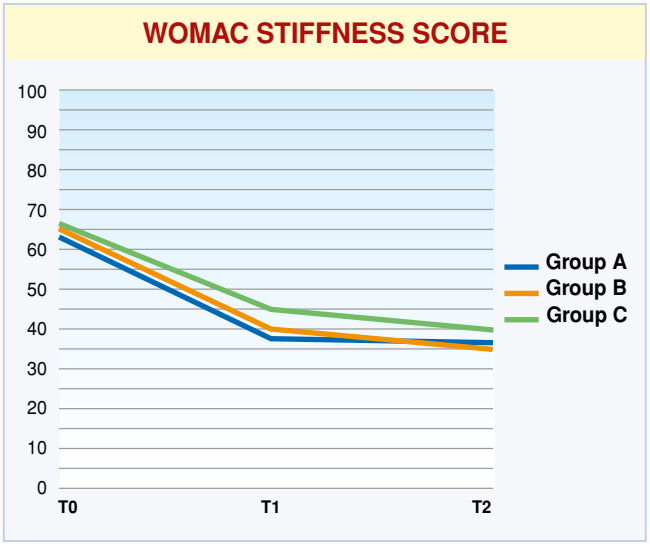
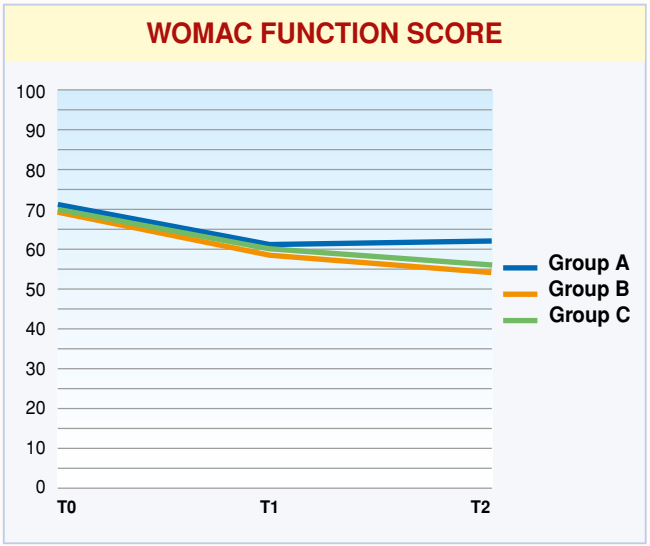


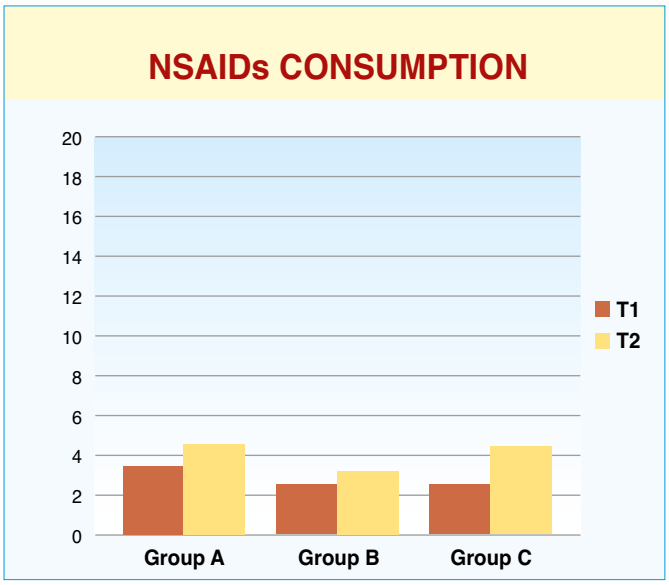




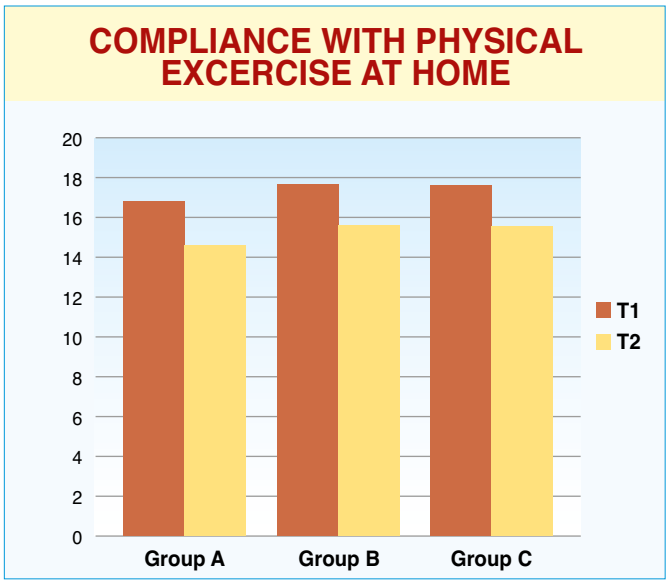


TAB. 7

TAB. 8



TAB. 9



CONCLUSIONS

The results obtained in this controlled, randomised, clinical study conducted on a homogeneous population with symptomatic osteoarthritis of the hip were those hypothesised during the initial study design phase.

– **HA + MD-Hip** combination therapy makes it possible to obtain **a more significant** and **longer-lasting** improvement in terms of **pain**, **overall range of movement** of the hip and, above all, its **function** than with treatment with HA alone.

The use of MD-Hip fills an unmet therapeutic need, making it possible to obtain **better clinical results**, by acting on the **periarticular tissues** that play a crucial role in the pathogenesis of osteoarthritic conditions.

– Moreover, this combination therapy also makes it possible to reduce the number of articular injections of HA, without compromising the therapeutic result, especially with regard to daily activities.

– As has already been highlighted several times in literature, good compliance in performing a specific home exercise programme with a certain constancy affects the final therapeutic result.

– During the clinical study, MD-Hip did not show any negative side effect and was seen to have an excellent safety profile. ■

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CLINICAL

M. Ottaviani

TREATMENT OF JOINT CONDITIONS WITH GUNA COLLAGEN MEDICAL DEVICES

– CLINICAL STUDY ON 257 PATIENTS

SUMMARY

Collagen is the main extracellular structural protein to be found in the connective tissue and bone tissue of most animals. In humans aged about 50 years its synthesis begins to reduce, with consequent cartilage and tendon degeneration and inevitable development of osteoarthritis and tendonitis. Since these degenerative conditions are very common and evolve towards pain and joint stiffness, there is an urgent need for tools that allow practitioners not only to limit this degenerative evolution, but also, in certain cases, to induce its regression.

This clinical study was conducted on 257 patients with joint and tendon disorders (impingement syndrome, shoulder tendinopathy, hip arthritis, knee arthritis, trapeziometacarpal osteoarthritis, Achilles' tendinopathy) frequently reflected in clinical evidence, such as pain and joint stiffness; they were all treated exclusively with local injections of Guna Collagen Medical Devices.

The data were collected through self-assessment scales, validated by the WHO and the results showed that Guna Collagen MD can give a useful contribution to containing the problems associated with joint degeneration.

PAROLE CHIAVE

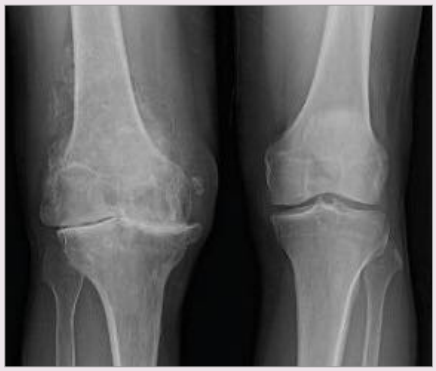
GUNA COLLAGEN MEDICAL DEVICES, COLLAGEN, OSTEOARTRHITIS, TENDINOPATHY, PAIN

INTRODUCTION

Collagen is a glycoprotein characterised by a structure in which a simple **basic module** is repeated: collagen molecules join together to form a collagen fibril; a union in which each molecule overlaps with that above by one quarter of its length.

This creates a kind of *wall*, in which the individual bricks that make it up are staggered in order to achieve considerable resistance to both incident tangential and perpendicular forces (FIG. 1).

– This characteristic arrangement gives the collagen significant sturdiness in terms of **resistance**, **extensibility** and **incompressibility**, whilst guaranteeing **plasticity**, **flexibility**, allowing **torsion**



http://www.georgeackermanmd.com/knee-osteoarthritis.html

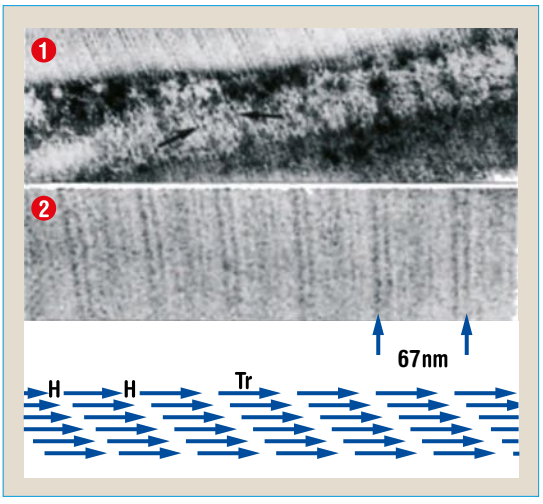
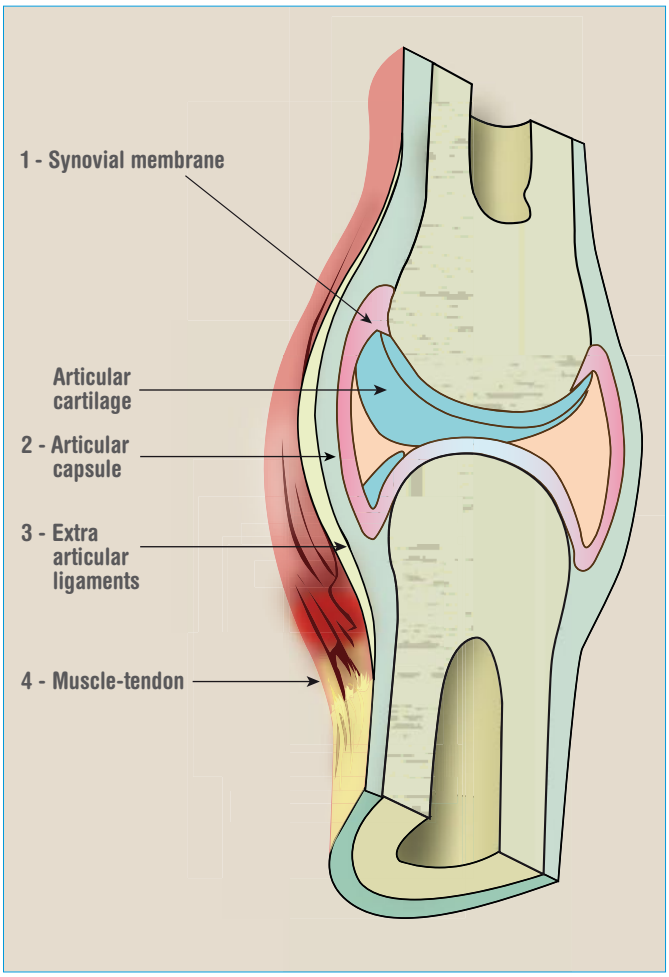


FIG. 1

Structure of collagen.
1: Sugars bound to collagen. Relationship between sugar (black precipitations) **and the density of collagen fibrils** (ME 112.000X)**;**
2: Section of a collagen fibril (ME 240.000X)**.**
A cycle of 67 nm (670 A) **forms on the base of collagen molecules, each of which is staggered by ¼ of their length.**

FIG. 2
Extra-articular containment system.



and **great resistance** to load.
In order to be functional, almost all joints must possess two, apparently contradictory, characteristics: stability and mobility.
The **articular stabilisation** systems consist of the structures pertaining to both the **extra-articular component** and the **intra-articular component**; collagen is present in abundance in both of these structures.

– The extra-articular component consists of ligaments, the articular capsule, tendons and muscles; the intra-articular component is formed of ligaments (for the knee and hip joints only) and of joint cartilage (FIG. 2).

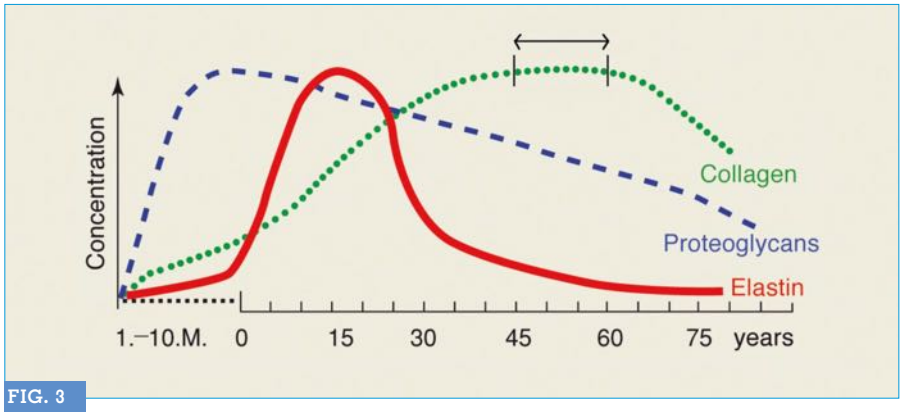


FIG. 3
Age-related biosynthesis of collagen, proteoglycans, and elastin.

One of the most important causes of joint pain is the **laxity** of the intra- and extra-articular stabilisation structures; lax containment systems result in **articular hypermobility**, especially in non-physiological directions and at non-physiological angles that, on the one hand, lead to greater, early wear of the containment systems themselves and, on the other, cause progressive cartilage degeneration.

The mechanical support provided by collagen represents an effective natural scaffolding.

– In humans, the biosynthesis of collagen starts to decrease at 55-60 years of age (FIG. 3);
From this age onwards, there is a quantitative and qualitative deterioration in the joint structures. More specifically, in the musculoskeletal system, the cartilage surfaces become thinner and degenerate to osteoarthritis, whereas the tendinous and ligamentous structures become less elastic and progress to tendinoses and tendinopathies of varying severities. Often in musculoskeletal conditions, the instrumental diagnostic evidence (x-ray, ultrasound, etc.) is not consistent with the clinical findings.

The term **Osteoarthritis state** is used to indicate physiological age-related articular ageing; it is a paraphysiological condition that does not cause any clinical situation and is often incidentally observed during imaging studies performed for other reasons (e.g. injury).
However, when osteoarthritis makes itself felt by causing the characteristic onset symptoms, such as *stiffness* and joint pain, we talk about osteoarthritis disease. Osteophytes are irregular beak- or crest-shaped proliferations of bone tissue that form in the vicinity of joints affected by a number of pathological processes, but above all in the presence of osteoarthritis. Their presence can involve disorders of various types, with restrictions to joint movement or the compression and irritation of nearby structures, in particular, nerve branches and tendon insertions. Osteophytes are the

bone tissue's attempt to increase the surface area of the heads of the articular bones damaged by osteoarthritis, in an attempt to stabilize the joint (FIG. 4).

In addition, it is common for ultrasound scans and MRI studies to show complete or multiple tendon damage, despite the presence of little or no signs and symptoms; conversely, in other cases, the tendon is intact but the patient experiences very severe pain and functional impairment.
As regards the tendinous-ligamentous sub-system, an anatomopathological distinction can be made between tendinites or tenosynovitis, tendinoses and tendon injuries of various degrees.

– Tendinites or tenosynovites are inflammatory states of the tendon and possibly also of its sheath, with or without peritendinous effusion; they may be a consequence of either a traumatic event or a functional overload.

When the repair process of the affected element starts in the presence of inflammation, the scar tissue that forms is a connective tissue that is devoid of the characteristics of elasticity and resistance that are typical of native tendons; this makes the structure more prone to partial or complete tears.

– For this reason, an inflammatory process affecting a tendinous or ligamentous structure should not be underestimated, rather it should be kept under close observation and resolved as soon as possible.

Also on the basis of our experience we can undoubtedly state that clinical and diagnostic evidence are not always consistent. In Italy, osteoarthritis accounts for **72.6%** of all rheumatic diseases and is responsible for **70%** of cases of chronic pain. The potential therapeutic approach to osteoarthritis, and tendinopathy, can be of different types:
– educational
– pharmacological
– rehabilitative
– surgical.

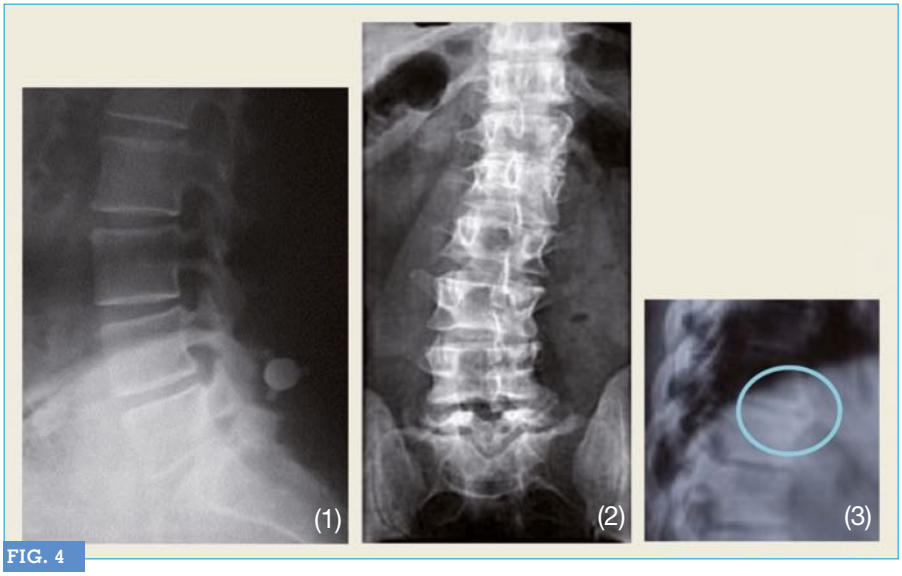


FIG. 4

X-ray of the L-S spine of an individual with severe low back pain without osteoarthritic skeletal alterations (1); of a L-S spine with significant radiological signs of osteoarthritic degeneration (2) in an asymptomatic patient; osteophytes (3).

The educational approach is represented by an improvement in quality of life including health education intervention, the use of braces, where necessary, and weight loss, when appropriate.
The conventional medicinal products used to treat osteoarthritis and tendinopathies (NSAIDs, Coxibs, Paracetamol, Steroids, and Opioids) have a symptomatic action and are used on both systemic and local levels (e.g. intra-articular steroid injections).
There are other medicinal products, whose real efficacy is not recognised by all Authors, which are thought to exert a slow chondroprotective action, these are: glucosamine sulphate, chondroitin sulphate, and hyaluronic acid.

The local use – and therefore – the intra-articular injection of hyaluronic acid boosts its efficacy; this kind of treatment is referred to as "visco-supplementation" and it has **only** a lubricating and shock-absorbing action.

Until just a few years ago, osteoarthritis was considered a progressive degenerative disease; subsequently, a prevention campaign against the progression of osteoarthritis with the use of "Cartilage integrators", was started.

– For some years now, it possible to state that osteoarthritis is a process that is, at least in part, reversible.
Given the ongoing rise in the population's average age, it goes without saying that having access to tools able to maintain high quality of life standards despite *chrono-aging* is an important breakthrough.

Guna Collagen Medical Devices are products for local injection constituted by **collagen** of porcine origin (porcine tissues have a very high collagen content) and a substance known as an *ancillary* or vehicle, of plant or mineral origin, characterised by a particular tropism for the specific articular segments.
A tangential filtration process, combined with sterilisation and control of the molecular weight, makes it possible to obtain a pure product with standard chemical and physical characteristics.
The availability of Guna Collagen Medical Devices for local injection is a determining factor in the repair process that follows anti-inflammatory intervention.
Lax joint support elements cause local nociceptor stimulation and excessive tension and stress: which explains why the reinforcement of these structures is **analgesic** as well as **regenerative**.

AREA	M	F	Total N.	Age - average	Age - range
SHOULDER, UPPER LIMB	30%	70%	**147**	53,5	34-78
KNEE	66%	34%	**53**	67,5	55-82
HIP	30%	70%	**30**	67	53-78
ACHILLES	20%	80%	**27**	43,3	32-63

TAB. 1

General caseload. Patient distribution according to gender and age.

– These characteristics translate directly into organoleptic properties: collagen is a **tissue structurer** (structural protein) and also possesses lubricating qualities.

– These bases form the significant difference between the properties of collagen and those of hyaluronic acid.

The latter is a lubricant (high viscosity) only of the articular cavity, that acts on the intra-articular component **only**, primarily in the large joints.
Collagen **also** and **primarily**, acts on the structures of the extra-articular component (capsule, ligaments, tendons) of small, medium, and large joints.
In addition, hyaluronic acid is efficacious in cases of modest and intermediate clinical severity, whereas collagen is also efficacious in those cases in which the patient's mobility is more severely impaired: it replaces the *bricks* where the *wall* had crumbled.

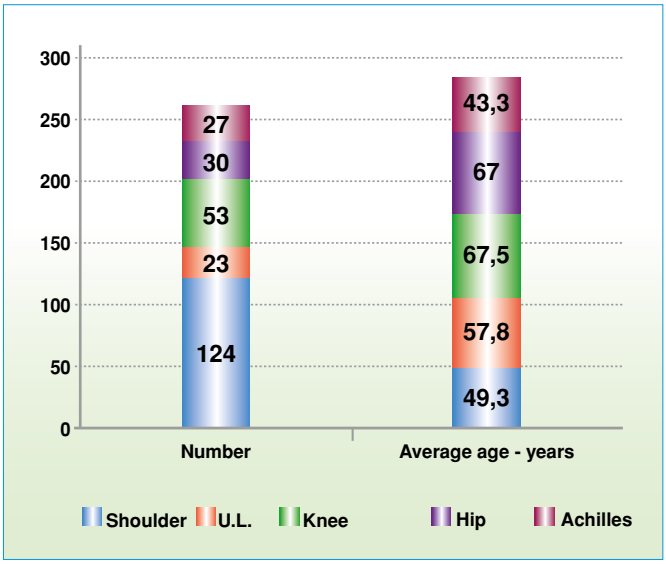
– Guna Collagen Medical Devices can be used alone or in home combinations with conventional or Physiological Regulating Medicine (PRM) products as **Guna-Arthro, Guna-Flam, Guna-Anti IL 1, Guna-Interleukin 10**; the treatment programme may also include other systemic pharmacological and rehabilitation treatments.

MATERIALS AND METHODS

A total of **257 patients** (36.5% M; 63.5% F) were enrolled in this clinical study. The mean age was 58.7 years, with a range of 32-82 years.
TAB. 1 shows the joint segments considered and treated and the corresponding epidemiological characteristics of the caseload.

FIG. 5

General caseload. – Number and mean age of patients included in the study per individual condition considered.



More specifically, because of the type of assessment scale used, the "Shoulder and upper limb (SUL)" Group included **124** patients with problems relating to the shoulder alone (rotator cuff syndrome, with possible tendon lesions); the remaining **23** had a number of other conditions, such as trapeziometacarpal osteoarthritis, epicondylitis and ganglion cysts of the wrist (U.L.).
It was consequently decided to analyse the results of these two sub-Groups independently (FIG. 5).

As far as the "Knee" Group was concerned, all **53** treated cases were classified as stage I, II and III osteoarthritis of the knee using the Kellgren-Lawrence radiological scale.
In the "Hip" Group, the treated hip joint (s) were affected by mild and moderate primary hip osteoarthritis (stage I and II); in this Group (**30** patients), patients were considered holistically, and only patients with a normal physique were included, so that the needle used was able to reach the pericapsular area.
In the "Achilles" Group, all the cases treated were mono- or bilateral Achilles' tendinopathies; **11** cases of tendonitis in the same area with ultrasound-documented exudate were also treated.
All patients were told about the type of treatment that they were being offered and the main differences that it would have compared to a similar injection therapy with hyaluronic acid or Guna Collagen MDs. They all signed the informed consent form.
The clinical and symptomatic findings of the patients enrolled were collected using assessment questionnaires validated by the WHO, more specifically:

- the Pain symptom was measured using a five-point visual-analogue scale (VAS), in which "0" = no pain and "5" = unbearable pain;
- D.A.S.H. (Disability for Arm, Shoulder and Hand) for the shoulder, elbow, hand, and wrist (range 0-100, in which 0 = no disability) (TAB. 2);
- O.K.S. (Oxford Knee Score) for the knee (range 48-0, in which 48 = no disability) (TAB. 3);
- O.H.S. (Oxford Hip Score) for the

hip (range 48-0, in which 48 = no disability) (TAB. 4);
- V.I.S.A.-A (Victorian Institute of Sport Assessment – Achilleus) for the Achilles' tendon (range 68-0, in which 68 = no disability) (TAB. 5).

The questionnaires were filled out by patients; the dedicated questionnaire was administered at the **first visit** and at the **end of treatment**.
Patients were administered **intra-articular** (shoulder, elbow, wrist, hand and knee), **pericapsular** (hip) and **local** (tendons) injections **with the appropriate** and **specific MDs**; 5 cc disposable syringes were used, with 23G x 1-1/2 - mm 0.60 x 40 needles for the hip, knee, and shoulder injections and 26G x 1/2 - mm 0.40 x 16 needles for hand, wrist, elbow, and foot injections.
Before administration, the skin was disinfected using a liquid product containing quaternary ammonium salt.

– In those segments in which administration was intra-articular, sterile surgical gloves were used and the injection area was disinfected thoroughly using sterile gauze soaked in surgical Betadine. In certain segments that are particularly rich in pain-sensitive nerve terminations, spray "ice" was used for analgesic purposes. The injections were administered **twice-weekly** for **5 consecutive weeks** (total = 10 injections).

– The patients treated for chronic degenerative diseases (knee osteoarthritis, hip osteoarthritis, trapeziometacarpal osteoarthritis and one case of severe Achilles' tendinopathy in a semi-professional dancer) continued with **maintenance therapy** (1 session a month for 6 consecutive months, then every 3 months). In no case was it suggested for the pharmacological therapy to be suspended or varied; patients taking NSAIDs or Paracetamol were asked to use this therapy only when absolutely necessary.
The evolution of the pain symptom in particular was monitored in the 8 patients who were taking opioid analgesics, in order to gradually reduce the posology of these drugs.

RESULTS

All the patients included in this study completed the treatment. None of them reported any side effect after the administration of the Guna Collagen Medical Devices. In those patients on antiplatelet or dicoumarol therapy, small areas of ecchymosis were observed at the injection site, but it reabsorbed rapidly without requiring any particular intervention.
All patients considerably **reduced** their use of conventional medicinal products and in **75%** ≈ of all cases their administration was not considered necessary.

– Of the 8 patients on treatment with opioid analgesics, 3 continued taking these medicinal products, albeit at considerably lower doses, whereas the remaining 5 gradually discontinued their use.

Generally speaking, the pain symptoms started to subside from the **4th** or **5th administration**; however, in cases of subacromial impingement and Achilles' or elbow tendinopathy the positive effects on pain were observed later.
In the osteoarthritic forms, affecting both the knee and the hip joint, the first effect reported by patients was a sensation of a **greater range of joint motion**; this sensation was perceived by patients after the first 2 - 3 sessions.

One particularly complex case was that of a male patient with polycythaemia, with concomitant severe osteoarthritis of the knee, hip and shoulder joint and significant functional impairment.
This was the case in which the improvement assessed by the questionnaires used in the study was poor; however, considering the initial clinical situation, it can be said that this was the patient who was most satisfied with the treatment received.

– We initially treated the shoulder alone and only subsequently, at the patient's insistence, also treated the knees. At a later date, we will decide if and when to treat the hips.

▶ Pain

The pain assessment scale showed a reduction from **3.06** (initial mean value including all the cases analysed) to a final value of **1.34**.
– The variation in the pain experienced in the various segments is shown in FIG. 6.

Shoulder and upper limb Group
(FIG. 7)

D.A.S.H. is an assessment questionnaire that considers a number of everyday situations facing the patient (disability concerning movements of the shoulder, hand, and elbow). The worst score is 100 and describes an extremely invalidating situation; a normal situation coincides with a score of 0.

In the caseload managed in this study regarding conditions of the **Shoulder**, the score dropped from an initial average of **78.7** to a final score of **17.3**.
As far as the **Upper limb** Group is concerned, from the initial mean of **66.8** the score dropped to **18.2**.

– In this case, the use of the D.A.S.H. questionnaire proved to be a disputable choice, as it pooled the results for a number of different segments. In the future, we intend to use a dedicated score, such as the *Oxford Shoulder Score* to assess shoulder function.

Knee Group

O.K.S. (The Oxford Knee Score) is an assessment scale including different common situations of everyday life.
The patient is invited to reply with regard to the 4 months prior to completion of the questionnaire; for obvious time reasons, post-treatment completion refers to the time at which it is filled out.
A score of 0 coincides with the most impaired situation, whereas a score of 48 coincides with a condition of full function. Of the 53 patients included (FIG. 8), the average initial score was **13.6**, whereas a score of **35.8** was achieved at the end of treatment.

D.A.S.H.

This questionnaire asks about your symptoms as well as your ability to perform certain activities. Please answer every question , based on your condition in the last week. If you did not have the opportunity to perform an activity in the past week, please make your best estimate on which response would be the most accurate. It doesn't matter which hand or arm you use to perform the activity; please answer based on you ability regardless of how you perform the task.

Please rate your ability to do the following activities in the last week

		NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1	Open a tight or new jar	1	2	3	4	5
2	Write	1	2	3	4	5
3	Turn a key	1	2	3	4	5
4	Prepare a meal	1	2	3	4	5
5	Push open a heavy door	1	2	3	4	5
6	Place an object on a shelf above your head	1	2	3	4	5
7	Do heavy household chores (e.g., wash walls, wash floors)	1	2	3	4	5
8	Garden or do yard work	1	2	3	4	5
9	Make a bed	1	2	3	4	5
10	Carry a shopping bag or briefcase	1	2	3	4	5
11	Carry a heavy object (over 10 lbs).	1	2	3	4	5
12	Change a lightbulb overhead	1	2	3	4	5
13	Wash or blow dry your hair	1	2	3	4	5
14	Wash your back	1	2	3	4	5
15	Put on pullover sweater	1	2	3	4	5
16	Use a knife to cut food	1	2	3	4	5
17	Recreational activities which require little effort (e.g., cardplaying, knitting, etc…)	1	2	3	4	5
18	Recreational activities in which you take some force or impact through your arm, shoulder or hand (e.g golf, hammering, tennis, etc…)	1	2	3	4	5
19	Recreational activities in which you move your arm freely (e.g., playing freesby, badminton, etc…)	1	2	3	4	5
20	Manage transportation needs (getting from one place to another)	1	2	3	4	5
21	Recreational activities which require considerable effort (e.g. push-ups, shaking a spray can, etc…)	1	2	3	4	5

22.During the past week, to what extend has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbours or groups? (circle number)

NOT AT ALL	SLIGHTLY	MODERATELY	QUITE A BIT	EXTREMELY
1	2	3	4	5

23.During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem? (circle number)

NO LIMITED AT ALL	SLIGHTLY LIMITED	MODERATELY LIMITED	VERY LIMITED	UNABLE
1	2	3	4	5

		NONE	MILD	MODERATE	SEVERE	EXTREME
24	Arm, Shoulder or hand pain	1	2	3	4	5
25	Arm, Shoulder or hand pain when you performed any specific activity	1	2	3	4	5
26	Tingling (pins and needles) in your arm, shoulder or hand	1	2	3	4	5
27	Weakness in your arm, shoulder or hand	1	2	3	4	5
28	Stiffness in your arm, shoulder or hand	1	2	3	4	5

29. During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand? (circle number)

NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	SO MUCH DIFFICULTY THAT I CAN'T SLEEP
1	2	3	4	5

30. I feel less capable, less confident or less useful because of my arm, shoulder or hand problem (circle number)

NONE	MILD	MODERATE	SEVERE	EXTREME
1	2	3	4	5

The following questions ask about the impact of your arms, shoulder or hand problem on your ability to work. Please circle the number that best describes your physical ability in the past week.

	Did you have difficulty:	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	EXTREME DIFFICULTY	UNABLE
31	Using your usual technique for your work?	1	2	3	4	5
32	Doing your usual work because of arm, shoulder or hand pain?					
33	Doing your work as well as you would like?					
34	Spending your usual amount of time doing your work?					

The following questions relate to the impact of your arms, shoulder or hand problem on playing your musical instrument or sport or both. If you play more than one sport or instrument (or play both), please answer with respect to that activity which is most important to you. Please circle the number that best describes your physical ability in the past week.

	Did you have difficulty:	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	EXTREME DIFFICULTY	UNABLE
35	Using your usual for playing your instrument or sport?	1	2	3	4	5
36	Playing your musical instrument or sport because of arm, shoulder or hand pain?	1	2	3	4	5
37	Playing your musical instrument or sport as well as you would like?	1	2	3	4	5
38	Spending your usual amount of time practicing or playing your instrument or sport?	1	2	3	4	5

Thank you for filling in this form.

TAB. 2

– D.A.S.H. (Disability for Arm, Shoulder and Hand) Questionnaire.

O.K.S. - OXFORD KNEE SCORE

NEW OXFORD KNEE SCORE QUESTIONNAIRE

Please answer the following 12 questions. Please only consider how you have been getting on during the past four weeks

1. How would you describe the pain you have usually from your knee? Score
None – 4
Very mild – 3
Mild – 2
Mild moderate – 1
Severe – 0

2. Have you had any trouble with washing and drying yourself all over because of your knee?
No trouble at all – 4
Very little trouble – 3
Moderate trouble – 2
Extreme difficulty – 1
Impossible to do – 0

3. Have you had any trouble getting in and out of a car or using public transport because of your knee?
No trouble at all – 4
Very little trouble – 3
Moderate trouble – 2
Extreme difficulty – 1
Impossible to do – 0

4. If you were to kneel down could you stand up afterwards?
Yes, easily – 4
With little difficulty – 3
With moderate difficulty – 2
With extreme difficulty – 1
No, impossible – 0

5. Have you been limping when walking because of your knee?
Rarely/never – 4
Sometimes or just at first – 3
Often, not just at first – 2
Most of the time – 1
All of the time – 0

6. Have you felt that your knee might suddenly give way or let you down?
Rarely/never – 4
Sometimes or just at first – 3
Often, not just at first – 2
Most of the time – 1
All of the time – 0

7. Could you kneel down and get up afterwards?
Rarely/never – 4
Sometimes or just at first – 3
Often, not just at first – 2
Most of the time – 1
All of the time – 0

8. Have you been able to do your own household shopping on your own? Score
Yes, easily – 4
With little difficulty – 3
With moderate difficulty – 2
With extreme difficulty – 1
No, impossible – 0

9. For how long have you been able to walk before the pain from your knee became severe (with or without a stick)?
No pain, even after more than 30 minutes – 4
16-30 minutes – 3
5-15 minutes – 2
Around the house only – 1
Unable to walk at all – 0

10. Have you been able to walk down a flight of stairs
Yes, easily – 4
With little difficulty – 3
With moderate difficulty – 2
With extreme difficulty – 1
No, impossible – 0

11. After a meal (sat at a table) how painful has it been for you to stand up from a chair because of your knee?
Not at all painful – 4
Slightly painful – 3
Moderately painful – 2
Very painful – 1
Unbearable – 0

12. How much pain from your knee interfered with your usual work (including housework)?
Not at all – 4
A little bit – 3
Moderately – 2
Greatly – 1
Totally – 0

13. Have you been troubled by pain from your knee in bed at night?
No nights – 4
Only 1 or 2 nights – 3
Some nights – 2
Most nights – 1
Every night – 0

TAB. 3
– O.K.S. (Oxford Knee Score) Questionnaire.

O.H.S. - OXFORD HIP SCORE

OXFORD HIP SCORE

Please answer the following 12 questions.

During the past 4 weeks...

1. How would you describe the pain you usually have in your hip?
4) None
3) Very mild
2) Mild
1) Moderate
0) Severe

2. Have you been troubled by pain from your hip in bed at night?
4) No nights
3) Only 1 or 2 nights
2) Some nights
1) Most nights
0) Every night

3. Have you had any sudden, severe pain-' shooting ', 'stabbing', or 'spasms' from your affected hip?
4) No days
3) Only 1 or 2 days
2) Some days
1)Most days
0) Every day

4. Have you been limping when walking because of your hip?
4) Rarely/never
3) Sometimes or just at first
2) Often, not just at first
1) Most of the time
0) All of the time

5. For how long have you been able to walk before the pain in your hip becomes severe (with or without a walking aid)?
4) No pain for 30 minutes or more.
3) 16 to 30 minutes
2) 5 to 15 minutes
1) Around the house only
0) Not at all

6. Have you been able to climb a flight of stairs?
4) Yes, easily
3) With little difficulty
2) With moderate difficulty
1) With extreme difficulty

7. Have you been able to put on a pair of socks, stockings or tights?
4) Yes, easily
3) With little difficulty
2) With moderate difficulty
1) With extreme difficulty
0) No, impossible

8. After a meal (sat at a table), how painful has it been for you to stand up from a chair because of your hip?
4) Not at all painful
3) Slightly painful
2) Moderately painful
1) Very painful
0) Unbearable

9. Have you had any trouble getting in and out of a car or using public transportation because of your hip?
4) No trouble at all
3) Very little trouble
2) Moderate trouble
1) Extreme difficulty
0) Impossible to do

10. Have you had any trouble with washing and drying yourself (all over) because of your hip?
4) No trouble at all
3) Very little trouble
2) Moderate trouble
1) Extreme difficulty
0) Impossible to do

11. Could you do the household shopping on your own?
4) Yes, easily
3) With little difficulty
2) With moderate difficulty
1) With extreme difficulty
0) No, impossible

12. How much has pain from your hip interfered with your usual work, including housework?
4)Not at all
3) A little bit
2) Moderately
1) Greatly
0) Totally

TAB. 4
– O.H.S. (Oxford Hip Score) Questionnaire.

TAB. 5
– V.I.S.A.-A (Victorian Institute of Sport Assesment- Achilles tendon) Questionnaire.

V.I.S.A.-A

IN THIS QUESTIONNAIRE, THE TERM PAIN REFERS SPECIFICALLY TO PAIN IN THE ACHILLES TENDON REGION

1. For how many minutes do you have stiffness in the Achilles region on first getting up?

100 mins ☐☐☐☐☐☐☐☐☐☐ 0 mins — POINTS ☐

0 1 2 3 4 5 6 7 8 9 10

2. Once you are warmed up for the day, do you have pain when stretching the Achilles tendon fully over the edge of a step? (keeping knee straight)

strong severe pain ☐☐☐☐☐☐☐☐☐☐ no pain — POINTS ☐

3. After walking on flat ground for 30 minutes, do you have pain within the next 2 hours?

strong severe pain ☐☐☐☐☐☐☐☐☐☐ no pain — POINTS ☐

4. Do you have pain walking downstairs with a normal gait cycle?

strong severe pain ☐☐☐☐☐☐☐☐☐☐ no pain — POINTS ☐

5. Do you have pain during or immediately after doing 10 (single leg) heel raises from a flat surface?

strong severe pain ☐☐☐☐☐☐☐☐☐☐ no pain — POINTS ☐

6. How many single leg hops can you do without pain?

0 ☐☐☐☐☐☐☐☐☐☐ 10 — POINTS ☐

7. Are you currently undertaking sport or other physical activity?

0 ☐ Not at all — POINTS

4 ☐ Modified training ± modified competition ☐

7 ☐ Full training ± competition but not at same level as when symptoms began

10 ☐ Competing at the same or higher level as when symptoms began

At the end of the treatment, patients were offered the chance to continue with maintenance therapy: all the patients agreed to continue the treatment, saying that they were satisfied and confident. The improvements achieved were maintained in the following months. In some cases, further improvements were seen; however, in order to quantify these data, the situation must be evaluated on a case-by-case basis.

Hip Group

O.H.S. (The Oxford Hip Score) is an assessment scale for hip joint function.
The patient must answer regarding his/her every day motor performance.
Once again, patients were invited to answer the end-of-treatment questionnaire, by entering their replies at the time of assessment. Full joint integrity coincides with a score of 48 points, whereas a clinical situation of maximum impairment coincides with a score of 0.
It is important to remember that the patients in this Group presented radiographic evidence of a stage I or II condition, the phases of the disease in which pain and functional impairment emerge.
In this Group, the mean score decreased from an initial value of **10.2** (indicating somewhat severe general impairment) to a final score of **37.2** (FIG. 9).

Achilles' Group

This Group of patients, suffering from an inflammation of the Achilles' tendon, answered the Victorian Institute of Sport Assessment (V.I.S.A.-A) questionnaire, which refers to the Achilles' tendon alone and provides a score of between 0 and 68 points; the latter value refers to a condition of complete and perfect function.
In this case, as shown by the data in FIG. 10, the score increased from an initial value of **21.0**, to a final value of **54.0** points.
The patients in this Group had an ultrasound study, with a finding of effusion between the tendon folds.
– As ultrasound is a non-invasive imaging technique, at the end of treatment the patients had a follow-up ultrasound scan, to show the reabsorption of the signs of inflammation (FIG.11).

CONCLUSIONS

All the treated patients declared that they were satisfied with the result achieved.
– There were no drop outs, despite the fact that the treatment lasted 5 - 6 weeks.
As far as all of the assessment questionnaires as a whole are concerned, there was a considerable, statistically significant, subjective improvement.
To this we must add the objective improvement, confirmed by imaging studies (follow-up ultrasound) for those patients with Achilles' tendon conditions, and clinically by range of joint motion tests.
After the first 3 - 4 administrations, almost all patients in the Shoulder, Hip and Knee Groups, expressed their surprise at the feeling of greater joint freedom.
The Hip Group was the Group that expressed the greatest and earliest satisfaction with the treatment. From a percentage standpoint, the best result was achieved in the Achilles' Group: this can be attributed to the fact that this Group was constituted by patients with the lowest average age and that in which the condition was not secondary to an overload or degenerative process.
The members of this Group and the Shoulder Group were not offered any maintenance therapy. A single addition-

al administration was required in just two cases, both in the Shoulder Group. For the patients in the Hip, Knee and Upper Limb Groups (in the latter, for cases of trapeziometacarpal osteoarthritis only) the treatment is still on-going. Administration is once-monthly for the first six months.

Subsequently, if stable remission is achieved, the treatment is administered once every two months and, later, once every three months.
Having been thoroughly informed of the role played by locally-administered collagen (Guna Collagen MDs), the patients readily understood that their attention to symptoms is fundamental to a successful outcome of treatment, in order to achieve long-lasting results.

– Another positive aspect of treatment with Guna Collagen MDs is the rapid effect on pain, even and above all in patients on dicoumarol anti-coagulant therapy, who cannot take NSAIDs or steroids.

A positive and somewhat rapid response was also observed in those patients with heavy pharmacological regimens due to comorbidities.
It is important to note that, in most of the cases observed in this study (as is the case for the majority of patients referred to a physiatrist), the patient was referred after at least two months of attempts using conventional pharmacological therapy (NSAIDs, Steroids, Paracetamol) without achieving any stable result. Their body was therefore intoxicated.

– The toxins from conventional anti-inflammatory drugs accumulate above all in the structures comprising the musculoskeletal system.

– Even subjects on heavy chronic pharmacological treatment (steroids, oral hypoglycaemic agents, insulin, anticoagulants), the positive response to therapy was achieved without any interference with their ongoing chronic therapies. ■

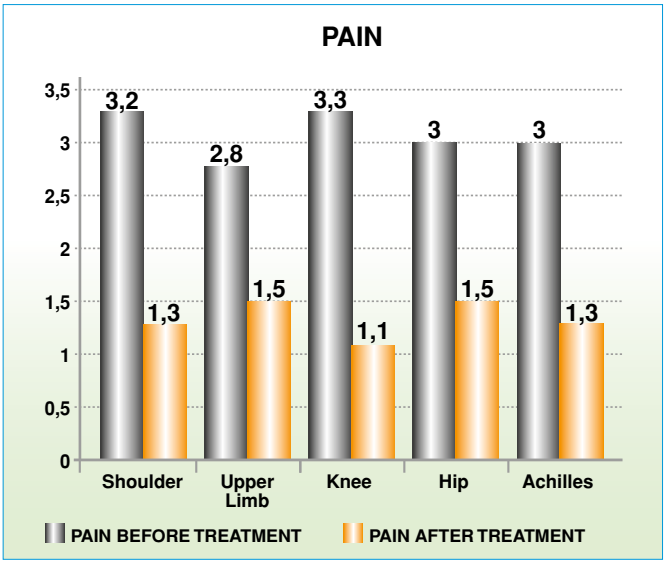
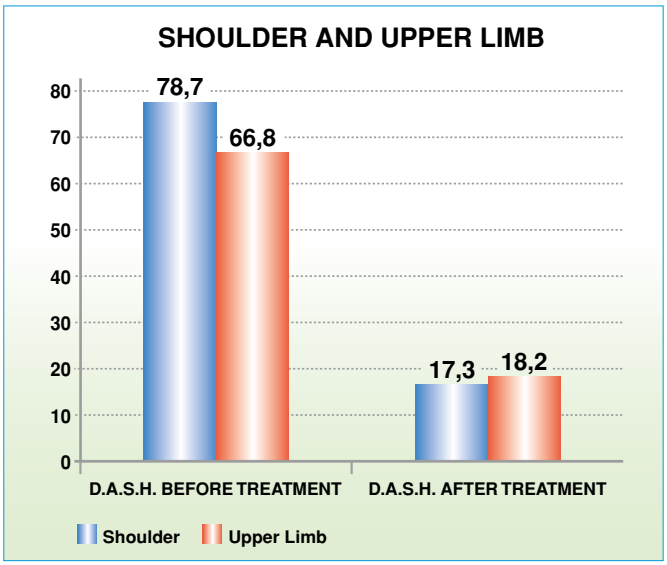


FIG. 6

Variation in the pain symptoms pre- and post-treatment in the different Groups treated with Guna Collagen MDs.

FIG. 7

Results of the analysis of the data collected using the D.A.S.H. questionnaire for conditions affecting the shoulder and upper limb (elbow, wrist, and hand).



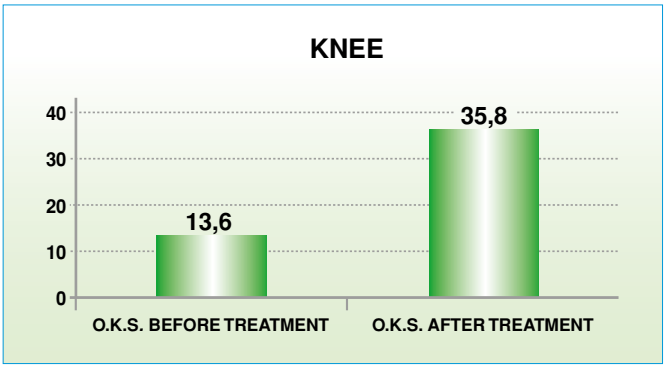


FIG. 8

Results of the analysis of the data collected using the O.K.S., for knee conditions.

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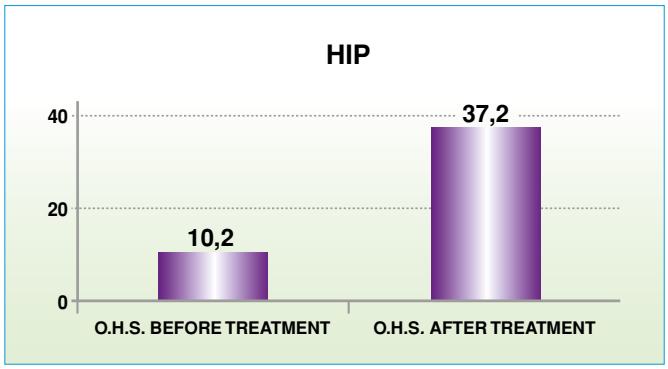
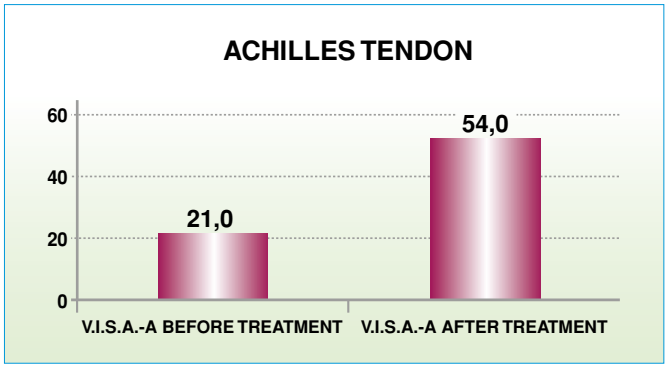


FIG. 9

Results of the analysis of the data collected using the O.H.S., for hip conditions.

FIG. 10

Results of the analysis of the data collected using the V.I.S.A.-A, for Achilles' tendon conditions.



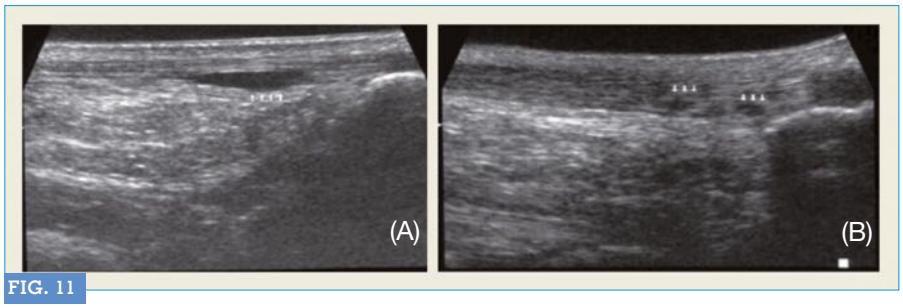


FIG. 11

(A) Achilles' tendon in the presence of effusion in the peritendineum; (B) The effusion is no longer visible. A situation of chronic tendinosis persists, with microcalcifications.

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FROM: Physiological Regulating Medicine. 2013; 31.

INTRA-ARTICULAR ADMINISTRATION OF MD-HIP IN 7 PATIENTS AFFECTED BY HIP OSTEOARTHRITIS UNRESPONSIVE TO VISCOSUPPLEMENTATION. SIX-MONTH MULTICENTER TRIAL

Authors: Migliore A., Massafra U., Bizzi E., Vacca F., Tormenta S.
– Clinical trial presented at the International Symposium Intra Articular Treatment; Rome (October 2011).

Experimental sites: UOS (Simple Operating Unit) of Rheumatology – San Pietro Fatebenefratelli Hospital, Rome.

Pathologies considered: osteoarthritis X-Ray I-III stage according to Kellgren-Lawrence affecting the hip joint unresponsive to viscosupplementation with hyaluronic acid (6 patients) or hylan (1 patient) (2 ultrasound guided injections at least).

Outcomes:
1)assessment of efficacy using VAS scale and Lequesne algofunctional Index;
2)NSAIDs consumption before treatment and during follow-up. 3)safety profile of MD-Hip.

Patients enrolled: 7

Treatment: **MD-Hip** (2 ampoules = 4 ml), 1 ultrasound guided intra-articular injection.

Results
1)VAS of osteoarthritis pain = from 6.15 (before treatment) to 4.23 (after 3 months), to 4.23 (after 6 months).
2)Lequesne Index = from 1.94 (before treatment) to 5.9 (after 3 months), to 5.83 (after 6 months).
3)NSAIDs consumption = from 7.57 (before treatment) to 4.25 (after 3 months), to 5.78 (after 6 months).

– **Author's conclusions:**
1)MD-Hip showed to be effective (all the average values of the results at 3 and at 6 months after the last treatment have been statistically significant) and safe in patients affected by hip osteoarthritis unresponsive to viscosupplementation.
2)The data suggest that the results can be evident from the very first injection and are stable for 6 months.
3)The preliminary data offer new research opportunities in the field of intra-articular therapy.

Abstract From: Milani L. THE COLLAGEN MEDICAL DEVICES IN THE LOCAL TREATMENT OF THE ALGIC ARTHRO-RHEUMOPATHIES – REVIEW OF THE CLINICAL STUDIES AND CLINICAL ASSESSMENTS 2010-2012Physiological Regulating Medicine. 2013; 21-36.

J. Staňa

3 YEARS IN LUHAČOVICE SPA WITH COLLAGEN MEDICAL DEVICES INJECTIONS IN THE TREATMENT OF PIRIFORMIS SYNDROME

SUMMARY

Luhačovice Spa is a Czech Spa Resort known worldwide with a nearly 200-year tradition and 12 springs of powerful mineral water.
In this clinic, in 2016 more than 800 Guna MDs injections were applied with approximately 90% superior effects.
The spectrum of application is: knee 51%, back pain 15%, shoulder 10%, carpal 10%, elbow, hip, Achilles tendinitis, heel, small joints and Piriformis Syndrome.
The technique used for Piriformis Syndrome injections includes:
• MD-Muscle or MD-Matrix
– Needle 20G, 0.9x70-90 mm
– Gentle manipulation of the needle – identification of the sacrum
– Aspiration – haematoma of *m. piriformis*
– Risk: N. ischiadicus damage, bleeding.

This deep application of Guna MDs in patients with Piriformis Syndrome is safe and effective. Further clinical studies are needed to confirm our results.

KEY WORDS

LUHAČOVICE SPA, GUNA COLLAGEN MD-MUSCLE, GUNA COLLAGEN MD-MATRIX, TRIGGER POINTS, PIRIFORMIS SYNDROME

INTRODUCTION

Luhačovice Spa is a Czech Spa Resort known worldwide with a nearly 200-year tradition and 12 springs of powerful mineral water.
It has been originally established to heal patients with asthma and tracheo-bronchial disorders. In most recent times the Spa is being visited by an increasing number of oncologic patients or patients with musculoskeletal disorders.
– The working team of the Spa Policlinic consists of the head and second graduated anesthesiologists, specialized in internal and emergency medicine, a rehabilitation doctor, an ENT specialist and an orthopedist; the staff includes 4-5 nurses and 5 physiotherapists.
The most favorite approach to the patient is individual and holistic.
Some new diagnostic methods as Computer Kinesiology and Hotman System are used for the evaluation of the Spa treatment efficacy.
The spectrum of Luhačovice Spa patients suffer from asthma + COPD (1/3), oncologic pathologies (1/3), and myoskeletal disorders (1/3).
The typical profile of patients with myoskeletal disorders is:

- F, aged 55+ suffering from back pain and mobility disorder
- Obesity, hypertension, thyreopathies, osteoporosis, hyperlipoproteinemia
- Stp.CHCE, HYE
- Assuming more than 5 medicaments
- Consulting more than 3 doctors.

– Guna MDs injections have been successfully used for 3 years.
In 2016 more than 800 Guna MDs injections were applied with approximately **90% superior effects**.

The spectrum of application concerns: **knee 51%**, **back pain 15%**, **shoulder 10%**, **carpal 10%**, **elbow**, **hip**, **Achilles tendinitis**, **heel**, **small joints** and **Piriformis Syndrome**.

We apply Guna MDs on the Trigger points **(TgP)**, especially periosteal.

In order to evaluate the results we use the

WOMAC Questionnaire filled in before and after the application of Guna MDs.

PIRIFORMIS SYNDROME

In clinical practice **Piriformis Syndrome (PS)** (FIGURE 1) is usually latent in diagnoses such as low back pain, sciatica, FBSS, L5/S1 nerve root irritation, SI syndrome, etc.
– These diagnoses are often supported by X-ray, CT or MRI scan showing spondylosis and osteochondrosis of LS spine or herniated disk.

CLINICAL HISTORY AND DIAGNOSIS OF PIRIFORMIS SYNDROME

Patient suffering from unilateral back and gluteal pain radiating downwards to the lower limbs and paresthesia of the affected branches of the sciatic nerve: *n. pudendus* and *n. gluteus* are often affected.

In fact, pain and discomfort are caused by the Compartment syndrome with compression of the sciatic nerve by oedema, haematoma or *Myositis ossificans* of the piriformis muscle.
The cause of PS could be multiple: sedentary job, overloading or trauma of rotators of the hip during sports or other physical activities, etc. Some authors suggest that PS is responsible for male impotence and female dyspareunia.
– PS diagnosis is based on the identification of painful gluteal muscle TPs practically in 100% of patients.
The Beatty test is positive in most cases and the Lasègue test is positive in more than 50% of patients.
It is important to note that, if neurologists state it is not herniated disk, and if orthopedists say it is not a hip, most likely the patient suffers from Piriformis Syndrome.

TREATMENTS OF PS

Non-invasive treatments include: Physiotherapy (exercises, yoga, stretching, massages, etc.); Electrotherapy (magnet, laser, ultrasound, etc.); Watertherapy, etc.
Semi-invasive treatments include: Acupuncture, Injection techniques.
Injection agents used to treat PS are:

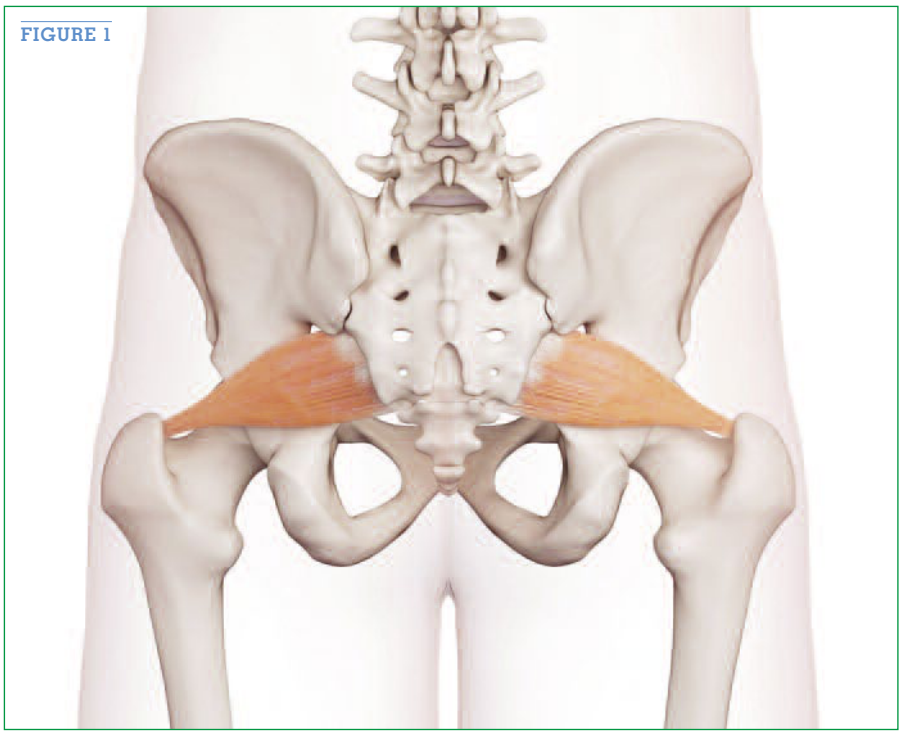
- Lidocaine (Marcaine)
- Steroids
- Combination of both the above mentioned substances
- Botulotoxin, under CT control
- Guna Collagen MDs injections are given in Luhačovice (CZ) since 2013.

The technique used for Piriformis Syndrome injections includes:

- **MD-Muscle** or **MD-Matrix**

– Needle 20G, 0.9x70-90 mm
– Gentle manipulation of the needle – identification of the sacrum
– Aspiration – haematoma of *m. piriformis*
– Risk: *N. ischiaticus* damage, bleeding.

FIGURE 1



RESULTS

A Group of **28 patients** (3 x surgery indicated) was administered **MD-Muscle** or **MD-Matrix**.

- 21 patients received "1-shot" therapy
- 7 patients received both 2 TgP treated
- 2 patients received more than 3 applications
- 2 x identified haematoma *m. piriformis*
- No one has worsened
- No one has undergone surgery.

Possible pitfalls and mistakes include the use of a needle not long enough, wrong handling, severe pain caused by nerve touch, and bleeding.
Patients suffering from haemophilia and taking anticoagulants should not be treated.

This deep application of Guna MDs in patients with Piriformis Syndrome is safe and effective.
Further clinical studies are needed to confirm our results. ■

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RESEARCH ARTICLE Open Access

A double blind randomized active-controlled clinical trial on the intra-articular use of Md-Knee versus sodium hyaluronate in patients with knee osteoarthritis ("Joint")

Luis Severino Martin Martin[1], Umberto Massafra[2], Emanuele Bizzi[2*] and Alberto Migliore[2]

Abstract

Background: To evaluate the clinical outcomes of a group of patients affected by knee osteoarthritis (OA) treated with MD-Knee (Guna S.p.a., Milan, Italy) versus a group of patients treated with sodium hyaluronate.

Method: This non-inferiority prospective randomized controlled trial involved 60 patients affected by knee OA, grade 2–3 of Kellgren-Lawrence scale. The MD-Knee Group, Group A ($n = 29$) was administered five intra-articular injections at 1 week interval; the sodium hyaluronate Group, Group B ($n = 31$), was administered five doses of intra-articular injection of sodium hyaluronate at 1 week interval. All patients were prospectively evaluated before and at 3 and 6 months after the treatment by the Lequesne Knee Index (LKI) as primary endpoint and the Visual Analogue Scale (VAS), Pain Killer consumption and SF-36 questionnaires as secondary endpoints.

Results: At the 3- and 6 month follow-up, LKI and VAS improved significantly in both groups compared to baseline and no statistically significant differences were observed between Group A and Group B. There was no statistically significant difference in the SF36 questionnaire score and pain killer consumption between two groups at any time point.

Conclusions: This study shows that both preparations exert similar clinical effects as assessed through multiple outcome measures. MD-Knee is effective on knee OA symptoms over 6 months after a 5-weekly injection course, and it is equally effective as the reference sodium hyaluronate.

Trial registration: Trial registration number: ISRCTN93862496. Registration date: January 18th, 2016

Keywords: Osteoarthritis, Knee, Intra-articular, Hyaluronic acid, MD-Knee

Background

Osteoarthritis (OA) is a chronic degenerative joint disease characterized by progressive damage of articular cartilage and underlying bone. It is a common rheumatic disease that affects both sexes and the majority of the elderly people; nevertheless, also the young are frequently affected by OA, thus becoming an important cause of lost workdays. Estimated prevalence in general adult population is of 11 and 24 % for hip and knee OA respectively [1]. Pain is accentuated by movements and decreases with rest but, with progression of disease, it may be present at rest and accompanied by short morning stiffness; moreover, joint damage causes a progressive functional limitation [2]. In order to reduce pain and to achieve an overall better clinical condition it is suggested to use a therapeutic strategy including physical therapy and rehabilitation, non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, chondroprotecting agents and intra-articular treatment with infiltrative substances such as hyaluronates and steroids. When the disease is at an advanced stage, orthopedic surgical solution can offer great benefits [3]. Over the past 10 years some double-blind controlled clinical trials have shown that administration by injection of hyaluronic acid (HA) for 3–5 weeks is superior in

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terms of efficacy, compared to saline, arthrocentesis, and treatments with NSAIDs [4–6]. In addition, HA has presented an excellent tolerability profile with a low incidence of complications at local level and a complete absence of systemic effects that are typically associated with anti-inflammatory drugs, steroid or surgery [7, 8]. Among HAs used, sodium hyaluronate SUPARTZ® (Seikagaku, Tokyo, Japan) is one of the most used and studied by clinical trials [9–15]. Other products for intra-articular use have been recently introduced for the treatment of OA; at present time there is no definitively effective treatment for this condition, but the very high cost of these therapies, however, fosters to test new treatments that could provide the same benefits at a lower cost. Among these, a medical device MD-Knee, produced by Guna S.p.a., Milan-Italy containing collagen of porcine origin has been investigated. Collagen content in MD-Knee has a molecular weight equal to 300,000 dalton, produced through a process of tangential filtration. It is a pure product, contaminant-free, with standardized chemical and physical characteristics. Collagen is the most abundant protein in the bodies of mammals, accounting for approximately 5–6 % of the body weight of an adult man. About 30 % of total protein mass of higher animals is collagen, found in bones, tendons, joint capsules, muscles, ligaments, teeth, skin and in general in extra-cellular matrix. Porcine tissues have a very high average collagen content, around 50 %. In collagen amino acid content is for Glycine 22.8, Proline 13.8 and Hydroxy-Proline 13 %. The average content of other amino acids is only 3 % (max Glutamic Acid 9.5 %; min Tyrosine 0.4 %). The purpose of an *in-situ* introduction of this device is structural; in fact, mechanical support provided by collagen is an effective natural scaffold support (bio-scaffold). Its degradation in the constituent aminoacids seems to constitute a nutritional support for tissues of the other joint structures [16–19].

The aim of this study is to evaluate the use of collagen MD-Knee versus sodium hyaluronate (SUPARTZ®) in patient with knee OA. The outcome has been clinically assessed through the OMERACT criteria (Outcome Measures in Rheumatology) [20].

Methods

Study design and patients

JOINT study is a prospective, double blind, multicentric, randomized clinical trial with active control. The trial was conducted in accordance with the Good Clinical Practice (GCP) and the Declaration of Helsinky; the protocol was approved by the local Ethical Committee (San Pietro Fatebenefratelli Hospital Bioethic Committee). Enrollment started in March 2013 and ended in September 2013. Patients were enrolled and followed in both participating Centers (San Pietro Fatebenefratelli Hospital, Rome, Italy, and Regina Apostolorum Hospital, Albano Laziale, Italy). Only patients affected by symptomatic knee OA were considered eligible for participating in the study. All patients signed an informed consent before entering the study. The randomization list was generated through a high-efficiency system (www.random.org). The list was created by generating eight blocks of eight subjects (1: 1) for a total of 64 enrolled patients. The use of the blocks has allowed to obtain balanced groups during the study. Two groups of subjects were identified; the first group (Group A) consisting of 32 patients has received the investigational product, MD-Knee (Guna S.p.a., Milan, Italy), The second group (Group B), consisting in 32 patients, was treated with SUPARTZ® (Seikagaku, Tokyo, Japan). MD-Knee (injectable ampoules of 2.0 ml) was administered at a dose of two vials for a total of 4 ml via intra-articular injection, once a week for a period of five consecutive weeks; one vial of 2.5 ml sodium hyaluronate (SUPARTZ®) was identically administered.

A total of three visits was performed. During the first one at time T0 (enrollment), the selected patients, after signing the informed consent, were assigned to the experimental group (Group A) or to the reference group (Group B) according to a randomization list. In the same visit the product under investigation was administered. All patients then underwent 1 weekly dosing of MD-Knee or SUPARTZ® for five consecutive weeks; patients were visited 3 months after enrollment (T3 follow-up) and 6 months after the start of the trial (T6 follow-up). The physician performing the intra-articular injection was aware of the product administered, while both physicians evaluating the algo-funcional indices, as well as the patients, were unaware of the product administered.

Inclusion criteria

In this trial were included male and female subjects who met the following criteria:

- ambulatory adult patients affected by knee OA
- diagnosis according to the ARA (American Rheumatism Association) criteria
- age > 40 years
- disease activity assessed by the Lequesne Knee Index ≥ 7.0 at T0
- disease activity assessed according to the VAS at T0 ≥ 4 cm and persistence of pain in the knee for at least the last 3 months.
- radiological degree II-III according to the Kellgren-Lawrence scale
- patients able to comply with study procedures.

Exclusion criteria

Patients who met the following criteria were excluded:

- presence of comorbidities (rheumatoid arthritis, spondyloarthritis, connective tissue disease,

polymyalgia rheumatica, gout, Paget's disease, septic arthritis, fractures, osteonecrosis, and fibromyalgia)
- patients with skin or subcutaneous tissue infection in the area of the joint to be treated
- patients who had used oral, parenteral or intra-articular corticosteroids in the 3 months prior to the T0 visit
- patients taking topical analgesics that may interfere with the evaluation of the study
- patients on anticoagulant therapy or suffering from thrombocytopenia and/or coagulopathy
- patients with allergy to products of porcine origins.

Primary endpoint

At T0 and during the clinical follow-up (FU) at 3 months and 6 months, it was performed the assessment of the physical function according to standardized parameters LKI (Lequesne Knee Index). This clinical trial was set up as a non-inferiority study of MD-Knee compared to sodium hyaluronate (SUPARTZ®) in reducing the LKI score at T3FU in patient with knee OA. At baseline, the average value of the LKI in both groups was assumed to be 7.0 ± 1.1. After 3 months, in Group B (SUPARTZ®), it was expected a reduction of the average value of the LKI to 4.2 ± 1.1 (e.g., a 40 % reduction from baseline). From this value of the LKI score, we accepted as non-inferior a possible value of LKI increased by less than 24 % for the Group A (MD-Knee), and thus the non-inferiority margin (NIM) was set equal to 4.2×1.24 = 5.21, with a standard deviation expected to remain equal to 1.1. Calling D the difference in LKI after 3 months between A and B (equal to 5:21 to 4:20 = 1.01) product, then null hypothesis is H0: $D \geq 1.01$, while alternative hypothesis is H1: $D < 1.01$. With these assumptions, the two groups of 29–31 subjects reached a power of 93.8 % in recognizing the non-inferiority using a one-tailed Student *t* test with significance level of $\alpha = 0.025$. In the case of non-applicability of the Student's test, it was estimated that the power of the non-parametric analogous test (one-tailed Mann–Whitney *U* test, with a significance level of 0.025) would have been 92.2 %.

Secondary endpoints

In order to demonstrate the non-inferiority of MD-Knee in reducing pain, the Visual Analogue Scale (VAS) (0–10 cm), the LKI score at T6FU, and the Pain Killer consumption assessment during the course of the study, were also performed.

Questionnaire SF-36 concerning the state of physical and mental health of the subjects, was administered and evaluated for all the patients at T0, T3FU, T6FU. Data were compared with those obtained by the reference group (Group B) and had to comply with the specified threshold for non-inferiority.

Finally, during the investigation period, all events related with intra-articular injection of the investigational product were analyzed.

Rescue medication

During the study, the only analgesic allowed was Acetaminophen 1000 mg (Pain Killer). Analgesic assumption was reported in a clinical diary.

Reporting adverse events

All information relating to possible adverse events (AEs), serious adverse events (SAEs) were reported.

Statistical methods

All variables collected were submitted to the appropriate descriptive analysis, based on their distribution within the sample recruited, assessed by visual inspection of distribution histograms and with the Shapiro-Wilk test for continuous variables, and frequency tables for the categorical variables. The primary endpoint of the possible non-inferiority efficacy in reducing the LKI score (measured at 3 months) in Group A, compared to Group B, was evaluated with Student's *t* test for independent data, in a one-tailed test, with the significance level of 0.025. The variations of scores between groups obtained from the LKI and the SF36 questionnaire at T0 versus T3FU and versus T6FU were analyzed with repeated measures ANOVA and Bonferroni-adjusted post-hoc test for pairwise comparisons. The changes in the LKI score intra-groups, at T0, versus T3FU and versus T6FU, were analyzed by repeated measures ANOVA plus Bonferroni post-hoc tests.

The change in VAS inter-groups at T0 versus T3FU and versus T6FU, were also analyzed by repeated measures ANOVA, with Bonferroni post-hoc tests. Pain Killer consumption was evaluated with the Mann–Whitney *U* test, after having standardized the values collected. The adverse events in each group were tabulated, and their frequency of occurrence was compared with Fisher's exact test.

Results of test were considered statistically significant if $p < 0.05$, unless for the primary endpoint, for which a one-tailed test with $p < 0.025$ was considered the level of statistical significance. All analyses were carried out with the statistical package Stata/SE 13.1 (The StataCorp LP, 4905 Lakeway Drive, College Station, Texas 77845 USA).

Results

Sixty-seven patients were assessed for eligibility. Three patients were excluded for not meeting the inclusion criteria, as affected by systemic inflammatory arhtritis (2 rheumatoid arthritis, 1 psoriatic arthritis). As reported previously 32 patients in Group A (MD-Knee) and 32 patients in Group B (SUPARTZ®) were enrolled. The

patients' demographic characteristics at T0 are shown in Table 1, evidencing no difference between groups. Women included in Group A were 86.2 and 64.5 % in Group B; mean age was similar in both groups (approximately 69 years). Body Mass Index (BMI) was also similar in both groups, with patients moderately overweight (average BMI approximately 27 kg/m^2). Kellgren and Lawrence radiological grades II and III were similarly distributed. Function evaluation showed LKI score approximately 12.5. Knee OA symptoms were moderate to severe (average VAS 7.5 cm circa). There was no difference between Group A and Group B in SF36 questionnaire score at T0 (Table 1) and NSAIDs consumption in the previous 3 months (Mann–Whitney *U* test: $p = 0.8439$) (data not shown). Three patients in the MD-Knee arm and one patient in the SUPARTZ arm dropped out before study conclusion. In the MD-Knee one patient experienced joint pain after the second intra-articular injection of MD-knee and decided to withdraw from the study, with knee pain regressing in 1 day without the need of any medicaments and no signs of joint effusion/inflammation, one patient experienced a direct blunt trauma in the knee after the second MD-knee injection and was then excluded from study prosecution and one patient was lost to followup. In the SUPARTZ group, one patient experienced an accidental fall with multiple contusions, involving studied knee, after the third injection of SUPARTZ and was then excluded from the study (Fig. 1).

Primary endpoint

Non-inferiority of LKI score at T3FU

LKI score was the same in the two groups at T0 (Student's *t* test: $p = 0.8871$) and at T3FU (Student's *t* test: $p = 0.3302$). Observed difference intra-groups (T3FU mean LKI - T0 mean LKI) was larger in absolute value in Group A (MD-Knee) than in Group B (SUPARTZ®), but this difference was not significant (Welch's test: $p = 0.3683$). The mean difference between Group A and Group B was equal to – 3.7778 - (–2.9483) = –0.8295, and the confidence interval (CI) 95 % of this difference ranged from – 2.6737 to +1.0147, while the standard error was 0.9110. Since the variances at T3FU did not differ between groups (F-test: $p = 0.7540$), the variance and the standard error pooled were used, keeping the non-inferiority limit by 24 % compared to the value measured in Group B, as established by the protocol. The precise difference between the average score was then – 1.2005, while the interval difference, taking into account the degrees of freedom of the system (dof = 54), was included with the 99 % confidence between – 4.47004 and +2.06904, and since the non-inferiority limit calculated for the differences between averages was +2.3503, we could conclude that the treatment with MD-Knee was not inferior of the treatment with SUPARTZ®, with a confidence level higher than 99 %. Table 2 – Fig. 2

Table 1 Patients' demographic characteristics at T0

	Group A (MD-Knee) = 32	Group B (SUPARTZ®) = 32
Age (years ± SD)	69.41 ± 8.42	69.97 ± 9.5
Women, n (%)	25 (86.2 %)	20 (64.5 %)
BMI (kg/m^2)	27.20 ± 3.78	27.3 ± 3.56
Kellgren and Lawrence, n (%)Grade II (%)	15 (51 %)	17 (55 %)
Kellgren and Lawrence, n (%)Grade III (%)	14 (49 %)	14 (45 %)
LKI ± SD	12.48 ± 2.63	12.6 ± 3.48
SF36 ± SD	91.41 ± 20.01	93.07 ± 17.3
Pain VAS (cm) ± SD	7.67 ± 1.41	7.42 ± 1.35

Data are mean ± *SD* Standard Deviation unless otherwise indicated. *BMI* Body Mass Index, *LKI* Lequesne Knee Index, *VAS* Visual Analogue Scale

Secondary endpoints

- *LKI variation inter- groups at T0* versus *T6FU*
  Repeated measures ANOVA of LKI showed a significant reduction intra-patient (F-test: $p < 0.01$), even assuming the non-sphericity of the data. It was observed no change due to membership in the treatment group (F-test: $p = 0.621$). Table 2 - Fig. 2
- *Pain VAS*
  Repeated measures ANOVA of VAS showed a intra-patient highly significant variation, while inter-groups variation ($p = 0.275$) and interaction (group x factor) ($p = 0.447$) are not significant. Therefore VAS variation does not seem to depend on the administered treatment. Table 2 – Fig. 3
- *SF36 questionnaire*
  Repeated measures ANOVA of SF36 questionnaire total score showed a significant change intra-patient (F-test: $p = 0.005$, without assuming the sphericity of the data), while no changes were observed due to treatment (F-test: $p = 0.462$) at T3FU and T6FU. Table 2 - Fig. 4
- *Pain Killer consumption (Rescue Medication)*
  Including dropouts, Acetaminophen was used by 13 of 29 patients (44,8 %) in Group A (MD-Knee) and by 12 of 31 patients (38,7 %) in Group B (SUPARTZ®). Acetominophen consumption during the trial did not change in the two Groups, considering both "only users" and "all patients" (Mann–Whitney test U: $p = 0.2198$ e $p = 0.9348$, respectively). Fig. 5a, b.

Safety

Adverse events (AE) observed by the investigators or reported by the patients spontaneously or following a non-

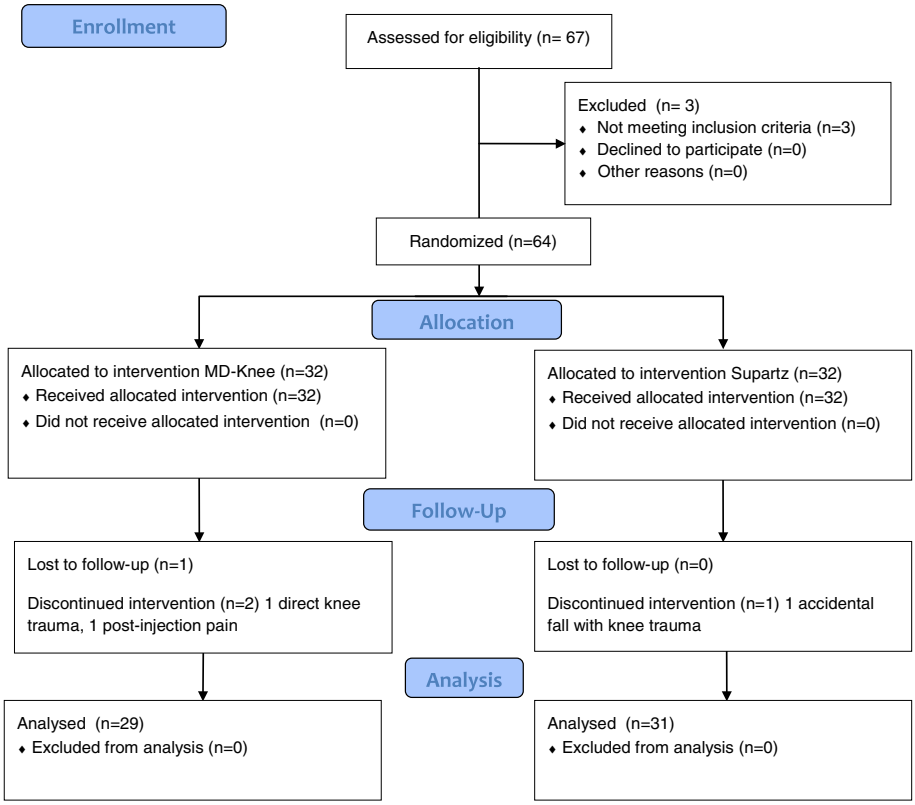

Fig. 1 Flow chart reporting patients' enrollment and study prosecution with drop outs and reasons for drop out

leading question, were investigated. Treatment with MD-Knee and with SUPARTZ® for up to 6 months was generally well tolerated. No systemic adverse events and septic complication were observed. Only one subject discontinued for a moderate post-injection reaction in Group A (MD-Knee) but symptoms disappeared without the need of medication. No joint effusion events were observed throughout the entire followup of patients in both groups.

Discussion

Intra-articular (IA) therapy in the treatment of OA knee is widespread in clinical practice, although much debated by the evidences of the most recent international recommendations. The IA therapy may consist of corticosteroids, of high or low molecular weight (MW) HA, of polynucleotited, pletelet-rich-plasma (PRP) or other substances including collagen extracts. Recent scientific evidences suggest that injecting treatment with porcin collagen could provide interesting improving clinical performances [16–19]. However IA therapy should be considered with the complex management of OA, such as medical and non- medical interventions. I The collagen administered at intra-articular level could stimulate and promote the healing process of the cartilage matrix, which is injured in the course of osteoarthritis, as demonstrated in animal models [17]. Collagen can promote repair processes of the cartilage matrix, interrupting the degenerative process and articular damage, which causes inflammation and pain.

In this double-blind, randomised, active-controlled clinical trial in patients affected by knee OA, five intra-articular injections of MD-Knee or sodium hyaluronate administered weekly are equally able to improve

Table 2 Data are mean ± SD (Standard Deviation) at T3FU and T6FU with *p* value

	T3 FU			T6 FU		
	Group A (MD-Knee)	Group B (SUPARTZ®)	*P*-value	Group A (MD-Knee)	Group B (SUPARTZ®)	*P*-value
LKI ± SD	8.59 ± 4.71	9.79 ± 4.43	0.33	9.12 ± 3.89	9.28 ± 4.28	0.621
Pain VAS ± SD	5.26 ± 2.52	5.13 ± 2.41	NE	5.42 ± 2.69	4.43 ± 2.63	0.275
SF36 ± SD	99.15 ± 8.95	101.32 ± 6.37	NE	88.37 ± 28.83	92.07 ± 23.37	0.462

NE Not evaluated

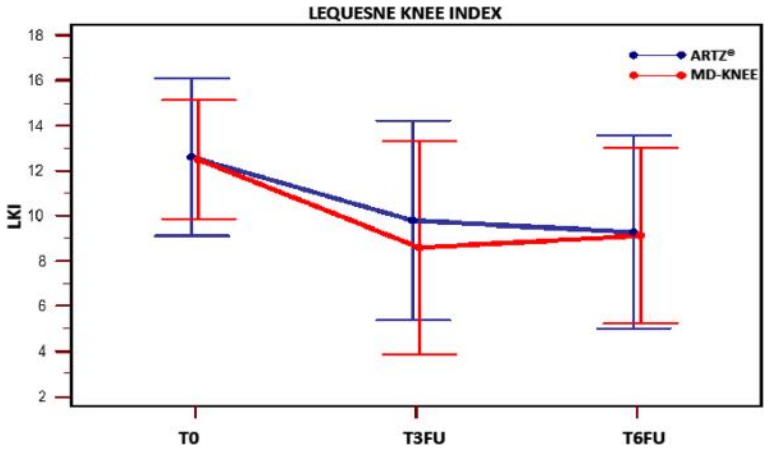

Fig. 2 Variation of LKI (Lequesne Knee Index) score intra-subject and inter-groups at time T0; T3FU; T6FU

function and reduce pain after 3 months till at least 6 months by the end of treatment. As shown VAS and LKI improved at T3FU and T6FU. SF36 questionnaire, and pain killer consumption did not change in both groups confirming non-inferiority hypothesis. We have to acknowledge limitations of this study. In this non inferiority prospective randomized controlled double blind study, for bio-ethical reasons, we have no placebo arm, therefore the confrontation was made between two active arms only. Also, followup time was limited to 6 months only, while longer followups are recommended for chronic pathologies such as OA.

Future trials should investigate the proportion of OARSI/OMERACT criteria responders which might be useful for an indirect comparison with other local or systemic treatments; also the effect on the progression of tissue damage could be looked into. The lack of a placebo control group is to be expected when IA injections of hyaluronic acid products are routinely used in clinical practice. A further issue concerns the nature of placebo for IA injections, ie. use of saline solution or sham injection. For these ethical and methodological reasons, it has been considered correct to compare MD-Knee with a marketed product, such as SUPARTZ®, that has been widely used in clinical practice and proved effective in previous studies. Moreover the lack of comparison with patients treated with other kind of HA (as high MW or cross-linked HA) doesn't allow us to draw final conclusion about the range of efficacy of MD-Knee Guna Medical Device, since the clinical equivalence of all HA products is not clear. Nevertheless a favourable feature of this trial is assessing OA knee symptoms effectiveness through several different measures, providing a wide clinical evaluation. Beside all Lequesne's items showing a similar advantage for both groups. Further studies are warranted in order to verify whether the symptomatic effect of MD-Knee is associated with a halting of knee OA progression.

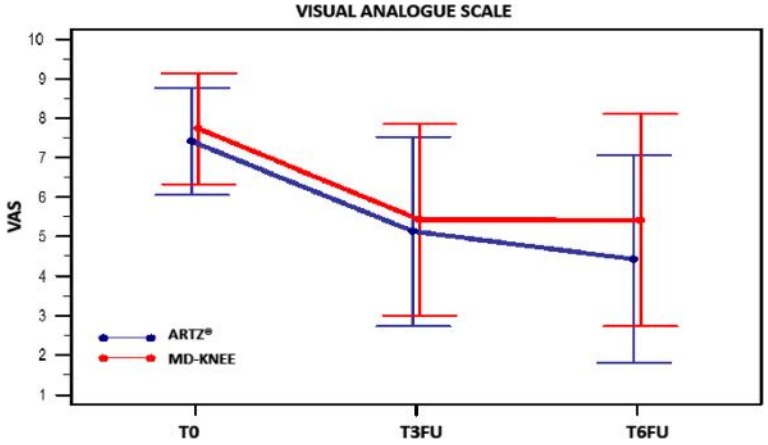

Fig. 3 Visual Analogue Scale (VAS) at time T0; T3FU; T6FU for Group ARTZ® and in Group MD-Knee

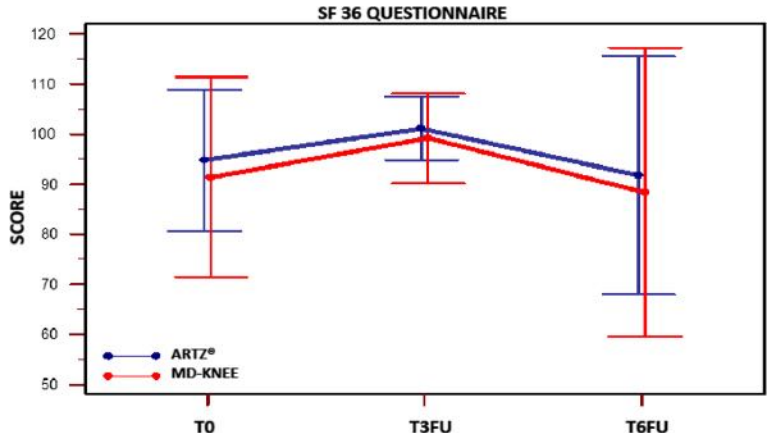

Fig. 4 SF36 questionnaire. Score at time T0; T3FU; T6FU for Group ARTZ®and Group MD-Knee

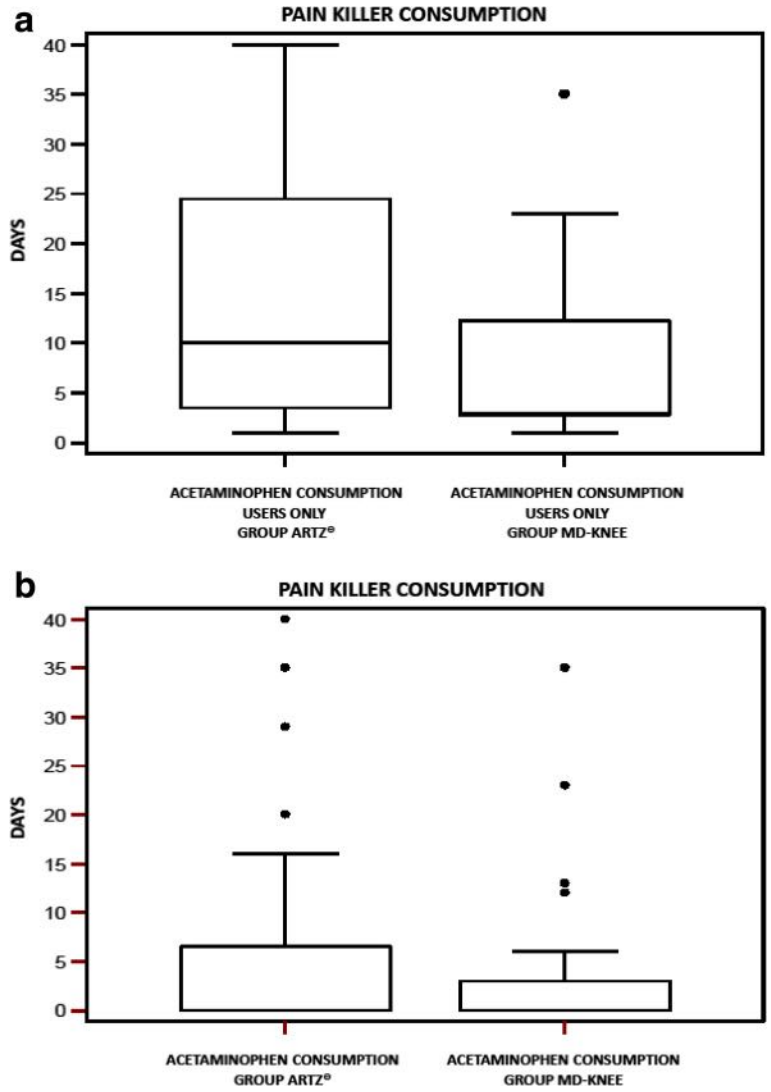

Fig. 5 a Pain Killer consumption (days), in users only, in both groups. **b** Pain Killer consumption (days),in all subject, in both groups

Conclusion

This trial shows that MD-Knee preparation is effective on knee OA symptoms over 6 months after a 5-week injection course, and it is equally effective in improving clinical performance as assessed through LKI, VAS, SF36 questionnaire and Pain Killer consumption, as the reference HA formulation.

MD-Knee and SUPARTZ® were equally well tolerated both locally and at a systemic level, therefore showing a satisfactory safety profile.

The reduced cost of MD-Knee compared to low or high MW HA could allow wider use of IA therapy, resulting in a NSAIDs intake reduction, as well as social cost reduction due to working days lost and caregivers time off work.

Competing interest

All authors state that Guna S.p.a did not participate in the interpretation of data, in the writing of the manuscript, nor in the decision to submit the manuscript for publication. The authors declare no conflict of interest with respect to the contents of this article.

Authors' contribution

LSMM and AM contributed to the ideation of the protocol and to data management and analysis, as well as to text drafting. EB and UM contributed to the study by recording patients' data and by performing intra-articular injections respectively, and both contributed to text drafting. All authors have read and approved the final version of the manuscript.

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RESEARCH ARTICLE Open Access

A double blind randomized active-controlled clinical trial on the intra-articular use of Md-Knee versus sodium hyaluronate in patients with knee osteoarthritis ("Joint")

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Abstract

Background: To evaluate the clinical outcomes of a group of patients affected by knee osteoarthritis (OA) treated with MD-Knee (Guna S.p.a., Milan, Italy) versus a group of patients treated with sodium hyaluronate.

Method: This non-inferiority prospective randomized controlled trial involved 60 patients affected by knee OA, grade 2–3 of Kellgren-Lawrence scale. The MD-Knee Group, Group A ($n = 29$) was administered five intra-articular injections at 1 week interval; the sodium hyaluronate Group, Group B ($n = 31$), was administered five doses of intra-articular injection of sodium hyaluronate at 1 week interval. All patients were prospectively evaluated before and at 3 and 6 months after the treatment by the Lequesne Knee Index (LKI) as primary endpoint and the Visual Analogue Scale (VAS), Pain Killer consumption and SF-36 questionnaires as secondary endpoints.

Results: At the 3- and 6 month follow-up, LKI and VAS improved significantly in both groups compared to baseline and no statistically significant differences were observed between Group A and Group B. There was no statistically significant difference in the SF36 questionnaire score and pain killer consumption between two groups at any time point.

Conclusions: This study shows that both preparations exert similar clinical effects as assessed through multiple outcome measures. MD-Knee is effective on knee OA symptoms over 6 months after a 5-weekly injection course, and it is equally effective as the reference sodium hyaluronate.

Trial registration: Trial registration number: ISRCTN93862496. Registration date: January 18th, 2016

Keywords: Osteoarthritis, Knee, Intra-articular, Hyaluronic acid, MD-Knee

Background

Osteoarthritis (OA) is a chronic degenerative joint disease characterized by progressive damage of articular cartilage and underlying bone. It is a common rheumatic disease that affects both sexes and the majority of the elderly people; nevertheless, also the young are frequently affected by OA, thus becoming an important cause of lost workdays. Estimated prevalence in general adult population is of 11 and 24 % for hip and knee OA respectively [1]. Pain is accentuated by movements and decreases with rest but, with progression of disease, it may be present at rest and accompanied by short morning stiffness; moreover, joint damage causes a progressive functional limitation [2]. In order to reduce pain and to achieve an overall better clinical condition it is suggested to use a therapeutic strategy including physical therapy and rehabilitation, non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, chondroprotecting agents and intra-articular treatment with infiltrative substances such as hyaluronates and steroids. When the disease is at an advanced stage, orthopedic surgical solution can offer great benefits [3]. Over the past 10 years some double-blind controlled clinical trials have shown that administration by injection of hyaluronic acid (HA) for 3–5 weeks is superior in

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terms of efficacy, compared to saline, arthrocentesis, and treatments with NSAIDs [4–6]. In addition, HA has presented an excellent tolerability profile with a low incidence of complications at local level and a complete absence of systemic effects that are typically associated with anti-inflammatory drugs, steroid or surgery [7, 8]. Among HAs used, sodium hyaluronate SUPARTZ® (Seikagaku, Tokyo, Japan) is one of the most used and studied by clinical trials [9–15]. Other products for intra-articular use have been recently introduced for the treatment of OA; at present time there is no definitively effective treatment for this condition, but the very high cost of these therapies, however, fosters to test new treatments that could provide the same benefits at a lower cost. Among these, a medical device MD-Knee, produced by Guna S.p.a., Milan-Italy containing collagen of porcine origin has been investigated. Collagen content in MD-Knee has a molecular weight equal to 300,000 dalton, produced through a process of tangential filtration. It is a pure product, contaminant-free, with standardized chemical and physical characteristics. Collagen is the most abundant protein in the bodies of mammals, accounting for approximately 5–6 % of the body weight of an adult man. About 30 % of total protein mass of higher animals is collagen, found in bones, tendons, joint capsules, muscles, ligaments, teeth, skin and in general in extra-cellular matrix. Porcine tissues have a very high average collagen content, around 50 %. In collagen amino acid content is for Glycine 22.8, Proline 13.8 and Hydroxy-Proline 13 %. The average content of other amino acids is only 3 % (max Glutamic Acid 9.5 %; min Tyrosine 0.4 %). The purpose of an *in-situ* introduction of this device is structural; in fact, mechanical support provided by collagen is an effective natural scaffold support (bio-scaffold). Its degradation in the constituent aminoacids seems to constitute a nutritional support for tissues of the other joint structures [16–19].

The aim of this study is to evaluate the use of collagen MD-Knee versus sodium hyaluronate (SUPARTZ®) in patient with knee OA. The outcome has been clinically assessed through the OMERACT criteria (Outcome Measures in Rheumatology) [20].

Methods

Study design and patients

JOINT study is a prospective, double blind, multicentric, randomized clinical trial with active control. The trial was conducted in accordance with the Good Clinical Practice (GCP) and the Declaration of Helsinky; the protocol was approved by the local Ethical Committee (San Pietro Fatebenefratelli Hospital Bioethic Committee). Enrollment started in March 2013 and ended in September 2013. Patients were enrolled and followed in both participating Centers (San Pietro Fatebenefratelli Hospital, Rome, Italy, and Regina Apostolorum Hospital, Albano Laziale, Italy). Only patients affected by symptomatic knee OA were considered eligible for participating in the study. All patients signed an informed consent before entering the study. The randomization list was generated through a high-efficiency system (www.random.org). The list was created by generating eight blocks of eight subjects (1: 1) for a total of 64 enrolled patients. The use of the blocks has allowed to obtain balanced groups during the study. Two groups of subjects were identified; the first group (Group A) consisting of 32 patients has received the investigational product, MD-Knee (Guna S.p.a., Milan, Italy), The second group (Group B), consisting in 32 patients, was treated with SUPARTZ® (Seikagaku, Tokyo, Japan). MD-Knee (injectable ampoules of 2.0 ml) was administered at a dose of two vials for a total of 4 ml via intra-articular injection, once a week for a period of five consecutive weeks; one vial of 2.5 ml sodium hyaluronate (SUPARTZ®) was identically administered.

A total of three visits was performed. During the first one at time T0 (enrollment), the selected patients, after signing the informed consent, were assigned to the experimental group (Group A) or to the reference group (Group B) according to a randomization list. In the same visit the product under investigation was administered. All patients then underwent 1 weekly dosing of MD-Knee or SUPARTZ® for five consecutive weeks; patients were visited 3 months after enrollment (T3 follow-up) and 6 months after the start of the trial (T6 follow-up). The physician performing the intra-articular injection was aware of the product administered, while both physicians evaluating the algo-funcional indices, as well as the patients, were unaware of the product administered.

Inclusion criteria

In this trial were included male and female subjects who met the following criteria:

- ambulatory adult patients affected by knee OA
- diagnosis according to the ARA (American Rheumatism Association) criteria
- age > 40 years
- disease activity assessed by the Lequesne Knee Index ≥ 7.0 at T0
- disease activity assessed according to the VAS at T0 ≥ 4 cm and persistence of pain in the knee for at least the last 3 months.
- radiological degree II-III according to the Kellgren-Lawrence scale
- patients able to comply with study procedures.

Exclusion criteria

Patients who met the following criteria were excluded:

- presence of comorbidities (rheumatoid arthritis, spondyloarthritis, connective tissue disease,

polymyalgia rheumatica, gout, Paget's disease, septic arthritis, fractures, osteonecrosis, and fibromyalgia)
- patients with skin or subcutaneous tissue infection in the area of the joint to be treated
- patients who had used oral, parenteral or intra-articular corticosteroids in the 3 months prior to the T0 visit
- patients taking topical analgesics that may interfere with the evaluation of the study
- patients on anticoagulant therapy or suffering from thrombocytopenia and/or coagulopathy
- patients with allergy to products of porcine origins.

Primary endpoint

At T0 and during the clinical follow-up (FU) at 3 months and 6 months, it was performed the assessment of the physical function according to standardized parameters LKI (Lequesne Knee Index). This clinical trial was set up as a non-inferiority study of MD-Knee compared to sodium hyaluronate (SUPARTZ®) in reducing the LKI score at T3FU in patient with knee OA. At baseline, the average value of the LKI in both groups was assumed to be 7.0 ± 1.1. After 3 months, in Group B (SUPARTZ®), it was expected a reduction of the average value of the LKI to 4.2 ± 1.1 (e.g., a 40 % reduction from baseline). From this value of the LKI score, we accepted as non-inferior a possible value of LKI increased by less than 24 % for the Group A (MD-Knee), and thus the non-inferiority margin (NIM) was set equal to 4.2×1.24 = 5.21, with a standard deviation expected to remain equal to 1.1. Calling D the difference in LKI after 3 months between A and B (equal to 5:21 to 4:20 = 1.01) product, then null hypothesis is H0: $D \geq 1.01$, while alternative hypothesis is H1: $D < 1.01$. With these assumptions, the two groups of 29–31 subjects reached a power of 93.8 % in recognizing the non-inferiority using a one-tailed Student *t* test with significance level of $\alpha = 0.025$. In the case of non-applicability of the Student's test, it was estimated that the power of the non-parametric analogous test (one-tailed Mann–Whitney *U* test, with a significance level of 0.025) would have been 92.2 %.

Secondary endpoints

In order to demonstrate the non-inferiority of MD-Knee in reducing pain, the Visual Analogue Scale (VAS) (0–10 cm), the LKI score at T6FU, and the Pain Killer consumption assessment during the course of the study, were also performed.

Questionnaire SF-36 concerning the state of physical and mental health of the subjects, was administered and evaluated for all the patients at T0, T3FU, T6FU. Data were compared with those obtained by the reference group (Group B) and had to comply with the specified threshold for non-inferiority.

Finally, during the investigation period, all events related with intra-articular injection of the investigational product were analyzed.

Rescue medication

During the study, the only analgesic allowed was Acetaminophen 1000 mg (Pain Killer). Analgesic assumption was reported in a clinical diary.

Reporting adverse events

All information relating to possible adverse events (AEs), serious adverse events (SAEs) were reported.

Statistical methods

All variables collected were submitted to the appropriate descriptive analysis, based on their distribution within the sample recruited, assessed by visual inspection of distribution histograms and with the Shapiro-Wilk test for continuous variables, and frequency tables for the categorical variables. The primary endpoint of the possible non-inferiority efficacy in reducing the LKI score (measured at 3 months) in Group A, compared to Group B, was evaluated with Student's *t* test for independent data, in a one-tailed test, with the significance level of 0.025. The variations of scores between groups obtained from the LKI and the SF36 questionnaire at T0 versus T3FU and versus T6FU were analyzed with repeated measures ANOVA and Bonferroni-adjusted post-hoc test for pairwise comparisons. The changes in the LKI score intra-groups, at T0, versus T3FU and versus T6FU, were analyzed by repeated measures ANOVA plus Bonferroni post-hoc tests.

The change in VAS inter-groups at T0 versus T3FU and versus T6FU, were also analyzed by repeated measures ANOVA, with Bonferroni post-hoc tests. Pain Killer consumption was evaluated with the Mann–Whitney *U* test, after having standardized the values collected. The adverse events in each group were tabulated, and their frequency of occurrence was compared with Fisher's exact test.

Results of test were considered statistically significant if $p < 0.05$, unless for the primary endpoint, for which a one-tailed test with $p < 0.025$ was considered the level of statistical significance. All analyses were carried out with the statistical package Stata/SE 13.1 (The StataCorp LP, 4905 Lakeway Drive, College Station, Texas 77845 USA).

Results

Sixty-seven patients were assessed for eligibility. Three patients were excluded for not meeting the inclusion criteria, as affected by systemic inflammatory arhtritis (2 rheumatoid arthritis, 1 psoriatic arthritis). As reported previously 32 patients in Group A (MD-Knee) and 32 patients in Group B (SUPARTZ®) were enrolled. The

patients' demographic characteristics at T0 are shown in Table 1, evidencing no difference between groups. Women included in Group A were 86.2 and 64.5 % in Group B; mean age was similar in both groups (approximately 69 years). Body Mass Index (BMI) was also similar in both groups, with patients moderately overweight (average BMI approximately 27 kg/m^2). Kellgren and Lawrence radiological grades II and III were similarly distributed. Function evaluation showed LKI score approximately 12.5. Knee OA symptoms were moderate to severe (average VAS 7.5 cm circa). There was no difference between Group A and Group B in SF36 questionnaire score at T0 (Table 1) and NSAIDs consumption in the previous 3 months (Mann–Whitney *U* test: $p = 0.8439$) (data not shown). Three patients in the MD-Knee arm and one patient in the SUPARTZ arm dropped out before study conclusion. In the MD-Knee one patient experienced joint pain after the second intra-articular injection of MD-knee and decided to withdraw from the study, with knee pain regressing in 1 day without the need of any medicaments and no signs of joint effusion/inflammation, one patient experienced a direct blunt trauma in the knee after the second MD-knee injection and was then excluded from study prosecution and one patient was lost to followup. In the SUPARTZ group, one patient experienced an accidental fall with multiple contusions, involving studied knee, after the third injection of SUPARTZ and was then excluded from the study (Fig. 1).

Primary endpoint

Non-inferiority of LKI score at T3FU

LKI score was the same in the two groups at T0 (Student's *t* test: $p = 0.8871$) and at T3FU (Student's *t* test: $p = 0.3302$). Observed difference intra-groups (T3FU mean LKI - T0 mean LKI) was larger in absolute value in Group A (MD-Knee) than in Group B (SUPARTZ®), but this difference was not significant (Welch's test: $p = 0.3683$). The mean difference between Group A and Group B was equal to – 3.7778 - (–2.9483) = –0.8295, and the confidence interval (CI) 95 % of this difference ranged from – 2.6737 to +1.0147, while the standard error was 0.9110. Since the variances at T3FU did not differ between groups (F-test: $p = 0.7540$), the variance and the standard error pooled were used, keeping the non-inferiority limit by 24 % compared to the value measured in Group B, as established by the protocol. The precise difference between the average score was then – 1.2005, while the interval difference, taking into account the degrees of freedom of the system (dof = 54), was included with the 99 % confidence between – 4.47004 and +2.06904, and since the non-inferiority limit calculated for the differences between averages was +2.3503, we could conclude that the treatment with MD-Knee was not inferior of the treatment with SUPARTZ®, with a confidence level higher than 99 %. Table 2 – Fig. 2

Table 1 Patients' demographic characteristics at T0

	Group A (MD-Knee) = 32	Group B (SUPARTZ®) = 32
Age (years ± SD)	69.41 ± 8.42	69.97 ± 9.5
Women, n (%)	25 (86.2 %)	20 (64.5 %)
BMI (kg/m^2)	27.20 ± 3.78	27.3 ± 3.56
Kellgren and Lawrence, n (%)Grade II (%)	15 (51 %)	17 (55 %)
Kellgren and Lawrence, n (%)Grade III (%)	14 (49 %)	14 (45 %)
LKI ± SD	12.48 ± 2.63	12.6 ± 3.48
SF36 ± SD	91.41 ± 20.01	93.07 ± 17.3
Pain VAS (cm) ± SD	7.67 ± 1.41	7.42 ± 1.35

Data are mean ± *SD* Standard Deviation unless otherwise indicated. *BMI* Body Mass Index, *LKI* Lequesne Knee Index, *VAS* Visual Analogue Scale

Secondary endpoints

- *LKI variation inter- groups at T0* versus *T6FU*
  Repeated measures ANOVA of LKI showed a significant reduction intra-patient (F-test: $p < 0.01$), even assuming the non-sphericity of the data. It was observed no change due to membership in the treatment group (F-test: $p = 0.621$). Table 2 - Fig. 2
- *Pain VAS*
  Repeated measures ANOVA of VAS showed a intra-patient highly significant variation, while inter-groups variation ($p = 0.275$) and interaction (group x factor) ($p = 0.447$) are not significant. Therefore VAS variation does not seem to depend on the administered treatment. Table 2 – Fig. 3
- *SF36 questionnaire*
  Repeated measures ANOVA of SF36 questionnaire total score showed a significant change intra-patient (F-test: $p = 0.005$, without assuming the sphericity of the data), while no changes were observed due to treatment (F-test: $p = 0.462$) at T3FU and T6FU. Table 2 - Fig. 4
- *Pain Killer consumption (Rescue Medication)*
  Including dropouts, Acetaminophen was used by 13 of 29 patients (44,8 %) in Group A (MD-Knee) and by 12 of 31 patients (38,7 %) in Group B (SUPARTZ®). Acetominophen consumption during the trial did not change in the two Groups, considering both "only users" and "all patients" (Mann–Whitney test U: $p = 0.2198$ e $p = 0.9348$, respectively). Fig. 5a, b.

Safety

Adverse events (AE) observed by the investigators or reported by the patients spontaneously or following a non-

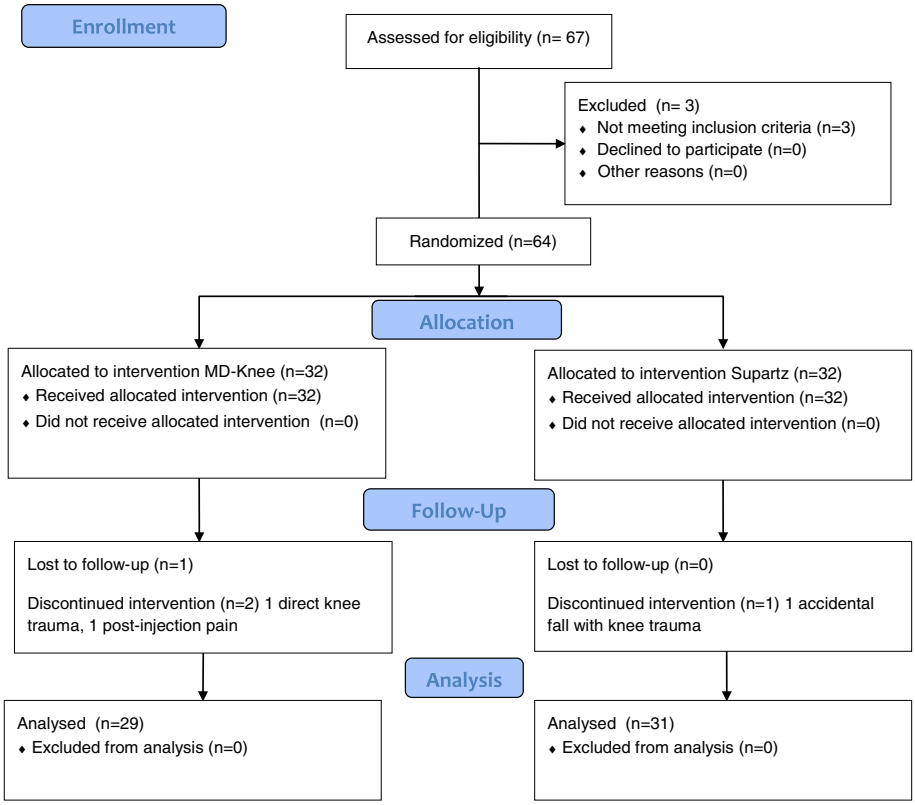

Fig. 1 Flow chart reporting patients' enrollment and study prosecution with drop outs and reasons for drop out

leading question, were investigated. Treatment with MD-Knee and with SUPARTZ® for up to 6 months was generally well tolerated. No systemic adverse events and septic complication were observed. Only one subject discontinued for a moderate post-injection reaction in Group A (MD-Knee) but symptoms disappeared without the need of medication. No joint effusion events were observed throughout the entire followup of patients in both groups.

Discussion

Intra-articular (IA) therapy in the treatment of OA knee is widespread in clinical practice, although much debated by the evidences of the most recent international recommendations. The IA therapy may consist of corticosteroids, of high or low molecular weight (MW) HA, of polynucleotited, pletelet-rich-plasma (PRP) or other substances including collagen extracts. Recent scientific evidences suggest that injecting treatment with porcin collagen could provide interesting improving clinical performances [16–19]. However IA therapy should be considered with the complex management of OA, such as medical and non- medical interventions. I The collagen administered at intra-articular level could stimulate and promote the healing process of the cartilage matrix, which is injured in the course of osteoarthritis, as demonstrated in animal models [17]. Collagen can promote repair processes of the cartilage matrix, interrupting the degenerative process and articular damage, which causes inflammation and pain.

In this double-blind, randomised, active-controlled clinical trial in patients affected by knee OA, five intra-articular injections of MD-Knee or sodium hyaluronate administered weekly are equally able to improve

Table 2 Data are mean ± SD (Standard Deviation) at T3FU and T6FU with *p* value

	T3 FU			T6 FU		
	Group A (MD-Knee)	Group B (SUPARTZ®)	*P*-value	Group A (MD-Knee)	Group B (SUPARTZ®)	*P*-value
LKI ± SD	8.59 ± 4.71	9.79 ± 4.43	0.33	9.12 ± 3.89	9.28 ± 4.28	0.621
Pain VAS ± SD	5.26 ± 2.52	5.13 ± 2.41	NE	5.42 ± 2.69	4.43 ± 2.63	0.275
SF36 ± SD	99.15 ± 8.95	101.32 ± 6.37	NE	88.37 ± 28.83	92.07 ± 23.37	0.462

NE Not evaluated

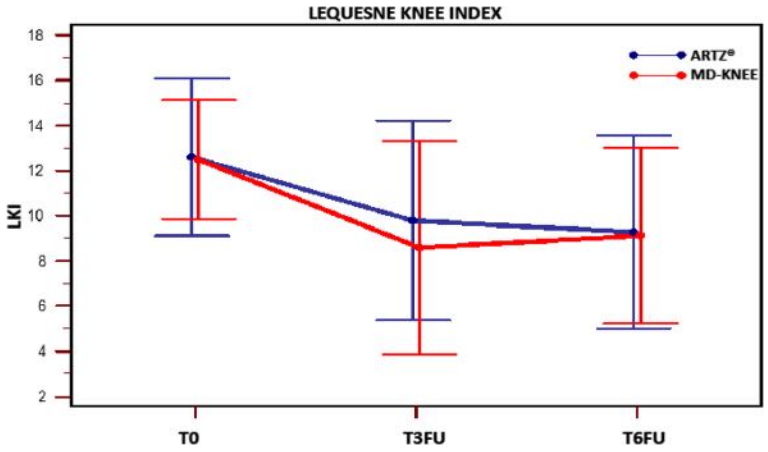

Fig. 2 Variation of LKI (Lequesne Knee Index) score intra-subject and inter-groups at time T0; T3FU; T6FU

function and reduce pain after 3 months till at least 6 months by the end of treatment. As shown VAS and LKI improved at T3FU and T6FU. SF36 questionnaire, and pain killer consumption did not change in both groups confirming non-inferiority hypothesis. We have to acknowledge limitations of this study. In this non inferiority prospective randomized controlled double blind study, for bio-ethical reasons, we have no placebo arm, therefore the confrontation was made between two active arms only. Also, followup time was limited to 6 months only, while longer followups are recommended for chronic pathologies such as OA.

Future trials should investigate the proportion of OARSI/OMERACT criteria responders which might be useful for an indirect comparison with other local or systemic treatments; also the effect on the progression of tissue damage could be looked into. The lack of a placebo control group is to be expected when IA injections of hyaluronic acid products are routinely used in clinical practice. A further issue concerns the nature of placebo for IA injections, ie. use of saline solution or sham injection. For these ethical and methodological reasons, it has been considered correct to compare MD-Knee with a marketed product, such as SUPARTZ®, that has been widely used in clinical practice and proved effective in previous studies. Moreover the lack of comparison with patients treated with other kind of HA (as high MW or cross-linked HA) doesn't allow us to draw final conclusion about the range of efficacy of MD-Knee Guna Medical Device, since the clinical equivalence of all HA products is not clear. Nevertheless a favourable feature of this trial is assessing OA knee symptoms effectiveness through several different measures, providing a wide clinical evaluation. Beside all Lequesne's items showing a similar advantage for both groups. Further studies are warranted in order to verify whether the symptomatic effect of MD-Knee is associated with a halting of knee OA progression.

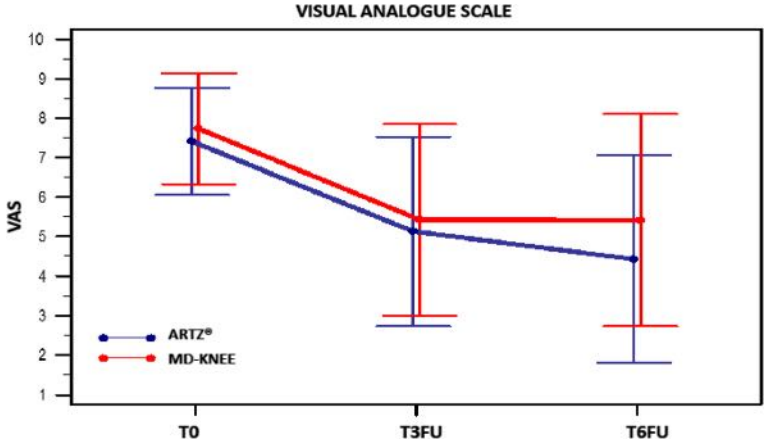

Fig. 3 Visual Analogue Scale (VAS) at time T0; T3FU; T6FU for Group ARTZ® and in Group MD-Knee

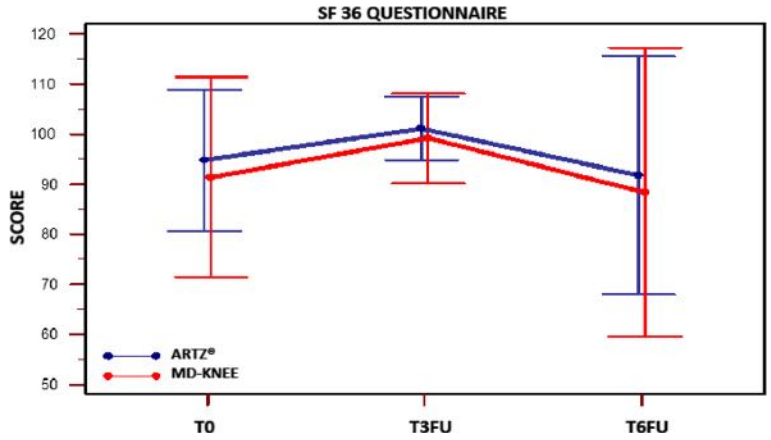

Fig. 4 SF36 questionnaire. Score at time T0; T3FU; T6FU for Group ARTZ®and Group MD-Knee

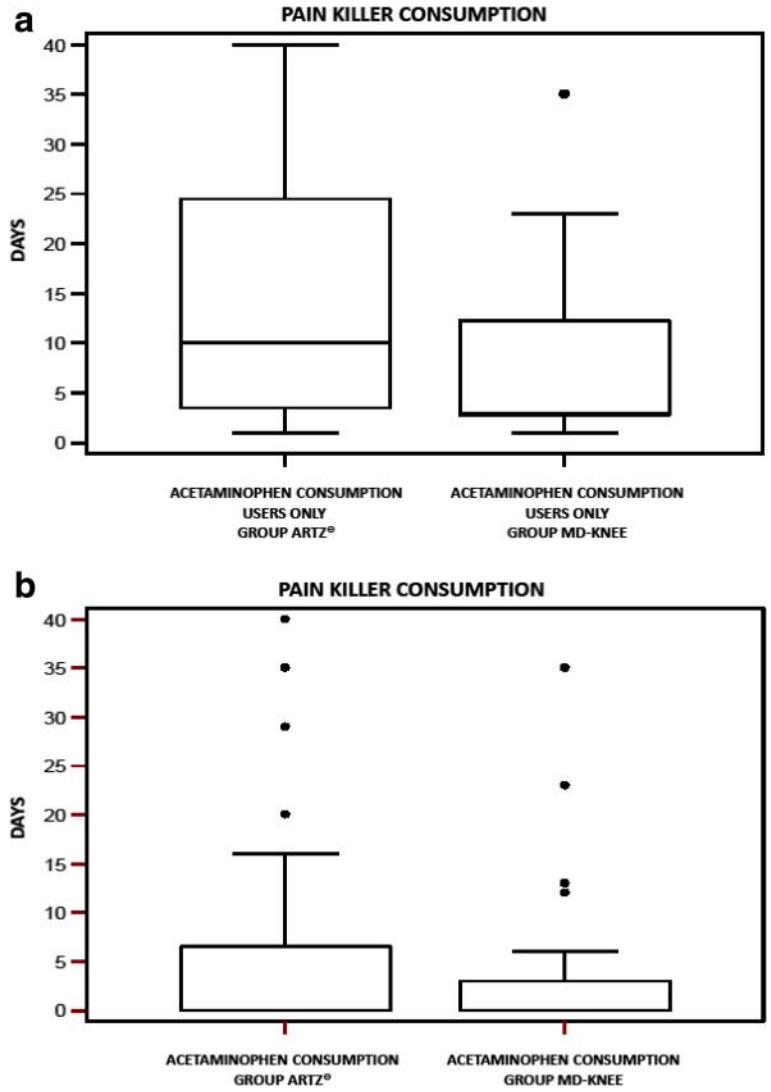

Fig. 5 a Pain Killer consumption (days), in users only, in both groups. **b** Pain Killer consumption (days),in all subject, in both groups

Conclusion

This trial shows that MD-Knee preparation is effective on knee OA symptoms over 6 months after a 5-week injection course, and it is equally effective in improving clinical performance as assessed through LKI, VAS, SF36 questionnaire and Pain Killer consumption, as the reference HA formulation.

MD-Knee and SUPARTZ® were equally well tolerated both locally and at a systemic level, therefore showing a satisfactory safety profile.

The reduced cost of MD-Knee compared to low or high MW HA could allow wider use of IA therapy, resulting in a NSAIDs intake reduction, as well as social cost reduction due to working days lost and caregivers time off work.

Competing interest

All authors state that Guna S.p.a did not participate in the interpretation of data, in the writing of the manuscript, nor in the decision to submit the manuscript for publication. The authors declare no conflict of interest with respect to the contents of this article.

Authors' contribution

LSMM and AM contributed to the ideation of the protocol and to data management and analysis, as well as to text drafting. EB and UM contributed to the study by recording patients' data and by performing intra-articular injections respectively, and both contributed to text drafting. All authors have read and approved the final version of the manuscript.

Acknowledgments

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SHORT COMMUNICATION

R. Nestorova, R. Rashkov,
V. Reshkova, N. Kapandjieva

EFFICIENCY OF COLLAGEN INJECTIONS OF GUNA MD IN PATIENTS WITH GONARTHROSIS, ASSESSED CLINICALLY AND BY ULTRASOUNDS

OBJECTIVE

This study has been planned to investigate the effectiveness of collagen injections of **GUNA MD-KNEE + GUNA MD-MATRIX** on pain and daily functioning in symptomatic knee osteoarthritis III-IV X-ray stages by Kellgren.
High frequency ultrasonography is an approved imaging technique for diagnosis of joint swelling and monitoring of the therapy.

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	6. Concomitant chondroprotectives
	7. Supporting physiotherapy

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STATISTICAL ANALYSIS

For the statistical processing of data and building graphics it was used the package IBM SPSS Statistics 19.
We used descriptive statistics and analysis with repeated observations (Repeated Measures Analysis).

RESULTS

– 10-point VAS
The average score for pain at rest decreased threefold at the end of treatment course /60 day/, the effect is maintained after treatment (FIG. 1). The mean score for pain on movement decreased almost twice at the end of treatment and continued to decrease 30 days after completion of the course (FIG. 2).

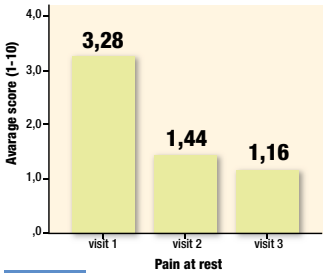

FIG. 1

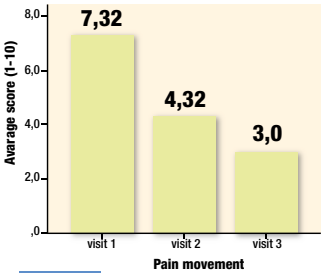

FIG. 2

– Algo-functional index of Lequesne

We observed improvements in all indicators of the index, but most significant are as follows:

– Morning stiffness decreased more than twice at the end of the course and the effect remained 30 days after therapy (FIG. 3).

– Average score of **pain on standing** was reduced threefold in the third visit - 90 days from the beginning (FIG. 4).

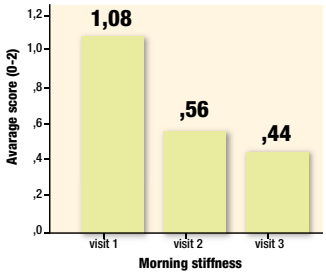

FIG. 3

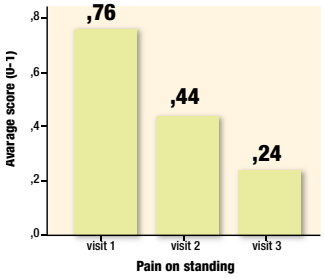

FIG. 4

– The mean assess for **pain during walking** decreased 1.5 times at the third visit compared with baseline (FIG. 5).

– The average score for the **maximum walking distance** was reduced 1.5 times at the third visit compared with baseline. This means that the actual distance that the patient can walk, thanks to GUNA MD-Knee and GUNA MD-Matrix, increased about 1.5 times (FIG. 6).

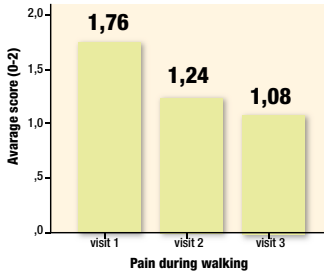

FIG.5

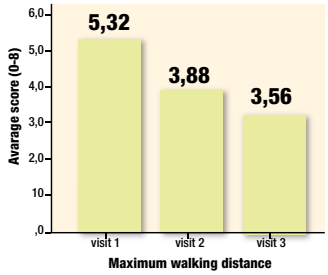

FIG. 6

– There were no side effects of application of collagen injections.

– Joint swelling, sonographically assessed:

We present some of the sonographic images of the knee prior to treatment with GUNA MD-Knee and GUNA MD-Matrix and 30 days thereafter (FIGG. 7a, b; 8a, b).

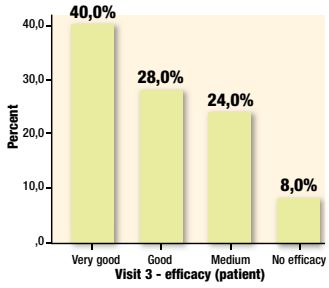

FIG.10

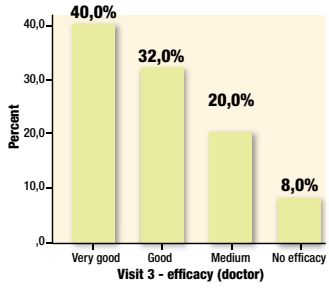

FIG. 11

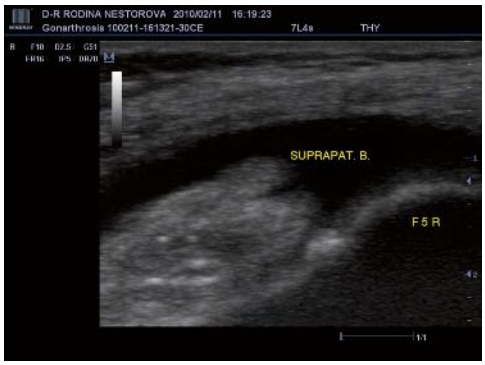

Fig. 7 a

Suprapatellar bursa was enlarged and swollen before treatment.

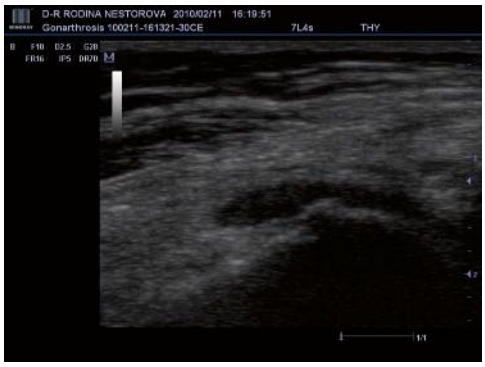

Fig. 7 b

Marked reduction of swelling after treatment.

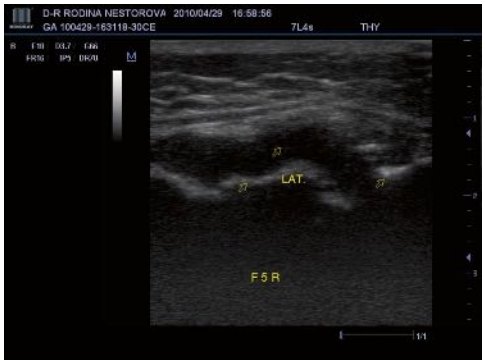

Fig. 8 a

Swelling of the joint space /lateral access/ prior to treatment.

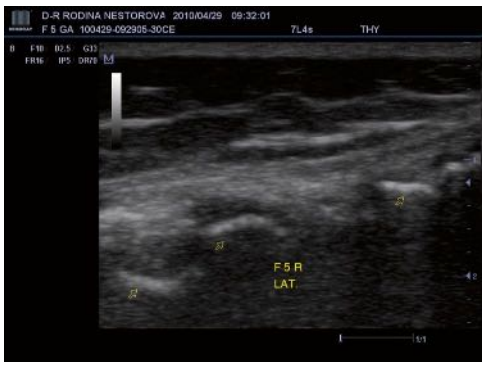

Fig. 8 b

Lack of edema after treatment.

Sonographic evaluation of swelling of the knee joint 30 days after treatment with the combination GUNA MD-Knee and GUNA MD-Matrix shows that 60% of the patients were without edema, and 30%were with reduction of swelling (FIG.9).

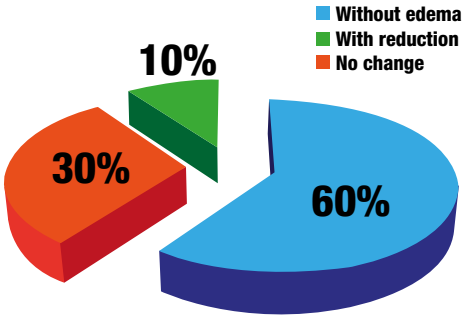

FIG. 9

Influence of joint swelling estimated by ultrasounds.

Efficacy of treatment according to patient and physician

Assessment of the patient and the physician of the efficacy of treatment with injectable collagen GUNA MDs on the 60th and 90th day matches, with the highest percentage is the highest rating, namely "very good".

FIG.10 and FIG.11 show the effect of treatment at visit 3 /90 day/. 68% of the evaluations of patients and 72% of doctors' assessments of the efficacy of treatment are "very good" and "good".

CONCLUSIONS

1. Periarticular administration of GUNA MD-Knee and GUNA MD-Matrix in Gonarthrosis III-IV X-Ray stage improves the status of the knee and thus improves the quality of life of patients due to:
   * Statistically significant reduction in pain at rest and pain on movement.
   * Statistically significant improvement in all indicators of the algo-functional Index of Lequesne.
   * Improvement in swollen syndrome in 90%, sonographically proven.
2. The effectiveness of GUNA MDs continues after stopping treatment.
3. The products have a very good safety profile.
4. 68% of the evaluations of patients and 72% of the evaluations of physicians on efficacy of the treatment have been defined as "very good" and "good".
5. Arthrosonography remains a proven technique for joint swelling assessment and monitoring of the therapy. ■

Abstract presented at the
9th Central European Congress of Rheumatology (CECR 2012)
3rd Annual Meeting of the Polish Rheumatologists
1st - 3rd September 2012, Kracow - Poland

First author

Dr. R. Nestorova, MD
– Rheumatology Centre St. Irina
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SHORT COMMUNICATION

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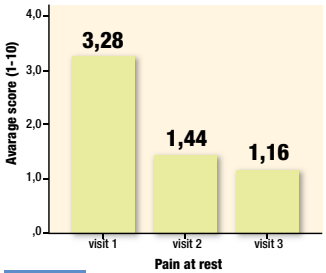

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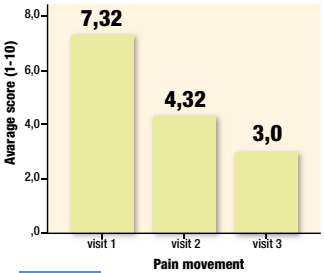

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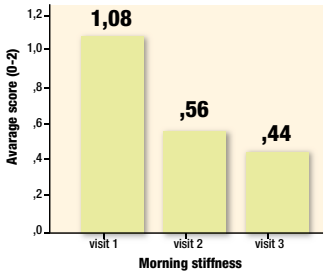

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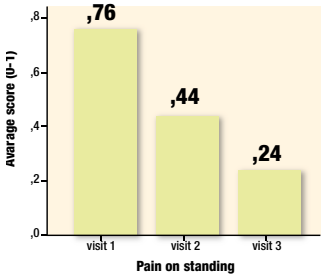

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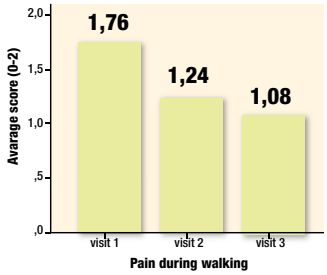

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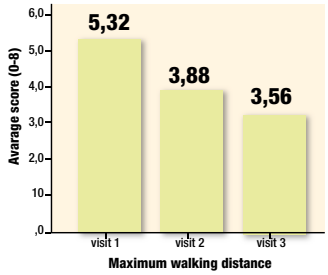

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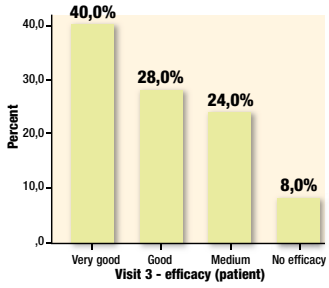

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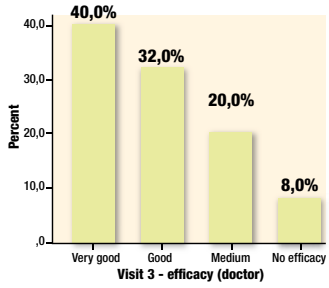

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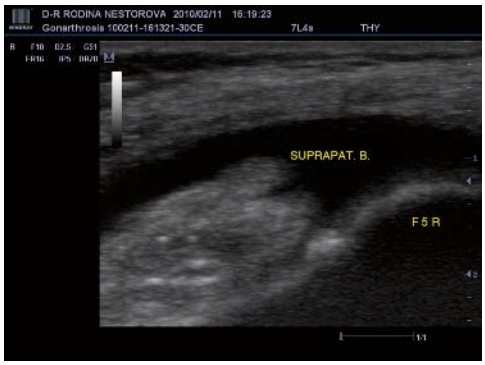

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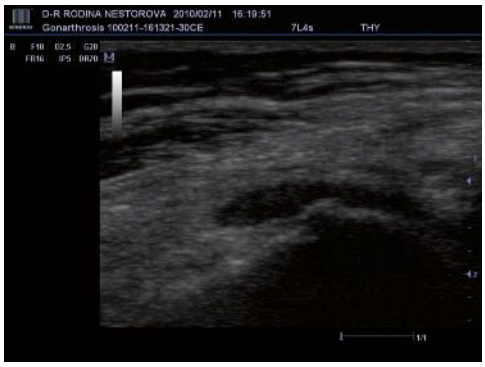


Fig. 7 b

Marked reduction of swelling after treatment.

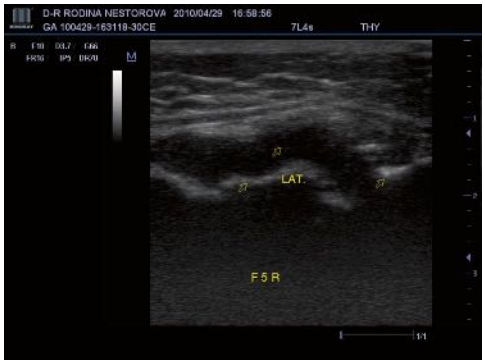


Fig. 8 a

Swelling of the joint space /lateral access/ prior to treatment.

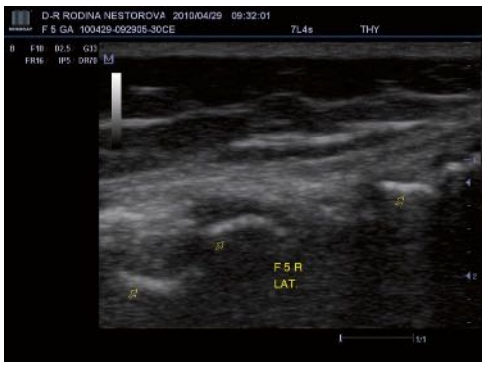


Fig. 8 b

Lack of edema after treatment.

Sonographic evaluation of swelling of the knee joint 30 days after treatment with the combination GUNA MD-Knee and GUNA MD-Matrix shows that 60% of the patients were without edema, and 30%were with reduction of swelling (FIG.9).

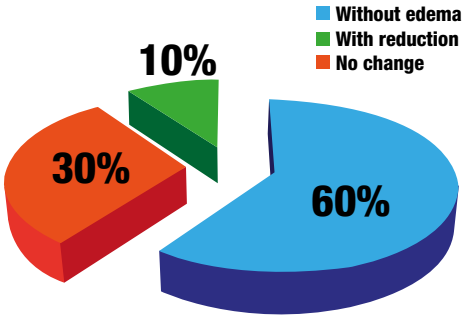


FIG. 9

Influence of joint swelling estimated by ultrasounds.

Efficacy of treatment according to patient and physician

Assessment of the patient and the physician of the efficacy of treatment with injectable collagen GUNA MDs on the 60th and 90th day matches, with the highest percentage is the highest rating, namely "very good".

FIG.10 and FIG.11 show the effect of treatment at visit 3 /90 day/. 68% of the evaluations of patients and 72% of doctors' assessments of the efficacy of treatment are "very good" and "good".

CONCLUSIONS

1. Periarticular administration of GUNA MD-Knee and GUNA MD-Matrix in Gonarthrosis III-IV X-Ray stage improves the status of the knee and thus improves the quality of life of patients due to:
   * Statistically significant reduction in pain at rest and pain on movement.
   * Statistically significant improvement in all indicators of the algo-functional Index of Lequesne.
   * Improvement in swollen syndrome in 90%, sonographically proven.
2. The effectiveness of GUNA MDs continues after stopping treatment.
3. The products have a very good safety profile.
4. 68% of the evaluations of patients and 72% of the evaluations of physicians on efficacy of the treatment have been defined as "very good" and "good".
5. Arthrosonography remains a proven technique for joint swelling assessment and monitoring of the therapy. ■

Abstract presented at the
9th Central European Congress of Rheumatology (CECR 2012)
3rd Annual Meeting of the Polish Rheumatologists
1st - 3rd September 2012, Kracow - Poland

First author

Dr. R. Nestorova, MD
– Rheumatology Centre St. Irina
Sofia, Bulgaria

APPLICATION AND ASSESSMENT OF EFFICACY OF COLLAGEN INJECTIONS GUNA MDs IN GONARTHROSIS.

Boshnakov D.

-Clinical Assessment presented at the XIX Days of Bulgarian Orthopedics and Traumatology, Tryavna, (September 2012).

Experimental sites: Saint Anne University Hospital, Varna (Bulgaria).

Pathologies considered: gonarthrosis.

Outcomes:
1)assessment of pain at rest and during movement (VAS = 0-10);
2)assessment of Lequesne Algofunctional Index for: a.pain when walking; b.maximum walking distance (in meters); c.daily activities;
3)assessment of efficacy of treatment from the patient's viewpoint.

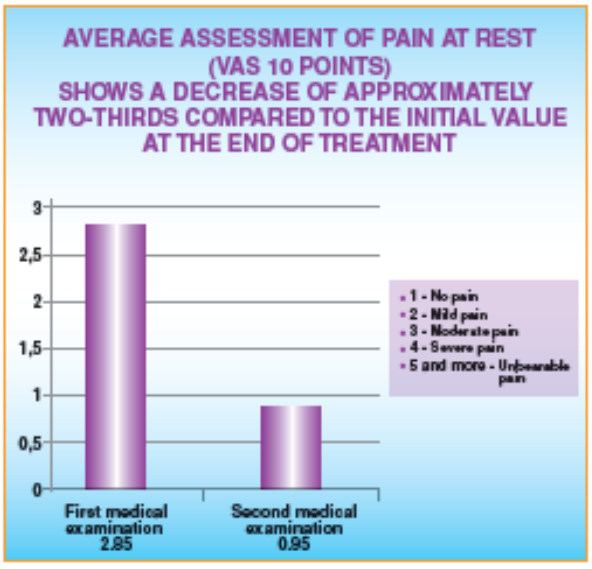
Inclusion/exclusion criteria: unstated.

Patients enrolled: 14 (8 M; 6 F; aged 51-72).

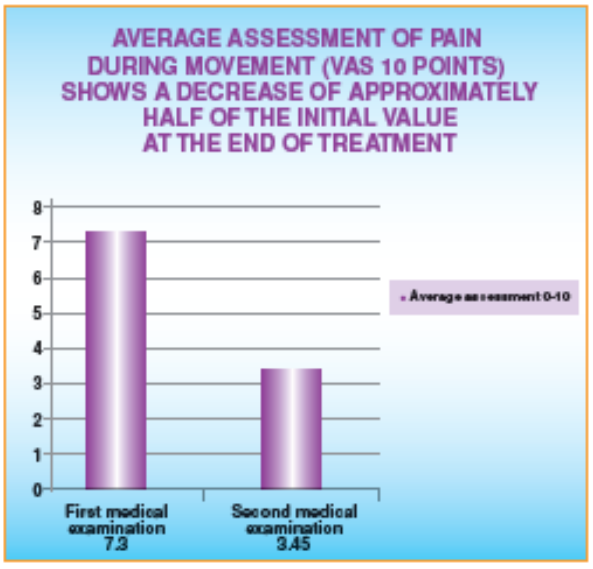
Treatment: **MD-Knee**, 1 ampoule + **MD-Muscle**, 1 ampoule: 2 intra-articular and peri-articular injections/week for 2 consecutive weeks + 1 intra-articular and peri-articular injection/ week for the following 6 weeks (total: 10 treatments in 2 months).

Results:
1) Pain at rest: VAS from 2.85 at treatment start (moderate pain) to 0.95 at the end of treatment (no pain) (TAB. 9).
2) Pain when moving: VAS from 7.3 at treatment start (unbearable pain) to 3.5 at the end of treatment (moderate/severe pain) (TAB. 10).
3) Lequesne Algofunctional Index: from 1.6 at treatment start to 1.1 at the end of treatment (TAB. 11); maximum walking distance from 100-300 meters before treatment (5.2 score) to 400-700 meters after treatment (3.6 score) (TA B. 12).

– **Author's conclusions:**
1)Intra-articular injections of Collagen MDs improve: a) localized pain; b) pain at movement; c) joint mobility.
2)Intra- and peri-articular injections improve the patients' functional activity and quality of life.
3)The injections of Collagen MDs are a new and effective method to treat gonarthrosis



TAB. 9



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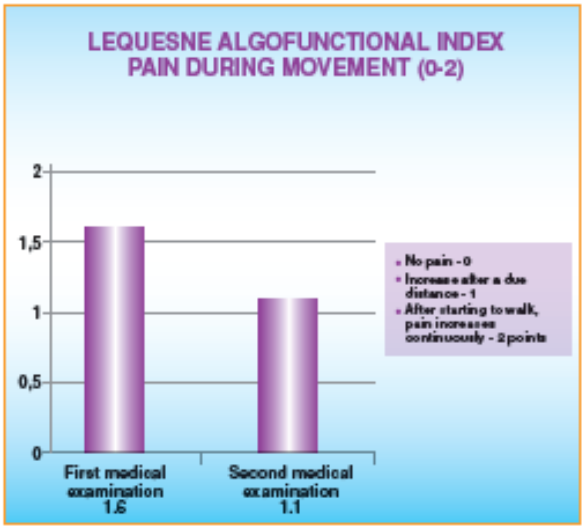
TAB. 11



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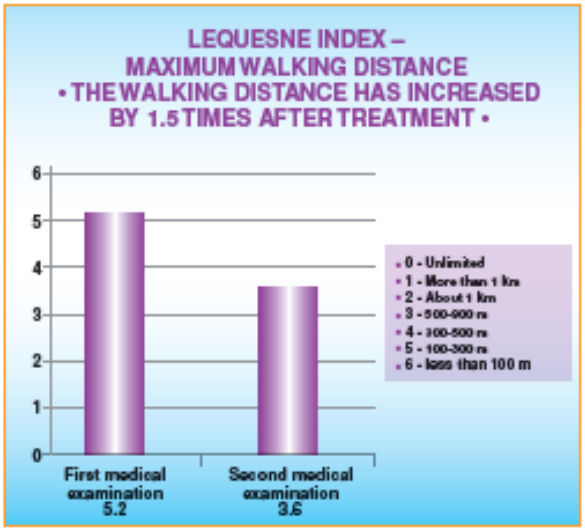

Abstract from:
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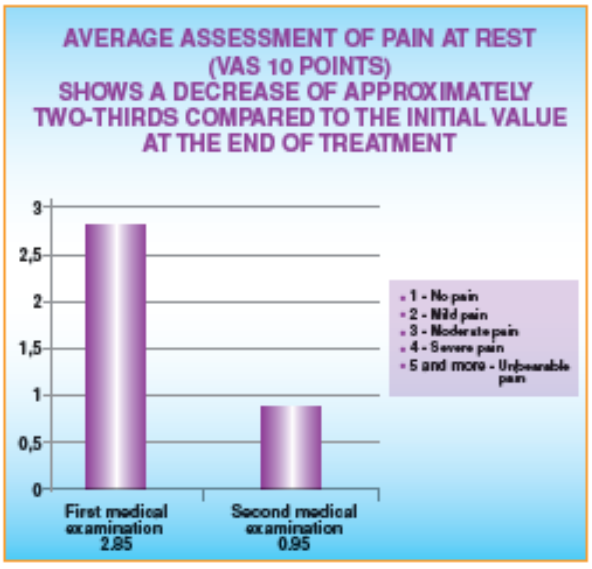

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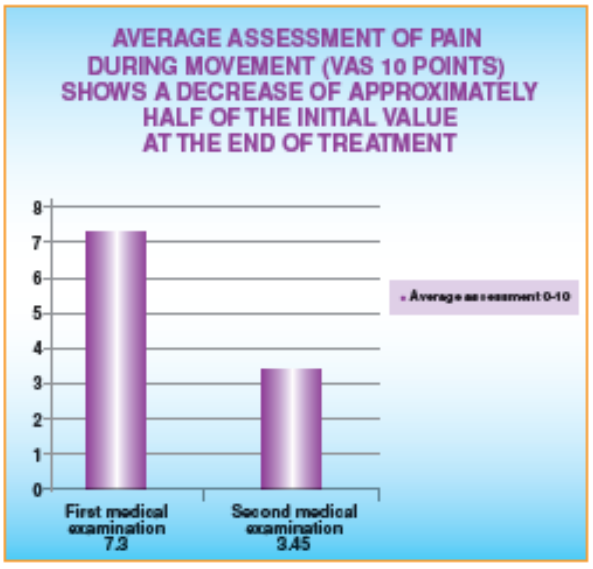

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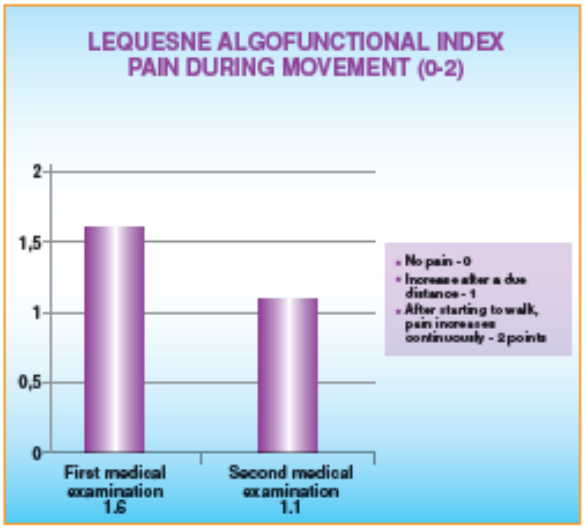

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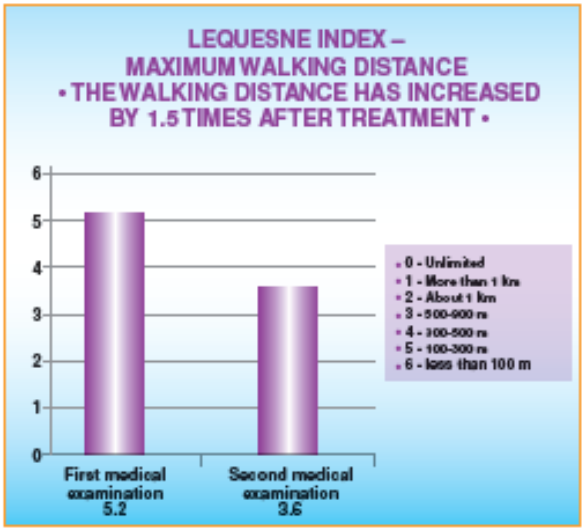

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V. Reshkova, R. Rashkov, R. Nestorova

EFFICACY AND SAFETY EVALUATION OF GUNA COLLAGEN MDs INJECTIONS IN KNEE OSTEOARTHRITIS – A CASE SERIES OF 30 PATIENTS

SUMMARY

Collagen is the most abundant protein (structural protein; molecular weight 300 KDa) in mammalian organisms, accounting for about 5-6% of an adult's body weight.

In this case series we have evaluated the efficacy and safety of intra-articular injections of Guna Collagen MD-Knee + Guna Collagen MD-Muscle in 30 patients (12 M, 18 F) affected by Radiological Knee Osteoarthritis (X-ray stage 2 or 3).

Patients have been administered 10 intra-articular injection with Guna Collagen MD-Knee + Guna Collagen MD-Muscle.

Evaluation was performed at baseline and then at week 8 (end of treatment) and at week 12 (4 weeks after treatment), in term of VAS pain at rest and during movement, Lequesne Index and patient and physician satisfaction.

– Intra-articular injections of Guna Collagen MDs resulted in a significant improvement of pain at rest, pain during movement and functional activity in patients with knee osteoarthritis. Guna Collagen MDs demonstrated to be safe; no side effect was reported in any patient.

KEY WORDS **KNEE OSTEOARTHRITIS, COLLAGEN INTRA-ARTICULAR INJECTION, COLLAGEN MEDICAL DEVICE, MD-KNEE, MD-MUSCLE**

INTRODUCTION

Collagen is the most abundant protein in the human body. Of the whole protein mass of higher Mammals, ¼ is composed of collagen: bones and tendons, joint capsules and muscles, ligaments and fascia, teeth and serous membranes, skin and extracellular matrix.

One of the most frequent reasons of local joint pain is the slackening of intra-articular (ligaments and articular cartilage) and extra-articular structures (ligaments, joint capsules, tendons, muscles) causing joint hypermobility (1).

– This mobility leads to further and early consumption of these systems on one hand, and on the other promotes progressive degeneration of the cartilage.

A special characteristic of Guna Collagen Medical Devices, which contain collagen and ancillary ingredients, is that they can offer an innovative approach to the treatment of painful diseases affecting the musculoskeletal system (2).

The ancillary ingredients of natural origin are combined with collagen in order to allow a better and more targeted positioning of collagen in the specific areas.

These collagen products may be used in periarticular, intra-articular, intramuscular and intradermal injections.
– Collagen provides a support which may have a positive impact in stabilizing the joint functionality, avoiding hypermobility and improving movement and pain.

Intra-articular administration of Guna Collagen Medical Devices could have a structural function: strengthening and protecting the structure of cartilage and joint capsules.
It is also supposed to provide mechanical support to the affected areas.
Strengthening these structures, Guna Collagen MDs may achieve regenerative and analgesic effects (3).
The purpose of this study is to confirm these hypothesis by evaluating the relief of localized pain or pain during movement.

MATERIALS AND METHODS

30 outpatients (12 M, 18 F) aged between 55 and 70 years, affected by **knee osteoarthritis** [X-ray stage 2 or 3, according to Kellgren-Lawrence Classification (4)] were included.

The main exclusion criteria were: inflammatory diseases, gout, and malignancy.
– Patients were administered **intra-articular** knee injections with Guna Collagen **MD-Knee** (10 amp.) + Guna Collagen **MD-Muscle** (10 amp.): 1 injection twice a week for 2 weeks, and 1 injection weekly for 6 weeks (course of treatment: 8 weeks).

Patients were evaluated before treatment (**Visit 1**), at week 8 (**Visit 2**, at the end of treatment), and at week 12 (**Visit 3**, 4 weeks after treatment) in term of pain at rest (VAS and a 5-point verbal scale) and during movement, Lequesne Algofunctional Index, assessment of efficacy by patients and physician (5).

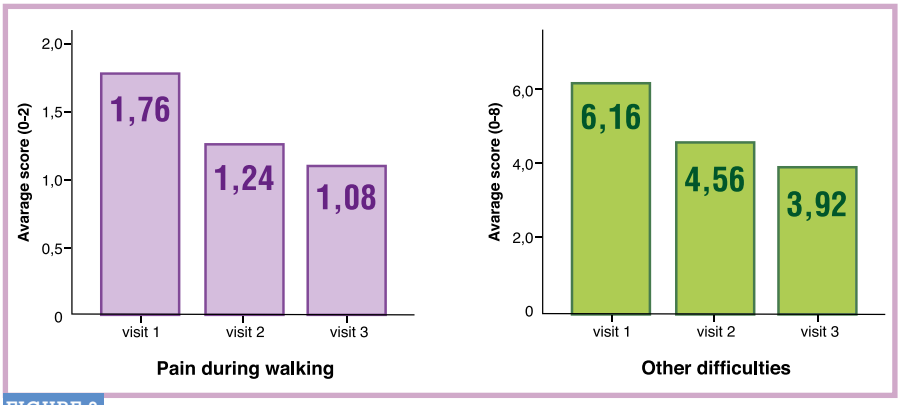

FIGURE 2

Left: Pain during walking, F (2,48) 19.750, p=0.000. Right: Other difficulties.

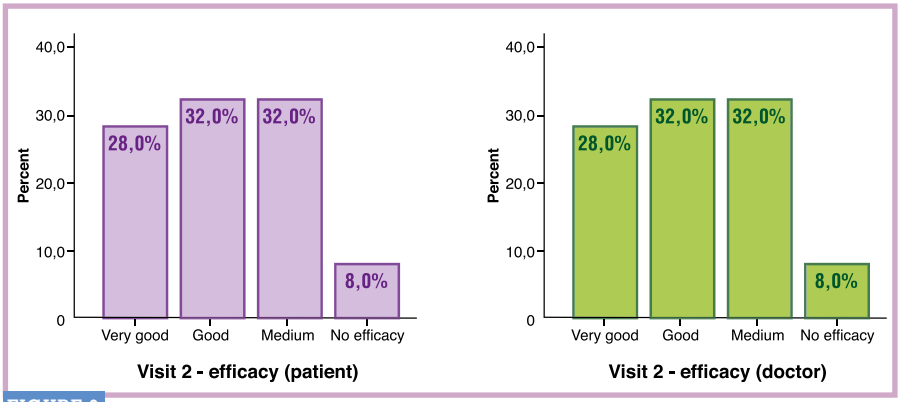

FIGURE 3

Assessment of efficacy by patients and by physicians.

RESULTS

A significant reduction of VAS pain at rest was observed at Visit 2 and Visit 3 (FIGURE 1).

– The average score for pain during movement was observed to decrease more than **twice** (2 times) at Visit 3 compared to baseline (FIGURE 1).

Pain at rest and during movement showed a statistically significant decrease after administration of the 2 Guna Collagen MDs.

The reduction continued 30 days after the end of treatment.
In terms of average score for pain during walking, at Visit 3 it was observed a reduction of 40%, compared to baseline (FIGURE 2).

At Visit 3, the average score for "other difficulties" (Lequesne Index) decreased approximately 2 times if compared to baseline (FIGURE 2). At Visit 2, the assessment of efficacy by patients and by doctors was **very good** in **28%** of cases, **good** in **32%**, **medium** in **32%** and the treatment was not considered effective in only **8%** (FIGURE 3).
At Visit 3 the percentages are even higher. The assessment of treatment efficacy at week 8 and 12 by patients and by doctors were similar. No side effects were reported during the follow-up.

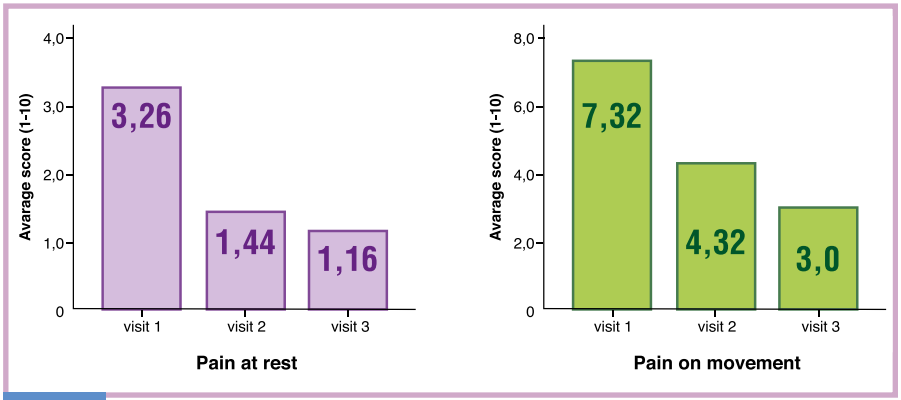

FIGURE 1

Left: Pain at rest, F (2,48) 35.871, p=0.000.
Right: Pain during movement, F (2,48) 69.630, p=0.000.

DISCUSSION

Current intra-articular treatment options for knee osteoarthritis (OA) include hya-

luronic acid (HA) and corticosteroids.

Viscosupplementation (HA) is a well-established treatment option in knee OA, and is included in the professional guidelines for treatment of the disease in this joint (6,7).

There are substantial data that exogenous HA may improve pain and function by non-mechanical, biologically-based mechanisms within the synovial and articular environment (8).

HA is comparable in efficacy with intra-articular corticosteroids, which have a faster onset of action but a shorter duration (9,10).
The conclusions of a Cochrane meta-analysis seem to be in favor of higher efficacy of HA for both pain and function; it is preferred to any other form of systemic intervention or intra-articular corticosteroids (11,12).

Despite its efficacy and safety, the use of viscosupplementation is limited by its cost, considering also the fact that most National Health Services do not reimburse such a treatment.

Also intra-articular placebo (saline solution) seems to be able to decrease pain in knee OA (13,14).

Zhang *et* Al. reported in a recent meta-analysis that IA placebo had effects above the average value of 0.51 ES (15).

Placebo in OA appeared to be effective only for all patient-related subjective outcomes such as pain, stiffness and self-reported function, but not for structural modification outcomes.

The results of this study seem to demonstrate that intra-articular administration of **Guna Collagen MDs** could be a safe and effective treatment in pain relief for patients affected by knee OA at stage 2 or 3 (Kellgren-Lawrence Classification).

– Therefore, Guna Collagen MDs might be an additional option in the intra-articular management of knee OA.

The limitation of this study is the absence of a comparative group; it would also be appropriate to carry out a comparative study firstly with placebo and then with the other products commonly used for intra-articular injections (hyaluronates, steroids, platelets rich plasma).

CONCLUSIONS

This case series suggests that intra-articular injection of Guna Collagen MDs in knee OA affects significantly pain at rest, pain during movement and functional activity.
– Due to its safety and efficacy Guna Collagen MDs may be considered an interesting and promising option for the intra-articular treatment of patients affected by intermediate knee OA. Further studies are to confirm these data. ■

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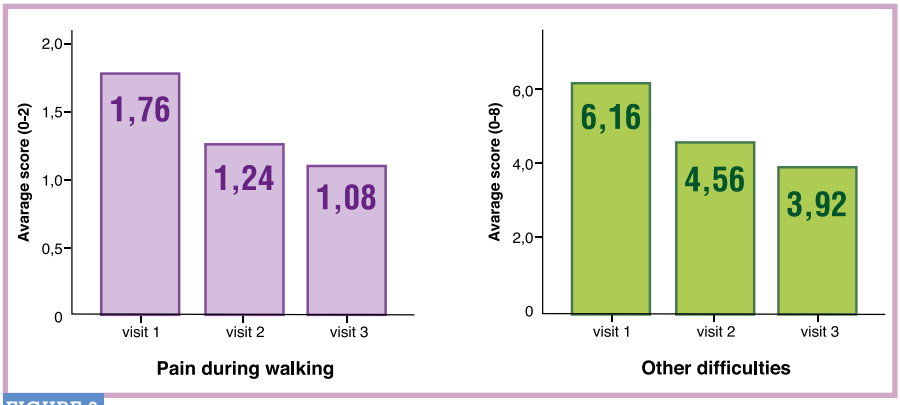

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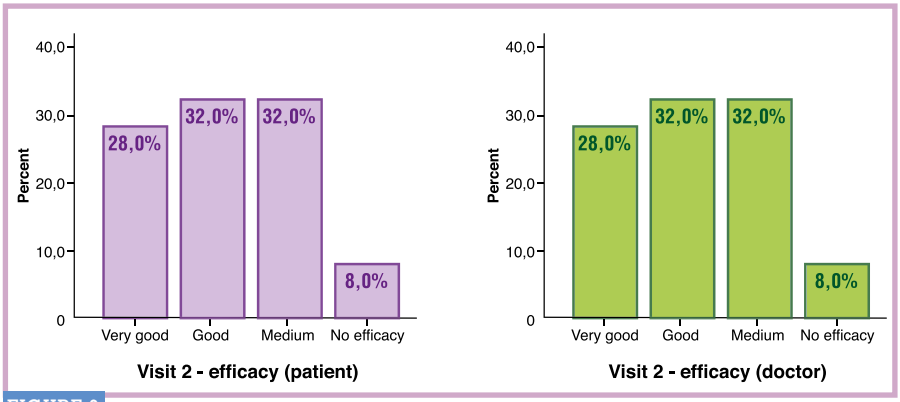

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– The average score for pain during movement was observed to decrease more than **twice** (2 times) at Visit 3 compared to baseline (FIGURE 1).

Pain at rest and during movement showed a statistically significant decrease after administration of the 2 Guna Collagen MDs.

The reduction continued 30 days after the end of treatment.
In terms of average score for pain during walking, at Visit 3 it was observed a reduction of 40%, compared to baseline (FIGURE 2).

At Visit 3, the average score for "other difficulties" (Lequesne Index) decreased approximately 2 times if compared to baseline (FIGURE 2). At Visit 2, the assessment of efficacy by patients and by doctors was **very good** in **28%** of cases, **good** in **32%**, **medium** in **32%** and the treatment was not considered effective in only **8%** (FIGURE 3).
At Visit 3 the percentages are even higher. The assessment of treatment efficacy at week 8 and 12 by patients and by doctors were similar. No side effects were reported during the follow-up.

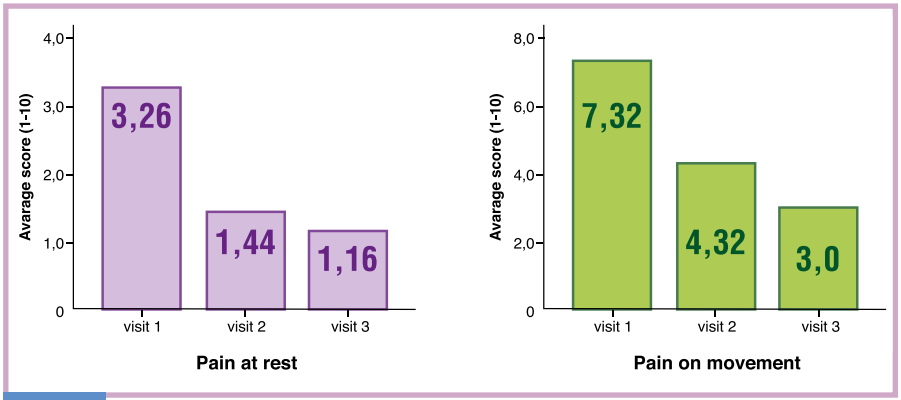

FIGURE 1

Left: Pain at rest, F (2,48) 35.871, p=0.000.
Right: Pain during movement, F (2,48) 69.630, p=0.000.

DISCUSSION

Current intra-articular treatment options for knee osteoarthritis (OA) include hya-

luronic acid (HA) and corticosteroids.

Viscosupplementation (HA) is a well-established treatment option in knee OA, and is included in the professional guidelines for treatment of the disease in this joint (6,7).

There are substantial data that exogenous HA may improve pain and function by non-mechanical, biologically-based mechanisms within the synovial and articular environment (8).

HA is comparable in efficacy with intra-articular corticosteroids, which have a faster onset of action but a shorter duration (9,10).
The conclusions of a Cochrane meta-analysis seem to be in favor of higher efficacy of HA for both pain and function; it is preferred to any other form of systemic intervention or intra-articular corticosteroids (11,12).

Despite its efficacy and safety, the use of viscosupplementation is limited by its cost, considering also the fact that most National Health Services do not reimburse such a treatment.

Also intra-articular placebo (saline solution) seems to be able to decrease pain in knee OA (13,14).

Zhang *et* Al. reported in a recent meta-analysis that IA placebo had effects above the average value of 0.51 ES (15).

Placebo in OA appeared to be effective only for all patient-related subjective outcomes such as pain, stiffness and self-reported function, but not for structural modification outcomes.

The results of this study seem to demonstrate that intra-articular administration of **Guna Collagen MDs** could be a safe and effective treatment in pain relief for patients affected by knee OA at stage 2 or 3 (Kellgren-Lawrence Classification).

– Therefore, Guna Collagen MDs might be an additional option in the intra-articular management of knee OA.

The limitation of this study is the absence of a comparative group; it would also be appropriate to carry out a comparative study firstly with placebo and then with the other products commonly used for intra-articular injections (hyaluronates, steroids, platelets rich plasma).

CONCLUSIONS

This case series suggests that intra-articular injection of Guna Collagen MDs in knee OA affects significantly pain at rest, pain during movement and functional activity.
– Due to its safety and efficacy Guna Collagen MDs may be considered an interesting and promising option for the intra-articular treatment of patients affected by intermediate knee OA. Further studies are to confirm these data. ■

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CLINICAL

M. Ottaviani

TREATMENT OF JOINT CONDITIONS WITH GUNA COLLAGEN MEDICAL DEVICES

– CLINICAL STUDY ON 257 PATIENTS

SUMMARY

Collagen is the main extracellular structural protein to be found in the connective tissue and bone tissue of most animals. In humans aged about 50 years its synthesis begins to reduce, with consequent cartilage and tendon degeneration and inevitable development of osteoarthritis and tendonitis. Since these degenerative conditions are very common and evolve towards pain and joint stiffness, there is an urgent need for tools that allow practitioners not only to limit this degenerative evolution, but also, in certain cases, to induce its regression.

This clinical study was conducted on 257 patients with joint and tendon disorders (impingement syndrome, shoulder tendinopathy, hip arthritis, knee arthritis, trapeziometacarpal osteoarthritis, Achilles' tendinopathy) frequently reflected in clinical evidence, such as pain and joint stiffness; they were all treated exclusively with local injections of Guna Collagen Medical Devices.

The data were collected through self-assessment scales, validated by the WHO and the results showed that Guna Collagen MD can give a useful contribution to containing the problems associated with joint degeneration.

PAROLE CHIAVE

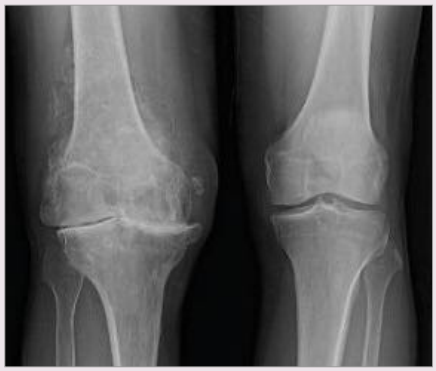
GUNA COLLAGEN MEDICAL DEVICES, COLLAGEN, OSTEOARTRHITIS, TENDINOPATHY, PAIN

INTRODUCTION

Collagen is a glycoprotein characterised by a structure in which a simple **basic module** is repeated: collagen molecules join together to form a collagen fibril; a union in which each molecule overlaps with that above by one quarter of its length.

This creates a kind of *wall*, in which the individual bricks that make it up are staggered in order to achieve considerable resistance to both incident tangential and perpendicular forces (FIG. 1).

– This characteristic arrangement gives the collagen significant sturdiness in terms of **resistance**, **extensibility** and **incompressibility**, whilst guaranteeing **plasticity**, **flexibility**, allowing **torsion**



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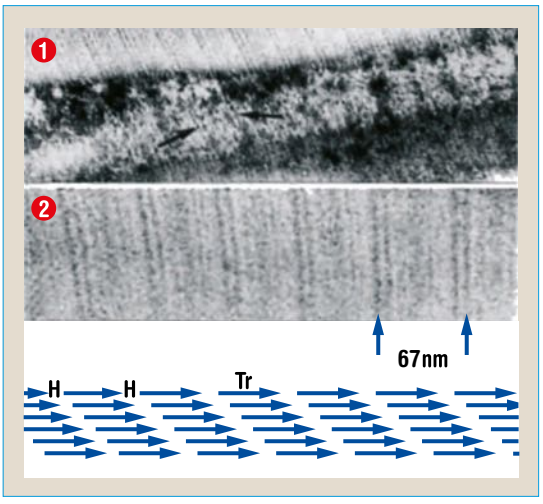
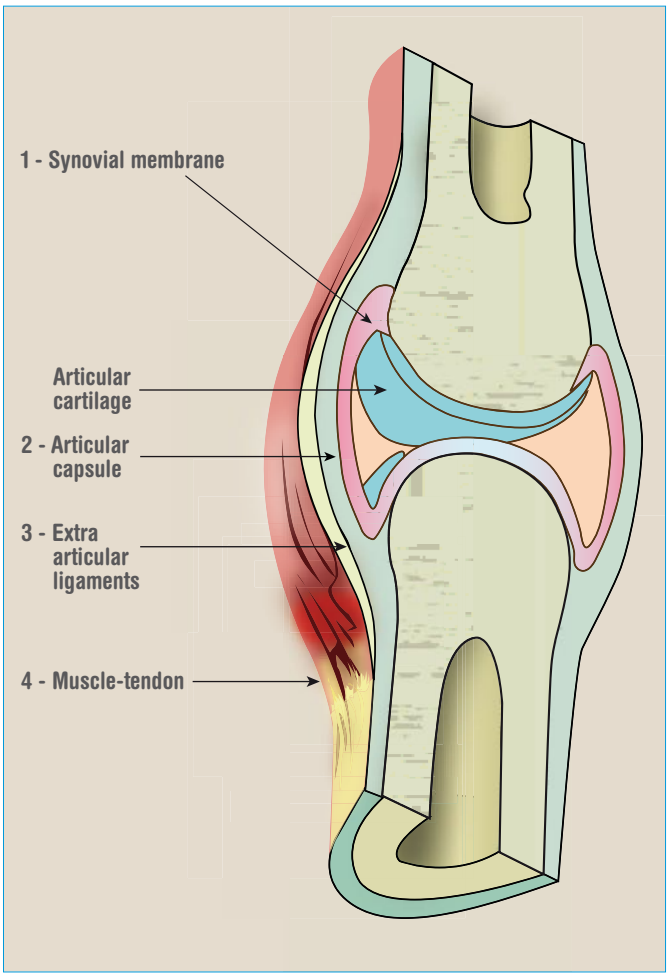


FIG. 1

Structure of collagen.
1: Sugars bound to collagen. Relationship between sugar (black precipitations) **and the density of collagen fibrils** (ME 112.000X)**;**
2: Section of a collagen fibril (ME 240.000X)**.**
A cycle of 67 nm (670 A) **forms on the base of collagen molecules, each of which is staggered by ¼ of their length.**

FIG. 2
Extra-articular containment system.



and **great resistance** to load.
In order to be functional, almost all joints must possess two, apparently contradictory, characteristics: stability and mobility.
The **articular stabilisation** systems consist of the structures pertaining to both the **extra-articular component** and the **intra-articular component**; collagen is present in abundance in both of these structures.

– The extra-articular component consists of ligaments, the articular capsule, tendons and muscles; the intra-articular component is formed of ligaments (for the knee and hip joints only) and of joint cartilage (FIG. 2).

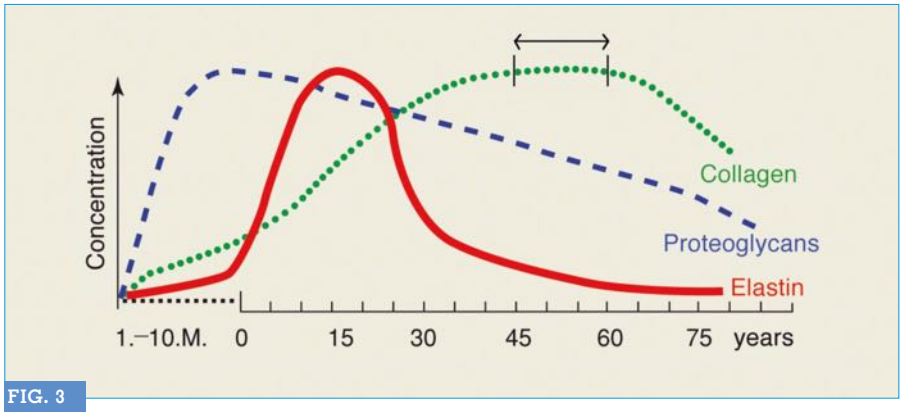


FIG. 3
Age-related biosynthesis of collagen, proteoglycans, and elastin.

One of the most important causes of joint pain is the **laxity** of the intra- and extra-articular stabilisation structures; lax containment systems result in **articular hypermobility**, especially in non-physiological directions and at non-physiological angles that, on the one hand, lead to greater, early wear of the containment systems themselves and, on the other, cause progressive cartilage degeneration.

The mechanical support provided by collagen represents an effective natural scaffolding.

– In humans, the biosynthesis of collagen starts to decrease at 55-60 years of age (FIG. 3);
From this age onwards, there is a quantitative and qualitative deterioration in the joint structures. More specifically, in the musculoskeletal system, the cartilage surfaces become thinner and degenerate to osteoarthritis, whereas the tendinous and ligamentous structures become less elastic and progress to tendinoses and tendinopathies of varying severities. Often in musculoskeletal conditions, the instrumental diagnostic evidence (x-ray, ultrasound, etc.) is not consistent with the clinical findings.

The term **Osteoarthritis state** is used to indicate physiological age-related articular ageing; it is a paraphysiological condition that does not cause any clinical situation and is often incidentally observed during imaging studies performed for other reasons (e.g. injury).
However, when osteoarthritis makes itself felt by causing the characteristic onset symptoms, such as *stiffness* and joint pain, we talk about osteoarthritis disease. Osteophytes are irregular beak- or crest-shaped proliferations of bone tissue that form in the vicinity of joints affected by a number of pathological processes, but above all in the presence of osteoarthritis. Their presence can involve disorders of various types, with restrictions to joint movement or the compression and irritation of nearby structures, in particular, nerve branches and tendon insertions. Osteophytes are the

bone tissue's attempt to increase the surface area of the heads of the articular bones damaged by osteoarthritis, in an attempt to stabilize the joint (FIG. 4).

In addition, it is common for ultrasound scans and MRI studies to show complete or multiple tendon damage, despite the presence of little or no signs and symptoms; conversely, in other cases, the tendon is intact but the patient experiences very severe pain and functional impairment.
As regards the tendinous-ligamentous sub-system, an anatomopathological distinction can be made between tendinites or tenosynovitis, tendinoses and tendon injuries of various degrees.

– Tendinites or tenosynovites are inflammatory states of the tendon and possibly also of its sheath, with or without peritendinous effusion; they may be a consequence of either a traumatic event or a functional overload.

When the repair process of the affected element starts in the presence of inflammation, the scar tissue that forms is a connective tissue that is devoid of the characteristics of elasticity and resistance that are typical of native tendons; this makes the structure more prone to partial or complete tears.

– For this reason, an inflammatory process affecting a tendinous or ligamentous structure should not be underestimated, rather it should be kept under close observation and resolved as soon as possible.

Also on the basis of our experience we can undoubtedly state that clinical and diagnostic evidence are not always consistent. In Italy, osteoarthritis accounts for **72.6%** of all rheumatic diseases and is responsible for **70%** of cases of chronic pain. The potential therapeutic approach to osteoarthritis, and tendinopathy, can be of different types:
– educational
– pharmacological
– rehabilitative
– surgical.

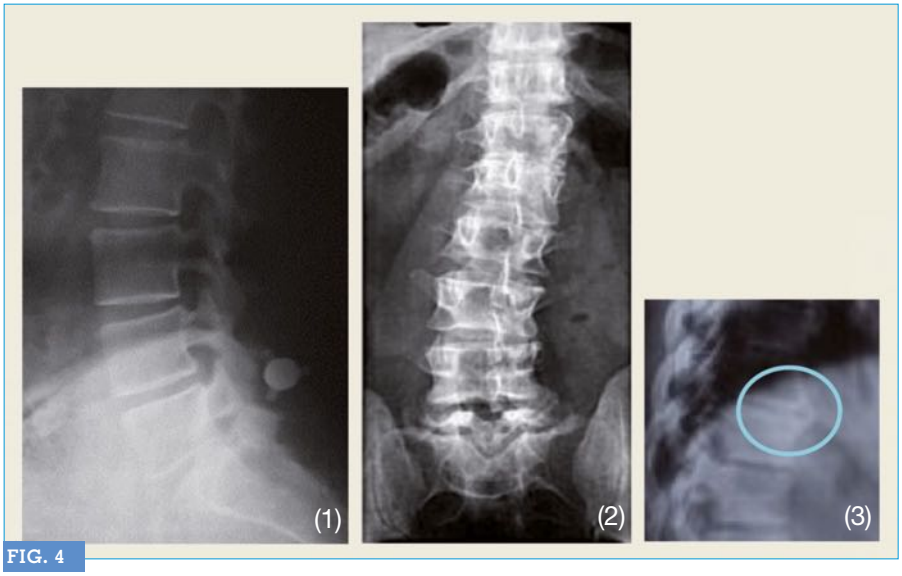


FIG. 4

X-ray of the L-S spine of an individual with severe low back pain without osteoarthritic skeletal alterations (1); of a L-S spine with significant radiological signs of osteoarthritic degeneration (2) in an asymptomatic patient; osteophytes (3).

The educational approach is represented by an improvement in quality of life including health education intervention, the use of braces, where necessary, and weight loss, when appropriate.
The conventional medicinal products used to treat osteoarthritis and tendinopathies (NSAIDs, Coxibs, Paracetamol, Steroids, and Opioids) have a symptomatic action and are used on both systemic and local levels (e.g. intra-articular steroid injections).
There are other medicinal products, whose real efficacy is not recognised by all Authors, which are thought to exert a slow chondroprotective action, these are: glucosamine sulphate, chondroitin sulphate, and hyaluronic acid.

The local use – and therefore – the intra-articular injection of hyaluronic acid boosts its efficacy; this kind of treatment is referred to as "visco-supplementation" and it has **only** a lubricating and shock-absorbing action.

Until just a few years ago, osteoarthritis was considered a progressive degenerative disease; subsequently, a prevention campaign against the progression of osteoarthritis with the use of "Cartilage integrators", was started.

– For some years now, it possible to state that osteoarthritis is a process that is, at least in part, reversible.
Given the ongoing rise in the population's average age, it goes without saying that having access to tools able to maintain high quality of life standards despite *chrono-aging* is an important breakthrough.

Guna Collagen Medical Devices are products for local injection constituted by **collagen** of porcine origin (porcine tissues have a very high collagen content) and a substance known as an *ancillary* or vehicle, of plant or mineral origin, characterised by a particular tropism for the specific articular segments.
A tangential filtration process, combined with sterilisation and control of the molecular weight, makes it possible to obtain a pure product with standard chemical and physical characteristics.
The availability of Guna Collagen Medical Devices for local injection is a determining factor in the repair process that follows anti-inflammatory intervention.
Lax joint support elements cause local nociceptor stimulation and excessive tension and stress: which explains why the reinforcement of these structures is **analgesic** as well as **regenerative**.

AREA	M	F	Total N.	Age - average	Age - range
SHOULDER, UPPER LIMB	30%	70%	**147**	53,5	34-78
KNEE	66%	34%	**53**	67,5	55-82
HIP	30%	70%	**30**	67	53-78
ACHILLES	20%	80%	**27**	43,3	32-63

TAB. 1

General caseload. Patient distribution according to gender and age.

– These characteristics translate directly into organoleptic properties: collagen is a **tissue structurer** (structural protein) and also possesses lubricating qualities.

– These bases form the significant difference between the properties of collagen and those of hyaluronic acid.

The latter is a lubricant (high viscosity) only of the articular cavity, that acts on the intra-articular component **only**, primarily in the large joints.
Collagen **also** and **primarily**, acts on the structures of the extra-articular component (capsule, ligaments, tendons) of small, medium, and large joints.
In addition, hyaluronic acid is efficacious in cases of modest and intermediate clinical severity, whereas collagen is also efficacious in those cases in which the patient's mobility is more severely impaired: it replaces the *bricks* where the *wall* had crumbled.

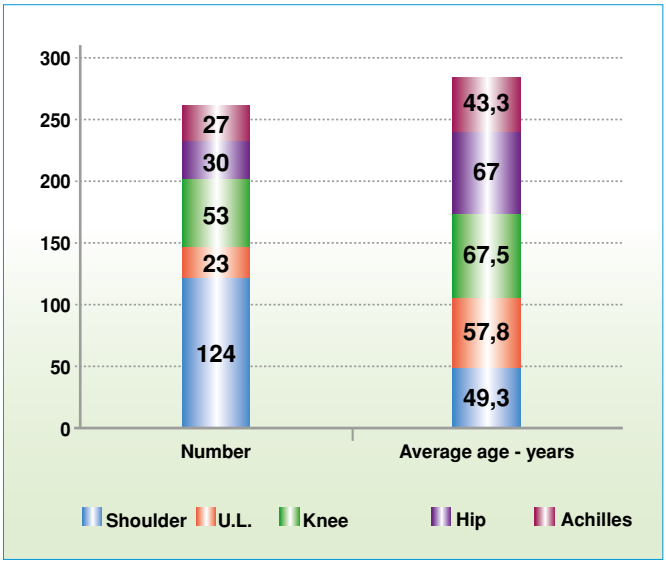
– Guna Collagen Medical Devices can be used alone or in home combinations with conventional or Physiological Regulating Medicine (PRM) products as **Guna-Arthro, Guna-Flam, Guna-Anti IL 1, Guna-Interleukin 10**; the treatment programme may also include other systemic pharmacological and rehabilitation treatments.

MATERIALS AND METHODS

A total of **257 patients** (36.5% M; 63.5% F) were enrolled in this clinical study. The mean age was 58.7 years, with a range of 32-82 years.
TAB. 1 shows the joint segments considered and treated and the corresponding epidemiological characteristics of the caseload.

FIG. 5

General caseload. – Number and mean age of patients included in the study per individual condition considered.



More specifically, because of the type of assessment scale used, the "Shoulder and upper limb (SUL)" Group included **124** patients with problems relating to the shoulder alone (rotator cuff syndrome, with possible tendon lesions); the remaining **23** had a number of other conditions, such as trapeziometacarpal osteoarthritis, epicondylitis and ganglion cysts of the wrist (U.L.).
It was consequently decided to analyse the results of these two sub-Groups independently (FIG. 5).

As far as the "Knee" Group was concerned, all **53** treated cases were classified as stage I, II and III osteoarthritis of the knee using the Kellgren-Lawrence radiological scale.
In the "Hip" Group, the treated hip joint (s) were affected by mild and moderate primary hip osteoarthritis (stage I and II); in this Group (**30** patients), patients were considered holistically, and only patients with a normal physique were included, so that the needle used was able to reach the pericapsular area.
In the "Achilles" Group, all the cases treated were mono- or bilateral Achilles' tendinopathies; **11** cases of tendonitis in the same area with ultrasound-documented exudate were also treated.
All patients were told about the type of treatment that they were being offered and the main differences that it would have compared to a similar injection therapy with hyaluronic acid or Guna Collagen MDs. They all signed the informed consent form.
The clinical and symptomatic findings of the patients enrolled were collected using assessment questionnaires validated by the WHO, more specifically:

- the Pain symptom was measured using a five-point visual-analogue scale (VAS), in which "0" = no pain and "5" = unbearable pain;
- D.A.S.H. (Disability for Arm, Shoulder and Hand) for the shoulder, elbow, hand, and wrist (range 0-100, in which 0 = no disability) (TAB. 2);
- O.K.S. (Oxford Knee Score) for the knee (range 48-0, in which 48 = no disability) (TAB. 3);
- O.H.S. (Oxford Hip Score) for the

hip (range 48-0, in which 48 = no disability) (TAB. 4);
- V.I.S.A.-A (Victorian Institute of Sport Assessment – Achilleus) for the Achilles' tendon (range 68-0, in which 68 = no disability) (TAB. 5).

The questionnaires were filled out by patients; the dedicated questionnaire was administered at the **first visit** and at the **end of treatment**.
Patients were administered **intra-articular** (shoulder, elbow, wrist, hand and knee), **pericapsular** (hip) and **local** (tendons) injections **with the appropriate** and **specific MDs**; 5 cc disposable syringes were used, with 23G x 1-1/2 - mm 0.60 x 40 needles for the hip, knee, and shoulder injections and 26G x 1/2 - mm 0.40 x 16 needles for hand, wrist, elbow, and foot injections.
Before administration, the skin was disinfected using a liquid product containing quaternary ammonium salt.

– In those segments in which administration was intra-articular, sterile surgical gloves were used and the injection area was disinfected thoroughly using sterile gauze soaked in surgical Betadine. In certain segments that are particularly rich in pain-sensitive nerve terminations, spray "ice" was used for analgesic purposes. The injections were administered **twice-weekly** for **5 consecutive weeks** (total = 10 injections).

– The patients treated for chronic degenerative diseases (knee osteoarthritis, hip osteoarthritis, trapeziometacarpal osteoarthritis and one case of severe Achilles' tendinopathy in a semi-professional dancer) continued with **maintenance therapy** (1 session a month for 6 consecutive months, then every 3 months). In no case was it suggested for the pharmacological therapy to be suspended or varied; patients taking NSAIDs or Paracetamol were asked to use this therapy only when absolutely necessary.
The evolution of the pain symptom in particular was monitored in the 8 patients who were taking opioid analgesics, in order to gradually reduce the posology of these drugs.

RESULTS

All the patients included in this study completed the treatment. None of them reported any side effect after the administration of the Guna Collagen Medical Devices. In those patients on antiplatelet or dicoumarol therapy, small areas of ecchymosis were observed at the injection site, but it reabsorbed rapidly without requiring any particular intervention.
All patients considerably **reduced** their use of conventional medicinal products and in **75%** ≈ of all cases their administration was not considered necessary.

– Of the 8 patients on treatment with opioid analgesics, 3 continued taking these medicinal products, albeit at considerably lower doses, whereas the remaining 5 gradually discontinued their use.

Generally speaking, the pain symptoms started to subside from the **4th** or **5th administration**; however, in cases of subacromial impingement and Achilles' or elbow tendinopathy the positive effects on pain were observed later.
In the osteoarthritic forms, affecting both the knee and the hip joint, the first effect reported by patients was a sensation of a **greater range of joint motion**; this sensation was perceived by patients after the first 2 - 3 sessions.

One particularly complex case was that of a male patient with polycythaemia, with concomitant severe osteoarthritis of the knee, hip and shoulder joint and significant functional impairment.
This was the case in which the improvement assessed by the questionnaires used in the study was poor; however, considering the initial clinical situation, it can be said that this was the patient who was most satisfied with the treatment received.

– We initially treated the shoulder alone and only subsequently, at the patient's insistence, also treated the knees. At a later date, we will decide if and when to treat the hips.

▶ Pain

The pain assessment scale showed a reduction from **3.06** (initial mean value including all the cases analysed) to a final value of **1.34**.
– The variation in the pain experienced in the various segments is shown in FIG. 6.

Shoulder and upper limb Group
(FIG. 7)

D.A.S.H. is an assessment questionnaire that considers a number of everyday situations facing the patient (disability concerning movements of the shoulder, hand, and elbow). The worst score is 100 and describes an extremely invalidating situation; a normal situation coincides with a score of 0.

In the caseload managed in this study regarding conditions of the **Shoulder**, the score dropped from an initial average of **78.7** to a final score of **17.3**.
As far as the **Upper limb** Group is concerned, from the initial mean of **66.8** the score dropped to **18.2**.

– In this case, the use of the D.A.S.H. questionnaire proved to be a disputable choice, as it pooled the results for a number of different segments. In the future, we intend to use a dedicated score, such as the *Oxford Shoulder Score* to assess shoulder function.

Knee Group

O.K.S. (The Oxford Knee Score) is an assessment scale including different common situations of everyday life.
The patient is invited to reply with regard to the 4 months prior to completion of the questionnaire; for obvious time reasons, post-treatment completion refers to the time at which it is filled out.
A score of 0 coincides with the most impaired situation, whereas a score of 48 coincides with a condition of full function. Of the 53 patients included (FIG. 8), the average initial score was **13.6**, whereas a score of **35.8** was achieved at the end of treatment.

D.A.S.H.

This questionnaire asks about your symptoms as well as your ability to perform certain activities. Please answer every question , based on your condition in the last week. If you did not have the opportunity to perform an activity in the past week, please make your best estimate on which response would be the most accurate. It doesn't matter which hand or arm you use to perform the activity; please answer based on you ability regardless of how you perform the task.

Please rate your ability to do the following activities in the last week

		NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1	Open a tight or new jar	1	2	3	4	5
2	Write	1	2	3	4	5
3	Turn a key	1	2	3	4	5
4	Prepare a meal	1	2	3	4	5
5	Push open a heavy door	1	2	3	4	5
6	Place an object on a shelf above your head	1	2	3	4	5
7	Do heavy household chores (e.g., wash walls, wash floors)	1	2	3	4	5
8	Garden or do yard work	1	2	3	4	5
9	Make a bed	1	2	3	4	5
10	Carry a shopping bag or briefcase	1	2	3	4	5
11	Carry a heavy object (over 10 lbs).	1	2	3	4	5
12	Change a lightbulb overhead	1	2	3	4	5
13	Wash or blow dry your hair	1	2	3	4	5
14	Wash your back	1	2	3	4	5
15	Put on pullover sweater	1	2	3	4	5
16	Use a knife to cut food	1	2	3	4	5
17	Recreational activities which require little effort (e.g., cardplaying, knitting, etc…)	1	2	3	4	5
18	Recreational activities in which you take some force or impact through your arm, shoulder or hand (e.g golf, hammering, tennis, etc…)	1	2	3	4	5
19	Recreational activities in which you move your arm freely (e.g., playing freesby, badminton, etc…)	1	2	3	4	5
20	Manage transportation needs (getting from one place to another)	1	2	3	4	5
21	Recreational activities which require considerable effort (e.g. push-ups, shaking a spray can, etc…)	1	2	3	4	5

22.During the past week, to what extend has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbours or groups? (circle number)

NOT AT ALL	SLIGHTLY	MODERATELY	QUITE A BIT	EXTREMELY
1	2	3	4	5

23.During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem? (circle number)

NO LIMITED AT ALL	SLIGHTLY LIMITED	MODERATELY LIMITED	VERY LIMITED	UNABLE
1	2	3	4	5

		NONE	MILD	MODERATE	SEVERE	EXTREME
24	Arm, Shoulder or hand pain	1	2	3	4	5
25	Arm, Shoulder or hand pain when you performed any specific activity	1	2	3	4	5
26	Tingling (pins and needles) in your arm, shoulder or hand	1	2	3	4	5
27	Weakness in your arm, shoulder or hand	1	2	3	4	5
28	Stiffness in your arm, shoulder or hand	1	2	3	4	5

29. During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand? (circle number)

NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	SO MUCH DIFFICULTY THAT I CAN'T SLEEP
1	2	3	4	5

30. I feel less capable, less confident or less useful because of my arm, shoulder or hand problem (circle number)

NONE	MILD	MODERATE	SEVERE	EXTREME
1	2	3	4	5

The following questions ask about the impact of your arms, shoulder or hand problem on your ability to work. Please circle the number that best describes your physical ability in the past week.

	Did you have difficulty:	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	EXTREME DIFFICULTY	UNABLE
31	Using your usual technique for your work?	1	2	3	4	5
32	Doing your usual work because of arm, shoulder or hand pain?					
33	Doing your work as well as you would like?					
34	Spending your usual amount of time doing your work?					

The following questions relate to the impact of your arms, shoulder or hand problem on playing your musical instrument or sport or both. If you play more than one sport or instrument (or play both), please answer with respect to that activity which is most important to you. Please circle the number that best describes your physical ability in the past week.

	Did you have difficulty:	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	EXTREME DIFFICULTY	UNABLE
35	Using your usual for playing your instrument or sport?	1	2	3	4	5
36	Playing your musical instrument or sport because of arm, shoulder or hand pain?	1	2	3	4	5
37	Playing your musical instrument or sport as well as you would like?	1	2	3	4	5
38	Spending your usual amount of time practicing or playing your instrument or sport?	1	2	3	4	5

Thank you for filling in this form.

TAB. 2

– D.A.S.H. (Disability for Arm, Shoulder and Hand) Questionnaire.

O.K.S. - OXFORD KNEE SCORE

NEW OXFORD KNEE SCORE QUESTIONNAIRE

Please answer the following 12 questions. Please only consider how you have been getting on during the past four weeks

1. How would you describe the pain you have usually from your knee? Score
None – 4
Very mild – 3
Mild – 2
Mild moderate – 1
Severe – 0

2. Have you had any trouble with washing and drying yourself all over because of your knee?
No trouble at all – 4
Very little trouble – 3
Moderate trouble – 2
Extreme difficulty – 1
Impossible to do – 0

3. Have you had any trouble getting in and out of a car or using public transport because of your knee?
No trouble at all – 4
Very little trouble – 3
Moderate trouble – 2
Extreme difficulty – 1
Impossible to do – 0

4. If you were to kneel down could you stand up afterwards?
Yes, easily – 4
With little difficulty – 3
With moderate difficulty – 2
With extreme difficulty – 1
No, impossible – 0

5. Have you been limping when walking because of your knee?
Rarely/never – 4
Sometimes or just at first – 3
Often, not just at first – 2
Most of the time – 1
All of the time – 0

6. Have you felt that your knee might suddenly give way or let you down?
Rarely/never – 4
Sometimes or just at first – 3
Often, not just at first – 2
Most of the time – 1
All of the time – 0

7. Could you kneel down and get up afterwards?
Rarely/never – 4
Sometimes or just at first – 3
Often, not just at first – 2
Most of the time – 1
All of the time – 0

8. Have you been able to do your own household shopping on your own? Score
Yes, easily – 4
With little difficulty – 3
With moderate difficulty – 2
With extreme difficulty – 1
No, impossible – 0

9. For how long have you been able to walk before the pain from your knee became severe (with or without a stick)?
No pain, even after more than 30 minutes – 4
16-30 minutes – 3
5-15 minutes – 2
Around the house only – 1
Unable to walk at all – 0

10. Have you been able to walk down a flight of stairs
Yes, easily – 4
With little difficulty – 3
With moderate difficulty – 2
With extreme difficulty – 1
No, impossible – 0

11. After a meal (sat at a table) how painful has it been for you to stand up from a chair because of your knee?
Not at all painful – 4
Slightly painful – 3
Moderately painful – 2
Very painful – 1
Unbearable – 0

12. How much pain from your knee interfered with your usual work (including housework)?
Not at all – 4
A little bit – 3
Moderately – 2
Greatly – 1
Totally – 0

13. Have you been troubled by pain from your knee in bed at night?
No nights – 4
Only 1 or 2 nights – 3
Some nights – 2
Most nights – 1
Every night – 0

TAB. 3
– O.K.S. (Oxford Knee Score) Questionnaire.

O.H.S. - OXFORD HIP SCORE

OXFORD HIP SCORE

Please answer the following 12 questions.

During the past 4 weeks...

1. How would you describe the pain you usually have in your hip?
4) None
3) Very mild
2) Mild
1) Moderate
0) Severe

2. Have you been troubled by pain from your hip in bed at night?
4) No nights
3) Only 1 or 2 nights
2) Some nights
1) Most nights
0) Every night

3. Have you had any sudden, severe pain-' shooting ', 'stabbing', or 'spasms' from your affected hip?
4) No days
3) Only 1 or 2 days
2) Some days
1)Most days
0) Every day

4. Have you been limping when walking because of your hip?
4) Rarely/never
3) Sometimes or just at first
2) Often, not just at first
1) Most of the time
0) All of the time

5. For how long have you been able to walk before the pain in your hip becomes severe (with or without a walking aid)?
4) No pain for 30 minutes or more.
3) 16 to 30 minutes
2) 5 to 15 minutes
1) Around the house only
0) Not at all

6. Have you been able to climb a flight of stairs?
4) Yes, easily
3) With little difficulty
2) With moderate difficulty
1) With extreme difficulty

7. Have you been able to put on a pair of socks, stockings or tights?
4) Yes, easily
3) With little difficulty
2) With moderate difficulty
1) With extreme difficulty
0) No, impossible

8. After a meal (sat at a table), how painful has it been for you to stand up from a chair because of your hip?
4) Not at all painful
3) Slightly painful
2) Moderately painful
1) Very painful
0) Unbearable

9. Have you had any trouble getting in and out of a car or using public transportation because of your hip?
4) No trouble at all
3) Very little trouble
2) Moderate trouble
1) Extreme difficulty
0) Impossible to do

10. Have you had any trouble with washing and drying yourself (all over) because of your hip?
4) No trouble at all
3) Very little trouble
2) Moderate trouble
1) Extreme difficulty
0) Impossible to do

11. Could you do the household shopping on your own?
4) Yes, easily
3) With little difficulty
2) With moderate difficulty
1) With extreme difficulty
0) No, impossible

12. How much has pain from your hip interfered with your usual work, including housework?
4)Not at all
3) A little bit
2) Moderately
1) Greatly
0) Totally

TAB. 4
– O.H.S. (Oxford Hip Score) Questionnaire.

TAB. 5
– V.I.S.A.-A (Victorian Institute of Sport Assesment- Achilles tendon) Questionnaire.

V.I.S.A.-A

IN THIS QUESTIONNAIRE, THE TERM PAIN REFERS SPECIFICALLY TO PAIN IN THE ACHILLES TENDON REGION

1. For how many minutes do you have stiffness in the Achilles region on first getting up?

100 mins ☐☐☐☐☐☐☐☐☐☐ 0 mins — POINTS ☐

0 1 2 3 4 5 6 7 8 9 10

2. Once you are warmed up for the day, do you have pain when stretching the Achilles tendon fully over the edge of a step? (keeping knee straight)

strong severe pain ☐☐☐☐☐☐☐☐☐☐ no pain — POINTS ☐

3. After walking on flat ground for 30 minutes, do you have pain within the next 2 hours?

strong severe pain ☐☐☐☐☐☐☐☐☐☐ no pain — POINTS ☐

4. Do you have pain walking downstairs with a normal gait cycle?

strong severe pain ☐☐☐☐☐☐☐☐☐☐ no pain — POINTS ☐

5. Do you have pain during or immediately after doing 10 (single leg) heel raises from a flat surface?

strong severe pain ☐☐☐☐☐☐☐☐☐☐ no pain — POINTS ☐

6. How many single leg hops can you do without pain?

0 ☐☐☐☐☐☐☐☐☐☐ 10 — POINTS ☐

7. Are you currently undertaking sport or other physical activity?

0 ☐ Not at all — POINTS

4 ☐ Modified training ± modified competition ☐

7 ☐ Full training ± competition but not at same level as when symptoms began

10 ☐ Competing at the same or higher level as when symptoms began

At the end of the treatment, patients were offered the chance to continue with maintenance therapy: all the patients agreed to continue the treatment, saying that they were satisfied and confident. The improvements achieved were maintained in the following months. In some cases, further improvements were seen; however, in order to quantify these data, the situation must be evaluated on a case-by-case basis.

Hip Group

O.H.S. (The Oxford Hip Score) is an assessment scale for hip joint function.
The patient must answer regarding his/her every day motor performance.
Once again, patients were invited to answer the end-of-treatment questionnaire, by entering their replies at the time of assessment. Full joint integrity coincides with a score of 48 points, whereas a clinical situation of maximum impairment coincides with a score of 0.
It is important to remember that the patients in this Group presented radiographic evidence of a stage I or II condition, the phases of the disease in which pain and functional impairment emerge.
In this Group, the mean score decreased from an initial value of **10.2** (indicating somewhat severe general impairment) to a final score of **37.2** (FIG. 9).

Achilles' Group

This Group of patients, suffering from an inflammation of the Achilles' tendon, answered the Victorian Institute of Sport Assessment (V.I.S.A.-A) questionnaire, which refers to the Achilles' tendon alone and provides a score of between 0 and 68 points; the latter value refers to a condition of complete and perfect function.
In this case, as shown by the data in FIG. 10, the score increased from an initial value of **21.0**, to a final value of **54.0** points.
The patients in this Group had an ultrasound study, with a finding of effusion between the tendon folds.
– As ultrasound is a non-invasive imaging technique, at the end of treatment the patients had a follow-up ultrasound scan, to show the reabsorption of the signs of inflammation (FIG.11).

CONCLUSIONS

All the treated patients declared that they were satisfied with the result achieved.
– There were no drop outs, despite the fact that the treatment lasted 5 - 6 weeks.
As far as all of the assessment questionnaires as a whole are concerned, there was a considerable, statistically significant, subjective improvement.
To this we must add the objective improvement, confirmed by imaging studies (follow-up ultrasound) for those patients with Achilles' tendon conditions, and clinically by range of joint motion tests.
After the first 3 - 4 administrations, almost all patients in the Shoulder, Hip and Knee Groups, expressed their surprise at the feeling of greater joint freedom.
The Hip Group was the Group that expressed the greatest and earliest satisfaction with the treatment. From a percentage standpoint, the best result was achieved in the Achilles' Group: this can be attributed to the fact that this Group was constituted by patients with the lowest average age and that in which the condition was not secondary to an overload or degenerative process.
The members of this Group and the Shoulder Group were not offered any maintenance therapy. A single addition-

al administration was required in just two cases, both in the Shoulder Group. For the patients in the Hip, Knee and Upper Limb Groups (in the latter, for cases of trapeziometacarpal osteoarthritis only) the treatment is still on-going. Administration is once-monthly for the first six months.

Subsequently, if stable remission is achieved, the treatment is administered once every two months and, later, once every three months.
Having been thoroughly informed of the role played by locally-administered collagen (Guna Collagen MDs), the patients readily understood that their attention to symptoms is fundamental to a successful outcome of treatment, in order to achieve long-lasting results.

– Another positive aspect of treatment with Guna Collagen MDs is the rapid effect on pain, even and above all in patients on dicoumarol anti-coagulant therapy, who cannot take NSAIDs or steroids.

A positive and somewhat rapid response was also observed in those patients with heavy pharmacological regimens due to comorbidities.
It is important to note that, in most of the cases observed in this study (as is the case for the majority of patients referred to a physiatrist), the patient was referred after at least two months of attempts using conventional pharmacological therapy (NSAIDs, Steroids, Paracetamol) without achieving any stable result. Their body was therefore intoxicated.

– The toxins from conventional anti-inflammatory drugs accumulate above all in the structures comprising the musculoskeletal system.

– Even subjects on heavy chronic pharmacological treatment (steroids, oral hypoglycaemic agents, insulin, anticoagulants), the positive response to therapy was achieved without any interference with their ongoing chronic therapies. ■

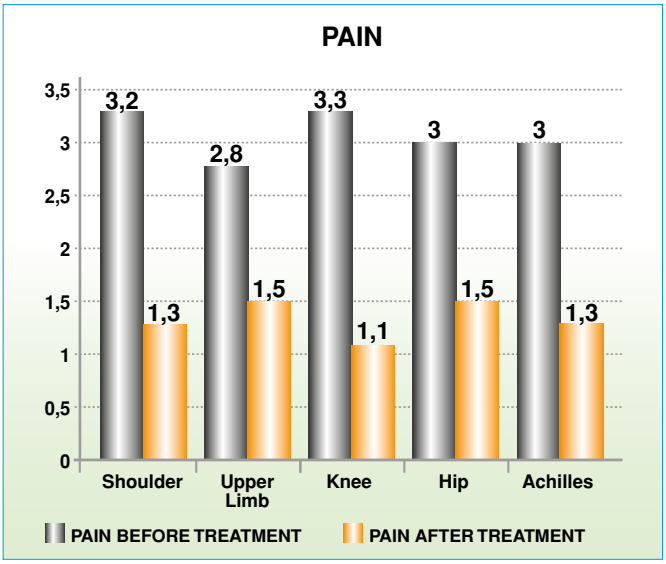
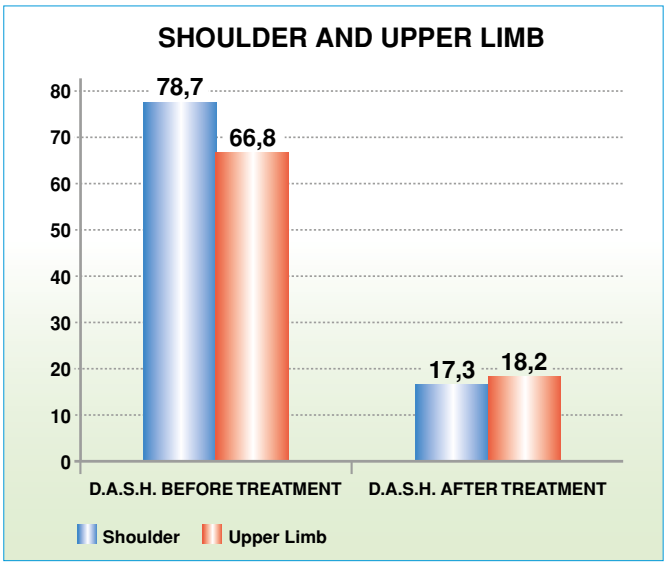


FIG. 6

Variation in the pain symptoms pre- and post-treatment in the different Groups treated with Guna Collagen MDs.

FIG. 7

Results of the analysis of the data collected using the D.A.S.H. questionnaire for conditions affecting the shoulder and upper limb (elbow, wrist, and hand).



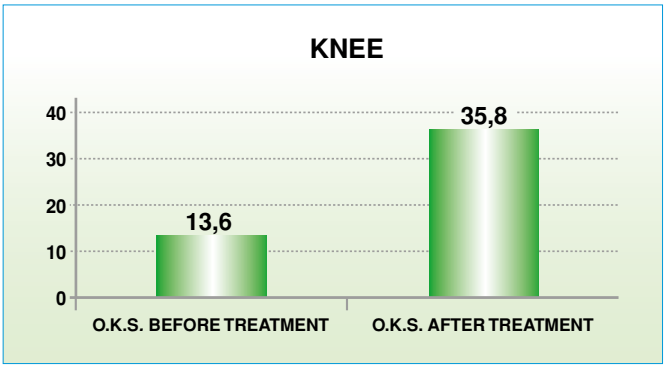


FIG. 8

Results of the analysis of the data collected using the O.K.S., for knee conditions.

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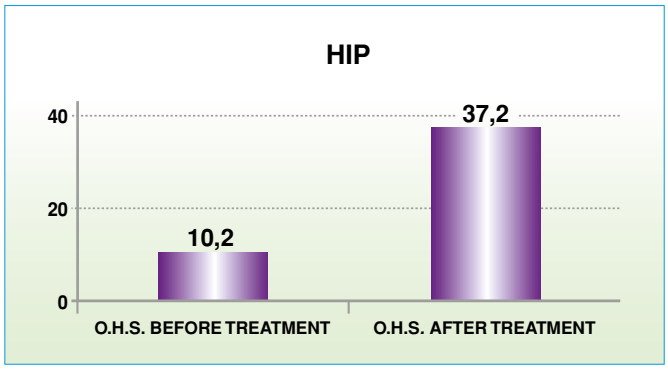
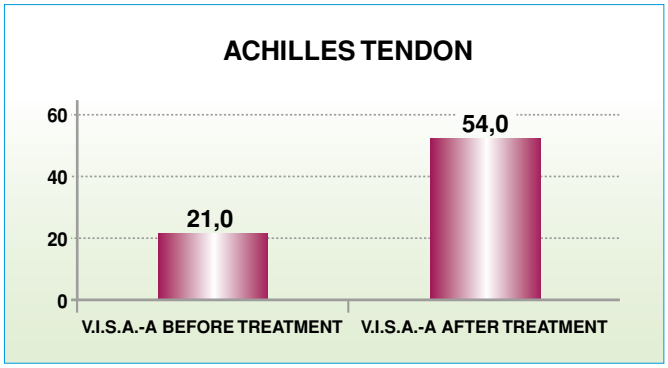


FIG. 9

Results of the analysis of the data collected using the O.H.S., for hip conditions.

FIG. 10

Results of the analysis of the data collected using the V.I.S.A.-A, for Achilles' tendon conditions.



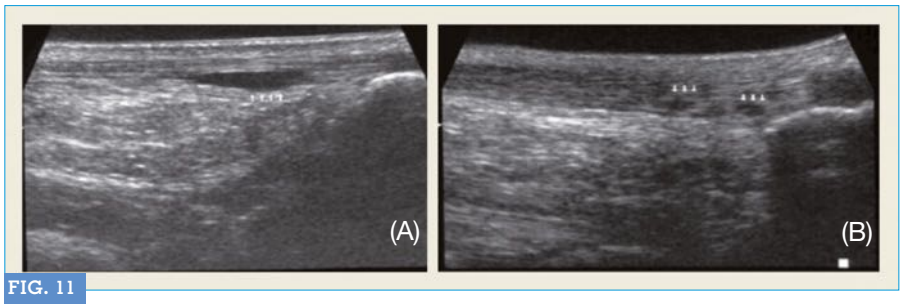


FIG. 11

(A) Achilles' tendon in the presence of effusion in the peritendineum; (B) The effusion is no longer visible. A situation of chronic tendinosis persists, with microcalcifications.

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USEFULNESS OF GUNA COLLAGEN MEDICAL DEVICES IN THE TREATMENT OF KNEE PAIN

SUMMARY

Guna Collagen Medical Devices contain swine-derived collagen and ancillary substances of natural origin.
A local administration both in acute cases and in subsequent phases speeds up the natural processes of recovery and provides an effective mechanical support.

– 20 patients aged 23, +/- 7 years, have been treated because suffering from sprained knee accompanied by a negative clinical involvement of the intra-articular ligaments and without significant intra-articular effusion.
10 patients were treated with peri-articular injections of Guna Collagen MD-Knee and Guna Collagen MD-Matrix twice/week x 3 consecutive weeks.

The Medical Devices group showed a rapid recovery and an excellent control of breakthrough pain, and VAS ≤ 1 after a two-week treatment.
This value remained still high in the group that was not treated (VAS ≥ 5).
– None of the patients treated with MDs injections used NSAIDs when needed.

KEY WORDS

COLLAGEN MEDICAL DEVICES, GUNA COLLAGEN MD-KNEE, GUNA COLLAGEN MD-MATRIX

The knee joint is the most frequently affected joint by sports-induced injuries.

Any adequate treatment should comply with the physiological processes of recovery, and any treatment should primarily influence the body processes of repair in a positive way so to obtain the best recovery in terms of joint mobility, muscle strength and endurance, neuromuscular control and cardio-respiratory efficiency.

Furthermore, recurrences should be avoided by trying to improve the endurance of damaged tissues against future strains.

From this perspective, any treatment should follow gradual stages.

Inside tissues, a mainly inflammatory phase is followed by a repair phase, during which the fibroblasts are urged to build a matrix of collagen fibers; then, a stabilization phase occurs where the collagen fibers spread according to the lines of force and sport-induced strains.

The possibility of applying specific easy-to-use **Collagen Medical Devices** without side effects in clinical practice in order to rebalance the loss of collagen, which always occurs in the above mentioned cases, is an **effective** and a **novel method of treatment**.

– The basic unit of collagen is tropocollagen, a glycoprotein made up of three intertwined left-handed polypeptide chains that are bound to molecules of glucose and galactose.

The three polypeptide chains are twisted in a tight helix. They are stabilized between aminoacids, which are hydroxylated by weak hydrogen bonds.
These bonds give collagen special characteristics, i.e. robustness as well as resistance and flexibility.

Guna Collagen Medical Devices contain swine-derived collagen and ancillary substances of natural origin.

A local administration both in acute cases and in subsequent phases speeds up the natural processes of recovery and provides an effective mechanical support.
There are different formulations to treat different joints, that are in any case appropriate for treating those tissues that are mostly mesoderm-derived.

– **20 patients** aged 23, +/-7 years, have been treated because suffering from

sprained knee accompanied by a negative clinical involvement of the intra-articular ligaments and without significant intra-articular effusion.

Such injuries, caused by physical activity, were regularly treated with NSAIDs for 4 days via systemic route.
The breakthrough pain was still high at the end of such treatment (VAS ≥ 7).
Therefore, NSAIDs were recommended only when needed.

10 patients were treated with **peri-articular injections** of **Guna Collagen MD-Knee** and **Guna Collagen MD-Matrix** twice/week x 3 consecutive weeks.

The Medical Devices group showed a **rapid recovery** and an excellent control of breakthrough pain, and VAS ≤ 1 after a two-week treatment.

– This value remained still high in the group that was not treated (VAS ≥ 5).
None of the patients treated with MDs injections used NSAIDs when needed.

– Therefore, the Guna Collagen Medical Devices turned out to be an effective method of treatment.

The possibility to combine a treatment based on Collagen Medical Devices with any other systemic or local treatment, or with physiotherapy or any other rehabilitation therapy offers various and useful fields of application to each single patient. ■

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COLLAGEN MEDICAL DEVICES AND CHELT IN SHOULDER AND KNEE OSTEOARTICULAR PAIN

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ABSTRACT: This observational study proposes an innovative method for treating osteoarticular pain, by combining Mesotherapy using Collagen MD-Shoulder or Collagen MD-Knee and CHELT (Cryo High Energy Laser Therapy) in rapid succession.
Individually, both techniques have a defined rationale with documented biological effects; this study describes the results of their close application in 40 patients studied over a 4-month period and divided into 2 groups: shoulder conditions (20) and knee conditions (20).
Observation was carried out at 3 timepoints - T0, T1 (at 1 month) and T2 (at 4 months) - with the administration of 3 tests: Visual Analogue Scale (VAS) for pain, and the Simple Shoulder Test (SST) or Oxford Knee Score (OKS) for shoulder and knee function, respectively.
The analysis of the data showed a significant improvement in all parameters: perceived pain, as rated using the VAS, improved by 50% after the first month of therapy (shoulder: 8.5 at T0; 4.55 at T1; 1.2 at T2; knee: 8.4 at T0, 4.65 at T1; 0.8 at T2);
joint functional in the first month improved by 48% in the shoulder group and by 22% in the knee group, as rated using the functional scales SST (6.55 at T0; 3.65 at T1; 1.15 at T2) and OKS (32.6 at T0; 39.8 at T1; 46.05 at T2).
The results suggest further studies should be conducted to evaluate the interactions between Collagen MDs injected using classical mesotherapy and photo-stimulation with laser and cryotherapy (CHELT).

INTRODUCTION

Osteoarticular pain accounts for a significant portion of requests for general medicine consultations and the various types of pain involving shoulder function alone account for 20% of such requests (1).
The purpose of this study conducted on a sample of **40 patients** was to establish to whether **MD-Shoulder** or **MD-Knee** administered using the conventional mesotherapy technique, in combination with an innovative physical energy technique (Cryo High Energy Laser Therapy, **CHELT**) is able to rapidly reduce acute and chronic pain symptoms, as well as to establish the improvement in shoulder and knee joint function.

This method could be an innovative alternative to conventional medical therapy with NSAIDs and pain killers in various formulations.

According to Karu (2), laser technology for therapeutic purposes can "be considered a true medicine, through the photobiostimulation of pathological tissues."
This provides the rationale for verifying the effectiveness of these physical energies in combination with mesotherapy (3) using Collagen MDs in order to achieve recovery through the adverse effect-free stimulation of repair processes.

- It is interesting to consider the better biological and curative effect produced with the combined application.

The patients were objectively assessed by administering a patient-reported functional test (Oxford Knee Score - OKS or Simple Shoulder Test - SST) (4, 5) and a Visual Analogue Scale **(VAS)** (6), at Time 0 (start of therapy), Time 1 (at 1 month) and time 2 (at 4 months).

The study showed that the perception of pain, rated using the VAS, improved in all cases from the first month of treatment, and that combining the two methods significantly reduces joint pain, and maintains and implements this outcome without recurrence, even 4 months after the start of treatment.

The results suggest that further studies should be conducted to evaluate the interactions between Collagen MDs and CHELT photostimulation.

MATERIALS AND METHODS

The patients were enrolled over a 6-month period: following careful assessment, **20 cases** with **shoulder** pain (average age 60 years, *range* 42-78, 9 M and 11 F) and **20 cases** with **knee** pain (average age 52 years, *range* 20-75, 13 M and 7 F) were enrolled amongst patients with acute and chronic single-joint pain, without recent injury sequelae.

The treatments were administered for most of the osteoarticular conditions affecting the shoulder and knee.
The sample was intentionally non-homogeneous in terms of age and the conditions considered, since the purpose of the study was to describe the effects of the therapy administered on pain and joint function.

The patients were first informed regarding the treatment they would be administered, as well as the need to pay great attention to the evolution of their symptoms, an aspect of fundamental importance to the success of both the treatment and the clinical trial

Patients were also reassured that the treatment was painless and free of adverse effects.

All patients were administered a self-reported functional test (Oxford Knee Scale - OKS or Simple Shoulder Test - SST) and the VAS at T0 (start of therapy), T1 (at 1 month) and T2 (at 4 months).

During each mesotherapy session, subjects were administered **MD-Shoulder** or **MD-Knee** by means of a 2.5 cc syringe with a 13-mm 30 G needle, using the classic access routes for the shoulder and knee, as described by Pistor Each Collagen MD application was followed by an administration of CHELT, in accordance with the regimens recommended for conditions in the subacute phase: Cryotherapy for 2 minutes, High-Energy Yag Laser in super-pulsed analgesia mode, cryotherapy for 2 minutes, High-Energy Laser in continuous biostimulation mode, cryotherapy for 2 minutes.

The full course of treatment consisted of 6-10 once- or twice-weekly sessions over a period of 4-6 weeks.

The results are provided in **TAB. 1** for patients with shoulder conditions and in **TAB. 2** for patients with knee conditions. (see below).

TAB. I
Shoulder patients: VAS and SST *(Simple Shoulder Test)* at T0 - T1 - T2.

	Patient	Age	Gender	VAS			SST		
				T0	T1	T2	T0	T1	T2
1	D.M.	52	F	8	4	0	4	2	1
2	Z.F.	62	M	8	3	0	4	1	0
3	C.G.	42	F	8	4	1	2	1	0
4	E.S.	64	M	10	5	2	6	5	1
5	L.M.	51	F	9	6	3	8	6	4
6	P.D.	70	F	10	8	7	8	5	3
7	V.A.	61	F	9	6	1	10	5	1
8	S.P.F.	78	M	10	5	2	10	6	2
9	C.A.	57	F	8	5	1	7	4	1
10	T.I.	71	F	8	3	0	8	3	0
11	B.S.	68	M	7	3	0	7	3	0
12	V.L.	45	M	7	5	1	6	3	1
13	B.F.	67	M	10	5	0	5	3	0
14	P.C.	78	F	10	5	2	10	5	3
15	P.C.	76	F	9	2	0	6	3	1
16	C.L.	42	M	7	4	0	6	4	0
17	C.R.	63	F	8	5	2	5	3	2
18	F.P.	44	M	7	3	0	5	3	0
19	R.G.B.	58	M	9	6	0	8	5	1
20	L.P.	54	F	8	4	2	6	3	2
	SIMPLE MEAN	**60.15**	***RATIO*** **M:F = 9:11**	**8.5**	**4.55**	**1.2**	**6.55**	**3.65**	**1.15**

MESOTHERAPY

Mesotherapy is a technique for administering medicinal products via an intraepidermal, superficial and deep intradermal, subcutaneous or hypodermic route (7).

The method was standardised and disseminated by the French physician Michel Pistor starting in 1952 (8). Mesotherapy is “a method for bringing the therapy closer to the disease site” (8).

Although its underlying concept is simple, mesotherapy requires adequate training in order to be carried out effectively (9).

The advantage of this technique consists in using minute doses of the active substance, which diffuse within the tissue surrounding the inoculation site and persist for longer than with intramuscular administration, bringing advantages that include:
1) long-lasting effect;
2) limited involvement of other organs;
3) lower risk of adverse events and side effects (10).
- It is used primarily for the treatment of osteoarticular and degenerative diseases

Mesotherapy has an adjuvant role; for example, in cases of moderate pain it helps to reduce the intake of systemic medicinal products.

For some of the above-mentioned indications there are significant clinical data supporting the efficacy of certain treatment protocols, for others the data are less significant

TAB. 2
Knee patients: VAS and OKS (*Oxford Knee Score*) at T0 - T1 - T2.

	Patient	Age	Gender	VAS			OKS		
				T0	T1	T2	T0	T1	T2
1	L.L.	68	M	10	6	2	31	40	46
2	L.M.	68	F	8	5	2	38	42	46
3	T.I.	71	F	10	5	0	21	38	47
4	C.F.	30	M	8	4	0	35	42	48
5	G.T.	48	F	7	4	0	39	43	48
6	C.M.	43	F	8	4	1	33	40	45
7	G.M.	75	F	8	6	2	40	43	45
8	V.L.	65	M	9	6	2	26	31	41
9	A.G.	30	M	7	5	1	38	42	46
10	B.P.	20	M	9	4	0	29	39	46
11	M.F.	32	M	9	4	0	30	40	48
12	B.S.	70	M	9	7	3	32	34	40
13	P.G.	66	M	10	5	0	28	35	48
14	P.P.	57	M	8	5	0	34	40	47
15	O.F.	58	F	9	4	1	32	40	45
16	F.P.	44	M	7	3	0	35	43	48
17	S.R.	51	F	10	5	1	31	41	46
18	T.C.	60	M	8	6	1	33	38	45
19	M.C.	51	M	7	3	0	34	42	48
20	C.F.	32	M	7	2	0	33	43	48
	SIMPLE MEAN	**51.95**	***RATIO*** **M:F = 13:7**	**8.4**	**4.65**	**0.8**	**32.6**	**39.8**	**46.05**

The Società Italiana di Mesoterapia [Italian Mesotherapy Society], which was founded in 1975, is therefore currently reviewing the criteria for the use of the technique in order to issue up-to-date guidelines on the various application settings. The Society recommends administering this therapy only once patients have been given adequate clinical information and have given informed consent to the treatment (11). In Italy, mesotherapy is considered a medical procedure.

In 1987, the Académie Française de Médicine acknowledged Mesotherapy part of traditional medicine and in many European countries, the USA and South America this technique has become practically routine practice.

CHELT

CHELT is the acronym of Cryo High Energy Laser Therapy, a treatment method that was developed starting in the 1990s and recently used in trials at Policlinico di Bari (12).

The rationale behind the method is the biostimulation of pathological tissue by applying high-energy laser and cryotherapy with cold dry air flows with a temperature of -30°C, following standardised sequences whose timings and powers depend on the depth of the tissue to be treated and the acute or chronic stage of the condition.
Combining laser therapy with cryotherapy led to the advent of CHELT, which is currently administered using the technology developed by Mectronic Medicale - Bergamo, Italy (13).

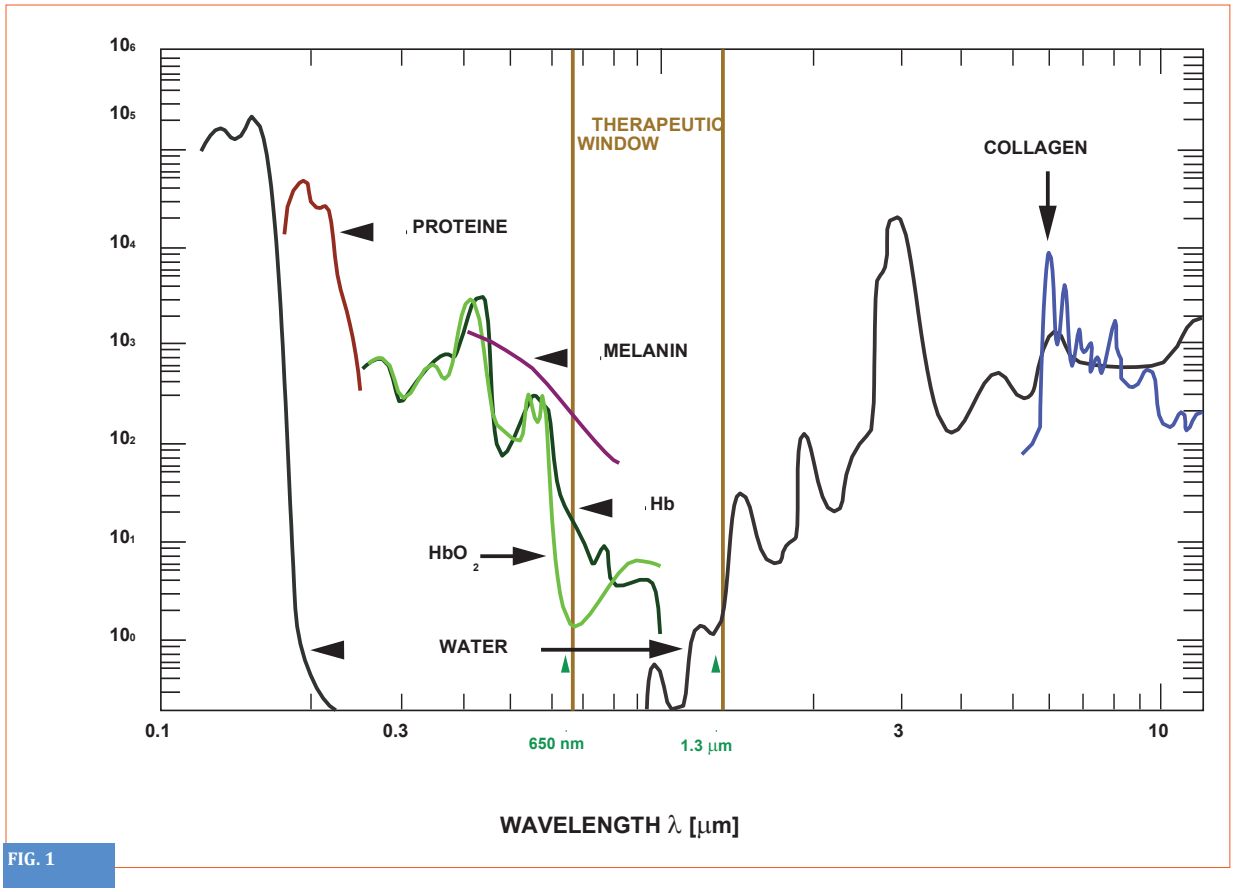


FIG. 1

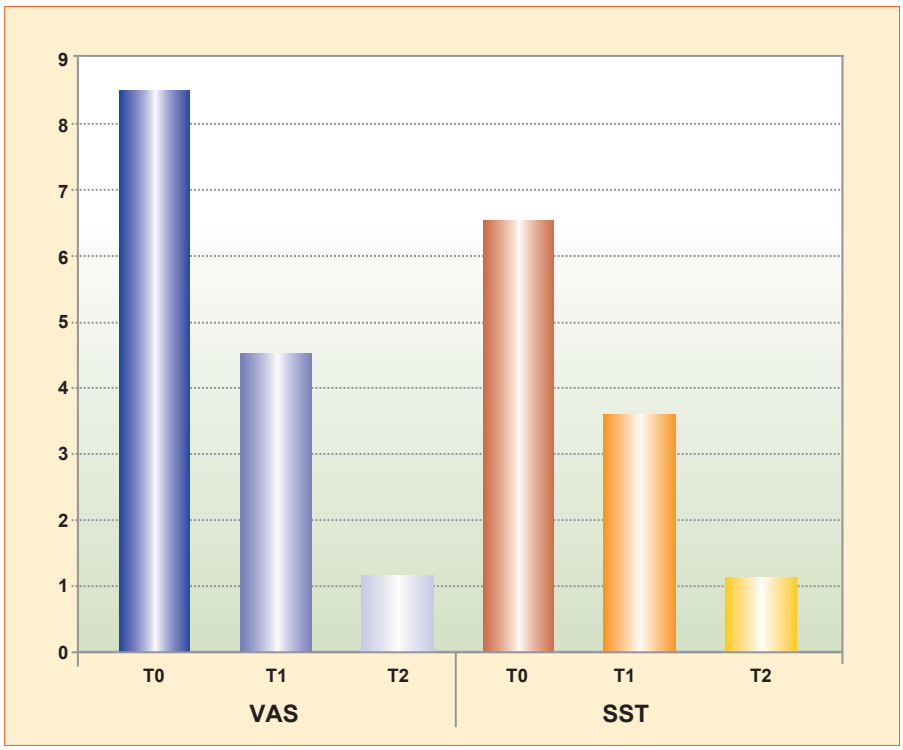
FIG.1 Optical absorption spectrum of various tissue components within the ultraviolet-infrared frequency range. From: The Warren Research Group, Duke University, Trinity College of Arts & Sciences-USA.

The laser energy produced by the deep interaction between the radiation and the damaged tissue has several therapeutic actions:
1) analgesic effect with the inhibition of the peripheral nociceptors (15,16); 2) modulation of inflammation and increase in cellular metabolic activity (17,18); 3) biostimulating effect with remodelling of the tissues due to the increase in cellular energy processes (19).

The power and wavelength of the laser are the technical characteristics that define the penetration of the quantity of energy required to activate biological responses in the target area (often located a few centimetres below the skin), due to the presence of cellular chromophore receptors that are sensitive to the radiation and photostimulation (20, 21, 22).

We conducted our trial using a 1064 nm single-frequency, high-energy laser, a source with a greater delivered energy density due to its limited scattering, as is shown in the Figure comparing the various therapeutic frequencies and their penetration into the tissues (FIG. 1). The greater output power is directly correlated with the amount of energy irradiated to the tissues by the biostimulating high intensity laser beam (23).

The term “cryotherapy” refers to a targeted exogenous cooling treatment. The superficial skin temperatures achieved during the transfer of negative energy (cooling) are between 2 °C and 15 ° C.



TAB. 3

The cold dry air flow used in cryotherapy has a rapid effect on oedema and pain: strong air flows with short action times produce immediate analgesia due to the thermal shock generated; weak flows with long application times have an effect on oedema and tissue inflammation due to their effect on the local microcirculation (24).
The cold air delivered during cryotherapy acts as a vector for the laser, as the vasoconstriction reduces the oedema and allows better energy absorption.

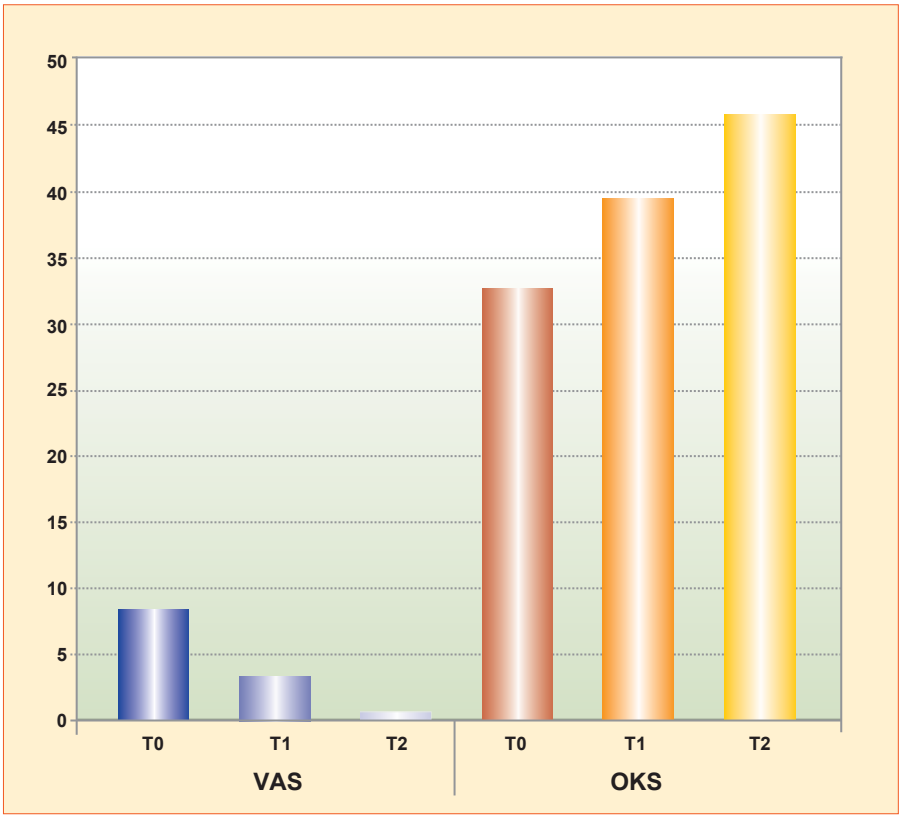
Cryotherapy was used with intermediate flows and application times before, during and after the laser applications, in order to favour tissue drainage and further activate cell metabolism (25, 26).

This is the methodological rationale that justifies the application of CHELT after each session of Mesotherapy with the Collagen Medical Devices (Guna S.p.A, Milan, Italy): activation of cellular metabolic processes and of the microcirculation with the delivery of physical energy (frequencies - photons – thermal) in order to accelerate the action of the collagen and optimise its absorption.

We calculated the simple mean of the data obtained, which were used to create the histograms for shoulder (TAB. 3) and knee (TAB. 4), which show the time trends of the values.

The study showed that the subjective perception of the pain, rated using the VAS, significantly improves in all cases from the first month of treatment, and that joint function (SST or OKS) also improves in line with the reduction in perceived pain.

The result in terms of improved joint function was significant even in the first month.



TAB. 4

CONCLUSIONS

The results achieved are positive and encourage further research.
The therapy administered, Collagen MD-Shoulder and Collagen MD-Knee injected using a conventional mesotherapy technique in combination with CHELT, undoubtedly brings a number of advantages:
1) rapid analgesic effectiveness;
2) functional recovery;
3) absence of adverse effects;
4) good patient compliance .

RESULTS AND DISCUSSION

The results are provided in the Table containing the data for each patient and subsequently in the two Tables containing the findings for patients with shoulder conditions (TAB. 1) and knee conditions (TAB. 2), showing the VAS scores and SST or OKS functional rating scale scores at T0 (time of the initial assessment), at T1 (after 1 month) and at T2 (4 months after the start of treatment).

It can be seen that the combination of the two methods results in a 50% average reduction in pain in the first month of treatment, as defined by the self-reported VAS (shoulder: 8.5 at T0; 4.55 at T1; 1.2 at T2; knee: 8.4 at T0; 4.65 at T1; 0.8 at T2) and maintains and implements this result without recurrence even 4 months after the first treatment (on average 2.5 months after the first treatment).

The therapeutic results obtained, without administering corticosteroids and/or local or systemic analgesics, suggest further research should be undertaken in order to adequately analyse the interactions between Collagen Medical Devices and photostimulation with cryotherapy and Yag laser (CHELT).

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CLINICAL

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PATELLO-FEMORAL CHONDROPATHY TREATED WITH MD-KNEE + ZEEL® T TRANSMITTED WITH O_2 *VS* NIMESULIDE + CHONDROITIN SULPHATE

SUMMARY

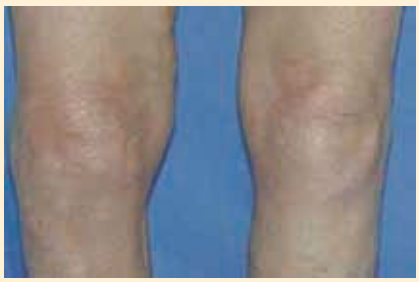
The aim of this study is to evaluate the effectiveness of the treatment with a new method, the propulsion of high pressure O_2 (2.5 atm) to transmit MD-KNEE + Zeel® T in patients with patello-femoral chondropathy vs controls receiving nimesulide + chondroitinsulphate. – 40 patients (divided into 2 Groups) were administered 2 questionnaires to record the degree of disability resulting from the chondropathy; it has been adopted the WOMAC Index for the pain scale, function and stiffness of lower limbs and the Lequesne Index concerning the functional limitation. The evaluation was performed before treatment and after 1, 2, 3, 6 and 12 weeks since the first administration. The conveyance of MD-KNEE + Zeel® T was performed with the propulsion of O_2 (98%), 2.5 atm pressure, supported by a device leaned on the skin, once a week for 12 weeks vs a daily oral administration of nimesulide + chondroitin.

– The results were evaluated with t Student and are statistically significant at $p < 0.0001$, both with the WOMAC index of pain, stiffness and joint function and with the scale, that assesses the Lequesne algo-functional Index in patients receiving O_2 + MD-KNEE + Zeel® T.

– It is noteworthy the absolute lack of side effects in the Group treated with O_2 infusion + low dose medication + medical device in addition to the low cost of treatment if compared to that of the Group treated with oral conventional medications.

KEY WORDS

PATELLO-FEMORAL CHONDROPATHY, MD-KNEE, ZEEL® T, NIMESULIDE, CHONDROPROTECTANS, PHYSIATRICS, ORTHOPAEDICS



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INTRODUCTION

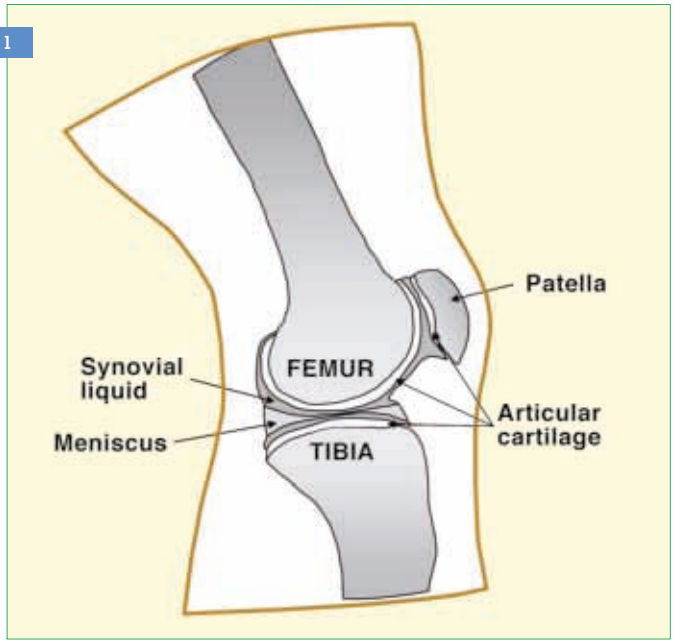
The chondropathies are broadly defined as a form of suffering of the cartilaginous tissue.
The patello-femoral chondropathy is a joint disease, whose etiopathogenesis is repeated, mechanical, and microtraumatic (FIG. 1).
The articular cartilage is formed by an elastic connective tissue covering the ends of the joint, characterized by considerable resistance to pressure and traction.

– An incorrect joint biomechanics – along with repeated microtrauma phenomena – may lead to the suffering of the cartilage of the femoral trochlea and of the patella.

The function of the cartilage is similar

FIG. 1

Schematic anatomy of the knee, lateral view. - For patellar chondromalacia it is meant the suffering of the cartilage of the patella. It rarely reaches the ulceration of the cartilage with exposure of the underlying bone.



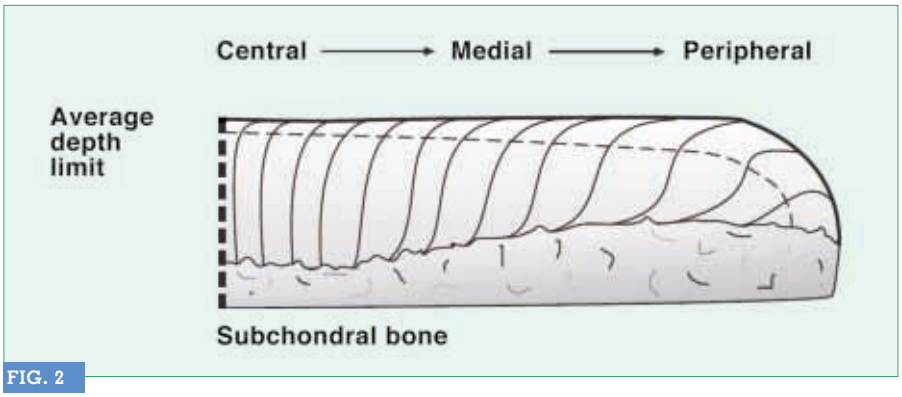


FIG. 2

Normal schematic architecture of collagen fibers.
- The layers are indicated according to the position in the joint.

to that of a bearing damper that protects the normal articular movements (FIG. 2).
– To further facilitate the flow without friction, the joint produces synovial fluid, mainly lubricating function.

A healthy cartilage allows scrolling mutual joint surfaces and can amortize well the load during movement.
– The patellar chondromalacia is, from an anatomopathological point of view, a form of suffering of the cartilage of the patella and of the femoral trochlea, which occurs on the patella.
Most frequently, the suffering cartilage is that of the lateral compartment.

Lesions vary with the severity of the cartilage injury (FIG. 3).
– Frequently, patients suffering from this disease have abnormalities in the biomechanics of the joint:
the **Q angle** of the knee (the angle between femur and tibia) is more open medially, tending to valgism; tibia tends to external rotation, it may occur excessive tension of ischio-crural muscles, causing stronger impact forces between trochlea and patella; the latter can be (anatomically) "high" (*retracted quadriceps tendon*) or "low" (*retracted patellar tendon*).
– A common area of intrinsic malalignment is the orientation of the patellar tendon in relation to the mechanism of extensors, defined as Q angle (FIG. 4).
This angle expresses the relationship between anterior tibial tuberosity and anterior superior iliac spine; it is determined – in distal direction – from the intersection of a segment from the anterior superior iliac spine to the center of the patella with a segment connecting the anterior tibial tuberosity to the center of the patella.

– The Q angle is usually inferior than 10° in males and inferior than 15° in females.
The upper limit of a Q angle is normally included between 13° and 15°.

A Q angle > 15° may depend on the rising of anteversion of the femur, on external tibial torsion and on the lateralization of anterior tibial tuberosity which increases the forces causing lateralization of the patella during muscle contraction, according to "the law of valgus".
– It is necessary to mention the concept of "static" Q angle and that of "dynamic" Q angle.
In this case, a hypotonic *vastus medialis obliquus* (VMO) can turn a static Q angle falling within the normal values in a dynamic Q angle, predisposing to patello femoral pathology.

The reduction of the angle Q does not cause the possible medial dislocation of the medial of the patella, but is responsible of compressive forces on medial tibiofemoral compartment, through an increase of the varus orientation of the knee joint and resulting in progressive damage of the medial joint compartment.

It should be remembered that the articular cartilage, in general and more easily, finds its original form after intense efforts, but temporally limited.
On the contrary, after efforts of lesser in-

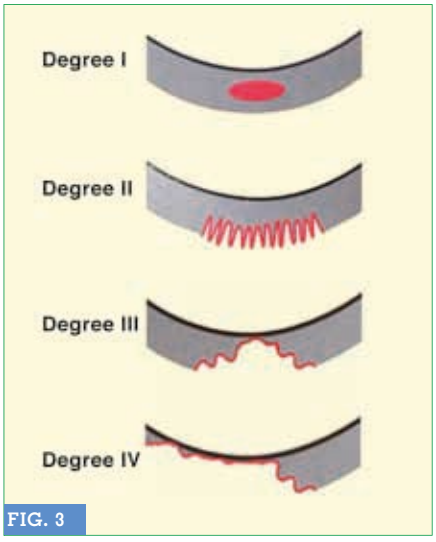


FIG. 3

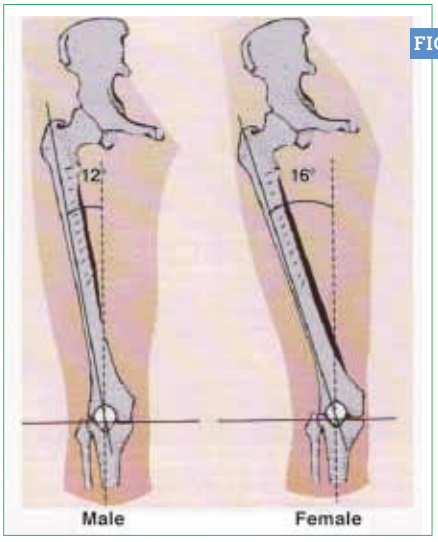


FIG. 4

The Q angle measurement allows to evaluate the alignment of the extensor system of the lower limb.

- In the badly aligned knee its value increases or decreases compared to normal ones, which differ slightly according to gender.
An increased valgus knee involves an increase of the Q angle.

tensity which are prolonged in time (eg. endurance sports or high endurance sports), cartilage shows a sharp mechanical suffering.

The femoral anteversion is a clinical sign that appears when the internal rotation of the diaphysis leads the femoral sulcus to a medial position considering the anterior tibial tuberosity and also leads the patellar tendon more laterally considering the patella, thus increasing the lateral vector force exerted on it during the contraction of the quadriceps muscle.

Another intrinsic factor is the laxity of the anterior medial quadrant of the patella (both static and dynamic).
Patellar stability is guaranteed by static patello femoral ligaments that surround the capsular tissue.
The decreased medial static stability, accompanied by excessive tension of the lateral compartment (*retinaculum*, iliotibial aponeurotic fascia), can lead to excessive tension of the structures.

– This malalignment is defined as "syndrome of side hyper pression" and is radiologically detectable at **30°** of knee flexion.

As for the dynamic component, patellar malalignment may be the result of a pathological mechanism of the VMO (underdevelopment, dysplastic disorders, post-lesional atrophy).
The VMO, in fact, guarantees the dynamic stabilization of the patello femoral joint (it is the only dynamic medial stabilizer).
– Its intersection is at III proximal of the patella with an angle of 55° in relation to the vertical axis of the patella.

▶ Its peculiar action is that of offsetting the *vastus lateralis* (VL) muscle during contraction and to provide tension of the ligaments.
In pathological conditions the VMO does not reach the III superior or the middle of the patella, and its line of action tends to be vertical and - therefore - less effective.

The combination of these anomalies undermines the medial stabilizing function of the VMO.
EMG tests of an healthy knee muscle show that the *ratio* between the activities of the VMO and those of the VL is **1:1** and that of the VMO is a tonic one.

Tests performed on the knee that has patello femoral syndrome highlight a ratio VMO / VL <1:1, as well as the fact that the activity of the VMO is a phasic one. This may be the result of a loss of asymmetry of the quadriceps (a 20-30 ml effusion may inhibit the VMO, while one of 50-60 ml can inhibit the activity of the VL) with consequent lateral shift of the patella.

Also the retraction or permanent hypertonia of the *rectus femoralis* muscle may cause a patellar hyperpression from 30° of flexion, also resulting in the tilt of the front pelvis, in which case the ischio-crural muscles stretch, decrease the tibiofemoral vertical "brake" thus encouraging the anterior translation of the tibia, which aggravates the patellar overload.
– A major retraction of the ischio-crural muscles can lead to knee flexed with disharmony of the rotatory movement.

▶ It is therefore understandable why most of the patellar syndromes are the consequence of a **dysfunction of the extensor system**, and, more generally, of the musculoskeletal structures, which must be corrected with rehabilitation or surgical treatment.

The patella, during the flexion and extension of the knee, flows inside the femoral trochlea (patellar trecking); it slides up in extension, and it slides down in flexion.
We remind briefly that the cartilage is made up of a fluid part (which gives the ability to absorb traumas) and a solid part (which increases its resistance).

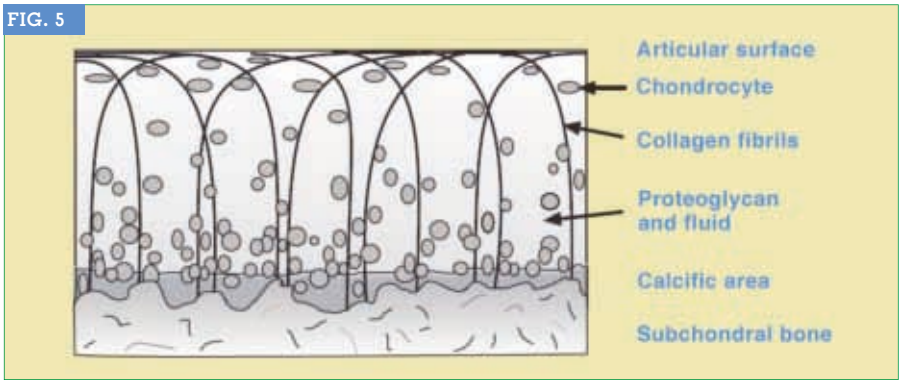
–The cartilaginous tissue are connective tissues, in which the extracellular matrix (ECM) is significantly dense, compact and consistent, so to imprison inside itself the chondrocytes (FIG. 5).

These, within their hosting niches, can face 1 or 2 mitoses maximum; therefore it can be observed the presence of small groups (isogenic groups) of 2, 3 or 4 chondrocytes.
– The most representative component of the cartilage is chondroitin sulfate, whose molecules are firmly bound by numerous sulfate bridges.
– The cartilage **is not vascularized**; therefore the cells can carry out metabolic exchanges by diffusion only through the ECM.

THE *CONSUMED CARTILAGE OF THE KNEE*

The clinical expression of osteoarthritis is manifested by various symptoms, the evolution is slow and quite unpredictable. The clinical symptoms of osteoarthritis are: osteoarticular pain, joint stiffness, crackles, joint deformity, functional limitations.

FIG. 5



Painful conditions
- occur when walking, going up and down the stairs;
- increase with the effort, accompanied by morning stiffness of short duration.

Inflammatory conditions
- sometimes particularly strong, with recrudescence during the night;
- presence of joint effusion, sometimes abundant.

In the current conception osteoarthritis is distinct from the physiological aging of the cartilage, and it is defined as a real disease, whose primary cause is represented by the metabolic alteration of the chondrocyte.

The patellofemoral joint chondropathy consists in a set of morphofunctional alterations that determine the onset of the pain of the front knee.
– In terms of etiology the alterations underlying this disease can essentially be attributed to a malalignment, or to dysplasia of the patella and / or of the femoral trochlea.

In addition to anatomical and biomechanical factors, there are a number of functional factors that, if determined in a "prone" person, may cause the onset or aggravation of symptoms (age, body weight, profession, sports activity, etc.).

The injury and pain to the structures of the knees are very common in the population because the patella lays in the system of the extensors and subject to large forces during physical activity.
1) the muscles
2) the patellar tendon
3) the patella (and its relationship with the femoral sulcus)
4) the meniscus and patella-femoral ligaments
5) the fat pads (infrapatellar and suprapatellar regions)
6) the bursa of the syuprapatellar and parapatellar regiones
7) the synovial membrane and the capsule in the anterior-medial and anterior-lateral areas of the joint.

The pain situated in the patella-femoral articulation is frequently found in clinical exams and requires the evaluation of various elements: anatomical alignment, static and dynamic stabilization system; activity level to determine mechanical joint load.

The femoral malalignment of the patella-femoral joint can result in a lateral patellar shift, which can be associated with subluxation, dislocation or both.

The patellar instability can be classified in 3 different degrees:

Degree 1: Patellar lateralization
Caused by the increase of the **Q angle**, during the contraction of the extensor muscles, a small contact area between the patellar articular surface and the trochlear one is formed.
– The consequence of this situation causes a lateral hyperpressure syndrome.

Degree 2: Marked inclination of the patella or subluxation of the patella
In case of excessive patellar tilt, a thickening occurs, as well as a retraction of the lateral *retinaculum* associated with capsular thickening.
– This determines, during knee flexion, patellar tilt, which results in lateral hyperpressure.
In the most severe cases there is a true lateral subluxation of the patella, usually caused by a sharp contraction of the quadriceps muscle with the extended knee.
– Recurrent subluxation in the long run cause severe suffering of the patellar and trochlear cartilage.

Degree 3: Dislocation of the patella
Condition that leads to severe and progressive suffering of the articular cartilage.

PURPOSE OF THE TRIAL

– The purpose of this controlled clinical randomized study is the evaluation of the clinical response to the administration of NSAID plus a cartilage protector vs. MD KNEE (Medical Device) + Zeel® T conveyed with the propulsion of O_2 in two homogeneous Groups of patients suffering from patellofemoral chondropathy.

MATERIALS AND METHODS

Several clinical studies published about O2 hyperbaric have shown the benefits of this treatment in various diseases concerning the ECM.
Hyperbaric O_2 therapy is used as support and as anti-inflammatory action in osteomyelitis,necrotic wounds and ulcers, necrotic fascitis, gangrene, pyodermitis, skin ulcers, diabetic foot, psoriasis, and purulent acne (1).
The effect of topical O_2 hyperbaric treatment is due to stimulation of the chemotaxis, of the phagocytosis, of the proliferation of fibroblasts and of the neosynthesis of collagen (especially Type I and Type III), of the epithelial proliferation and the final remodeling, with cascade processes (2).
The O_2 in the atmosphere penetrates the superficial layers of the skin to a maximum depth of 0.25 - 0.40 mm, while O_2 transported by the blood flow has less influence on the more superficial layers (3, 4).

TAB. 1

WOMAC Inferior limb – PAIN
How painful is it: • Walking? • Going up or down the stairs? • In bed, at night? • Standing up from a chair or sitting down on it? • Standing?

– A *in vivo* study [animal model (adult pig)] by Atrux-Tallau *et Al.* (5) showed that the O2 reaches the dermis, through:
1) **penetration** (uptake)
2) **permeation**.

Hyperbaric O_2 therapy does not reduce the vitality of neutrophils and functions such as degranulation and phagocytosis, oxidative lysis in response to chemoattractors remains unchanged (6).

▶ **20** randomized **patients** (**Group A**: 15 M, 5 F) received daily **Nimesulide + chondroitin sulfate.**

▶ **20** randomized **patients** (**Group B**: 15 M, 5 F) received a weekly dose of **MD-KNEE** (Guna Laboratories, Milan - I) + **Zeel® T** (-Heel, Baden Baden-D) conveyed using O_2 propulsion.

All patients were informed regarding the purposes and methods of the study and were required a written informed consent.

– Upon inclusion, all patients were administered 2 questionnaires aimed at defining the degree of incapacity following the chondropathy.

WOMAC Scale (*Western Ontario and McMaster Universities Osteoarthritis Index*) for pain, stiffness and lower limb function (TABB. 1, 2, 3) and the **Lequesne Index** for the functional limitation (TAB. 4) were used.

– WOMAC is probably the reference test for the evaluation of the results of the treatments of knee pathologies.
Each WOMAC item has 5 possible responses (from "none" to "very strong ").
The Lequesne Index assigns a score to each response up to a total that is recorded and which is the reference value for the following evaluation.

These assessments were made **before** the beginning of the treatment and at **1**, **2**, **3**, **6**, and **12 weeks**.
Statistical analysis was performed with Student's t.

– Each patient was subjected to clinical examination for the evaluation of criteria correspondence for **patello-femoral chondropathy**.
Each patient, upon inclusion, produced recent x-ray of the joints.
– These were classified according to the Kellgren-Lawrence scale.

The scale describes 4 stages of osteoarthritis:
Stage 1: not well-determined initial thinning of the joint space with the possible presence of osteophytes;
Stage 2: osteophytes and possible narrowing of the joint space;
Stage 3: moderate osteophytosis, well-defined thinning of the joint space, subchondral sclerosis, and possible sub-

TAB. 2

WOMAC
Inferior limb – RIGIDITY

What is the degree of rigidity of your joint:
- Getting up in the morning?
- When you move after having been sitting, in bed or at rest during the day?

TAB. 3

WOMAC
Inferior limb – FUNCTIONALITY

How difficult is it:
- Going down the stairs?
- Going up the stairs?
- Standing up from a chair?
- Standing?
- Leaning forward?
- Walking on a flat ground?
- Getting into/out of a car?
- Doing your usual activities?
- Putting on your socks?
- Getting out of bed?
- Lying on the bed?
- Entering/leaving the bathtub?
- Doing your daily housework?

TAB. 4

LEQUESNE INDEX

- ***Knee pain***

A) At night
None / According to movements / Also when staying still
B) Morning block
<1 min. / 1-15 min. / >15 min.
C) Standing or walking on a way down for half an hour
Yes / No.
D) Walking
No / after a certain distance / Immediately and progressively
E) Standing up from a chair without the help of the arms
No / Yes / >15 min.

- ***Maximum walking length***

No limitation / Limited, < 1 km / About 1 km (about 15 min.) / 500-900 m. (8-15 min.) / 300-500 m. / 100-300 m. / < 100 m. / with a stick or a crutch / with two sticks or crutches

- ***Difficulty in the daily life***

Going up a floor / Going down a floor / Crouching / Walking on an even ground

chondral bone deformities;
Stage 4: severe arthritis.

– The study included patients with patellar femoral chondropathy, clinically and radiographically documented at Stage 1, 2 or 3 according to Kellgren-Lawrence.

Patients included in the study did not report any previous knee surgery, nor rheumatic diseases or auto-immune ones, being underway or documented.

– The 20 patients in **Group A** received Nimesulide 100 mg sachet + galactosaminglucoronoglicane sulfate sodium salt 400 mg (Condral®) once a day orally.

– The 20 patients in **Group B** received **MD-KNEE** 1 ampoule + **Zeel® T** 1ampoule applied to the skin of the knee, O_2-propelled.

Patients were treated 1 time / week, after careful disinfection of the skin (alcohol or iodine based antiseptic solution).

The propulsion technique with pure O_2 (98%) was performed with an equipment that concentrates the O_2 from the air environment (zeolite filters) and that – through a compressor – provides O_2 at the pressure of 2.5 atm, using a device placed on the skin (Maya Beauty Engineering, Oxyendodermia Medicale).
– The patient lays in supine position with the affected knee slightly flexed through a popliteal pad; on the area to be treated were applied MD-KNEE + Zeel® T, mixed together with a neutral serum solution.
- Immediately afterward O_2 was delivered at 2.5 atm, for 20 minutes.
• **Group A** (Nimesulide + chondroitin) consists of 15 M and 5 F, average age 46.9 years (min 28, max 65), with Standard Deviation (SD) 11.8; average BMI of 25.4 with SD 2.45.
It was also calculated the average body fat, equal to 20.32% DS 7.04,evaluating the circumference of the neck, abdomen and, in females, hips too.

– The average pre-treatment WOMAC score was **59 points** (34 min, max 80), on a scale from 0 to 96.
- The average algo-dysfunctional Index of Lequesne was **18 points** (12 min, max 22) on a scale from 0 to 24.
The right knee was affected in 15 cases, the left one in 5 cases.

• **Group B** (MD-KNEE + Zeel® T + O_2 propulsion) is also composed of 15 M and 5 F, average age 49.4 years (min 31, max 66) with DS 9.1;average BMI of 24.4 with SD 2.4.
It was also calculated the average body fat, equal to 26.11% with SD 17.8, considering the circumference of the neck, abdomen and, in females, the hips too.
- The average pre-treatment WOMAC score was **58 points** (min. 42, max 89).
- The average algo-dysfunctional Index of Lequesne was **18 points** (min. 12, max 22).
The right knee was affected in 10 cases, the left one in 10 cases.

RESULTS

All patients completed the prearranged treatment. The results are reported according to the Group membership of the patients (A, B); these were recorded during **5** ***follow-ups*** performed at **1**, **2**, **3**, **6**, and **12 weeks** after initial administration.

• After the **first** week: patients belonging to both groups showed a reduction of the total WOMAC score, compared to "basal" score, not statistically significant.
- The average score of the Group A patients was **54** WOMAC points (min 30, max 78), p <0.374.
- The average score of the Group B patients was **50** WOMAC points (min 34, max 74), p <0.087.

• **Second** week: patients of both Groups showed a reduction of the WOMAC total score, compared to the previous score.
- The average score of the Group A patients was **53** WOMAC points (min 30, max 78), p <0.217.
- The average score of the Group B patients was **47** WOMAC points (min 30, max 68), p <0.0047.

• **Third** week: patients of both Groups showed a reduction of the WOMAC total score, compared to the previous score.
- The average score of the Group A patients was **51** WOMAC points (min 30, max 74), p <0.0109.
- The average score of the Group B patients was **44** WOMAC points (min 30, max 66), p <0.0031.

• **Sixth** week: between 3rd and 6th week since the first treatment, there was no change in the WOMAC average score of Group A patients, while the WOMAC average score of Group B patients is statistically significant, marking a decrease in pain, stiffness, and functionality.
- The average score of the Group A patients was **50** WOMAC points (min 32, max 72), p <0.097.
- The average score of the Group B patients was **41** WOMAC points (min 30, max 68), p <0.0004.
The difference is statistically significant (p <0.001).

• **Twelfth** week: the last follow-up showed that the WOMAC average score of the Group A patients is **47** points (32 min, max 70), p <0.014.
- The WOMAC average score of the Group B patients has further decreased to **39** points (min. 24, max 60), p <0.0001.
The difference between the 2 experimental Groups is statistically significant (p <0.001).
As far as the algo-dysfunctional Lequesne Index is concerned, it has increased from **18** to **15 points** among the Group A patients; it has increased from **17** to **10** among the Group B patients (TABB. 8, 9).

CONCLUSIONS

Conservative treatment of patellofemoral chondropathy has a well documented background in the scientific literature of the last fifty years.

The use of NSAIDs, corticosteroids and chondro-protectants is common in conventional medicine.

The mechanism of action of corticosteroids is very clear: inhibition of the synthesis of prostaglandins, decrease of the collagenase activity and reduction of the production of IL-1, TNFα, and various proteases that attack the cartilage.

– NSAIDs and corticosteroids act only on the painful symptoms.

	BASIC WOMAC	WOMAC 1st week	WOMAC 2nd week	WOMAC 3rd week	WOMAC 6th week	WOMAC 12th week
M	36	30	30	30	34	34
	34	30	30	30	32	34
	66	54	54	50	52	48
	34	30	30	32	34	34
	72	68	64	64	66	55
	68	62	62	58	60	54
	68	62	64	62	60	56
	68	62	60	60	60	50
	70	68	60	58	52	48
	68	60	58	50	50	46
	68	60	58	54	50	46
	70	68	60	54	54	46
	66	60	60	58	60	48
	39	34	34	34	32	32
	70	70	68	66	66	64
F	80	78	76	74	72	70
	36	34	34	34	30	32
	34	30	34	34	34	32
	48	44	40	40	42	42
	78	74	70	70	68	66
	58,65	**53,9**	**52,3**	**50,6**	**50,4**	**46,85**
	16,68	**16,74**	**15,29**	**14,29**	**13,80**	**11,69**
	p	**0,374401**	**0,217196**	**0,109516**	**0,096581**	**0,013509**

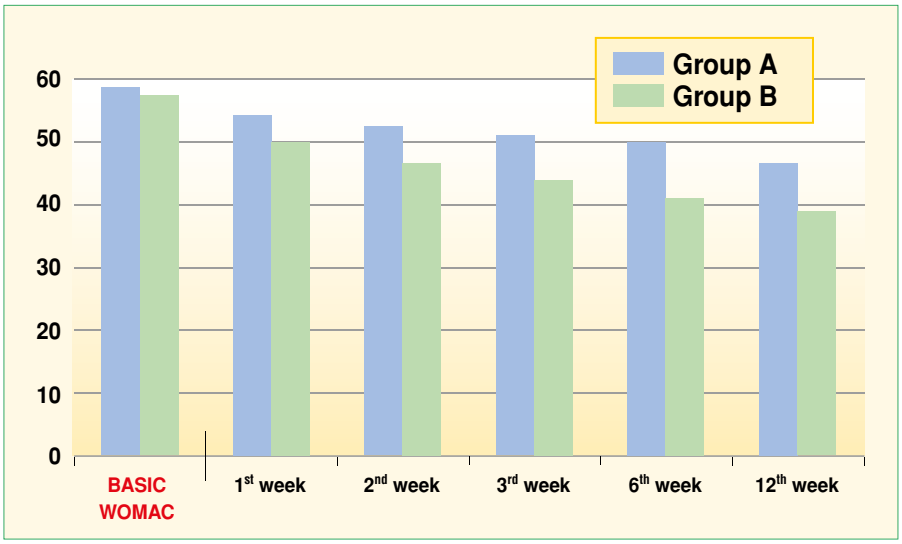
TAB. 5

Group A - Analytical WOMAC (basic evaluation, and at 1st, 2nd, 3rd, 6th and 12th week since the beginning of the therapy).

TAB. 6

Group B - Analytical WOMAC (basic evaluation, and at 1st, 2nd, 3rd, 6th and 12th week since the beginning of the therapy).

	BASIC WOMAC	WOMAC 1st week	WOMAC 2nd week	WOMAC 3rd week	WOMAC 6th week	WOMAC 12th week
M	42	38	38	36	34	28
	46	38	34	30	36	32
	64	60	48	48	52	44
	44	38	38	36	34	36
	89	74	68	66	68	60
	60	60	56	50	44	46
	46	44	44	42	40	40
	42	40	34	34	30	28
	86	72	68	66	64	60
	46	36	30	30	28	24
	46	38	40	42	38	34
	80	74	68	60	54	50
	77	70	60	52	45	38
	76	60	60	58	54	50
	64	49	45	40	34	34
F	49	38	34	30	24	24
	42	34	34	34	30	32
	50	42	42	40	34	34
	68	60	60	58	50	52
	52	34	34	36	34	32
	58	**49,95**	**46,75**	**44,4**	**41,35**	**38,9**
	15,91	**14,63**	**13,17**	**12,03**	**12,14**	**10,98**
	p	**0,086603**	**0,01551837**	**0,00317**	**0,0004773**	**0,00005**



TAB. 7

Progressive differences of average WOMAC in the 2 Groups of patients.

14	12	20	15	22	16	18	16	18	20	18	20	20	14	20	22	14	19	18	22	Average **17,9**	DS 2,99
10	10	15	14	15	11	14	15	18	18	18	15	14	11	18	18	14	18	18	22	Average **15,3**	DS 3,21

TAB. 8

Group A - Lequesne score before and after 12-week treatment.

12	15	19	14	20	18	16	15	20	16	16	20	22	19	18	22	18	14	15	12	Average **17,05**	DS 3,00
9	8	12	10	12	12	11	10	10	11	11	10	12	12	10	12	10	8	8	10	Average **10,4**	DS 1,39

TAB. 9

Group B - Lequesne score before and after 12-week treatment.

The use of chondro-protectants should aim to restore the natural rheological and metabolic homeostasis of the joint affected by arthritis, enhancing the protective effect, lubricating and "shock-absorbing" the synovial fluid.

– Both groups (A, B) showed – in the lapse of the period considered, i.e. 12 weeks – a significant improvement due to a decrease of pain and of limited functionally linked to the gonarthrosic process.

– The data show that the improvement of the clinical-functional situation is **more immediate in patients treated with O_2 (98%) conveyed at 2.5 atm + MD-KNEE + Zeel® T**: the Group B patients have shown a decrease in the average WOMAC score in joint stiffness and function more relevant from a statistical point of view than the score obtained by the Group A patients treated with nimesulide + chondro-protectants.

– The total absence of negative side effects recorded in the Group B patients and the use of a non-invasive, painless and very easy therapy, one treatment only per week) has allowed better acceptance and an expenditure definitely more advantageous. ■

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CLINICAL

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PATELLO-FEMORAL CHONDROPATHY TREATED WITH MD-KNEE + ZEEL® T TRANSMITTED WITH O_2 *VS* NIMESULIDE + CHONDROITIN SULPHATE

SUMMARY

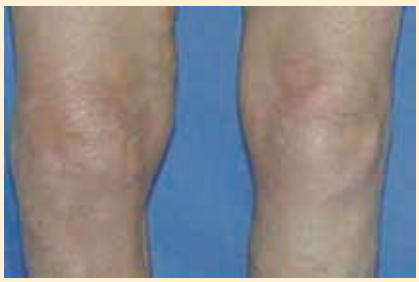
The aim of this study is to evaluate the effectiveness of the treatment with a new method, the propulsion of high pressure O_2 (2.5 atm) to transmit MD-KNEE + Zeel® T in patients with patello-femoral chondropathy vs controls receiving nimesulide + chondroitinsulphate. – 40 patients (divided into 2 Groups) were administered 2 questionnaires to record the degree of disability resulting from the chondropathy; it has been adopted the WOMAC Index for the pain scale, function and stiffness of lower limbs and the Lequesne Index concerning the functional limitation. The evaluation was performed before treatment and after 1, 2, 3, 6 and 12 weeks since the first administration. The conveyance of MD-KNEE + Zeel® T was performed with the propulsion of O_2 (98%), 2.5 atm pressure, supported by a device leaned on the skin, once a week for 12 weeks vs a daily oral administration of nimesulide + chondroitin.

– The results were evaluated with t Student and are statistically significant at $p < 0.0001$, both with the WOMAC index of pain, stiffness and joint function and with the scale, that assesses the Lequesne algo-functional Index in patients receiving O_2 + MD-KNEE + Zeel® T.

– It is noteworthy the absolute lack of side effects in the Group treated with O_2 infusion + low dose medication + medical device in addition to the low cost of treatment if compared to that of the Group treated with oral conventional medications.

KEY WORDS

PATELLO-FEMORAL CHONDROPATHY, MD-KNEE, ZEEL® T, NIMESULIDE, CHONDROPROTECTANS, PHYSIATRICS, ORTHOPAEDICS



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INTRODUCTION

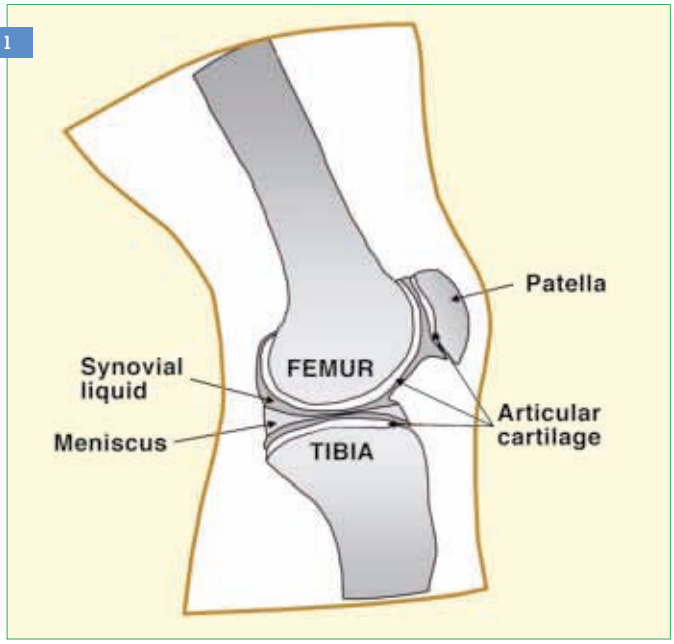
The chondropathies are broadly defined as a form of suffering of the cartilaginous tissue.
The patello-femoral chondropathy is a joint disease, whose etiopathogenesis is repeated, mechanical, and microtraumatic (FIG. 1).
The articular cartilage is formed by an elastic connective tissue covering the ends of the joint, characterized by considerable resistance to pressure and traction.

– An incorrect joint biomechanics – along with repeated microtrauma phenomena – may lead to the suffering of the cartilage of the femoral trochlea and of the patella.

The function of the cartilage is similar

FIG. 1

Schematic anatomy of the knee, lateral view. - For patellar chondromalacia it is meant the suffering of the cartilage of the patella. It rarely reaches the ulceration of the cartilage with exposure of the underlying bone.



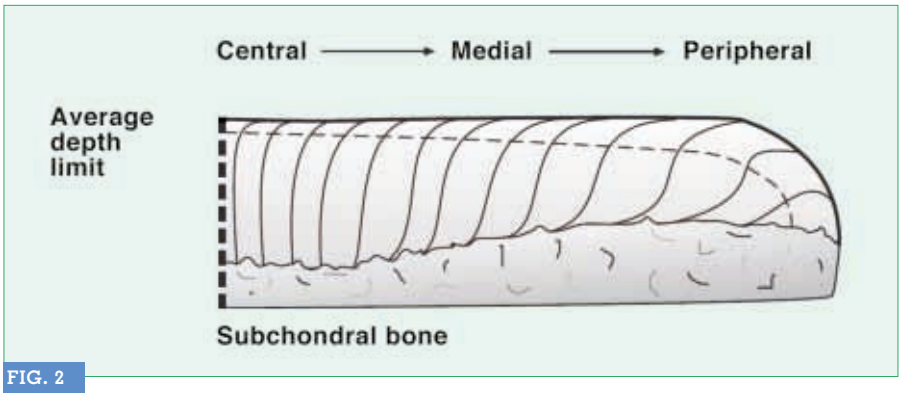


FIG. 2

Normal schematic architecture of collagen fibers.
- The layers are indicated according to the position in the joint.

to that of a bearing damper that protects the normal articular movements (FIG. 2).
– To further facilitate the flow without friction, the joint produces synovial fluid, mainly lubricating function.

A healthy cartilage allows scrolling mutual joint surfaces and can amortize well the load during movement.
– The patellar chondromalacia is, from an anatomopathological point of view, a form of suffering of the cartilage of the patella and of the femoral trochlea, which occurs on the patella.
Most frequently, the suffering cartilage is that of the lateral compartment.

Lesions vary with the severity of the cartilage injury (FIG. 3).
– Frequently, patients suffering from this disease have abnormalities in the biomechanics of the joint:
the **Q angle** of the knee (the angle between femur and tibia) is more open medially, tending to valgism; tibia tends to external rotation, it may occur excessive tension of ischio-crural muscles, causing stronger impact forces between trochlea and patella; the latter can be (anatomically) "high" (*retracted quadriceps tendon*) or "low" (*retracted patellar tendon*).
– A common area of intrinsic malalignment is the orientation of the patellar tendon in relation to the mechanism of extensors, defined as Q angle (FIG. 4).
This angle expresses the relationship between anterior tibial tuberosity and anterior superior iliac spine; it is determined – in distal direction – from the intersection of a segment from the anterior superior iliac spine to the center of the patella with a segment connecting the anterior tibial tuberosity to the center of the patella.

– The Q angle is usually inferior than 10° in males and inferior than 15° in females.
The upper limit of a Q angle is normally included between 13° and 15°.

A Q angle > 15° may depend on the rising of anteversion of the femur, on external tibial torsion and on the lateralization of anterior tibial tuberosity which increases the forces causing lateralization of the patella during muscle contraction, according to "the law of valgus".
– It is necessary to mention the concept of "static" Q angle and that of "dynamic" Q angle.
In this case, a hypotonic *vastus medialis obliquus* (VMO) can turn a static Q angle falling within the normal values in a dynamic Q angle, predisposing to patello femoral pathology.

The reduction of the angle Q does not cause the possible medial dislocation of the medial of the patella, but is responsible of compressive forces on medial tibiofemoral compartment, through an increase of the varus orientation of the knee joint and resulting in progressive damage of the medial joint compartment.

It should be remembered that the articular cartilage, in general and more easily, finds its original form after intense efforts, but temporally limited.
On the contrary, after efforts of lesser in-

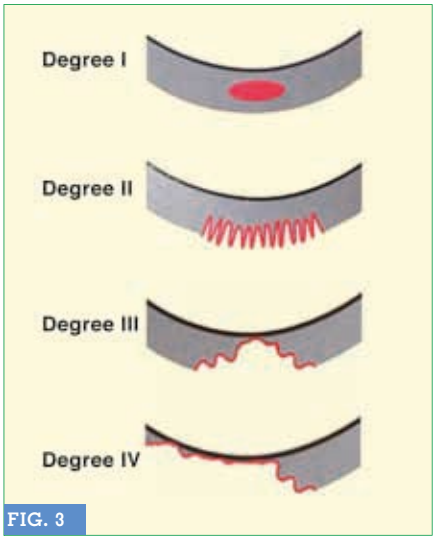


FIG. 3

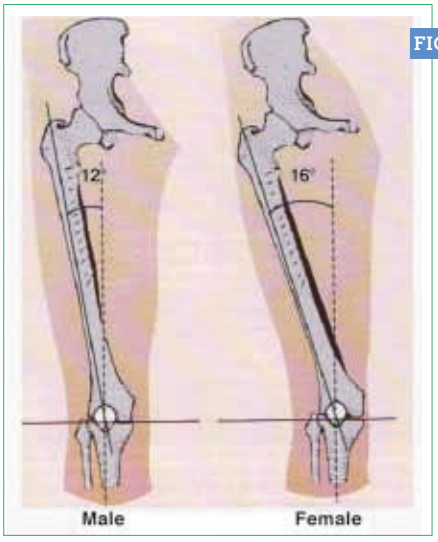


FIG. 4

The Q angle measurement allows to evaluate the alignment of the extensor system of the lower limb.

- In the badly aligned knee its value increases or decreases compared to normal ones, which differ slightly according to gender.
An increased valgus knee involves an increase of the Q angle.

tensity which are prolonged in time (eg. endurance sports or high endurance sports), cartilage shows a sharp mechanical suffering.

The femoral anteversion is a clinical sign that appears when the internal rotation of the diaphysis leads the femoral sulcus to a medial position considering the anterior tibial tuberosity and also leads the patellar tendon more laterally considering the patella, thus increasing the lateral vector force exerted on it during the contraction of the quadriceps muscle.

Another intrinsic factor is the laxity of the anterior medial quadrant of the patella (both static and dynamic).
Patellar stability is guaranteed by static patello femoral ligaments that surround the capsular tissue.
The decreased medial static stability, accompanied by excessive tension of the lateral compartment (*retinaculum*, iliotibial aponeurotic fascia), can lead to excessive tension of the structures.

– This malalignment is defined as "syndrome of side hyper pression" and is radiologically detectable at **30°** of knee flexion.

As for the dynamic component, patellar malalignment may be the result of a pathological mechanism of the VMO (underdevelopment, dysplastic disorders, post-lesional atrophy).
The VMO, in fact, guarantees the dynamic stabilization of the patello femoral joint (it is the only dynamic medial stabilizer).
– Its intersection is at III proximal of the patella with an angle of 55° in relation to the vertical axis of the patella.

▶ Its peculiar action is that of offsetting the *vastus lateralis* (VL) muscle during contraction and to provide tension of the ligaments.
In pathological conditions the VMO does not reach the III superior or the middle of the patella, and its line of action tends to be vertical and - therefore - less effective.

The combination of these anomalies undermines the medial stabilizing function of the VMO.
EMG tests of an healthy knee muscle show that the *ratio* between the activities of the VMO and those of the VL is **1:1** and that of the VMO is a tonic one.

Tests performed on the knee that has patello femoral syndrome highlight a ratio VMO / VL <1:1, as well as the fact that the activity of the VMO is a phasic one. This may be the result of a loss of asymmetry of the quadriceps (a 20-30 ml effusion may inhibit the VMO, while one of 50-60 ml can inhibit the activity of the VL) with consequent lateral shift of the patella.

Also the retraction or permanent hypertonia of the *rectus femoralis* muscle may cause a patellar hyperpression from 30° of flexion, also resulting in the tilt of the front pelvis, in which case the ischio-crural muscles stretch, decrease the tibiofemoral vertical "brake" thus encouraging the anterior translation of the tibia, which aggravates the patellar overload.
– A major retraction of the ischio-crural muscles can lead to knee flexed with disharmony of the rotatory movement.

▶ It is therefore understandable why most of the patellar syndromes are the consequence of a **dysfunction of the extensor system**, and, more generally, of the musculoskeletal structures, which must be corrected with rehabilitation or surgical treatment.

The patella, during the flexion and extension of the knee, flows inside the femoral trochlea (patellar trecking); it slides up in extension, and it slides down in flexion.
We remind briefly that the cartilage is made up of a fluid part (which gives the ability to absorb traumas) and a solid part (which increases its resistance).

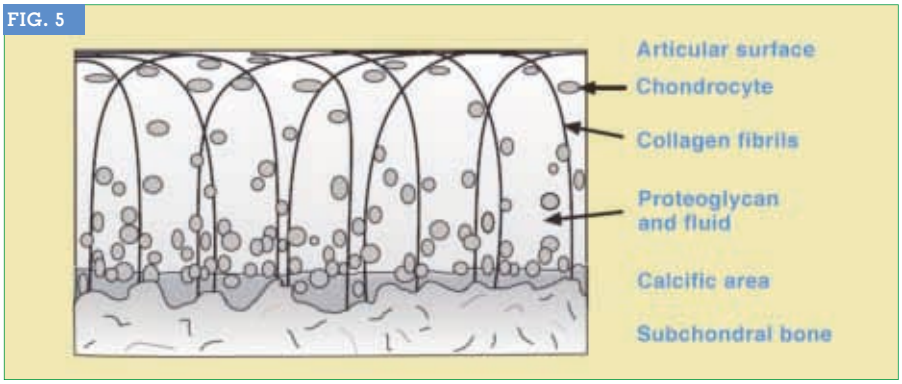
–The cartilaginous tissue are connective tissues, in which the extracellular matrix (ECM) is significantly dense, compact and consistent, so to imprison inside itself the chondrocytes (FIG. 5).

These, within their hosting niches, can face 1 or 2 mitoses maximum; therefore it can be observed the presence of small groups (isogenic groups) of 2, 3 or 4 chondrocytes.
– The most representative component of the cartilage is chondroitin sulfate, whose molecules are firmly bound by numerous sulfate bridges.
– The cartilage **is not vascularized**; therefore the cells can carry out metabolic exchanges by diffusion only through the ECM.

THE *CONSUMED CARTILAGE OF THE KNEE*

The clinical expression of osteoarthritis is manifested by various symptoms, the evolution is slow and quite unpredictable. The clinical symptoms of osteoarthritis are: osteoarticular pain, joint stiffness, crackles, joint deformity, functional limitations.

FIG. 5



Painful conditions
- occur when walking, going up and down the stairs;
- increase with the effort, accompanied by morning stiffness of short duration.

Inflammatory conditions
- sometimes particularly strong, with recrudescence during the night;
- presence of joint effusion, sometimes abundant.

In the current conception osteoarthritis is distinct from the physiological aging of the cartilage, and it is defined as a real disease, whose primary cause is represented by the metabolic alteration of the chondrocyte.

The patellofemoral joint chondropathy consists in a set of morphofunctional alterations that determine the onset of the pain of the front knee.
– In terms of etiology the alterations underlying this disease can essentially be attributed to a malalignment, or to dysplasia of the patella and / or of the femoral trochlea.

In addition to anatomical and biomechanical factors, there are a number of functional factors that, if determined in a "prone" person, may cause the onset or aggravation of symptoms (age, body weight, profession, sports activity, etc.).

The injury and pain to the structures of the knees are very common in the population because the patella lays in the system of the extensors and subject to large forces during physical activity.
1) the muscles
2) the patellar tendon
3) the patella (and its relationship with the femoral sulcus)
4) the meniscus and patella-femoral ligaments
5) the fat pads (infrapatellar and suprapatellar regions)
6) the bursa of the syuprapatellar and parapatellar regiones
7) the synovial membrane and the capsule in the anterior-medial and anterior-lateral areas of the joint.

The pain situated in the patella-femoral articulation is frequently found in clinical exams and requires the evaluation of various elements: anatomical alignment, static and dynamic stabilization system; activity level to determine mechanical joint load.

The femoral malalignment of the patella-femoral joint can result in a lateral patellar shift, which can be associated with subluxation, dislocation or both.

The patellar instability can be classified in 3 different degrees:

Degree 1: Patellar lateralization
Caused by the increase of the **Q angle**, during the contraction of the extensor muscles, a small contact area between the patellar articular surface and the trochlear one is formed.
– The consequence of this situation causes a lateral hyperpressure syndrome.

Degree 2: Marked inclination of the patella or subluxation of the patella
In case of excessive patellar tilt, a thickening occurs, as well as a retraction of the lateral *retinaculum* associated with capsular thickening.
– This determines, during knee flexion, patellar tilt, which results in lateral hyperpressure.
In the most severe cases there is a true lateral subluxation of the patella, usually caused by a sharp contraction of the quadriceps muscle with the extended knee.
– Recurrent subluxation in the long run cause severe suffering of the patellar and trochlear cartilage.

Degree 3: Dislocation of the patella
Condition that leads to severe and progressive suffering of the articular cartilage.

PURPOSE OF THE TRIAL

– The purpose of this controlled clinical randomized study is the evaluation of the clinical response to the administration of NSAID plus a cartilage protector vs. MD KNEE (Medical Device) + Zeel® T conveyed with the propulsion of O_2 in two homogeneous Groups of patients suffering from patellofemoral chondropathy.

MATERIALS AND METHODS

Several clinical studies published about O2 hyperbaric have shown the benefits of this treatment in various diseases concerning the ECM.
Hyperbaric O_2 therapy is used as support and as anti-inflammatory action in osteomyelitis,necrotic wounds and ulcers, necrotic fascitis, gangrene, pyodermitis, skin ulcers, diabetic foot, psoriasis, and purulent acne (1).
The effect of topical O_2 hyperbaric treatment is due to stimulation of the chemotaxis, of the phagocytosis, of the proliferation of fibroblasts and of the neosynthesis of collagen (especially Type I and Type III), of the epithelial proliferation and the final remodeling, with cascade processes (2).
The O_2 in the atmosphere penetrates the superficial layers of the skin to a maximum depth of 0.25 - 0.40 mm, while O_2 transported by the blood flow has less influence on the more superficial layers (3, 4).

TAB. 1

WOMAC Inferior limb – PAIN
How painful is it: • Walking? • Going up or down the stairs? • In bed, at night? • Standing up from a chair or sitting down on it? • Standing?

– A *in vivo* study [animal model (adult pig)] by Atrux-Tallau *et Al.* (5) showed that the O2 reaches the dermis, through:
1) **penetration** (uptake)
2) **permeation**.

Hyperbaric O_2 therapy does not reduce the vitality of neutrophils and functions such as degranulation and phagocytosis, oxidative lysis in response to chemoattractors remains unchanged (6).

▶ **20** randomized **patients** (**Group A**: 15 M, 5 F) received daily **Nimesulide + chondroitin sulfate.**

▶ **20** randomized **patients** (**Group B**: 15 M, 5 F) received a weekly dose of **MD-KNEE** (Guna Laboratories, Milan - I) + **Zeel® T** (-Heel, Baden Baden-D) conveyed using O_2 propulsion.

All patients were informed regarding the purposes and methods of the study and were required a written informed consent.

– Upon inclusion, all patients were administered 2 questionnaires aimed at defining the degree of incapacity following the chondropathy.

WOMAC Scale (*Western Ontario and McMaster Universities Osteoarthritis Index*) for pain, stiffness and lower limb function (TABB. 1, 2, 3) and the **Lequesne Index** for the functional limitation (TAB. 4) were used.

– WOMAC is probably the reference test for the evaluation of the results of the treatments of knee pathologies.
Each WOMAC item has 5 possible responses (from "none" to "very strong ").
The Lequesne Index assigns a score to each response up to a total that is recorded and which is the reference value for the following evaluation.

These assessments were made **before** the beginning of the treatment and at **1**, **2**, **3**, **6**, and **12 weeks**.
Statistical analysis was performed with Student's t.

– Each patient was subjected to clinical examination for the evaluation of criteria correspondence for **patello-femoral chondropathy**.
Each patient, upon inclusion, produced recent x-ray of the joints.
– These were classified according to the Kellgren-Lawrence scale.

The scale describes 4 stages of osteoarthritis:
Stage 1: not well-determined initial thinning of the joint space with the possible presence of osteophytes;
Stage 2: osteophytes and possible narrowing of the joint space;
Stage 3: moderate osteophytosis, well-defined thinning of the joint space, subchondral sclerosis, and possible sub-

TAB. 2

WOMAC
Inferior limb – RIGIDITY

What is the degree of rigidity of your joint:
- Getting up in the morning?
- When you move after having been sitting, in bed or at rest during the day?

TAB. 3

WOMAC
Inferior limb – FUNCTIONALITY

How difficult is it:
- Going down the stairs?
- Going up the stairs?
- Standing up from a chair?
- Standing?
- Leaning forward?
- Walking on a flat ground?
- Getting into/out of a car?
- Doing your usual activities?
- Putting on your socks?
- Getting out of bed?
- Lying on the bed?
- Entering/leaving the bathtub?
- Doing your daily housework?

TAB. 4

LEQUESNE INDEX

- ***Knee pain***

A) At night
None / According to movements / Also when staying still
B) Morning block
<1 min. / 1-15 min. / >15 min.
C) Standing or walking on a way down for half an hour
Yes / No.
D) Walking
No / after a certain distance / Immediately and progressively
E) Standing up from a chair without the help of the arms
No / Yes / >15 min.

- ***Maximum walking length***

No limitation / Limited, < 1 km / About 1 km (about 15 min.) / 500-900 m. (8-15 min.) / 300-500 m. / 100-300 m. / < 100 m. / with a stick or a crutch / with two sticks or crutches

- ***Difficulty in the daily life***

Going up a floor / Going down a floor / Crouching / Walking on an even ground

chondral bone deformities;
Stage 4: severe arthritis.

– The study included patients with patellar femoral chondropathy, clinically and radiographically documented at Stage 1, 2 or 3 according to Kellgren-Lawrence.

Patients included in the study did not report any previous knee surgery, nor rheumatic diseases or auto-immune ones, being underway or documented.

– The 20 patients in **Group A** received Nimesulide 100 mg sachet + galactosaminglucoronoglicane sulfate sodium salt 400 mg (Condral®) once a day orally.

– The 20 patients in **Group B** received **MD-KNEE** 1 ampoule + **Zeel® T** 1ampoule applied to the skin of the knee, O_2-propelled.

Patients were treated 1 time / week, after careful disinfection of the skin (alcohol or iodine based antiseptic solution).

The propulsion technique with pure O_2 (98%) was performed with an equipment that concentrates the O_2 from the air environment (zeolite filters) and that – through a compressor – provides O_2 at the pressure of 2.5 atm, using a device placed on the skin (Maya Beauty Engineering, Oxyendodermia Medicale).
– The patient lays in supine position with the affected knee slightly flexed through a popliteal pad; on the area to be treated were applied MD-KNEE + Zeel® T, mixed together with a neutral serum solution.
- Immediately afterward O_2 was delivered at 2.5 atm, for 20 minutes.
• **Group A** (Nimesulide + chondroitin) consists of 15 M and 5 F, average age 46.9 years (min 28, max 65), with Standard Deviation (SD) 11.8; average BMI of 25.4 with SD 2.45.
It was also calculated the average body fat, equal to 20.32% DS 7.04,evaluating the circumference of the neck, abdomen and, in females, hips too.

– The average pre-treatment WOMAC score was **59 points** (34 min, max 80), on a scale from 0 to 96.
- The average algo-dysfunctional Index of Lequesne was **18 points** (12 min, max 22) on a scale from 0 to 24.
The right knee was affected in 15 cases, the left one in 5 cases.

• **Group B** (MD-KNEE + Zeel® T + O_2 propulsion) is also composed of 15 M and 5 F, average age 49.4 years (min 31, max 66) with DS 9.1;average BMI of 24.4 with SD 2.4.
It was also calculated the average body fat, equal to 26.11% with SD 17.8, considering the circumference of the neck, abdomen and, in females, the hips too.
- The average pre-treatment WOMAC score was **58 points** (min. 42, max 89).
- The average algo-dysfunctional Index of Lequesne was **18 points** (min. 12, max 22).
The right knee was affected in 10 cases, the left one in 10 cases.

RESULTS

All patients completed the prearranged treatment. The results are reported according to the Group membership of the patients (A, B); these were recorded during **5** ***follow-ups*** performed at **1**, **2**, **3**, **6**, and **12 weeks** after initial administration.

• After the **first** week: patients belonging to both groups showed a reduction of the total WOMAC score, compared to "basal" score, not statistically significant.
- The average score of the Group A patients was **54** WOMAC points (min 30, max 78), p <0.374.
- The average score of the Group B patients was **50** WOMAC points (min 34, max 74), p <0.087.

• **Second** week: patients of both Groups showed a reduction of the WOMAC total score, compared to the previous score.
- The average score of the Group A patients was **53** WOMAC points (min 30, max 78), p <0.217.
- The average score of the Group B patients was **47** WOMAC points (min 30, max 68), p <0.0047.

• **Third** week: patients of both Groups showed a reduction of the WOMAC total score, compared to the previous score.
- The average score of the Group A patients was **51** WOMAC points (min 30, max 74), p <0.0109.
- The average score of the Group B patients was **44** WOMAC points (min 30, max 66), p <0.0031.

• **Sixth** week: between 3rd and 6th week since the first treatment, there was no change in the WOMAC average score of Group A patients, while the WOMAC average score of Group B patients is statistically significant, marking a decrease in pain, stiffness, and functionality.
- The average score of the Group A patients was **50** WOMAC points (min 32, max 72), p <0.097.
- The average score of the Group B patients was **41** WOMAC points (min 30, max 68), p <0.0004.
The difference is statistically significant (p <0.001).

• **Twelfth** week: the last follow-up showed that the WOMAC average score of the Group A patients is **47** points (32 min, max 70), p <0.014.
- The WOMAC average score of the Group B patients has further decreased to **39** points (min. 24, max 60), p <0.0001.
The difference between the 2 experimental Groups is statistically significant (p <0.001).
As far as the algo-dysfunctional Lequesne Index is concerned, it has increased from **18** to **15 points** among the Group A patients; it has increased from **17** to **10** among the Group B patients (TABB. 8, 9).

CONCLUSIONS

Conservative treatment of patellofemoral chondropathy has a well documented background in the scientific literature of the last fifty years.

The use of NSAIDs, corticosteroids and chondro-protectants is common in conventional medicine.

The mechanism of action of corticosteroids is very clear: inhibition of the synthesis of prostaglandins, decrease of the collagenase activity and reduction of the production of IL-1, TNFα, and various proteases that attack the cartilage.

– NSAIDs and corticosteroids act only on the painful symptoms.

	BASIC WOMAC	WOMAC 1st week	WOMAC 2nd week	WOMAC 3rd week	WOMAC 6th week	WOMAC 12th week
M	36	30	30	30	34	34
	34	30	30	30	32	34
	66	54	54	50	52	48
	34	30	30	32	34	34
	72	68	64	64	66	55
	68	62	62	58	60	54
	68	62	64	62	60	56
	68	62	60	60	60	50
	70	68	60	58	52	48
	68	60	58	50	50	46
	68	60	58	54	50	46
	70	68	60	54	54	46
	66	60	60	58	60	48
	39	34	34	34	32	32
	70	70	68	66	66	64
F	80	78	76	74	72	70
	36	34	34	34	30	32
	34	30	34	34	34	32
	48	44	40	40	42	42
	78	74	70	70	68	66
	58,65	**53,9**	**52,3**	**50,6**	**50,4**	**46,85**
	16,68	**16,74**	**15,29**	**14,29**	**13,80**	**11,69**
	p	**0,374401**	**0,217196**	**0,109516**	**0,096581**	**0,013509**

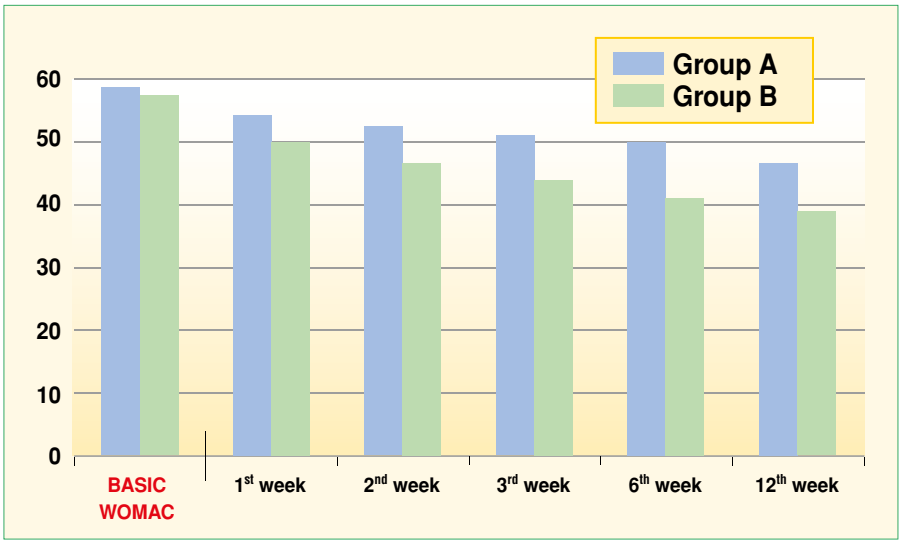
TAB. 5

Group A - Analytical WOMAC (basic evaluation, and at 1st, 2nd, 3rd, 6th and 12th week since the beginning of the therapy).

TAB. 6

Group B - Analytical WOMAC (basic evaluation, and at 1st, 2nd, 3rd, 6th and 12th week since the beginning of the therapy).

	BASIC WOMAC	WOMAC 1st week	WOMAC 2nd week	WOMAC 3rd week	WOMAC 6th week	WOMAC 12th week
M	42	38	38	36	34	28
	46	38	34	30	36	32
	64	60	48	48	52	44
	44	38	38	36	34	36
	89	74	68	66	68	60
	60	60	56	50	44	46
	46	44	44	42	40	40
	42	40	34	34	30	28
	86	72	68	66	64	60
	46	36	30	30	28	24
	46	38	40	42	38	34
	80	74	68	60	54	50
	77	70	60	52	45	38
	76	60	60	58	54	50
	64	49	45	40	34	34
F	49	38	34	30	24	24
	42	34	34	34	30	32
	50	42	42	40	34	34
	68	60	60	58	50	52
	52	34	34	36	34	32
	58	**49,95**	**46,75**	**44,4**	**41,35**	**38,9**
	15,91	**14,63**	**13,17**	**12,03**	**12,14**	**10,98**
	p	**0,086603**	**0,01551837**	**0,00317**	**0,0004773**	**0,00005**



TAB. 7

Progressive differences of average WOMAC in the 2 Groups of patients.

14	12	20	15	22	16	18	16	18	20	18	20	20	14	20	22	14	19	18	22	Average **17,9**	DS 2,99
10	10	15	14	15	11	14	15	18	18	18	15	14	11	18	18	14	18	18	22	Average **15,3**	DS 3,21

TAB. 8

Group A - Lequesne score before and after 12-week treatment.

12	15	19	14	20	18	16	15	20	16	16	20	22	19	18	22	18	14	15	12	Average **17,05**	DS 3,00
9	8	12	10	12	12	11	10	10	11	11	10	12	12	10	12	10	8	8	10	Average **10,4**	DS 1,39

TAB. 9

Group B - Lequesne score before and after 12-week treatment.

The use of chondro-protectants should aim to restore the natural rheological and metabolic homeostasis of the joint affected by arthritis, enhancing the protective effect, lubricating and "shock-absorbing" the synovial fluid.

– Both groups (A, B) showed – in the lapse of the period considered, i.e. 12 weeks – a significant improvement due to a decrease of pain and of limited functionally linked to the gonarthrosic process.

– The data show that the improvement of the clinical-functional situation is **more immediate in patients treated with O_2 (98%) conveyed at 2.5 atm + MD-KNEE + Zeel® T**: the Group B patients have shown a decrease in the average WOMAC score in joint stiffness and function more relevant from a statistical point of view than the score obtained by the Group A patients treated with nimesulide + chondro-protectants.

– The total absence of negative side effects recorded in the Group B patients and the use of a non-invasive, painless and very easy therapy, one treatment only per week) has allowed better acceptance and an expenditure definitely more advantageous. ■

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ORIGINALIA

SUMMARY

– Introduction: The administration by injection of hyaluronic acid (HA) for 3-5 weeks is effective in the treatment of patients with knee osteoarthritis (OA). Other products for intra-articular use have been recently introduced for the treatment of OA. Among these, a medical device, MD-Knee, produced by Guna S.p.A.; this study aims to estimate the cost-minimization of MD-Knee versus HA in the treatment of knee osteoarthritis.

– Methods and Results: We performed a cost-minimization analysis (CMA). The CMA was conducted from the perspective of the Italian National Health Service (NHS). Only direct medical costs (MD-Knee and HA) were considered. We performed a sensitivity analysis to test the robustness of the results. The mean 6-month cost per patient was € 75,00 with MD-Knee and € 185,00 with HA.

– Conclusion: From the Italian National Health Service's perspective, MD-Knee appears to be the cost-saving therapeutic option compared with HA in the treatment of patients with knee osteoarthritis.

KEY WORDS **COST, HYALURONIC ACID, ITALIAN NHS, MD-KNEE, SUPARTZ®**

A COST-MINIMISATION ANALYSIS OF MD-KNEE VERSUS HYALURONIC ACID IN THE TREATMENT OF PATIENTS WITH KNEE OSTEOARTHRITIS

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– ORIGINAL RESEARCH ARTICLE

INTRODUCTION

Osteoarthritis **(OA)** is a chronic degenerative disease of the joints that typically causes progressive damage to the articular cartilage and underlying bone (1).
It is one of the most common chronic diseases, with a prevalence of 11% and 24% in the adult population for the hip and knee OA, respectively (1).
It was estimated that approximately 303 million people worldwide were affected by OA in 2017 (2).
OA, which is more prevalent in the elderly population, is the most common cause of disability, including limitation of daily activities, and particularly pain (1). The pain is exacerbated by movement and decreases on resting, but as the disease advances, it can also occur when at rest.
The burden of disease associated with musculoskeletal diseases is continually increasing, becoming the second leading cause of disability in 2015 (years lived with disability, YLDs) (3).
Various studies have also investigated the existence of a possible relationship between OA of the knee and premature mortality.
These have identified an indicator of unfavourable results due to the limitations caused by musculoskeletal disease on the daily activities and physical functionality of the patients affected (4-8).
The FDA define the term "serious" as a disease or condition associated with morbidity that has substantial negative

impact on the day-to-day functioning of the individual (9).
OA shows all the characteristics of a serious condition. It restricts the essential daily activities of the person (walking, eating, communicating or taking care of themselves or other family members), causes premature ageing due to the loss of functionality within society, and increases the risk of mortality compared with the general population (9).
Since the life expectancy of the general population is continually increasing, the number of people with OA is also expected to grow.

– For the purpose of relieving pain and achieving an optimal clinical condition for the management of OA, International Guidelines recommend a therapeutic strategy that includes: **1)** non-pharmacological treatment (physiotherapy and rehabilitation), **2)** pharmacological treatment (non-steroidal anti-inflammatory drugs, analgesics, chondroprotective agents and intra-articular treatments), and **3)** surgical treatment (advanced stages of the disease) (10-15).

Much emphasis has been placed on non-pharmacological management over the past decade (1).
However, perhaps because the associated recommendations have not been sufficiently clear in terms of the timing, intensity, frequency, duration and implementation of procedures, various studies have shown that the non-pharmacological management of OA has not always led to optimal care results (16,17).
Although scientific evidence suggests low efficacy, paracetamol is widely recommended for the analgesic treatment of OA in the initial stages.
However, because this is associated with adverse events affecting the gastrointestinal system, cardiovascular system, liver and kidneys in the general population (especially in patients taking high dosages), its use must be carefully evaluated (18).

Among the pharmacological options, hyaluronic acid administered by infiltration plays a major role because it enables pain control and improves joint mobility, especially that of the knee (19). Double-blind controlled clinical studies have demonstrated its superior efficacy when compared with saline solution, arthrocentesis and NSAID treatments, along with an excellent tolerability profile (20,21). Hyaluronic acid has a well-known mechanism of action.
As well as safeguarding the viscoelastic properties of the synovial fluid, it plays an important part in maintaining the structural and functional characteristics of the articular cartilage (20,21).
Viscosupplementation is a procedure that involves the intra-articular infiltration of hyaluronic acid. Among the hyaluronic acid products currently available, **SUPARTZ®** is the most extensively analysed in clinical studies and the most widely used in practice (22).

– Since 2010, the treatment of painful and degenerative diseases of the musculoskeletal system has included an innovative therapeutic approach involving injectable medical devices (MD) based on porcine collagen.
Among those that are currently on the market is **MD-Knee** (Guna S.p.A.), a medical device available in vials of injectable solution based on porcine collagen. Porcine collagen is a good choice because of its biochemical similarity and the fact that porcine tissues have a very high average collagen content (19).
The reason for introducing collagen locally is structural, since the mechanical support provided by collagen constitutes an effective natural support scaffold (bio-scaffold).
This is because collagen replaces, strengthens and protects the cartilage, tendons, ligaments and joint capsules (23-26).

OBJECTIVE

The purpose of this economic assessment is to compare the benefits and costs of treatment associated with MD-Knee and SUPARTZ® in the treatment of knee OA in a hospital setting.

MATERIALS AND METHODS

Premise

The first phase of this economic assessment was based on a literature review carried out by consulting the PubMed database, to determine whether there were any clinical studies that had directly compared the two pharmacological treatment options (head-to-head).
There was only one study that satisfied this requirement (22). Its main features are summarised in the section on "clinical data".

Clinical data

The clinical study (randomised, double blind, prospective and multicentre), conducted in Italy by Martin-Martin *et* Al. assessed the non-inferiority of MD-Knee versus hyaluronic acid (SUPARTZ®) in the treatment of patients with knee OA.

– Enrolment onto the study began in March 2013 and ended in September 2013. Only patients with symptomatic OA of the knee were considered (please refer to the publication for specific inclusion and exclusion criteria). A total of 64 patients were enrolled, 32 of whom were treated with MD-Knee and 32 with SUPARTZ®. The study involved a total of 3 consultations per patient, one at the time of enrolment and a further two at 3 months and 6 months after enrolment.
The dosage regimen adopted for the two options was as follows: for MD-Knee, intra-articular injection of 4 ml collagen (two 2 ml-vials) once a week for 5 consecutive weeks; for SUPARTZ®, intra-articular injection of 2.5 ml hyaluronic acid once a week for 5 consecutive weeks.
The primary endpoint of the study was the Lequesne index of severity for osteoarthritis of the knee (ISK), while the Visual Analogue Scale (VAS) and the SF-36 questionnaire were the secondary endpoints (27). The ISK assessed the

severity of the knee OA, while the VAS and the SF-36 questionnaire assessed, respectively, variations in the pain and physical-mental state of the patients treated.
The main demographic features of the two treatment groups proved well balanced on enrolment and are described in TAB. 1.
At the time of the 3 and 6 month follow-ups, the ISK and VAS values highlighted a significant improvement in both groups compared with those measured during enrolment, with no statistically significant differences observed.
Furthermore, there was no statistically significant difference in the scores on the SF-36 questionnaire.
The results show that both pharmacological options are equally effective in relieving the symptoms of knee OA as measured 6 months after the start of treatment.

Parameters	MD-Knee (n. = 32)	SUPARTZ® (n. = 32)
Age (years ± SD)	69.41 ± 8.42	69.97 ± 9.5
Females, n. (%)	25 (86.2%)	20 (64.5%)
BMI (Kg/m²)	27.2 ± 3.78	27.3 ± 3.56
Kellgren and Lawrence grade II, n. (%)	15 (51%)	17 (55%)
Kellgren and Lawrence grade III, n. (%)	14 (44%)	14 (44%)
ISK± SD	12.45 ± 2.63	12.6 ± 3.48
SF-36 ± SD	91.41 ± 20.01	93.07 ± 17.3
VAS ± SD	7.67 ± 1.41	7.42 ± 1.35

TAB. 1

Main demographic characteristics at enrolment (22).

Assessment technique

Given that the clinical study (22) showed no differences in efficacy, it was considered appropriate to compare MD-Knee and SUPARTZ® through a **cost-minimisation analysis (CMA)**, thus placing the emphasis on the drug costs only.

Timeframe

In accordance with the observation period of the reference clinical study (22), an analysis time period of 6 months, or 26 weeks, was adopted.

Analysis perspective

Since the two drugs are not currently reimbursed by the Italian National Health System, and the respective administrations tend to be carried out in a hospital setting (outpatient department or day hospital), the analysis perspective adopted here is that of the hospital, on the assumption that the same facility will be responsible for the purchase.

Consumption of resources and unit costs

The consumption of the two treatment regimens was calculated by multiplying the dosages indicated in the clinical study (22) by the corresponding market prices (retail price). A retail price of **€ 75.00** for a pack of ten 2 ml-vials of **MD-Knee** and a retail price of **€ 185.00** for a pack of five 2.5 ml pieces of **SUPARTZ®** were taken into account.

In accordance with the objective of the study (to estimate the incremental costs between the two therapies) and with the economic assessment technique adopted (CMA), no cost associated with administration was considered, insofar as it was assumed to be the same in both cases (weekly administration for 5 consecutive weeks).

Since no significant differences in terms of tolerability had been identified in the reference clinical study (22), no costs for the management of adverse events relating to the treatment administered were taken into account.

Sensitivity analysis

As stated in the Guidelines drawn up by the AIES group (Associazione Italiana di Economia Sanitaria) [Italian Association of Health Economics] (28), the sensitivity analysis should involve detailed analysis of the uncertainty of the result of the base case (or reference case, CDR).

In this assessment, the uncertainty analysis was carried out exclusively with reference to the purchase prices of the two pharmacological options. In this regard, to estimate the uncertainty relating to this variable, a threshold analysis was conducted in order to estimate the reductions in purchase price for which the two options would be cost-neutral.

RESULTS

Cost minimisation analysis

TAB. 2 shows the CMA results illustrating the average treatment costs for the two therapeutic alternatives.
– It is clear that, in view of the lower cost per single administration (**€ 15.00** vs **€ 37.00**), the patient treated with MD-Knee is associated with a lower average cost of treatment (**€ 75.00** vs **€ 185.00**), resulting in a saving of **€ 110.00** over the entire treatment cycle.

Sensitivity analysis

The threshold analysis conducted to estimate the uncertainty associated with the retail price shows how, if the price of MD-Knee is kept constant (base case), then only if there were a signifi-

TAB. 2

Results of the cost minimisation analysis.

Parameters	A	B
	MD-Knee	SUPARTZ®
Dose per administration	4 ml	2.5 ml
Cost per administration	€ 15.00	€ 37.00
Total No. administrations	5	5
Average cost of treatment	€ 75.00	€ 185.00
Difference (A-B)	**-€ 110.00**	

cant reduction in the price of SUPARTZ® **(-59.5%)** would the two therapeutic alternatives be cost-neutral, i.e. they would add up to the same average cost per patient treated (FIG. 1).

DISCUSSION

OA is a clinical condition that features in a large section of the population, especially the elderly. The constant and continuous ageing of the population due to the increase in life expectancy suggests that, in the near future, the number of patients affected by this disease will rise, and of these, approximately one quarter will suffer from knee osteoarthritis.

– As highlighted in other studies published in the literature, the adoption of a non-pharmacological strategy does not always prove an effective measure in countering OA (16,17).
For this reason, the identification of a pharmacological option that provides a satisfactory clinical response and, at the same time, delays or prevents surgical intervention, is becoming fundamental to addressing the problems associated with OA.
Among the pharmacological treatments, the administration of hyaluronic acid has proved to be more effective than using nonsteroidal anti-inflammatory drugs or analgesia (20,21).
The subsequent arrival on the market of injectable medical devices based on porcine collagen constituted an equally effective option in the management of knee OA, as also shown by the direct comparison study conducted in Italy by Martin-Martin *et al.* (22).

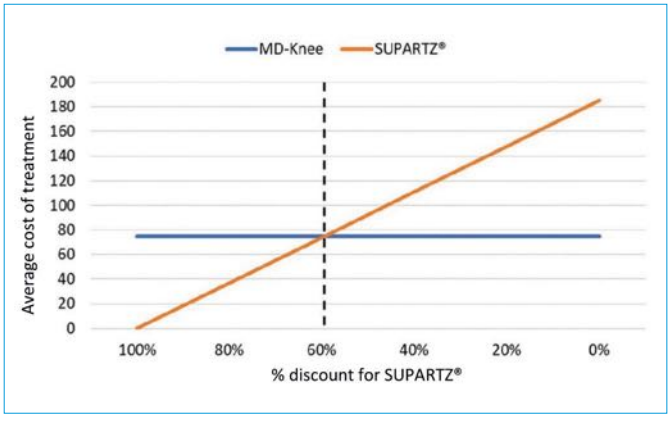
For the same effectiveness (22), the cost of treatment might be a subsequent driver of therapeutic choice, especially if considered within a broader discussion on the sustainability of healthcare spending.

In the light of the above, the intention here was to conduct a cost minimisation analysis aimed at comparing the cost associated with MD-Knee, an injectable Medical Device based on porcine collagen, with SUPARTZ®, a solution based on hyaluronic acid, over a **six-month period**.
Since neither of the drugs is reimbursed by the SSN, the hospital environment was adopted as the analytical setting, assuming that the same facility would be responsible for purchasing the drugs.
The result of the minimisation analysis showed a reduction in the average treatment cost for MD-Knee **(€ 75.00)** of **€ 110.00**, compared with SUPARTZ® **(€ 185.00)**.
Since the respective retail prices were considered, in order to take into account any discounts granted to hospitals in the event of bulk purchases of the drug, a threshold analysis was carried out to verify the price reduction for SUPARTZ® at which, if the MD-Knee were kept constant, the two alternatives would be cost-neutral.
As things stand, a reduction in the price of SUPARTZ® of almost **60%** would be required to make the average treatment cost the same for both alternatives.
It has not been done here, but it would be interesting to conduct a brief investigation to determine the average prices actually charged to hospitals for the purchase of the two drugs.
The result in favour of MD-Knee, expressed in terms of the lower average cost of treatment, could also be extended to include an analysis carried out from the point of view of the patient, thereby assuming that the patients themselves would be responsible for the drug purchase rather than the hospital.
In this case, we would be dealing with a lower impact on the social cost of knee OA.

This analysis must be read in light the of some observations.
To begin with, the comparison was carried out over a time period of just six months, as opposed to the probably longer follow-up period required for the management of knee OA.
The economic comparison actually reflects the observation timeframe adopted by the reference clinical study (22), and it was therefore considered more correct not to extrapolate the results of this to a longer time period.

FIG. 1

Threshold analysis.



A second observation concerns the fact that, in the economic assessment between the hyaluronic acid products available, only SUPARTZ® was considered.

There were two reasons for this choice: the first is that SUPARTZ® is widely used in clinical practice, with proven efficacy in previous studies, and the second is that, in the literature, there are no direct comparisons of MD-knee in relation to other types of hyaluronic acid (e.g., cross-linked, high molecular weight), which means that we cannot draw definitive conclusions on the efficacy of the MD-Knee medical device in relation to the latter.

CONCLUSIONS

Based on the results found here, it is believed that, in terms of managing knee osteoarthritis, MD-Knee constitutes a more efficient option than a medium molecular weight hyaluronic acid product such as SUPARTZ® for hospitals (or patients) since, with the same toxicity and efficacy, it leads to a lower average cost of treatment over a 6-month time period.

Disclosures

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Ultrasound-guided collagen injections for treatment of plantar fasciopathy in runners: A pilot study and case series

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ABSTRACT

Background. Plantar fasciopathy is a frequent source of foot pain in athletes, and it is caused by the degeneration of the proximal insertion of the plantar fascia, usually triggered by repetitive microtrauma. Type I porcine collagen was shown to enhance tendon repair in vitro, and collagen injections are currently used to treat different tendinopathies. The aim of this study is to verify the effectiveness of collagen injections on pain and function in runners with plantar fasciopathy. Methods. Runners, who have been suffering from plantar fasciopathy for at least 6 months, were treated with a series of 4 ultrasound-guided type I porcine collagen injections, at weekly intervals. The Visual Analogue Scale, American Orthopedic Foot and Ankle Society-Ankle Hindfoot score and pressure algometry were used to verify the effects of collagen injections at 1-month and 3-month follow-up. Results. Compared to baseline, minor ($p \geq .05$) and major ($p \leq .001$) improvements on pain and function were registered at 1-month and 3-month follow-up, respectively. Conclusion. This is the first study that evaluates the effectiveness of collagen injections in the treatment of plantar fasciopathy in runners. Despite the limitations of this study, the positive findings could represent the starting point for further clinical trials.

Keywords: Plantar fasciitis; Plantar fasciopathy; Chronic plantar fasciitis; Athletes; Runners; Collagen injections.

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INTRODUCTION

Plantar fasciopathy (PF) is a musculoskeletal condition that affects the plantar fascia, which is a thick band made by connective tissue that runs from the calcaneal tuberosity forward to the heads of the metatarsal bones, helping to maintain the stability and the arch of the foot (Hormozi et al., 2011; Petraglia et al., 2017). The plantar fascia is divided into three cords, with the central one being the thickest and the most often injured (Meyer et al., 2018). PF was formerly known as "plantar fasciitis", but this term is obsolete, since inflammation is absent in this condition. Nowadays PF is considered a degenerative pathology, more similar to tendinopathy and to a chronic disease, which involves the site of the attachment of the plantar fascia at the medial tubercle of the calcaneus (Petraglia et al., 2017).

PF is a common cause of foot pain in adults, usually a plantar-medial heel pain, typically after a long weight-bearing phase, and it usually worsens the patients' quality of life (Alrashidi et al., 2016; Irving et al., 2008). It has been reported that 10% of people may suffer from symptoms of PF during their lifetime (Monteagudo et al., 2018; Riddle et al., 2003). PF affects both sexes, ranging from sedentary individuals to athletes, with women being affected slightly more often than men (Orchard, 2012; Taunton et al., 2002). The peak incidence of PF occurs in people aged between 45 and 65 years (Riddle and Schappert, 2004). PF is experienced in both recreational and elite athletes and is reported in different sports (Orchard, 2012). A recent review concerning ankle and foot injuries in sport pointed out that PF is mainly reported in runners (Sobhani et al., 2013). The incidence of PF in runners ranges from 4.5 to 10%, and represents the third most frequently experience running-related musculoskeletal injuries (Lopes et al., 2012). A recent prospective study analysed the novice running-related injuries, revealing that PF accounts for about 5% (Nielsen et al., 2014). In ultra-marathon runners PF has an incidence of about 11% (Hoffman and Krishnan, 2014). In runners, PF seems to be associated with overuse, training errors, and improper or excessively worn footwear (Rompe, 2009).

Diagnosis of PF is essentially clinical (Oliva et al., 2017). The cardinal symptom of PF is the intense and acute heel pain localized primarily where plantar fascia attaches to the anterior calcaneus (Petraglia et al., 2017). A runner typically reports a sensation of pain over the plantar aspect of the foot, typically worse with initial morning ambulation and improved during the course of a run, with worsening pain after discontinuation of activity (Tenforde et al., 2016). Foot stiffness and heel swelling are also present (Goff and Crawford, 2011). The Windlass test can be performed to confirm the diagnosis, although it has a low sensitivity (De Garceau et al., 2003).

In the case of uncertain diagnosis or when patient presents a persistent heel pain, instrumental analysis can be performed (Petraglia et al., 2017). Diagnostic imaging is recommended when patient suffers of persistent heel pain after 4-6 months of conservative approaches or in case of atypical symptoms or signs (Neufeld and Cerrato, 2008). Plain radiography, magnetic resonance imaging (MRI), diagnostic ultrasonography (US), nerve conduction study and bone scans can be carried out for differential diagnosis (Petraglia et al., 2017). US is a very useful, non-invasive, well-tolerated and reliable tool to confirm the diagnosis (Alrashidi et al., 2016; Lim et al., 2016). It can be used for follow-up and monitoring the improvement after initiation of therapy (Alrashidi et al., 2016). US features of PF include a thickened (> 4 mm) and hypoechoic aponeurosis close to its calcaneal attachment (Elias et al., 2013). Shear wave elastography (SWE) allows quantitative assessment of the stiffness of the plantar fascia and can highlights the classic alterations of PF (Corrado et al., 2019; Schillizzi et al., 2020; Vola et al., 2018). Contrary to popular belief, recent studies have demonstrated no correlation between fascial thickness and degree of symptoms (Meyer et al., 2018).

The crucial aims of PF management are the reduction of pain, the improvement of quality of life, including both the return to daily physical activity and physical fitness (; (Petraglia et al., 2017). Around 90% of patients with PF will find that their symptoms resolve within 12 months with conservative treatment (Crawford and Thomson, 2003), but about one tenth of cases may fail to respond to it. The first level of treatment would include the use of non-steroidal anti-inflammatory drugs (NASAIDs), specific physical exercises (such as stretching of the plantar fascia), foot insoles, night splints, ice massage, and patient's instructions to lose weight, activity modifications, and not to use flat shoes or walk barefoot (Akınoğlu and Köse, 2018; Celik et al., 2016; Cinar et al., 2018; Huffer et al., 2017; Lim et al., 2016, 2016; Montesano et al., 2020; Oliva et al., 2017; Palermi et al., 2020; Sirico et al., 2018). Other treatment options are local injections of corticosteroids (CSs) (Gurcay et al., 2017), anaesthetic, and botulinum toxin (Ahmad et al., 2017); extracorporeal shock wave therapy (Corrado et al., 2019; Hsu et al., 2018; Reilly et al., 2018); ultrasound scanning; radiofrequency ablation (Akınoğlu and Köse, 2018; Ozan et al., 2017); cryopreserved human amniotic membrane injections (Hanselman et al., 2015); prolotherapy (Kim and Lee, 2014; Ryan et al., 2009); ozone injections (Bahrami et al., 2019); hyaluronic acid injections (Kumai et al., 2018); platelet-rich plasma injections (PRP) (Chen et al., 2019; Franceschi et al., 2014; Singh et al., 2017; Sirico et al., 2017; Soraganvi et al., 2019); and surgical, such as endoscopic release (Al-Ashhab et al., 2018; Bernhard et al., 2018; Oliva et al., 2017). However, as yet, there is no consensus regarding the optimal treatment method (Corrado et al., 2019, Eftekharsadat et al., 2016; Kiter et al., 2006; Say et al., 2014).

To our knowledge, only one study by Kim et al. (Kim et al., 2016) explored the effects of collagen injections for PF after unsuccessful conservative treatment with NSAIDs, night splints, and stretching exercises for at least 3 months, reporting an increased tissue elasticity after treatment. Given the degenerative nature of PF, that encompasses collagen degeneration, the rationale behind the use of collagen injections is that collagen is a major extracellular matrix component in tendons and ligaments, and it contributes to the entrapment, local storage, and delivery of growth factors and cytokines. Collagen also plays an important role in organ development, wound healing, and tissue repair (Hay, 1981). Injectable collagen is used to treat different tendinopathies (Corrado et al., 2020; Corrado et al., 2019), because of its ability to stimulate synthesis, maturation and secretion of endogenous type I collagen (Randelli et al., 2018).

The aims of this prospective pilot study and case series are: (a) to evaluate the effectiveness of US-guided collagen injections in the treatment of PF in a group of runners, and (b) to examine the feasibility of such an intervention that is intended to be used in a larger scale and higher quality studies.

No studies on the effectiveness of collagen injections in treating PF in runners have been published to date.

MATERIALS AND METHODS

This is a prospective observational pilot study carried out at the Federico II University Hospital of Naples, Italy. The subjects of our study were all outpatients, enrolled from September 2019 to November 2019. The patients were non-professional marathon runners who have been suffering from PF for at least 6 months. All patients underwent US and X-ray before the enrolment.

The inclusion criteria were: age > 18 years, pain over the plantar aspect of the foot (typically worse with initial morning ambulation and improved while running), sharp pain elicited by palpation of the medial plantar calcaneal region, a positive Windlass test, US evidence of increased plantar fascia thickness, and lack of therapy in the last 6 months.

The exclusion criteria were: previous foot and ankle surgery, inflammatory arthritis, X-ray evidence of heel spur, and previous fractures, bone tumours or osteonecrosis of the ankle and foot.

After a full and clear description of the study protocol, all the enrolled patients were invited to sign the informed consent. The study was carried out in accordance with the principles of the Declaration of Helsinki and met the ethical standards of the local ethics committee.

Ten patients were enrolled (7 males and 3 females), with an average age of 34 ± 8 years. Regarding the treatment, four US-guided injections of 2 ml porcine type I collagen were planned once a week. All injections were performed by a single physician with over ten years of experience. There is strong evidence that the accuracy of US guidance is greater than that of palpation guidance (Hall, 2013). Injections were performed with the patients lying face down on the examination table. A 22-gauge needle was inserted with a medial approach under US guidance, aligned to the long axis of the US transducer. The needle was directed anteriorly to the insertion of the plantar fascia on the calcaneal bone, in the region of the maximal thickness of the fascia. When the tip of the needle was seen in the correct position, then collagen was slowly injected.

Patients were invited to not rest after each injection, but only to avoid foot and ankle overloading for 24 hours. Patients were advised to interrupt their sporting activities during the treatment and until the last follow-up. No other treatment was associated with collagen injections.

Patients were evaluated at the time of enrolment (T0), one month (T1) and three months (T2) after the last injection. Pain was assessed using the 10 cm-Visual Analogue Scale (VAS) and the pressure algometry. Assessment of function was conducted using the Italian version of the American Orthopedic Foot and Ankle Society – Ankle-Hindfoot (AOFAS-AH) score.

Pressure algometry is a semiquantitative method used to evaluate the pain threshold in tissues. The pressure algometry has been validated to determine pain threshold (Walton et al., 2011; Ylinen et al., 2007), and it has been found repeatable and stable (Frank et al., 2013). The pressure algometer used in this study was a Force Dial™ FDK 20 (Wagner Instruments, Greenwich USA). The pressure was measured in kilogram per square centimetre (Kg/cm^2). The measurement was conducted on the most sensitive point of the plantar fascia. The algometer contact head was aligned perpendicularly to the skin and the pressure gradually increased until the patient reported pain (i.e. pain tolerance). This process was repeated three times at the same point on the plantar fascia, then an average of the three readings was recorded. Higher algometer scores indicated greater pressure threshold and less tenderness, and vice versa.

The AOFAS-AH score comprises nine questions and covers three categories: pain (40 points), function (50 points) and alignment (10 points), for a total of 100 points. Although it has yet to be validated, the AOFAS-AH is one of the most widely-used score in clinical studies concerning ankle and foot, and it remains in use at a substantially higher rate than other scales that have been validated (Leigheb et al., 2016).

Results were calculated as mean and standard deviation. Statistical significance was analysed by one-way nonparametric ANOVA (Kruskal Wallis test). The confidence interval was established at 95% ($p < .05$). Statistical analysis was performed using IBM SPSS version 20 for Windows.

RESULTS

Means and standard deviations of VAS, pressure algometry, and AOFAS-AH are listed in Table 1.

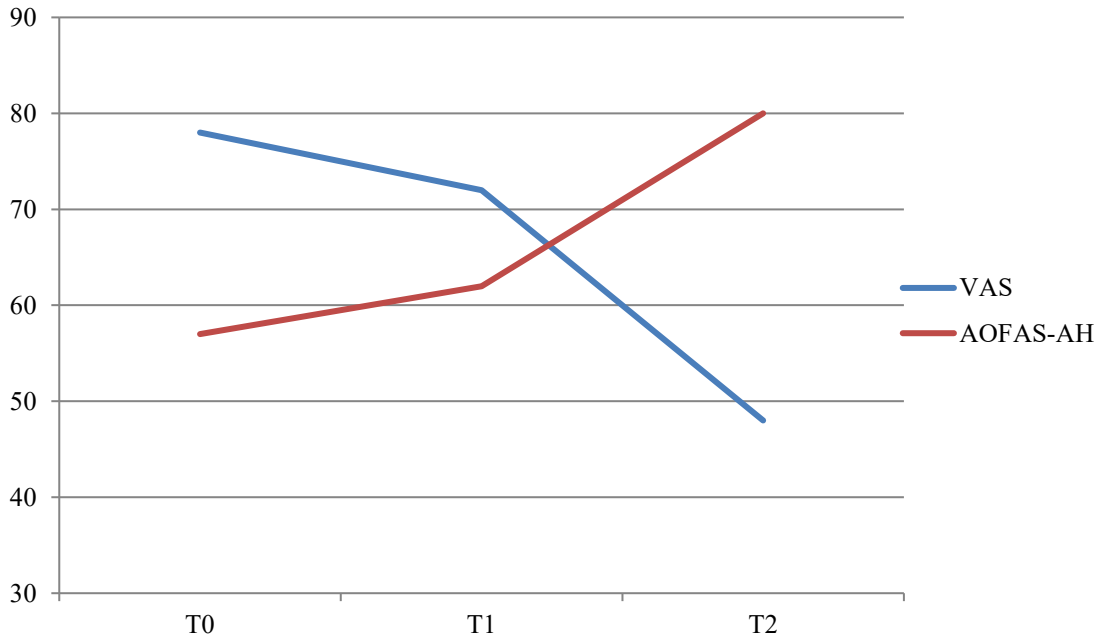
Table 1. Means and standard deviations of VAS, pressure algometry, and AOFAS-AH at different follow-up times.

Outcome measures	T0	T1	T2
VAS 0-10	7.8 ± 0.79	7.2 ± 0.63 Δ = 7.7% p = .98	4.8 ± 0.79 Δ = 38.5% p < .001
Pressure algometry kg/cm^2	4.45 ± 0.29	4.65 ± 0.26 Δ = 4.5% p = .11	5.2 ± 0.2 Δ = 16.9% p < .001
AOFAS-AH 0-100	57.4 ± 4.09	62.3 ± 3.74 Δ = 8.5% p = .19	80.8 ± 3.26 Δ = 40.8% p < .001

Note: VAS = Visual Analogue Scale; AOFAS-HF = American Orthopedic Foot Ankle Society – Hind Foot; Δ = relative delta.

At the baseline, mean scores of VAS, pressure algometry, and AOFAS-AH were 7.8, 4.45 Kg/cm^2, and 57.4, respectively.

At 1-month follow up, evaluation of VAS and pressure algometry showed a not statistically significant improvement in pain relief (mean VAS score = 7.2; mean algometry score = 4.65 Kg/cm^2). Regarding the improvement of function, the average AOFAS-AH at T1 was 63.3, and even in this case the difference was not statistically significant (p = .19).



Note: VAS = Visual Analogue Scale; AOFAS-HF = American Orthopedic Foot Ankle Society – Hind Foot.

Figure 1. Trends of VAS and AOFAS-AH over time.

At 3-month follow up, improvement in pain and function became greater and statistically significant. The average scores of VAS, pressure algometry, and AOFAS-AH were 4.8, 5.2 Kg/cm^2, and 80.8, respectively ($p < .001$). Trends of VAS and AOFAS-AH over time are shown in Figure 1.

No adverse event was reported after collagen injections, except for some cases of burning sensation at the injection site which resolved spontaneously in a few hours.

DISCUSSION

PF is a common cause of heel pain and foot impairment in both élite and recreational athletes. Different approaches are available for the treatment of PF, either conservative and surgical. Approximately 90% of patients with PF can be successfully treated without surgery (Monteagudo et al., 2018).

Injections are one of the several conservative interventions used to treat PF, with CSs and PRP being the most commonly administered drugs.

Several studies showed that CSs injections provide pain relief in the short term, but they do not provide a long-lasting effect (no more than one month) and could carry some risk of complications such as plantar fascia rupture and plantar fat pad atrophy (David et al., 2017; Tatli and Kapasi, 2009).

PRP injections seem to be a safer modality when compared to CSs injections, and it was suggested that PRP affects collagen catabolism and irregular vascularization in chronic PF (Monto, 2013). A recent systematic review pointed out that PRP injections were associated with improved pain and function at 3-month follow-up (Singh et al., 2017). However, adverse event rates and costs of PRP injections for the treatment of PF have not been properly analysed.

To our knowledge, in the current scientific literature only one study by Kim et al. reported the outcomes of collagen injections for treating PF, but not in athletes (Kim et al., 2016). Kim and colleagues evaluated the effectiveness of a series of three collagen injections in the treatment of PF using US elastography. Patients showed significantly increased strain ratios in their calcaneal insertions after collagen injections, proving the regenerative effect of such a therapy (Kim et al., 2016).

In our pilot study, we wanted to evaluate the effectiveness of collagen injection therapy in a group of ten runners affected by chronic PF (four injections of type I porcine collagen, once a week).

A direct comparison of results is possible only with the study by Kim et al., even if the assessment tool is a little bit different. In the study by Kim et al., the pain relief was assessed using the 100 mm-VAS three months after the last collagen injection (Kim et al., 2016). The mean 100 mm-VAS scores were, before and after treatment, respectively 71.8 and 43.9. A 38.9% reduction of the pain score was registered. In our study, the mean VAS scores were 7.8 and 4.8 at T0 and T2 (3-month follow-up), respectively. We observed a 38.5% reduction of the pain after treatment. Therefore, the results between our study and the one by Kim and colleagues are totally comparable (M. Kim et al., 2016).

Our results can be also compared with those of different injectable therapies frequently used for the management of PF.

Jain et al. aimed to compare the efficacy of PRP to traditional CS injection in the treatment of chronic PF at three, six and twelve months after injection (Jain et al., 2015). Patients were assessed using the 10 cm-VAS for pain and the AOFAS-AH score for function.

The CSs group had a pre-treatment average score of 8.27 and 56.70 for VAS and AOFAS-AH respectively, while the PRP group had a pre-treatment average score of 8.30 e 58.63 for VAS and AOFAS-AH respectively. At three months post-treatment, the VAS and AOFAS-AH average scores improved, respectively, to 2.83 and 86.37 as regards to the CS group, and improved, respectively, to 3.50 and 83.70 as regards to the PRP group.

Comparing our results with those achieved by Jain et al., we can state that collagen injections at 3-month follow-up reach the same pain relief and function restoration similar to those of PRP injections (Jain et al., 2015).

Mahindra et al. compared the effects of PRP and CSs injections in the treatment of chronic PF. Patients were assessed using the 10 cm-VAS for pain and the AOFAS-AH score before injection, at three weeks, and at 3-month follow-up (Mahindra et al., 2016).

Mean VAS score in the PRP and CSs groups decreased, respectively, from 7.44 and 7.72 at the pre-injection time to 3.76 and 2.84 at 3-week follow-up and, respectively, to 2.52 and 3.64 at 3-month final follow-up. Mean AOFAS-AH score in the PRP and CSs groups improved, respectively, from 51.56 and 55.72 at the pre-injection time to 83.92 and 86.6 at 3-week follow-up and, respectively, to 88.24 and 81.32 at the final 3-month follow-up. The authors concluded that PRP injection is as effective or more effective than CSs injection in treating chronic PF.

In comparison to our findings, we can state that CSs are slightly more effective for pain relief and functional improvement in the short term compared to PRP and much more effective compared to collagen but, at an intermediate term, PRP and collagen are more effective than CSs, especially regarding the disability reduction.

Summarizing, CSs injection resulted in short-term benefit (no more than 1 month) with an associated increased risk of rupture of the plantar fascia and fat pad atrophy especially if frequently repeated, whereas PRP injections were associated with improved pain and function at 3-month follow-up even if no clear information regarding adverse event rates or costs have been provided until now.

In our pilot study, adverse events were not observed neither during nor after the treatment, and the cost-benefit ratio was judged positive by the enrolled patients.

The preliminary findings of our study let us suppose that collagen injections are useful for treating PF. Since collagen is a structural protein of the plantar fascia, injectable collagen works not just healing, but also restoring the tissue's native function. Endogenous collagen synthesis, maturation, and secretion are also stimulated by injectable collagen, thus favouring plantar fascia repair. The effectiveness at the intermediate term and the lack of side effects could be explained on the basis of the above-mentioned reasons.

The present study has some limitations: (a) a small sample, (b) the lack of a control group, and (c) the short follow-up time. However, it should be highlighted that this is a pilot study and that is, to our knowledge, the only study on the effectiveness of collagen injection therapy for PF in athletes.

In conclusion, our pilot study pointed out that a series of four type I porcine collagen US-guided injections, at weekly intervals, is able to reduce significantly pain symptoms and to improve function in a group of 10 runners with PF at 3-month follow-up.

Higher quality studies with a greater number of patients are needed to confirm our preliminary studies and draw more definitive conclusions on the role of collagen injections in the management of PF.

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CLINICAL

M. Ottaviani

TREATMENT OF JOINT CONDITIONS WITH GUNA COLLAGEN MEDICAL DEVICES

– CLINICAL STUDY ON 257 PATIENTS

SUMMARY

Collagen is the main extracellular structural protein to be found in the connective tissue and bone tissue of most animals. In humans aged about 50 years its synthesis begins to reduce, with consequent cartilage and tendon degeneration and inevitable development of osteoarthritis and tendonitis. Since these degenerative conditions are very common and evolve towards pain and joint stiffness, there is an urgent need for tools that allow practitioners not only to limit this degenerative evolution, but also, in certain cases, to induce its regression.

This clinical study was conducted on 257 patients with joint and tendon disorders (impingement syndrome, shoulder tendinopathy, hip arthritis, knee arthritis, trapeziometacarpal osteoarthritis, Achilles' tendinopathy) frequently reflected in clinical evidence, such as pain and joint stiffness; they were all treated exclusively with local injections of Guna Collagen Medical Devices.

The data were collected through self-assessment scales, validated by the WHO and the results showed that Guna Collagen MD can give a useful contribution to containing the problems associated with joint degeneration.

PAROLE CHIAVE

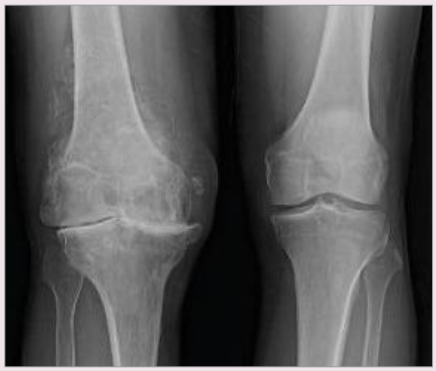
GUNA COLLAGEN MEDICAL DEVICES, COLLAGEN, OSTEOARTRHITIS, TENDINOPATHY, PAIN

INTRODUCTION

Collagen is a glycoprotein characterised by a structure in which a simple **basic module** is repeated: collagen molecules join together to form a collagen fibril; a union in which each molecule overlaps with that above by one quarter of its length.

This creates a kind of *wall*, in which the individual bricks that make it up are staggered in order to achieve considerable resistance to both incident tangential and perpendicular forces (FIG. 1).

– This characteristic arrangement gives the collagen significant sturdiness in terms of **resistance**, **extensibility** and **incompressibility**, whilst guaranteeing **plasticity**, **flexibility**, allowing **torsion**



http://www.georgeackermanmd.com/knee-osteoarthritis.html

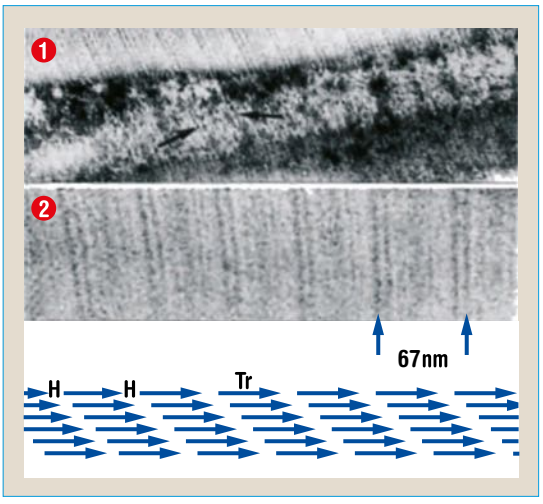
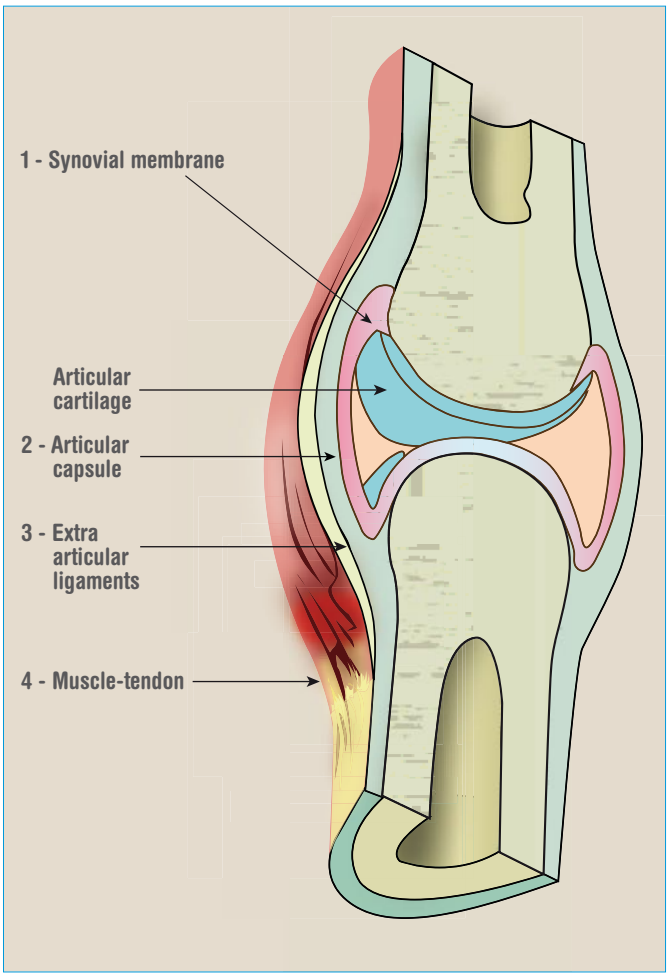


FIG. 1

Structure of collagen.
1: Sugars bound to collagen. Relationship between sugar (black precipitations) **and the density of collagen fibrils** (ME 112.000X)**;**
2: Section of a collagen fibril (ME 240.000X)**.**
A cycle of 67 nm (670 A) **forms on the base of collagen molecules, each of which is staggered by ¼ of their length.**

FIG. 2
Extra-articular containment system.



and **great resistance** to load.
In order to be functional, almost all joints must possess two, apparently contradictory, characteristics: stability and mobility.
The **articular stabilisation** systems consist of the structures pertaining to both the **extra-articular component** and the **intra-articular component**; collagen is present in abundance in both of these structures.

– The extra-articular component consists of ligaments, the articular capsule, tendons and muscles; the intra-articular component is formed of ligaments (for the knee and hip joints only) and of joint cartilage (FIG. 2).

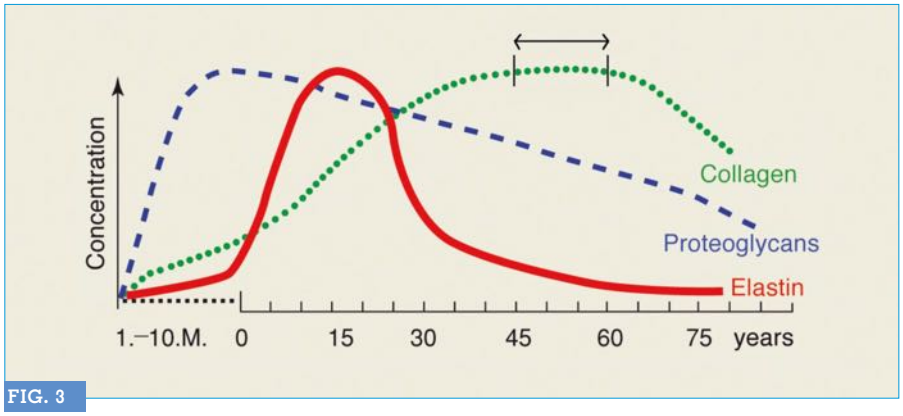


FIG. 3
Age-related biosynthesis of collagen, proteoglycans, and elastin.

One of the most important causes of joint pain is the **laxity** of the intra- and extra-articular stabilisation structures; lax containment systems result in **articular hypermobility**, especially in non-physiological directions and at non-physiological angles that, on the one hand, lead to greater, early wear of the containment systems themselves and, on the other, cause progressive cartilage degeneration.

The mechanical support provided by collagen represents an effective natural scaffolding.

– In humans, the biosynthesis of collagen starts to decrease at 55-60 years of age (FIG. 3);
From this age onwards, there is a quantitative and qualitative deterioration in the joint structures. More specifically, in the musculoskeletal system, the cartilage surfaces become thinner and degenerate to osteoarthritis, whereas the tendinous and ligamentous structures become less elastic and progress to tendinoses and tendinopathies of varying severities. Often in musculoskeletal conditions, the instrumental diagnostic evidence (x-ray, ultrasound, etc.) is not consistent with the clinical findings.

The term **Osteoarthritis state** is used to indicate physiological age-related articular ageing; it is a paraphysiological condition that does not cause any clinical situation and is often incidentally observed during imaging studies performed for other reasons (e.g. injury).
However, when osteoarthritis makes itself felt by causing the characteristic onset symptoms, such as *stiffness* and joint pain, we talk about osteoarthritis disease. Osteophytes are irregular beak- or crest-shaped proliferations of bone tissue that form in the vicinity of joints affected by a number of pathological processes, but above all in the presence of osteoarthritis. Their presence can involve disorders of various types, with restrictions to joint movement or the compression and irritation of nearby structures, in particular, nerve branches and tendon insertions. Osteophytes are the

bone tissue's attempt to increase the surface area of the heads of the articular bones damaged by osteoarthritis, in an attempt to stabilize the joint (FIG. 4).

In addition, it is common for ultrasound scans and MRI studies to show complete or multiple tendon damage, despite the presence of little or no signs and symptoms; conversely, in other cases, the tendon is intact but the patient experiences very severe pain and functional impairment.
As regards the tendinous-ligamentous sub-system, an anatomopathological distinction can be made between tendinites or tenosynovitis, tendinoses and tendon injuries of various degrees.

– Tendinites or tenosynovites are inflammatory states of the tendon and possibly also of its sheath, with or without peritendinous effusion; they may be a consequence of either a traumatic event or a functional overload.

When the repair process of the affected element starts in the presence of inflammation, the scar tissue that forms is a connective tissue that is devoid of the characteristics of elasticity and resistance that are typical of native tendons; this makes the structure more prone to partial or complete tears.

– For this reason, an inflammatory process affecting a tendinous or ligamentous structure should not be underestimated, rather it should be kept under close observation and resolved as soon as possible.

Also on the basis of our experience we can undoubtedly state that clinical and diagnostic evidence are not always consistent. In Italy, osteoarthritis accounts for **72.6%** of all rheumatic diseases and is responsible for **70%** of cases of chronic pain. The potential therapeutic approach to osteoarthritis, and tendinopathy, can be of different types:
– educational
– pharmacological
– rehabilitative
– surgical.

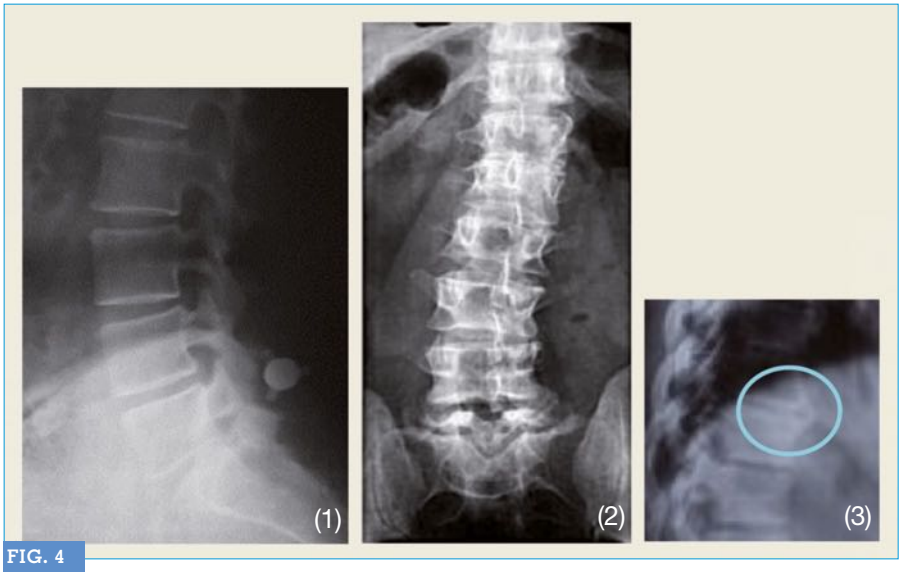


FIG. 4

X-ray of the L-S spine of an individual with severe low back pain without osteoarthritic skeletal alterations (1); of a L-S spine with significant radiological signs of osteoarthritic degeneration (2) in an asymptomatic patient; osteophytes (3).

The educational approach is represented by an improvement in quality of life including health education intervention, the use of braces, where necessary, and weight loss, when appropriate.
The conventional medicinal products used to treat osteoarthritis and tendinopathies (NSAIDs, Coxibs, Paracetamol, Steroids, and Opioids) have a symptomatic action and are used on both systemic and local levels (e.g. intra-articular steroid injections).
There are other medicinal products, whose real efficacy is not recognised by all Authors, which are thought to exert a slow chondroprotective action, these are: glucosamine sulphate, chondroitin sulphate, and hyaluronic acid.

The local use – and therefore – the intra-articular injection of hyaluronic acid boosts its efficacy; this kind of treatment is referred to as "visco-supplementation" and it has **only** a lubricating and shock-absorbing action.

Until just a few years ago, osteoarthritis was considered a progressive degenerative disease; subsequently, a prevention campaign against the progression of osteoarthritis with the use of "Cartilage integrators", was started.

– For some years now, it possible to state that osteoarthritis is a process that is, at least in part, reversible.
Given the ongoing rise in the population's average age, it goes without saying that having access to tools able to maintain high quality of life standards despite *chrono-aging* is an important breakthrough.

Guna Collagen Medical Devices are products for local injection constituted by **collagen** of porcine origin (porcine tissues have a very high collagen content) and a substance known as an *ancillary* or vehicle, of plant or mineral origin, characterised by a particular tropism for the specific articular segments.
A tangential filtration process, combined with sterilisation and control of the molecular weight, makes it possible to obtain a pure product with standard chemical and physical characteristics.
The availability of Guna Collagen Medical Devices for local injection is a determining factor in the repair process that follows anti-inflammatory intervention.
Lax joint support elements cause local nociceptor stimulation and excessive tension and stress: which explains why the reinforcement of these structures is **analgesic** as well as **regenerative**.

AREA	M	F	Total N.	Age - average	Age - range
SHOULDER, UPPER LIMB	30%	70%	**147**	53,5	34-78
KNEE	66%	34%	**53**	67,5	55-82
HIP	30%	70%	**30**	67	53-78
ACHILLES	20%	80%	**27**	43,3	32-63

TAB. 1

General caseload. Patient distribution according to gender and age.

– These characteristics translate directly into organoleptic properties: collagen is a **tissue structurer** (structural protein) and also possesses lubricating qualities.

– These bases form the significant difference between the properties of collagen and those of hyaluronic acid.

The latter is a lubricant (high viscosity) only of the articular cavity, that acts on the intra-articular component **only**, primarily in the large joints.
Collagen **also** and **primarily**, acts on the structures of the extra-articular component (capsule, ligaments, tendons) of small, medium, and large joints.
In addition, hyaluronic acid is efficacious in cases of modest and intermediate clinical severity, whereas collagen is also efficacious in those cases in which the patient's mobility is more severely impaired: it replaces the *bricks* where the *wall* had crumbled.

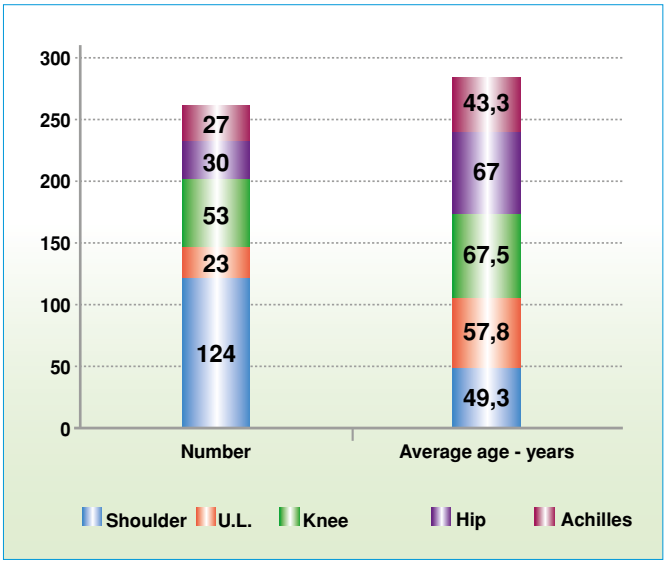
– Guna Collagen Medical Devices can be used alone or in home combinations with conventional or Physiological Regulating Medicine (PRM) products as **Guna-Arthro, Guna-Flam, Guna-Anti IL 1, Guna-Interleukin 10**; the treatment programme may also include other systemic pharmacological and rehabilitation treatments.

MATERIALS AND METHODS

A total of **257 patients** (36.5% M; 63.5% F) were enrolled in this clinical study. The mean age was 58.7 years, with a range of 32-82 years.
TAB. 1 shows the joint segments considered and treated and the corresponding epidemiological characteristics of the caseload.

FIG. 5

General caseload. – Number and mean age of patients included in the study per individual condition considered.



More specifically, because of the type of assessment scale used, the "Shoulder and upper limb (SUL)" Group included **124** patients with problems relating to the shoulder alone (rotator cuff syndrome, with possible tendon lesions); the remaining **23** had a number of other conditions, such as trapeziometacarpal osteoarthritis, epicondylitis and ganglion cysts of the wrist (U.L.).
It was consequently decided to analyse the results of these two sub-Groups independently (FIG. 5).

As far as the "Knee" Group was concerned, all **53** treated cases were classified as stage I, II and III osteoarthritis of the knee using the Kellgren-Lawrence radiological scale.
In the "Hip" Group, the treated hip joint (s) were affected by mild and moderate primary hip osteoarthritis (stage I and II); in this Group (**30** patients), patients were considered holistically, and only patients with a normal physique were included, so that the needle used was able to reach the pericapsular area.
In the "Achilles" Group, all the cases treated were mono- or bilateral Achilles' tendinopathies; **11** cases of tendonitis in the same area with ultrasound-documented exudate were also treated.
All patients were told about the type of treatment that they were being offered and the main differences that it would have compared to a similar injection therapy with hyaluronic acid or Guna Collagen MDs. They all signed the informed consent form.
The clinical and symptomatic findings of the patients enrolled were collected using assessment questionnaires validated by the WHO, more specifically:

- the Pain symptom was measured using a five-point visual-analogue scale (VAS), in which "0" = no pain and "5" = unbearable pain;
- D.A.S.H. (Disability for Arm, Shoulder and Hand) for the shoulder, elbow, hand, and wrist (range 0-100, in which 0 = no disability) (TAB. 2);
- O.K.S. (Oxford Knee Score) for the knee (range 48-0, in which 48 = no disability) (TAB. 3);
- O.H.S. (Oxford Hip Score) for the

hip (range 48-0, in which 48 = no disability) (TAB. 4);
- V.I.S.A.-A (Victorian Institute of Sport Assessment – Achilleus) for the Achilles' tendon (range 68-0, in which 68 = no disability) (TAB. 5).

The questionnaires were filled out by patients; the dedicated questionnaire was administered at the **first visit** and at the **end of treatment**.
Patients were administered **intra-articular** (shoulder, elbow, wrist, hand and knee), **pericapsular** (hip) and **local** (tendons) injections **with the appropriate** and **specific MDs**; 5 cc disposable syringes were used, with 23G x 1-1/2 - mm 0.60 x 40 needles for the hip, knee, and shoulder injections and 26G x 1/2 - mm 0.40 x 16 needles for hand, wrist, elbow, and foot injections.
Before administration, the skin was disinfected using a liquid product containing quaternary ammonium salt.

– In those segments in which administration was intra-articular, sterile surgical gloves were used and the injection area was disinfected thoroughly using sterile gauze soaked in surgical Betadine. In certain segments that are particularly rich in pain-sensitive nerve terminations, spray "ice" was used for analgesic purposes. The injections were administered **twice-weekly** for **5 consecutive weeks** (total = 10 injections).

– The patients treated for chronic degenerative diseases (knee osteoarthritis, hip osteoarthritis, trapeziometacarpal osteoarthritis and one case of severe Achilles' tendinopathy in a semi-professional dancer) continued with **maintenance therapy** (1 session a month for 6 consecutive months, then every 3 months). In no case was it suggested for the pharmacological therapy to be suspended or varied; patients taking NSAIDs or Paracetamol were asked to use this therapy only when absolutely necessary.
The evolution of the pain symptom in particular was monitored in the 8 patients who were taking opioid analgesics, in order to gradually reduce the posology of these drugs.

RESULTS

All the patients included in this study completed the treatment. None of them reported any side effect after the administration of the Guna Collagen Medical Devices. In those patients on antiplatelet or dicoumarol therapy, small areas of ecchymosis were observed at the injection site, but it reabsorbed rapidly without requiring any particular intervention.
All patients considerably **reduced** their use of conventional medicinal products and in **75%** ≈ of all cases their administration was not considered necessary.

– Of the 8 patients on treatment with opioid analgesics, 3 continued taking these medicinal products, albeit at considerably lower doses, whereas the remaining 5 gradually discontinued their use.

Generally speaking, the pain symptoms started to subside from the **4th** or **5th administration**; however, in cases of subacromial impingement and Achilles' or elbow tendinopathy the positive effects on pain were observed later.
In the osteoarthritic forms, affecting both the knee and the hip joint, the first effect reported by patients was a sensation of a **greater range of joint motion**; this sensation was perceived by patients after the first 2 - 3 sessions.

One particularly complex case was that of a male patient with polycythaemia, with concomitant severe osteoarthritis of the knee, hip and shoulder joint and significant functional impairment.
This was the case in which the improvement assessed by the questionnaires used in the study was poor; however, considering the initial clinical situation, it can be said that this was the patient who was most satisfied with the treatment received.

– We initially treated the shoulder alone and only subsequently, at the patient's insistence, also treated the knees. At a later date, we will decide if and when to treat the hips.

▶ Pain

The pain assessment scale showed a reduction from **3.06** (initial mean value including all the cases analysed) to a final value of **1.34**.
– The variation in the pain experienced in the various segments is shown in FIG. 6.

Shoulder and upper limb Group
(FIG. 7)

D.A.S.H. is an assessment questionnaire that considers a number of everyday situations facing the patient (disability concerning movements of the shoulder, hand, and elbow). The worst score is 100 and describes an extremely invalidating situation; a normal situation coincides with a score of 0.

In the caseload managed in this study regarding conditions of the **Shoulder**, the score dropped from an initial average of **78.7** to a final score of **17.3**.
As far as the **Upper limb** Group is concerned, from the initial mean of **66.8** the score dropped to **18.2**.

– In this case, the use of the D.A.S.H. questionnaire proved to be a disputable choice, as it pooled the results for a number of different segments. In the future, we intend to use a dedicated score, such as the *Oxford Shoulder Score* to assess shoulder function.

Knee Group

O.K.S. (The Oxford Knee Score) is an assessment scale including different common situations of everyday life.
The patient is invited to reply with regard to the 4 months prior to completion of the questionnaire; for obvious time reasons, post-treatment completion refers to the time at which it is filled out.
A score of 0 coincides with the most impaired situation, whereas a score of 48 coincides with a condition of full function. Of the 53 patients included (FIG. 8), the average initial score was **13.6**, whereas a score of **35.8** was achieved at the end of treatment.

D.A.S.H.

This questionnaire asks about your symptoms as well as your ability to perform certain activities. Please answer every question , based on your condition in the last week. If you did not have the opportunity to perform an activity in the past week, please make your best estimate on which response would be the most accurate. It doesn't matter which hand or arm you use to perform the activity; please answer based on you ability regardless of how you perform the task.

Please rate your ability to do the following activities in the last week

		NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1	Open a tight or new jar	1	2	3	4	5
2	Write	1	2	3	4	5
3	Turn a key	1	2	3	4	5
4	Prepare a meal	1	2	3	4	5
5	Push open a heavy door	1	2	3	4	5
6	Place an object on a shelf above your head	1	2	3	4	5
7	Do heavy household chores (e.g., wash walls, wash floors)	1	2	3	4	5
8	Garden or do yard work	1	2	3	4	5
9	Make a bed	1	2	3	4	5
10	Carry a shopping bag or briefcase	1	2	3	4	5
11	Carry a heavy object (over 10 lbs).	1	2	3	4	5
12	Change a lightbulb overhead	1	2	3	4	5
13	Wash or blow dry your hair	1	2	3	4	5
14	Wash your back	1	2	3	4	5
15	Put on pullover sweater	1	2	3	4	5
16	Use a knife to cut food	1	2	3	4	5
17	Recreational activities which require little effort (e.g., cardplaying, knitting, etc…)	1	2	3	4	5
18	Recreational activities in which you take some force or impact through your arm, shoulder or hand (e.g golf, hammering, tennis, etc…)	1	2	3	4	5
19	Recreational activities in which you move your arm freely (e.g., playing freesby, badminton, etc…)	1	2	3	4	5
20	Manage transportation needs (getting from one place to another)	1	2	3	4	5
21	Recreational activities which require considerable effort (e.g. push-ups, shaking a spray can, etc…)	1	2	3	4	5

22.During the past week, to what extend has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbours or groups? (circle number)

NOT AT ALL	SLIGHTLY	MODERATELY	QUITE A BIT	EXTREMELY
1	2	3	4	5

23.During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem? (circle number)

NO LIMITED AT ALL	SLIGHTLY LIMITED	MODERATELY LIMITED	VERY LIMITED	UNABLE
1	2	3	4	5

		NONE	MILD	MODERATE	SEVERE	EXTREME
24	Arm, Shoulder or hand pain	1	2	3	4	5
25	Arm, Shoulder or hand pain when you performed any specific activity	1	2	3	4	5
26	Tingling (pins and needles) in your arm, shoulder or hand	1	2	3	4	5
27	Weakness in your arm, shoulder or hand	1	2	3	4	5
28	Stiffness in your arm, shoulder or hand	1	2	3	4	5

29. During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand? (circle number)

NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	SO MUCH DIFFICULTY THAT I CAN'T SLEEP
1	2	3	4	5

30. I feel less capable, less confident or less useful because of my arm, shoulder or hand problem (circle number)

NONE	MILD	MODERATE	SEVERE	EXTREME
1	2	3	4	5

The following questions ask about the impact of your arms, shoulder or hand problem on your ability to work. Please circle the number that best describes your physical ability in the past week.

	Did you have difficulty:	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	EXTREME DIFFICULTY	UNABLE
31	Using your usual technique for your work?	1	2	3	4	5
32	Doing your usual work because of arm, shoulder or hand pain?					
33	Doing your work as well as you would like?					
34	Spending your usual amount of time doing your work?					

The following questions relate to the impact of your arms, shoulder or hand problem on playing your musical instrument or sport or both. If you play more than one sport or instrument (or play both), please answer with respect to that activity which is most important to you. Please circle the number that best describes your physical ability in the past week.

	Did you have difficulty:	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	EXTREME DIFFICULTY	UNABLE
35	Using your usual for playing your instrument or sport?	1	2	3	4	5
36	Playing your musical instrument or sport because of arm, shoulder or hand pain?	1	2	3	4	5
37	Playing your musical instrument or sport as well as you would like?	1	2	3	4	5
38	Spending your usual amount of time practicing or playing your instrument or sport?	1	2	3	4	5

Thank you for filling in this form.

TAB. 2

– D.A.S.H. (Disability for Arm, Shoulder and Hand) Questionnaire.

O.K.S. - OXFORD KNEE SCORE

NEW OXFORD KNEE SCORE QUESTIONNAIRE

Please answer the following 12 questions. Please only consider how you have been getting on during the past four weeks

1. How would you describe the pain you have usually from your knee? Score
None – 4
Very mild – 3
Mild – 2
Mild moderate – 1
Severe – 0

2. Have you had any trouble with washing and drying yourself all over because of your knee?
No trouble at all – 4
Very little trouble – 3
Moderate trouble – 2
Extreme difficulty – 1
Impossible to do – 0

3. Have you had any trouble getting in and out of a car or using public transport because of your knee?
No trouble at all – 4
Very little trouble – 3
Moderate trouble – 2
Extreme difficulty – 1
Impossible to do – 0

4. If you were to kneel down could you stand up afterwards?
Yes, easily – 4
With little difficulty – 3
With moderate difficulty – 2
With extreme difficulty – 1
No, impossible – 0

5. Have you been limping when walking because of your knee?
Rarely/never – 4
Sometimes or just at first – 3
Often, not just at first – 2
Most of the time – 1
All of the time – 0

6. Have you felt that your knee might suddenly give way or let you down?
Rarely/never – 4
Sometimes or just at first – 3
Often, not just at first – 2
Most of the time – 1
All of the time – 0

7. Could you kneel down and get up afterwards?
Rarely/never – 4
Sometimes or just at first – 3
Often, not just at first – 2
Most of the time – 1
All of the time – 0

8. Have you been able to do your own household shopping on your own? Score
Yes, easily – 4
With little difficulty – 3
With moderate difficulty – 2
With extreme difficulty – 1
No, impossible – 0

9. For how long have you been able to walk before the pain from your knee became severe (with or without a stick)?
No pain, even after more than 30 minutes – 4
16-30 minutes – 3
5-15 minutes – 2
Around the house only – 1
Unable to walk at all – 0

10. Have you been able to walk down a flight of stairs
Yes, easily – 4
With little difficulty – 3
With moderate difficulty – 2
With extreme difficulty – 1
No, impossible – 0

11. After a meal (sat at a table) how painful has it been for you to stand up from a chair because of your knee?
Not at all painful – 4
Slightly painful – 3
Moderately painful – 2
Very painful – 1
Unbearable – 0

12. How much pain from your knee interfered with your usual work (including housework)?
Not at all – 4
A little bit – 3
Moderately – 2
Greatly – 1
Totally – 0

13. Have you been troubled by pain from your knee in bed at night?
No nights – 4
Only 1 or 2 nights – 3
Some nights – 2
Most nights – 1
Every night – 0

TAB. 3
– O.K.S. (Oxford Knee Score) Questionnaire.

O.H.S. - OXFORD HIP SCORE

OXFORD HIP SCORE

Please answer the following 12 questions.

During the past 4 weeks...

1. How would you describe the pain you usually have in your hip?
4) None
3) Very mild
2) Mild
1) Moderate
0) Severe

2. Have you been troubled by pain from your hip in bed at night?
4) No nights
3) Only 1 or 2 nights
2) Some nights
1) Most nights
0) Every night

3. Have you had any sudden, severe pain-' shooting ', 'stabbing', or 'spasms' from your affected hip?
4) No days
3) Only 1 or 2 days
2) Some days
1)Most days
0) Every day

4. Have you been limping when walking because of your hip?
4) Rarely/never
3) Sometimes or just at first
2) Often, not just at first
1) Most of the time
0) All of the time

5. For how long have you been able to walk before the pain in your hip becomes severe (with or without a walking aid)?
4) No pain for 30 minutes or more.
3) 16 to 30 minutes
2) 5 to 15 minutes
1) Around the house only
0) Not at all

6. Have you been able to climb a flight of stairs?
4) Yes, easily
3) With little difficulty
2) With moderate difficulty
1) With extreme difficulty

7. Have you been able to put on a pair of socks, stockings or tights?
4) Yes, easily
3) With little difficulty
2) With moderate difficulty
1) With extreme difficulty
0) No, impossible

8. After a meal (sat at a table), how painful has it been for you to stand up from a chair because of your hip?
4) Not at all painful
3) Slightly painful
2) Moderately painful
1) Very painful
0) Unbearable

9. Have you had any trouble getting in and out of a car or using public transportation because of your hip?
4) No trouble at all
3) Very little trouble
2) Moderate trouble
1) Extreme difficulty
0) Impossible to do

10. Have you had any trouble with washing and drying yourself (all over) because of your hip?
4) No trouble at all
3) Very little trouble
2) Moderate trouble
1) Extreme difficulty
0) Impossible to do

11. Could you do the household shopping on your own?
4) Yes, easily
3) With little difficulty
2) With moderate difficulty
1) With extreme difficulty
0) No, impossible

12. How much has pain from your hip interfered with your usual work, including housework?
4)Not at all
3) A little bit
2) Moderately
1) Greatly
0) Totally

TAB. 4
– O.H.S. (Oxford Hip Score) Questionnaire.

TAB. 5
– V.I.S.A.-A (Victorian Institute of Sport Assesment- Achilles tendon) Questionnaire.

V.I.S.A.-A

IN THIS QUESTIONNAIRE, THE TERM PAIN REFERS SPECIFICALLY TO PAIN IN THE ACHILLES TENDON REGION

1. For how many minutes do you have stiffness in the Achilles region on first getting up?

100 mins ☐☐☐☐☐☐☐☐☐☐ 0 mins — POINTS ☐

0 1 2 3 4 5 6 7 8 9 10

2. Once you are warmed up for the day, do you have pain when stretching the Achilles tendon fully over the edge of a step? (keeping knee straight)

strong severe pain ☐☐☐☐☐☐☐☐☐☐ no pain — POINTS ☐

3. After walking on flat ground for 30 minutes, do you have pain within the next 2 hours?

strong severe pain ☐☐☐☐☐☐☐☐☐☐ no pain — POINTS ☐

4. Do you have pain walking downstairs with a normal gait cycle?

strong severe pain ☐☐☐☐☐☐☐☐☐☐ no pain — POINTS ☐

5. Do you have pain during or immediately after doing 10 (single leg) heel raises from a flat surface?

strong severe pain ☐☐☐☐☐☐☐☐☐☐ no pain — POINTS ☐

6. How many single leg hops can you do without pain?

0 ☐☐☐☐☐☐☐☐☐☐ 10 — POINTS ☐

7. Are you currently undertaking sport or other physical activity?

0 ☐ Not at all — POINTS

4 ☐ Modified training ± modified competition ☐

7 ☐ Full training ± competition but not at same level as when symptoms began

10 ☐ Competing at the same or higher level as when symptoms began

At the end of the treatment, patients were offered the chance to continue with maintenance therapy: all the patients agreed to continue the treatment, saying that they were satisfied and confident. The improvements achieved were maintained in the following months. In some cases, further improvements were seen; however, in order to quantify these data, the situation must be evaluated on a case-by-case basis.

Hip Group

O.H.S. (The Oxford Hip Score) is an assessment scale for hip joint function.
The patient must answer regarding his/her every day motor performance.
Once again, patients were invited to answer the end-of-treatment questionnaire, by entering their replies at the time of assessment. Full joint integrity coincides with a score of 48 points, whereas a clinical situation of maximum impairment coincides with a score of 0.
It is important to remember that the patients in this Group presented radiographic evidence of a stage I or II condition, the phases of the disease in which pain and functional impairment emerge.
In this Group, the mean score decreased from an initial value of **10.2** (indicating somewhat severe general impairment) to a final score of **37.2** (FIG. 9).

Achilles' Group

This Group of patients, suffering from an inflammation of the Achilles' tendon, answered the Victorian Institute of Sport Assessment (V.I.S.A.-A) questionnaire, which refers to the Achilles' tendon alone and provides a score of between 0 and 68 points; the latter value refers to a condition of complete and perfect function.
In this case, as shown by the data in FIG. 10, the score increased from an initial value of **21.0**, to a final value of **54.0** points.
The patients in this Group had an ultrasound study, with a finding of effusion between the tendon folds.
– As ultrasound is a non-invasive imaging technique, at the end of treatment the patients had a follow-up ultrasound scan, to show the reabsorption of the signs of inflammation (FIG.11).

CONCLUSIONS

All the treated patients declared that they were satisfied with the result achieved.
– There were no drop outs, despite the fact that the treatment lasted 5 - 6 weeks.
As far as all of the assessment questionnaires as a whole are concerned, there was a considerable, statistically significant, subjective improvement.
To this we must add the objective improvement, confirmed by imaging studies (follow-up ultrasound) for those patients with Achilles' tendon conditions, and clinically by range of joint motion tests.
After the first 3 - 4 administrations, almost all patients in the Shoulder, Hip and Knee Groups, expressed their surprise at the feeling of greater joint freedom.
The Hip Group was the Group that expressed the greatest and earliest satisfaction with the treatment. From a percentage standpoint, the best result was achieved in the Achilles' Group: this can be attributed to the fact that this Group was constituted by patients with the lowest average age and that in which the condition was not secondary to an overload or degenerative process.
The members of this Group and the Shoulder Group were not offered any maintenance therapy. A single addition-

al administration was required in just two cases, both in the Shoulder Group. For the patients in the Hip, Knee and Upper Limb Groups (in the latter, for cases of trapeziometacarpal osteoarthritis only) the treatment is still on-going. Administration is once-monthly for the first six months.

Subsequently, if stable remission is achieved, the treatment is administered once every two months and, later, once every three months.
Having been thoroughly informed of the role played by locally-administered collagen (Guna Collagen MDs), the patients readily understood that their attention to symptoms is fundamental to a successful outcome of treatment, in order to achieve long-lasting results.

– Another positive aspect of treatment with Guna Collagen MDs is the rapid effect on pain, even and above all in patients on dicoumarol anti-coagulant therapy, who cannot take NSAIDs or steroids.

A positive and somewhat rapid response was also observed in those patients with heavy pharmacological regimens due to comorbidities.
It is important to note that, in most of the cases observed in this study (as is the case for the majority of patients referred to a physiatrist), the patient was referred after at least two months of attempts using conventional pharmacological therapy (NSAIDs, Steroids, Paracetamol) without achieving any stable result. Their body was therefore intoxicated.

– The toxins from conventional anti-inflammatory drugs accumulate above all in the structures comprising the musculoskeletal system.

– Even subjects on heavy chronic pharmacological treatment (steroids, oral hypoglycaemic agents, insulin, anticoagulants), the positive response to therapy was achieved without any interference with their ongoing chronic therapies. ■

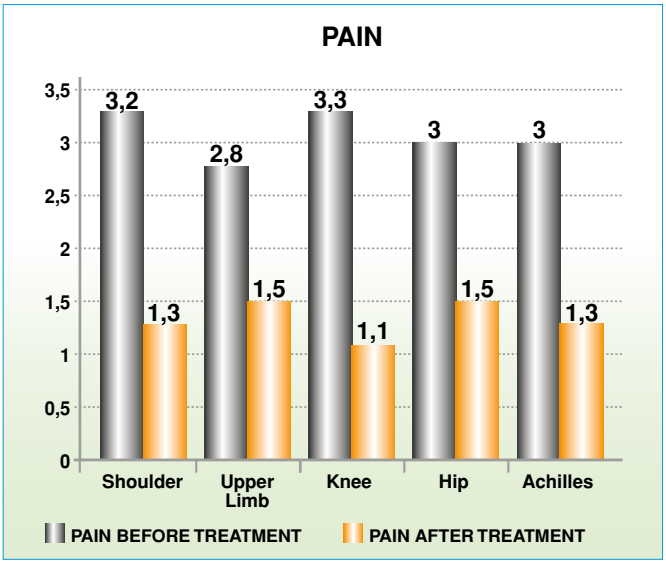
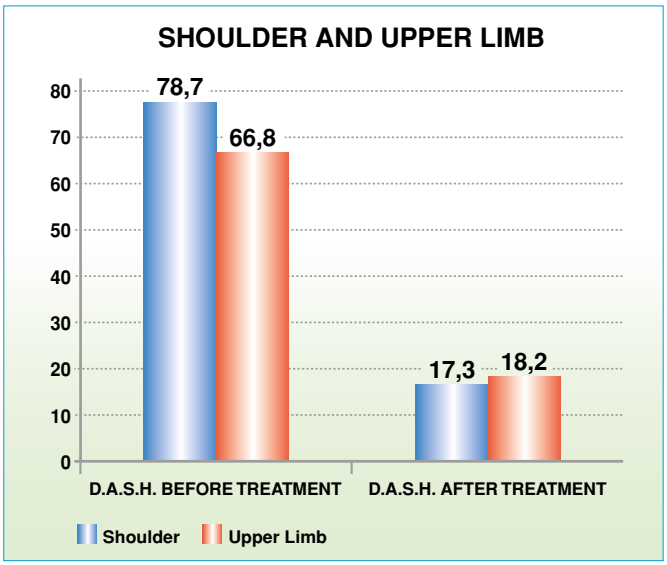


FIG. 6

Variation in the pain symptoms pre- and post-treatment in the different Groups treated with Guna Collagen MDs.

FIG. 7

Results of the analysis of the data collected using the D.A.S.H. questionnaire for conditions affecting the shoulder and upper limb (elbow, wrist, and hand).



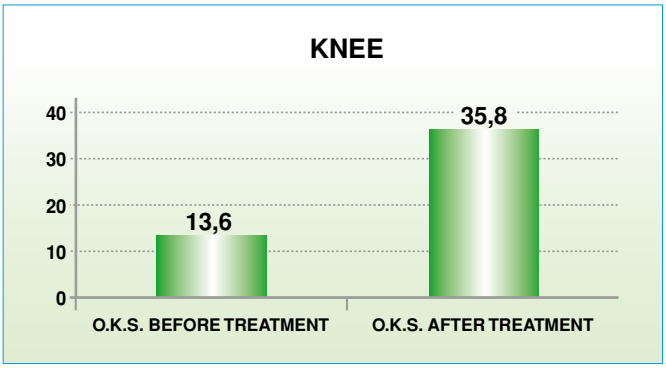


FIG. 8

Results of the analysis of the data collected using the O.K.S., for knee conditions.

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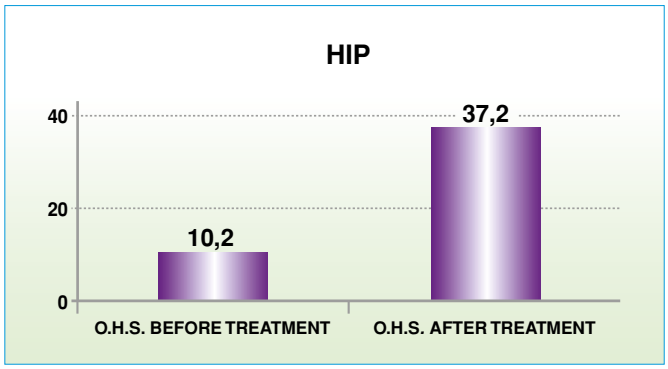
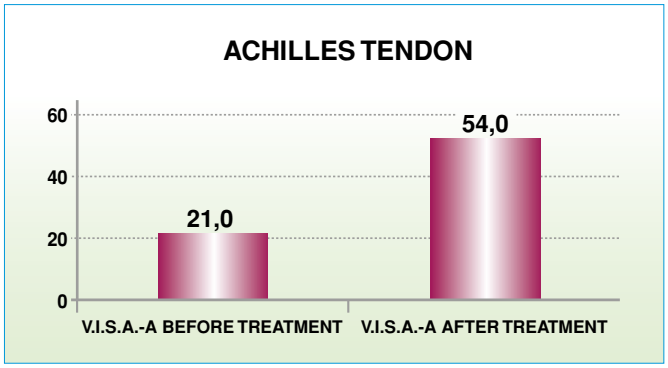


FIG. 9

Results of the analysis of the data collected using the O.H.S., for hip conditions.

FIG. 10

Results of the analysis of the data collected using the V.I.S.A.-A, for Achilles' tendon conditions.



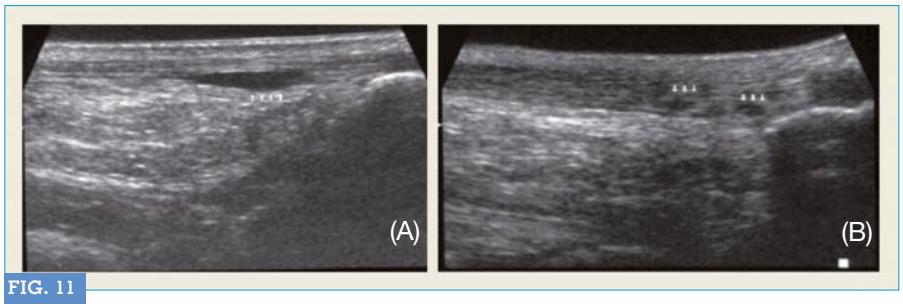


FIG. 11

(A) Achilles' tendon in the presence of effusion in the peritendineum; (B) The effusion is no longer visible. A situation of chronic tendinosis persists, with microcalcifications.

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Medical Device iniettabili a base di collagene

Stato dell'arte e *overview* degli studi clinici

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Parole chiave
Collagene
Medical device
Viscosupplementazione
Infiltrazioni intrarticolari e periarticolari
Studi clinici

Riassunto
I continui progressi in campo medico-scientifico hanno sicuramente garantito un sostanziale allungamento della vita ma anche un conseguente aumento della tendenza alla cronicizzazione degli eventi morbosi. Uno degli Apparati in cui è più evidente questo *trend* è l'Apparato locomotore e di sostegno e patologie come l'artrosi rappresentano solo una delle espressioni di questo *trend*. Le strutture connettivali recitano un ruolo fondamentale nell'etiopatogenesi delle malattie infiammatorie e degenerative delle articolazioni e di tessuti come ossa, tendini, legamenti, muscoli: con il progredire dell'età, infatti, il tessuto connettivo, ed il collagene in particolare, tendono fisiologicamente a degradarsi in modo progressivo, fino a risultare inadeguati ad assolvere le loro specifiche e molteplici funzioni. Di particolare interesse la constatazione che tutte le strutture extra- ed intra-articolari sono costituite fondamentalmente da collagene.
Ed è partendo proprio da questa considerazione che, negli ultimi anni, la ricerca farmacologica si è focalizzata su nuovi approcci terapeutici che pongono questa sostanza al centro dell'attenzione.
Attualmente uno degli interventi terapeutici sicuramente più studiati ed utilizzati è rappresentato dalla viscosupplementazione con acido jaluronico per via intra-articolare, utile anche nel controllo del dolore e della flogosi e per il recupero funzionale dell'articolazione.
Ma una preziosa alternativa all'iniezione intra-articolare di acido jaluronico è rappresentata dall'iniezione intra-articolare o peri-articolare di *collagene di origine naturale*, con la funzione di rimpiazzare, rinforzare, strutturare e proteggere (barriera di adesione) cartilagini e capsule articolari, migliorando l'assetto anatomico e funzionale delle fibre collagene e di tutte le strutture in cui il collagene è presente e di fornire un supporto di tipo meccanico al distretto interessato.

Introduzione

In Italia le malattie reumatiche colpiscono circa 5 milioni e mezzo di individui, e l'artrosi è di gran lunga l'affezione più frequente, rappresentando da sola il 72,6% delle malattie reumatiche[1]; secondo le Linee Guida EULAR *(European League Against Rheumatism)*, risulterebbero affetti da osteoartrosi sintomatica circa 4 milioni di persone[2]. L'indagine *"Pain in Europe Survey"*, condotta su un campione di 50 mila persone in tutta Europa, ha dimostrato che il dolore cronico (che nel 70% dei casi è legato a reumartropatie) ha una maggiore prevalenza in Norvegia, Italia (26%) e Polonia, mentre la Spagna è il Paese con la minor prevalenza (19%). Negli U.S.A. si stima che ca. 27 milioni di persone siano affette, per esempio, da coxartrosi.
L'osteoartrosi è la più comune patologia cronica articolare e la sua prevalenza è destinata ad aumentare a causa dell'incremento dell'età media della popolazione; le articolazioni più colpite risultano, nell'ordine: ginocchio, mano, anca. Negli U.S.A. si stima che circa 27 milioni di persone siano affette, per esempio, di coxartrosi.

Opzioni terapeutiche

La terapia del dolore osteo-artro-mio-fasciale benigno prevede il ricorso a differenti tipi di trattamento:

- non farmacologico
- farmacologico
- riabilitativo
- chirurgico

Il trattamento non farmacologico prevede programmi di educazione sanitaria, l'uso di eventuali tutori e infine, quando necessario, la riduzione del peso corporeo[2,3,4].
La terapia farmacologica prevede il ricorso sia a farmaci sintomatici ad azione rapida (paracetamolo, FANS, oppioidi, COXIB e, per via infiltrativa, i corsticosterioidi), che agiscono come antidolorifici e/o antinfiammatori, sia a farmaci sintomatici ad azione lenta (glucosamina solfato, condroitin-solfato, acido jaluronico), che agiscono come condro-protettori in quanto normali costituenti della cartilagine articolare. Le linee guida EULAR e le raccomandazioni OARSI *(Osteoarthritis Research Society International)*

prevedono anche il trattamento riabilitativo sia strumentale che chinesiterapico. Tra gli approcci riabilitativi la chinesiterapia è quella che presenta il maggior grado di evidenza negli studi relativi alla gestione del dolore e al miglioramento della funzione articolare[5].
Tra i farmaci sintomatici ad azione lenta un ruolo da protagonista è giocato dall'acido jaluronico. Generalmente viene somministrato per via infiltrativa, dando buoni risultati nel controllo del dolore e nel miglioramento dell'articolarità, soprattutto del ginocchio.
Il suo meccanismo d'azione è oggi ben conosciuto: le molecole di acido jaluronico del liquido sinoviale si organizzano a formare una vasta rete, grazie alla quale il liquido sinoviale stesso si comporta come un lubrificante viscoso durante i movimenti lenti dell'articolazione, come la deambulazione, e come un ammortizzatore elastico durante i movimenti rapidi quali la corsa[6].
Oltre a garantire le proprietà viscoelastiche del liquido sinoviale, l'acido jaluronico svolge un importante ruolo nel mantenere le caratteristiche strutturali e funzionali della cartilagine articolare, regolando varie attività cellulari attraverso specifici recettori di membrana (CD44)[7].
L'intervento terapeutico che prevede l'infiltrazione intra-articolare di acido jaluronico è detto viscosupplementazione. Gli obbiettivi sono:

- ripristinare la viscoelasticità del liquido sinoviale,
- ridurre la sintomatologia dolorosa a carico dell'articolazione,
- migliorare la funzione articolare,
- ripristinare le funzioni protettive dell'acido jaluronico stesso nell'articolazione[8].

Dal 2010, il trattamento delle patologie dolorose e degenerative dell'Apparato locomotore e di sostegno si avvale di un innovativo approccio terapeutico con l'uso di **Medical Device iniettabili a base di collagene suino***.

Il Collagene[9]
Il collagene è la proteina più abbondante nei Mammiferi: ca. il 5-6% del peso corporeo di un uomo adulto; un terzo o un quarto di tutta la massa proteica degli animali superiori è costituita da collagene: dalle ossa ai tendini, dalle capsule articolari ai muscoli, dai legamenti alle fasce, dai denti alle sierose, dalla cute alla matrice extra-cellulare (ECM).
Questo implica l'importanza, per l'organismo umano, che tutti i meccanismi biologici e metabolici, legati alla sintesi ed alla funzione del collagene in ogni sua localizzazione, siano perfettamente efficienti, pena l'insorgenza di patologie in uno o più distretti corporei.
Nell'uomo, il picco di biosintesi collagenica avviene dal 45° al 60° anno di età: successivamente la sua produzione scende molto rapidamente, insieme a quella di elastina e di proteoglicani.
L'unità-base del collagene è il **tropo-collagene**, glicoproteina formata dall'intreccio di tre catene polipeptidiche sinistrorse portatrici di molecole di glucosio e galattosio, fissate sulla molecola dell'aminoacido Idrossilisina (Hyl), uno dei quattro aminoacidi costituenti il tropo-collagene con Glicina (Gly), Prolina (Pro) e 4-Idrossiprolina (Hyp). Questa tripla elica stretta garantisce la **robustezza strutturale** e la **rigidità**, ma anche la **resistenza** e la **flessibilità** necessarie alla perfetta funzionalità del collagene.
La mancata idrossilazione a Hyp e a Hyl porta alla formazione di collagene non strutturalmente adeguato alla funzioni.
La disposizione delle fibrille nella formazione delle fibre collagene, garantisce alla struttura una grande robustezza in termini di *resistenza, inestensibilità, incomprimibilità,* ma anche di p*lasticità, flessibilità, resistenza al carico, resistenza alla torsione.*
Queste caratteristiche fanno del collagene una "struttura" estremamente versatile che la Natura ha selezionato in centinaia di milioni di anni e confermato come il miglior mezzo per adempiere le sue numerose funzioni.
In Ortopedia e Traumatologia queste evidenze sul ruolo strutturale del collagene ricoprono una particolare importanza dal momento che tutte le strutture extra ed intra-articolari sono costituite fondamentalmente da questa molecola.

Collagen Medical Device
Un nuovo approccio sostanziale e raffinato alle patologie algiche-disfunzionali dell'Apparato di sostegno ed alle funzioni motorie correlate è offerto dall'utilizzo, nella pratica ambulatoriale e nelle strutture specialistiche, dei *Collagen Medical Device*. I 13 *Collagen Medical Device* (MD) contengono **collagene (di tipo I) e sostanze ancillari di origine naturale**. Queste ultime consentono un più efficace e specifico posizionamento *in loco* del collagene con la funzione di veicolazione e di stabilizzazione.
Di questi 13 MD, 8 sono specifici distrettuali per i singoli comparti anatomici scheletrici e le loro patologie [MD-NECK (Colonna Cervicale); MD-THORACIC (Colonna Toracica); MD-LUMBAR (Colonna Lombare); MD-SHOULDER (Spalla); MD-HIP (Anca); MD-KNEE (Ginocchio); MD-SMALL JOINTS (Piccole articolazioni); MD-POLY (Pluri-articolarità)]; uno è specifico distrettuale per il nervo sciatico [MD-ISCHIAL], e altri quattro sono specifici tissutaliper le patologie dei tessuti somatici di derivazione prevalentemente mesodermica [MD-MUSCLE (Muscolo); MD-NEURAL (Nervi); MD-MATRIX (Matrice Extra-Cellulare); MD-TISSUE (Tessuti molli)]. Tutti i 13 Guna MD contengono, oltre all'eccipiente veicolante (*ancillare*), collagene di origine suina.
La scelta di preferire collagene di suino è dettata, oltre che dalla somiglianza biochimica e filogenetica, dal fatto che i tessuti di suino hanno mediamente un contenuto di collage-

* Collagen Medical Device - Guna S.p.a. (Italy).

ne molto elevato (Glicina = 22,8%; Prolina = 13,8%; Idrossi-Prolina = 13%). Il contenuto medio degli altri aminoacidi è solo del 3% (max. Ac. glutammico = 9,5%; min. Tirosina = 0,4%).
Il collagene utilizzato nei *Collagen Medical Device* è sottoposto ad un particolare processo di filtrazione tangenziale, sterilizzazione e controllo del peso molecolare, che permette di ottenere un prodotto puro (senza contaminanti) e con caratteristiche chimico-fisiche standardizzate per la buona sicurezza clinica.

I SISTEMI DI STABILIZZAZIONE ARTICOLARE
Ogni articolazione deve possedere 2 caratteristiche fondamentali, apparentemente in contrasto tra loro: la stabilità e la mobilità articolare.
I sistemi di stabilizzazione sono rappresentati da strutture che, in misura diversa, concorrono all'ottimale funzionalità articolare.

1 – Comparto extra-articolare
– LEGAMENTI
Dispositivi intra- (solo grosse articolazioni) ed extra-articolari costituiti da una disposizione parallela di fasci di collagene.
– CAPSULA ARTICOLARE
Dispositivo di copertura-protezione e rinforzo dell'articolazione, fissato vicino ad essa sui due elementi ossei contigui.
– TENDINI
– MUSCOLI
Anche il muscolo concorre alla "tenuta articolare".

2 – Comparto intra-articolare
– LEGAMENTI
Intra-articolari delle grandi articolazioni .
– CARTILAGINE ARTICOLARE
Fibrille collagene della cartilagine ialina disposte in fasci verticali nello strato profondo e in fasci tangenziali nello strato superficiale.

Lo scopo dell'introduzione *in loco* del collagene di suino purificato e sterilizzato, che costituisce i *Collagen Medical Device*, "dove serve" è strutturale: rimpiazzare, rinforzare, strutturare e proteggere (barriera di adesione) cartilagini, tendini, legamenti, capsule articolari, etc. migliorando l'assetto delle fibre collagene e – di conseguenza – di tutte le strutture anatomiche in cui esso è presente e fornire un supporto di tipo meccanico al distretto interessato.
Una delle cause più importanti di dolore distrettuale articolare è la lassità delle strutture intra- ed extra-articolari di stabilizzazione; i sistemi di contenimento lassi determinano ipermobilità articolare, soprattutto in direzioni ed angolature non fisiologiche che, da un lato, usurano precocemente ed ulteriormente i sistemi di contenimento stessi, e, dall'altro, operano verso una progressiva degenerazione cartilaginea.
Il supporto meccanico fornito dal collagene rappresenta un'efficace impalcatura naturale di sostegno (*bio-scaffold*).
L'infiltrazione di collagene e dei singoli eccipienti ancillari, perfettamente tollerata dal paziente e priva di effetti collaterali negativi, agisce nel rispetto della fisiologia.
Inoltre i PGs della ECM cementanti le fibre collagene migliorano le proprietà visco-elastiche del liquido sinoviale.
Infine è possibile ascrivere ai *Collagen Medical Device* azione antalgica: gli elementi di sostegno articolare lassi e ipermobili provocano stimolazione dei nocicettori locali, tensioni e sollecitazioni eccessive; stabilizzare queste strutture equivale a ridurre la spina irritativa algica. I *Collagen Medical Device* migliorano la mobilità articolare fisiologica, favorendo la distensione muscolare zonale, alleviando il dolore localizzato o provocato dal movimento articolare o da vizi posturali.

***Overview* degli Studi clinici condotti in Europa sui Collagen Medical Device**

In uno studio clinico (Rashkov R, Nestorova R, Reshkova V. Efficacy and safety of collagen injection Guna Mds in osteoarthrosis treatment of knee. IOF-ECCEO12 – March 21-24, 2012 – Bordeaux, France) sono stati trattati 30 pazienti (12 M, 16 F, età compresa tra 55 e 70 anni) affetti da gonartrosi clinicamente determinata, al II o III stadio radiologico, senza gonfiore. Sono state escluse le infiammazioni dell'articolazione, la gotta e le malattie maligne.
La terapia è stata condotta per mezzo di iniezioni intra-articolari di dispositivi medici iniettabili a base di collagene (MD-Knee e MD-Muscle), nella misura di 2 iniezioni settimanali per 2 settimane e successivamente 1 iniezione settimanale per 6 settimane, per un totale di 8 settimane di trattamento. I pazienti hanno compilato un questionario e i medici hanno espresso un giudizio prima del trattamento (prima visita), all'ottava settimana (termine del trattamento – seconda visita) e al novantesimo giorno (30 giorni dopo il termine del trattamento – terza visita).
Gli obiettivi del lavoro sono stati:
• valutazione del grado di dolore a riposo e durante il movimento nei pazienti affetti da gonartrosi prima e dopo il trattamento con i dispositivi medici iniettabili a base di collagene;
• valutazione delle variazioni dell'indice algo-funzionale di Lequesne prima e dopo il trattamento;
• valutazione dell'efficacia dei *Collagen Medical Device* nella gonartrosi secondo il giudizio dei pazienti e secondo il giudizio dei medici.

Il dolore a riposo e il dolore durante il movimento si sono ridotti in modo statisticamente significativo e la riduzione del dolore a riposo si è mantenuta tale anche 30 giorni dopo il termine della terapia, mentre il dolore durante il movimento è continuato ad attenuarsi anche dopo il termine della terapia (Grafico 1, Grafico 2).

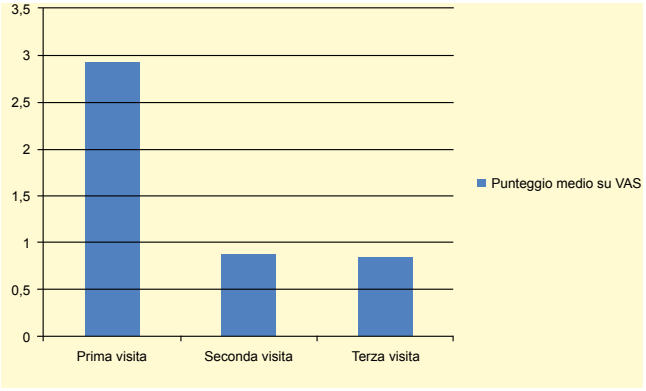

Grafico 1: Valutazione del dolore a riposo da parte dei pazienti su scala VAS (da 0 a 10).

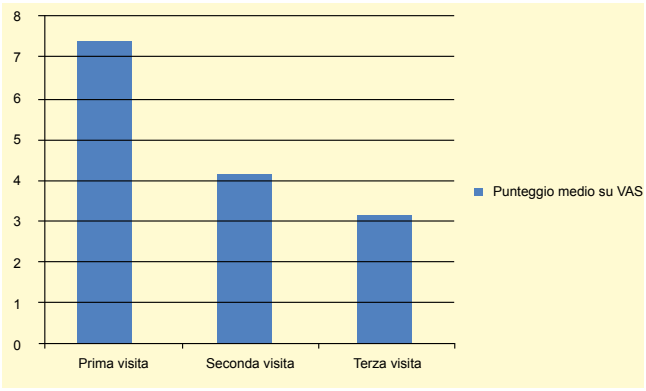

Grafico 2: Valutazione del dolore durante il movimento da parte dei pazienti su scala VAS (da 0 a 10).

L'impiego dei *Collagen Medical Device* nel trattamento della gonartrosi ha anche consentito un miglioramento statisticamente significativo dell'Indice Algofunzionale di Lequesne (Grafico 3, Grafico 4).

La valutazione dell'efficacia della terapia con i *Collagen Medical Device* nel trattamento dell'artrosi del ginocchio alla seconda e alla terza visita da parte dei pazienti e da parte dei medici è sovrapponibile e la percentuale maggiore ha giudicato la terapia molto buona (Grafico 5).

Le conclusioni tratte dagli autori dello studio clinico sono:

- l'applicazione intra-articolare di MD-Knee e MD-Muscle riduce significativamente il dolore a riposo e durante il movimento e migliora l'attività funzionale dei pazienti;
- i *Collagen Medical Device* si dimostrano altamente efficaci in tutti i pazienti;
- non si sono manifestati effetti collaterali.

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Uno studio clinico (Nestorova R, Rashkov R, Reshkova V,

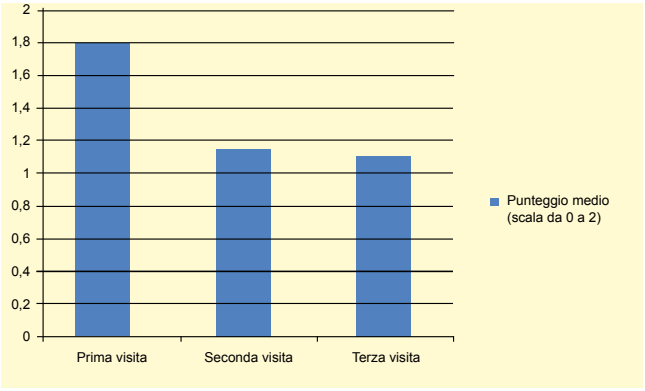

Grafico 3: Valutazione del dolore al ginocchio durante la deambulazione (0 = assente; 1 = crescente dopo una certa distanza; 2 = crescente all'avvio).

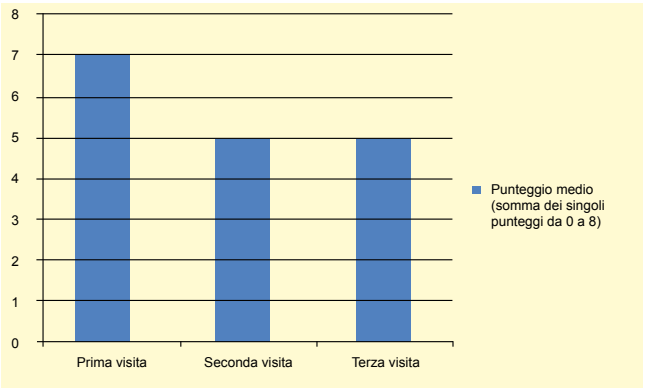

Grafico 4: Valutazione del dolore nel compiere altre attività (salire le scale, scendere le scale, inginocchiarsi e accosciarsi, camminare su terreno accidentato, tutti da 0 a 2 punti).

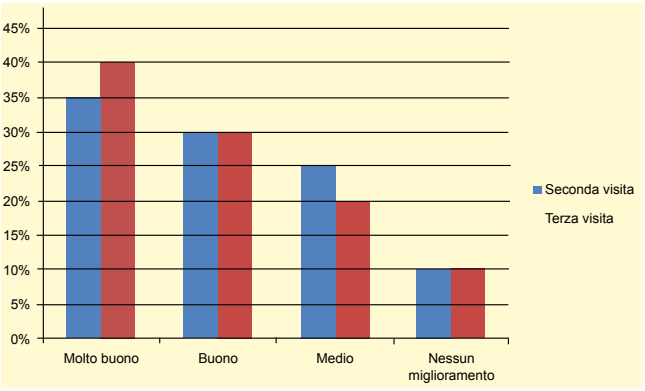

Grafico 5: Giudizio sulla terapia espresso dai pazienti alla seconda (60 giorni dall'inizio della terapia) e alla terza visita (90 giorni dall'inizio della terapia).

Kapandjieva N. Efficiency of Collagen injections "Guna MDs" in patients with gonarthrosis, assessed clinically and by ultrasound. IOF-ECCEO12 – March 21-24, 2012 – Bordeaux, France) è stato condotto per investigare l'efficacia dei dispositivi medici iniettabili a base di collagene, MD-Knee e

MD-Matrix, nella riduzione del dolore e nel miglioramento della funzionalità nell'osteoartrosi del ginocchio sintomatica, al III e IV stadio radiologico secondo Kellgren. E' stata impiegata l'ecografia per la diagnosi del gonfiore articolare e per il monitoraggio della terapia.
Sono stati trattati 25 pazienti con età compresa tra 62 e 79 anni. I criteri di inclusione e di esclusione sono riportati nella Tabella 1.

Tutti i pazienti sono stati analizzati clinicamente per mezzo di una valutazione radiografica e ecografica dell'articolazione. I pazienti hanno compilato questionari prima del trattamento, a 60 giorni dall'inizio del trattamento e a 90 giorni, esprimendo un giudizio sul dolore a riposo e sul dolore durante il movimento, utilizzando una scala VAS a 10 punti. Inoltre, è stata fatta una stima tramite l'Indice Algofunzionale di Lequesne sulla gonartrosi e i pazienti e i medici hanno espresso un giudizio sull'efficacia del trattamento. Le ginocchia di tutti i pazienti sono state esaminate con ecografia prima dell'inizio della terapia, dopo 30 giorni e al termine della terapia.
E' stata iniettata a livello periarticolare una combinazione di MD-Knee e MD-Matrix secondo il seguente schema: 2 volte alla settimana per le prime due settimane, 1 volta alla settimana per le 6 settimane successive, per un totale di 8 settimane di trattamento.
Il punteggio medio sulla VAS del dolore a riposo si riduce a un terzo al termine del trattamento e si mantiene anche dopo il trattamento (Grafico 6).
Il punteggio medio sulla VAS del dolore durante il movimento si riduce alla metà al termine del trattamento e continua a diminuire 30 giorni dopo il termine del trattamento (Grafico 7).
Si osserva un miglioramento in tutti gli indicatori dell'Indice Algofunzionale di Lequesne. I più significativi sono la rigidità mattutina, che diminuisce a meno della metà al termine della terapia e si mantiene anche 30 giorni dopo il termine (Grafico 8), e il dolore stando in piedi, che si riduce a un terzo alla terza visita (Grafico 9).

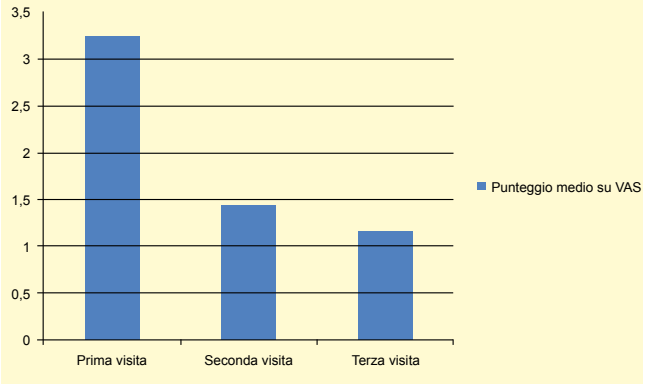

Grafico 6: Valutazione del dolore a riposo da parte dei pazienti su scala VAS (da 0 a 10).

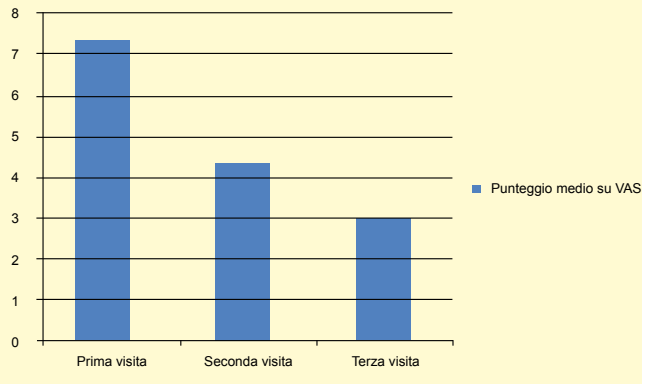

Grafico 7: Valutazione del dolore durante il movimento da parte dei pazienti su scala VAS (da 0 a 10).

Il punteggio medio per il dolore alla deambulazione dimi-

Criteri di inclusione	Criteri di esclusione
1. Gonartrosi al III e IV stadio radiologico secondo Kellgren	1. Malattie infiammatorie articolari
2. Gonfiore articolare ecograficamente comprovato	2. Malattie autoimmunitarie
3. VAS del dolore > 25 mm	3. Gotta
4. Indice Algofunzionale di Lequesne > 7	4. Malattie maligne
	5. Pregressi traumi o interventi chirurgici al ginocchio
	6. Terapie condroprotettive concomitanti
	7. Supporto fisioterapico

Tabella 1: Criteri di inclusione e di esclusione.

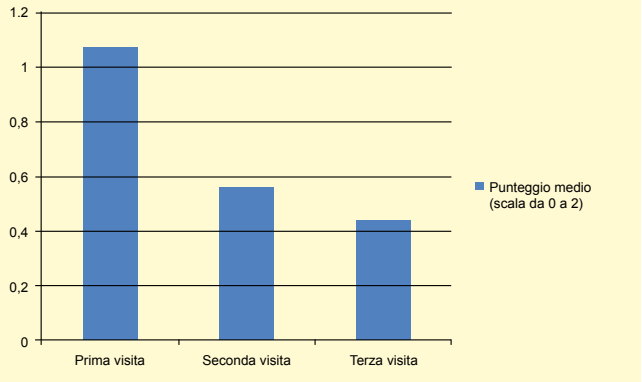

Grafico 8: Valutazione della rigidità mattutina.

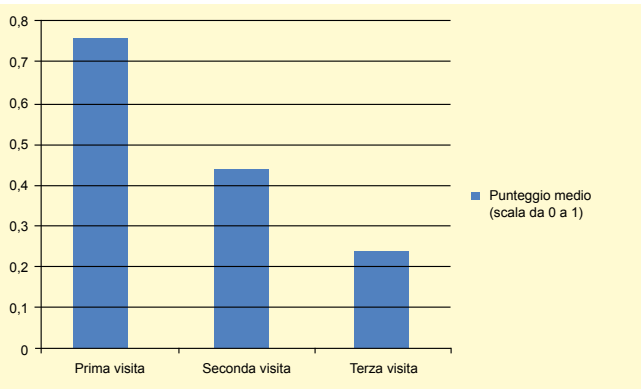

Grafico 9: Valutazione del dolore stando in piedi.

nuisce di 1,5 volte alla terza visita, rispetto al valore medio iniziale (Grafico 10).

Il punteggio medio per la massima distanza percorribile

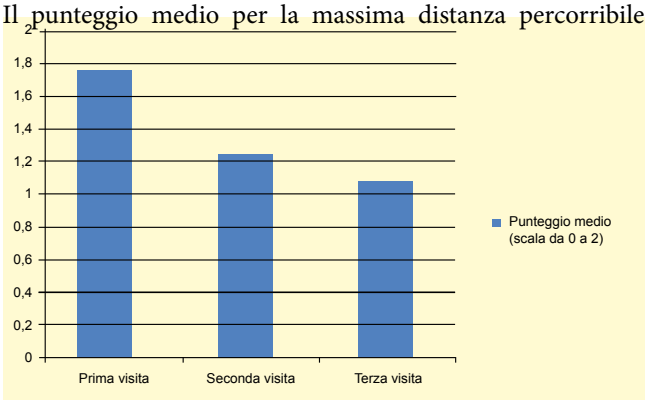

Grafico 10: Valutazione del dolore alla deambulazione.

camminando si riduce di 1,5 volte alla terza visita, rispetto al valore medio iniziale (Grafico 11).
Non si sono riscontrati effetti collaterali a seguito della terapia.

Alcune immagini ecografiche consentono di apprezzare l'an-

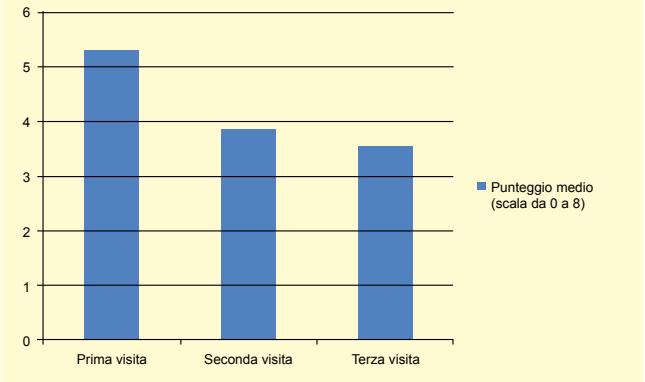

Grafico 11: Valutazione della massima distanza percorribile camminando.

damento del gonfiore articolare (Figure 1 e 2).
La valutazione ecografica dell'edema articolare del ginocchio

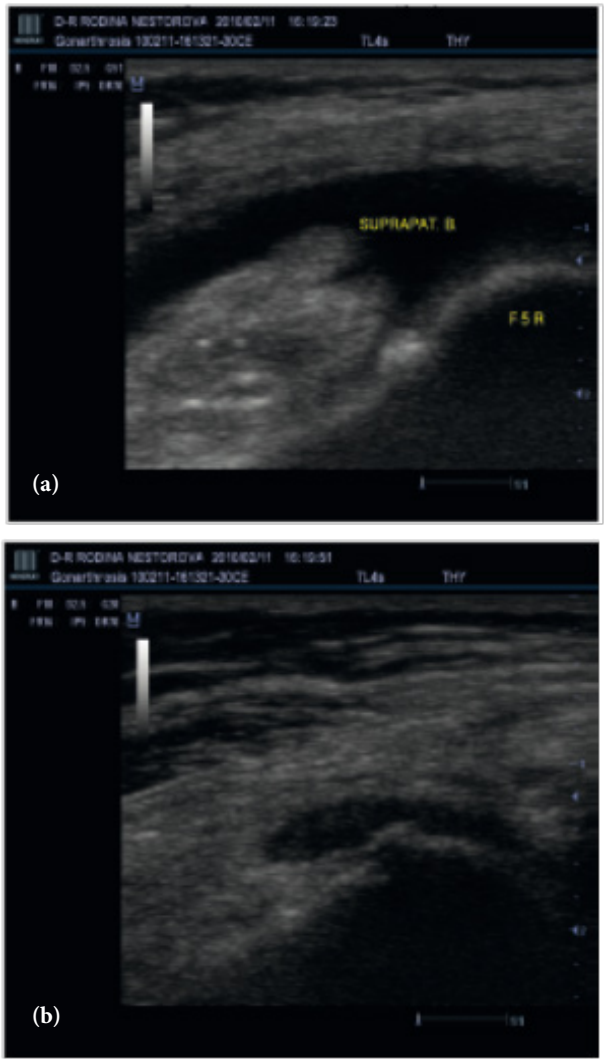

Figura 1: La borsa sovrapatellare appare ampliata ed edematosa prima del trattamento (a), mentre si osserva una marcata riduzione dopo il trattamento (b).

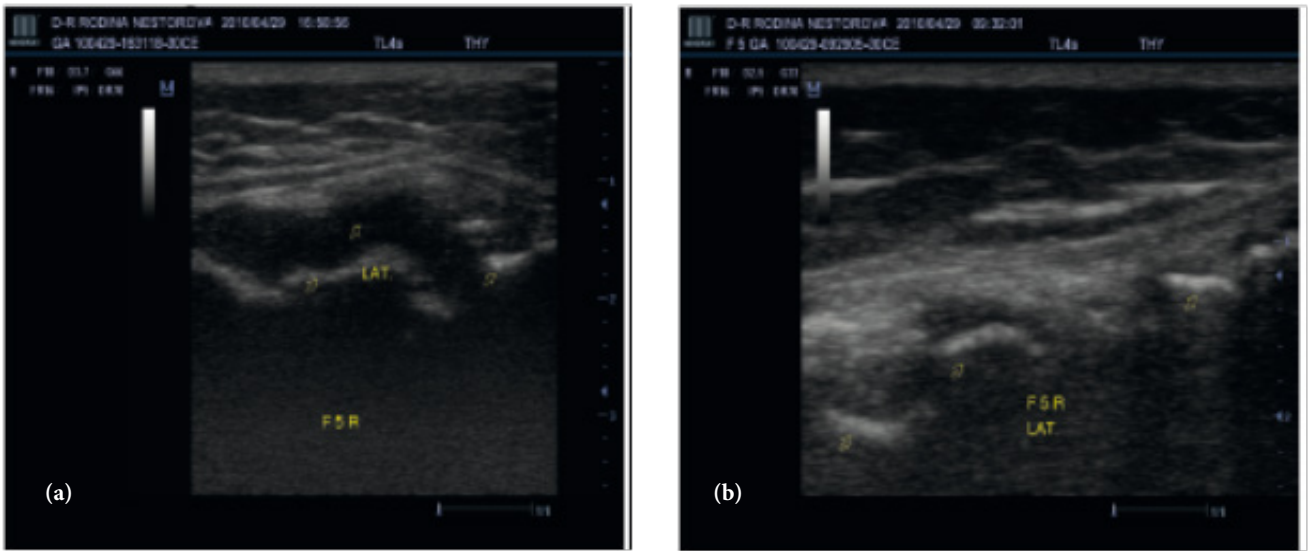

Figura 2: Si nota l'edema nello spazio articolare – accesso laterale – prima del trattamento (a). L'edema è scomparso al termine del trattamento (b).

condotta 30 giorni dopo il trattamento con la combinazione di MD-Knee e MD-Matrix mostra che il 60% dei pazienti risulta privo di edema e il 30% di essi ha avuto una riduzione (Grafico 12).
La valutazione dell'efficacia del trattamento con i *Collagen Medical Device* al 60° e al 90° giorno mostra che il giudizio più ricorrente è "molto buono" (Grafico 13 e Grafico 14).
Le conclusioni tratte dagli autori dello studio clinico sono:

- la somministrazione periarticolare di Md-Knee e MD-Matrix nella gonartrosi al III e IV stadio radiologico migliora lo stato del ginocchio e la qualità di vita dei pazienti. Si osserva:
  - riduzione statisticamente significativa del dolore a riposo e durante il movimento;
  - miglioramento statisticamente significativo di tutti gli indicatori dell'Indice Algofunzionale di Lequesne;
  - miglioramento dello stato edematoso nel 90% dei casi, comprovato ecograficamente;
- l'effetto continua a sussistere dopo il termine del trattamento;
- i dispositivi medici in oggetto hanno un profilo di sicurezza molto buono;
- il giudizio sull'efficacia è stato "molto buono" o "buono" per il 68% dei pazienti e per il 72% dei medici;
- l'ecografia rimane una tecnica comprovata per la valutazione dell'edema articolare e per il monitoraggio della terapia.

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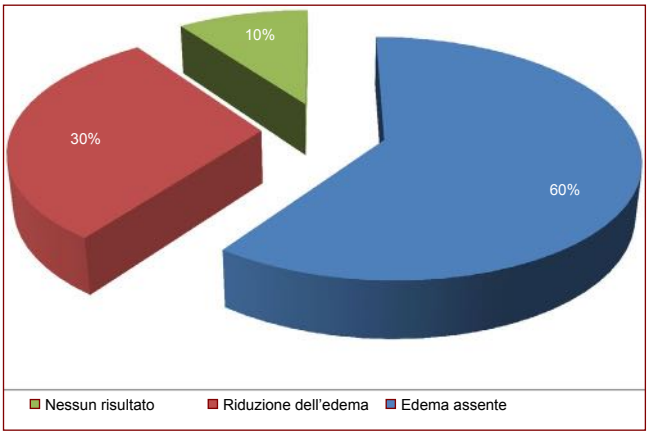

Grafico 12: Effetti della terapia sull'edema articolare stimati per mezzo di controllo ecografico.

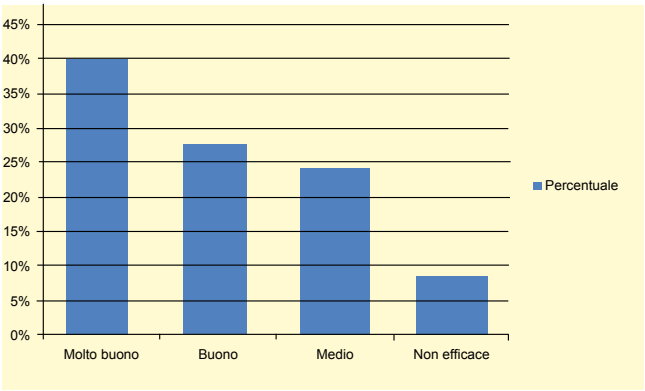

Grafico 13: Giudizio sull'efficacia espresso dai pazienti alla terza visita.

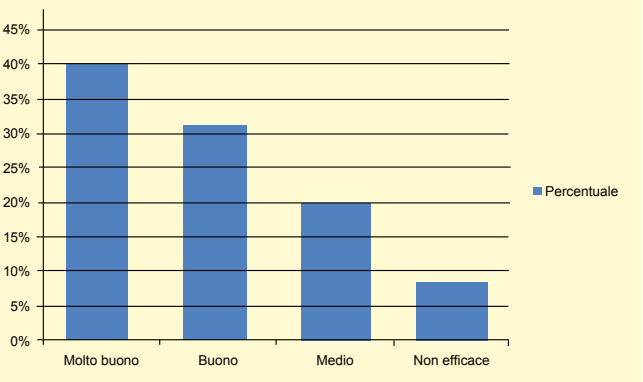

Grafico 14: Giudizio sull'efficacia espresso dai medici alla terza visita.

Uno studio di coorte (Migliore A, Massafra U, Bizzi E, Vacca F, Tormenta S. Intra-articular administrations of MD-Hip in 7 patients with symptomatic osteoarthritis of the hip unresponsive to viscosupplementation. A 6 month cohort study. International Symposium Intra Articular Treatment. 6-8 october 2011 – Rome, Italy) durato sei mesi è stato realizzato per verificare l'efficacia e il profilo di sicurezza di MD-Hip in 7 pazienti affetti da osteoartrosi dell'articolazione dell'anca non responsivi nei confronti della viscosupplementazione con acido jaluronico (6 pazienti) o hylan (1 paziente). Sono stati trattati pazienti adulti sofferenti di osteoartrosi di grado da I a III secondo Kellgren e Lawrence, già trattati precedentemente con almeno 2 iniezioni ecoguidate di acido jaluronico o hylan senza che si riscontrassero benefici.
A 7 pazienti è stata praticata 1 iniezione ecoguidata di MD-Hip (2 fiale per un totale di 4ml). Il periodo di *follow-up* è stato di 6 mesi. La valutazione dell'efficacia è stata condotta per mezzo dell'indice di Lequesne e di una scala VAS per il dolore. Si è anche tenuto conto del consumo di FANS comparando il dato precedente il trattamento con il dato riguardante il periodo di *follow-up* (Tabella 2).
Non si sono manifestate complicanze di tipo infettivo. Un paziente ha riportato un transitorio stato di disagio nell'articolazione trattata, spontaneamente regredito nell'arco di un giorno dall'iniezione.
Le conclusioni tratte dagli autori dello studio clinico sono:

- i dati raccolti suggeriscono che i benefici risultati ottenuti con le iniezioni intra-articolari ecoguidate nell'articolazione dell'anca possono essere notati sin dalla prima iniezione e si mantengono per 6 mesi;
- MD-Hip ha dimostrato di essere efficace e sicuro in pazienti affetti da OA dell'articolazione dell'anca non responsivi nei confronti di precedenti terapie viscosupplementative con acido jaluronico o hylan;
- i dati preliminari introducono nuovi scenari per l'investigazione nel campo della terapia intra-articolare.
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Uno studio clinico (Posabella G. Utilità di Medical Device nella terapia post traumatica della spalla. Secondo Convegno di Traumatologia Clinica e Forense – 9° Corso di Ortopedia, Traumatologia e Medicina Legale. 25 – 26 Novembre 2011. Salsomaggiore Terme (PR), Italy) è stato condotto con lo scopo di valutare l'efficacia di un trattamento con MD-Shoulder, nella riduzione del dolore a riposo e nel miglioramento della funzionalità della spalla, in pazienti praticanti attività sportiva, che abbiano subito un trauma.

I criteri di inclusione nello studio sono stati:
- dolore post traumatico alla spalla;
- alterata escursione articolare passiva e alterata funzionalità della spalla.

I criteri di esclusione:
- pazienti post intervento chirurgico;
- lesioni ossee e legamentose, accertate tramite RX ed ecografia.

Sono stati studiati 18 pazienti, atleti amatori e dilettanti di varie discipline sportive, che avevano subito un trauma da caduta o da incidente di gioco.
Età media 34 D.S. ± 8,9 altezza D.S. ± 5,7 peso 69 D.S. ± 7,3 .
Tutti i pazienti hanno riferito dolore a riposo e durante il movimento, nessun paziente aveva effettuato in precedenza un programma riabilitativo.

I pazienti sono stati trattati 2 volte alla settimana con MD-

Parametro	Valore prima del trattamento	Valore medio dopo 3 mesi	Valore medio dopo 6 mesi
VAS dolore OA	6,15	4,23*	4,23*
Indice di Lequesne	7,94	5,9*	5,83*
Consumo di FANS	7,57	4,25*	5,78*

Tabella 2: Risultati (* miglioramento statisticamente significativo).

Shoulder, somministrato con propulsione di ossigeno puro fino al 98% e a 3,5 atm di pressione, per un periodo di 5 settimane equivalente a 10 somministrazioni complessive. La durata di ogni seduta di trattamento è stata di 30 minuti.
All'inizio e alla fine del periodo di trattamento, ogni paziente ha compilato un questionario sulla funzionalità e sintomatologia della spalla *(Shoulder Rating Questionnaire)*.
Il questionario prevedeva sia domande riguardanti le caratteristiche e l'intensità del dolore sia il grado di difficoltà nell'utilizzo della spalla durante attività funzionali e lavorative.
Il punteggio del questionario compilato dai pazienti prima del trattamento andava da un minimo di 12 (situazione peggiore) ad un massimo di 75 (situazione migliore).
Le conclusioni tratte dall'autore sono state:

- tutti i pazienti hanno indicato un aumento nel punteggio del questionario al termine delle 10 sedute di trattamento (Grafico 15);
- l'analisi statistica del campione ha evidenziato una differenza significativa tra i dati raccolti prima e dopo il trattamento.
- il trattamento si è rivelato utile nel diminuire il dolore dal quale dipendevano le limitazioni funzionali;
- le caratteristiche e l'intensità del dolore descritte dai soggetti inseriti nello studio, ossia prevalentemente a riposo e con accentuazione durante il movimento, sono migliorate.

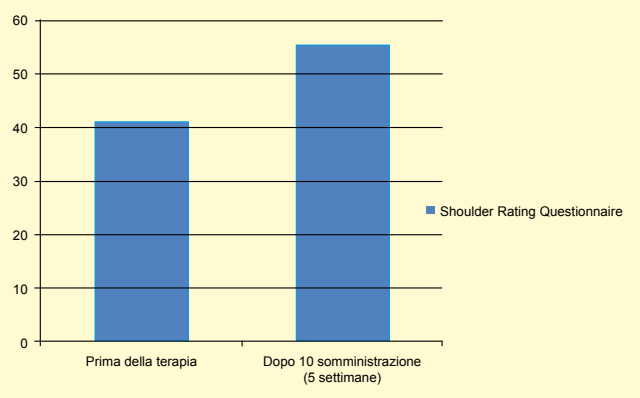

Grafico 15: confronto tra il punteggio medio del Shoulder Rating Questionnaire prima e dopo la somministrazione di MD-Shoulder (media prima della terapia = 42 ± 14,2; media dopo la terapia 55 ± 11,0).

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Uno studio clinico (Zocco R, Criscuolo S, Lorenzetti N, Senesi M. Effectiveness of integrated medicine in the control of pain in vertebral disorders: observational study. Poster Presentation 5th European Congress for Integrative Medicine. European Journal of Integrative Medicine 2012; 4S: 140) è stato condotto con lo scopo di valutare l'efficacia della Medicina Integrata (terapie manipolative secondo Maigne e Agopuntura associate a Collagen Medical Devices) nel controllo del dolore nelle patologie del rachide.
Tra gennaio 2010 e giugno 2011, 60 pazienti (19 maschi e 41 femmine, età compresa tra 19 e 70 anni, età media 45,08±13,52) affetti da patologie della colonna (disturbi intervertebrali minori lombari - MIDs - 92%, MID dorsali 68%, MID sacrali 39%; nel 37% dei soggetti erano compresenti MID lombari e dorsali, mentre il coinvolgimento dorsale e sacrale era presente nel 13%) da almeno 6 mesi e resistenti alle terapie fisiche e farmacologiche sono stati arruolati nell'U.O. Riabilitazione e Rieducazione Funzionale e presso l'Ambulatorio di Medicina Integrata per il Dolore dell'ASL 7 di Siena.
La terapia manipolativa prevedeva sessioni di 3 settimane consecutive. L'agopuntura e i trattamenti con Collagen Medical Device sono stati somministrati settimanalmente per 10 settimane. Le valutazioni sono state condotte al 3°, al 6°e al 12° mese dopo il termine dell'ultima seduta di terapia.
Alla prima valutazione il 40% dei soggetti con limitazione funzionale localizzata al periostio degli elementi del rachide dorsale mostravano SVS (cell-syndrome-myalgic-spinal-segmental), presente solo nel 20% dei pazienti a 3 mesi dal termine del trattamento. Dopo 6 e 12 mesi si è osservata un'inversione dell'andamento (60%). Il 57,9% dei soggetti con alterazioni algiche del distretto dorsale presentavano UAT (lumbar-myalgia syndrome cell-periosteum-spinal-segmental) prima del trattamento; tale percentuale si è ridotta al 36,8% dopo 12 mesi. Disordini funzionali della cerniera lombo-sacrale sono stati riscontrati nel 46,2% dei casi alla prima visita, nel 30,8% dopo 3 e 6 mesi e nel 38,5% dopo 12 mesi. Prima del trattamento il 75% dei soggetti presentava dolore severo, mentre la percentuale è scesa al 19,1% dopo 3 mesi e all'11,8% al sesto e al dodicesimo mese. Nei soggetti con esclusivo coinvolgimento delle vertebre dorsali il controllo del dolore è variato dal 40% dei soggetti prima del trattamento al 20% al terzo mese, al 40% al sesto mese e al 20% al dodicesimo mese. Nei pazienti con coinvolgimento lombare la presenza del dolore è stata registrata nell'80,4% dei casi prima del trattamento, al 18,5% tra 3 e 6 mesi e al 10,9% dopo un anno.
Gli autori concludono che il beneficio derivante dalle manipolazioni secondo Maigne appare più evidente a breve termine, mentre i benefici derivanti da agopuntura e Collagen Medical Device appaiono più evidenti a lungo termine.

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A latere si vogliono citare 2 lavori clinici di particolare interesse, non inclusi in questa overview poiché i *Collagen Medical Device* utilizzati sono stati impiegati non da soli ma in associazione con farmaci omeopatici iniettabili:

- Posabella G. Terapia della condropatia femoro-

rotulea con MD-Knee+ZEEL® T veicolati con propulsione di O_2 vs nimesulide+condroitinsolfato. La Med. Biol., 2011/3; 3-11

- Mariconti P., Milani L. Terapia infiltrativa *low dose* della tendinopatia degenerativa di caviglia in danzatori professionisti. La Med. Biol., 2012/3; 15-34

CONCLUSIONI

L'introduzione in terapia dei *Collagen Medical Device* rappresenta un'interessante novità nel panorama del trattamento delle affezioni osteo-artro-mio-fasciali benigne.
I *Collagen Medical Device* offrono un'alta versatilità d'uso: possono essere utilizzati da soli o in associazione con farmaci antinfiammatori di sintesi o omeopatici, o in associazione con trattamenti di viscosupplementazione con acido jaluronico.
Dall'analisi della rassegna di 4 degli studi condotti tra il 2010 ed il 2012 in Europa sui *Collagen Medical Device* emerge:

- altissima tollerabilità e sicurezza d'uso;
- efficacia non inferiore a trattamenti di viscosupplementazione;
- durata degli effetti positivi del trattamento oltre i 6 mesi.

Ringraziamenti

Si ringrazia il Dr. Enrico Baldini per la consultazione della sua tesi di specializzazione in Medicina Fisica e Riabilitazione presso la facoltà di Medicina e Chirurgia dell'Università degli Studi di Firenze, dal titolo: "Terapia iniettiva intrarticolare nella gonartrosi. Confronto tra acido jaluronico e collagene".

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SHORT COMMUNICATION

R. Zocco, S. Criscuolo, N. Lorenzetti, M. Senesi

EFFECTIVENESS OF INTEGRATED MEDICINE IN THE CONTROL OF PAIN IN VERTEBRAL DISORDERS: OSSERVATIONAL STUDY

AIM

To evaluate the effectiveness of integrated medicine [manipulative therapies according to R. Maigne and acupuncture associated to Medical Device (MD-Lumbar)], in the control of pain in vertebral disorders.

MATERIALS AND METHODS

From January 2010 to June 2011, **60 patients** with vertebral disorders lasting at least for six months and resistant to pharmacological and physical therapies, were enrolled at the UO Riabilitazione e Rieducazione Funzionale (Hospital Department for Rehabilitation and Functional Rehabilitation) and at the Ambulatorio di Medicina Integrata per il Dolore (Consulting room of Integrated Medicine) of the ASL 7 of Siena, Italy. Manipulative therapies comprised of three consecutive weekly sessions. Acupuncture and MD-Lumbar treatments were done weekly for ten weeks. Therapy effects were valuated three, six and twelve months after the end of the last session.

RESULTS

19 males and **41 females**, aged between 19 and 70 years (mean age 45.08 ± 13.52 SD) were included in the study. Lumbar minor intervertebral disorders (MID) were observed in 92% of cases; dorsal in 68%; sacral in 39. Lumbar and dorsal MID were present in 37% of subjects, while both the lumbar-sacral involved 13% of patients. At first evaluation, 40% of patients with functional impairment at the dorsal periosteum location showed cell-syndrome-myalgic-spinal-segmental (SVS), reduced to 20% at three months from the end of treatments.
Six and twelve months after, we observed a reverse trend (60%).
57.9% of patients with dispatch of the district had lumbar-myalgia syndrome cell-periosteum-spinal-segmental (UAT) before treatments (36.8% at 12 months).
Functional disorders of the hinge lumbo-sacral segmental clinical manifestations were found in 46.2% of cases at the first visit (30.8% at three months, 30.8% at six months, 38.5% at one).

CONCLUSION

The benefits arising from the manipulative treatment according to Maigne are more evident in the short term, while those concerning acupuncture and Collagen MD were more evident in the long term. ■

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ОРИГИНАЛНИ СТАТИИ / oRIGINAL PAPERS

ОЦЕНКА НА ЕФЕКТА И ПОНОСИМОСТТА НА КОМБИНИРАНО ЛЕЧЕНИЕ С АМПУЛИ КОЛАГЕН GUNA MD - LUMBAR И GUNA MD - ISCHIAL ПРИ БОЛНИ С ЛУМБАЛНА ДИСКОВА ХЕРНИЯ

РЕЗЮМЕ

ОЦЕНКА НА ЕФЕКТА И ПОНОСИМОСТТА НА КОМБИНИРАНО ЛЕЧЕНИЕ С АМПУЛИ КОЛАГЕН GUNA MD - LUMBAR И GUNA MD - ISCHIAL ПРИ БОЛНИ С ЛУМБАЛНА ДИСКОВА ХЕРНИЯ

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Колагенът е най-широко разпространения протеин в човешкия организъм. Колагеновата решетка (матрикс) се съдържа в междупрешленните дискове, лигаментите, мускулите и сухожилията, осигуряващи подвижността и стабилността на гръбначния стълб. Нарушенията в структурата на екстрацелуларния матрикс улесняват дисковото херниране в лумбалната област, което е честа причина за поява на болка в кръста. Терапията с ампули колаген е нов физиологичен подход за нейното лечение.

При 25 болни с дискови херии в лумбалната област са прилагани интрамускулно паравертебрално два вида ампули, съдържащи колаген - GUNA MD - Lumbar и GUNA MD - Ischial. Лечението е провеждано в амбулаторни условия по схема, която включва общо 10 процедури. При 64% от пациентите болката е хронична, с давност над 6 месеца. Интензитетът й по VAS в началото на лечението е средно 6,6 т., а в края - 1,6 т. ($p < 0,001$), като при 12 пациенти (52%) липсва болка.

79% от пациентите оценяват ефекта от лечението като «много добър» и «добър».

Не са наблюдавани странични ефекти и нежелании лекарствени реакции.

Ключови думи: дискова херния, колаген, GUNA

ABSTRACT

EFFICACY AND SAFETY OF COMBINED TREATMENT WITH COLLAGEN INJECTIONS GUNA MD - LUMBAR AND GUNA - MD ISCHIAL IN PATIENTS WITH LUMBAR DISC HERNIATION

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Collagen is the most abundant protein in the human body. The collagen reticulum (matrix) is widely spread in the intervertebral discs, ligaments, muscles and tendons. These structures are responsible for the mobility and stability of the spinal column. Structural impairments of the extracellular matrix facilitate lumbar disc herniation and collagen injections are a new physiological therapeutical approach.

GUNA MD Lumbar and GUNA MD Ischial are used as paravertebral intramuscular injections in 25 patients with lumbar disc herniations. The treatment is performed as outpatient by special protocol including 10 procedures.

64% of patients have chronic low back pain (more than 6 months of duration). According to VAS intensity of low back pain is 6.6 scores in the treatmen's begining and 1.6 scores ($p < 0,001$) in the end of observation (52% have 0 points).

79% of patients estimate efficacy as «very good» or «good» and no side effects are observed.

Key words: collagen, disc herniation, GUNA

Болката в лумбална област е сред най-често срещаните оплаквания в ежедневната неврологична практика. Обичайно тя е проява на структурни и дегенеративни промени на тъканите около и между прешлените - междупрешленни дискове, междупрешленни стави, връзките около гръбначния стълб, мускулите и техните сухожилия. Лумбалната дискова херния е причина за остро настъпили болки в кръста при около 8% -10% от пациентите с лумбалгия. Този процент обаче нараства до 40% за хроничната болка в тази анатомична област (1). Междупрешленните дискове са хрущялни структури, които придават гъвкавост на гръбначния стълб и поемат натоварванията на гръбнака при ходене, скачане, навеждане, вдигане на различни по тежест предмети. Носещата мрежа (матрикс) в тези хрущялни сруктури е изградена от колаген. Колагеновата решетка е в основата и на връзките (лигаментите), мускулите и сухожилията, обграждащи и даващи стабилност на гръбначния стълб. В обвивките на нерва също има колагенова мрежа, както и в меките тъкани около структурите на гръбнака (междуклетъчното пространство, съединителната тъкан). С възрастта или под влияние на други фактори колагеновата решетка отслабва, дефрагментира се, което води до намаляване здравината на структурите, които изгражда (2). Това скъсява времето до появата на първите болки в кръста и първите симптоми на радикулопатия от дискова херниране. Болката и ограничението на движенията в кръста са основните симптоми при дискова херния. Ензимът фосфолипаза А2 освобождава арахидонова киселина от клетъчните мембрани, а тя е основния медиатор на неврогенното възпаление и отока на нервните коренчета. Болката се дължи на цитокините в съдържанието на интервертебралния диск (1, 5).

Лечението на острата болка в кръста (ноцицептивна или невропатна) обичайно включва миорелаксанти, НСПВС, аналгетици, вкл. опиатни такива, кортикостероиди, физиотерапия. Хронифицираната лумбалгия най-често е със смесена патогенеза (ноцицептивна и невропатна) и за нейното терапевтично повлияване е необходимо към комплексното лечение да се добавят антиконвулсанти (Gabapentine, Pregabalin) и антидепресанти (трициклични и SNRI).

Терапията с ампули, съдържащи колаген и допълнителни съставки от природен произход, е един нов физиологичен подход при повишаването на качеството на живот на тези пациенти (4). За разлика от всички гореспоменати стандартни лечебни въздействия, инжекционният колаген укрепва и усилва хрущялните структури, изграждащи междупрешленния диск, както и всички околопрешленни структури - връзки, сухожилия, междуклетъчно пространство на съединителната тъкан. Укрепва се и обвивката на нерва, което спомага за възстановяването му при компресия (3).

Ампулите колаген се прилагат инжекционно: локално подкожно, локално мускулно, вътреставно и околоставно. Благодарение на допълнителните съставки в тях, колагенът достига до желаната прицелна локализация. Освен това ампулите колаген могат да се използват и с физиотерапевтичен апарат - Гунафореза, който посредством резонансна магнитофореза, дава възможност за голяма дълбочина на проникване в тъкани и стави, и висок процент на абсорбция на препарата (4).

Целта на настоящото открито пост-маркетингово проучване е да се оценят ефикастността и поносимостта от локалното паравертебрално интрамускулно приложение на ампули колаген (GUNA MD - Lumbar и GUNA MD - Ischial) при болни с лумбална дискова херния.

Контингент и методики

В проучването бях включени 25 болни - 9 жени и 16 мъже на възраст от 27 г. до 83 г. (средна възраст 51.36 г.) с дискови хернии в лумбалния отдел на гръбначния стълб, установени посредством невроизобразяващи методи - компютърна томография или магнитно-резонансна томография. При 6 от тях дисковата херния е на ниво L4-L5, при 5 - на ниво L5-S1, а при 14 са установени дискови хернии на две и повече нива (от L2-3 до L5-S1). Давността на заболяването е както следва: до 1 месец - при 4 болни (16%); до 6 месеца - при 5 болни (20%) и над 6 месеца- при 16 болни (64%), като при някои от тях хронично рецидивиращата болка е от 10 и повече години. Участието в проучването се осъществяваше по определен, създаден за целта протокол, след подписване на информирано съгласие. Оценявани бяха давността на заболяването, наличието на предхождаща медикаментозна и/или физиотерапия (преустановени най-малко 72 часа преди началото на лечението с ампули колаген), интензитета на болката по визуалната аналогова скала (VAS) от 0 до 10 точки, наличието на разтежни феномени, вертебрален синдром, разстояние «пръсти-под».

Ампулите колаген се прилагаха като монотерапия, локално паравертебрално в лумбалната област, в точката на максимална изразеност на палпаторната болезненост, предизвикана от дозиран натиск. Схемата на приложение включваше общо 10 еднократни апликации, първоначално в три поредни дни, последвани от две инжектирания седмично за две седмици и по една процедура седмично в следващите три седмици. При всичките включени в проучването пациенти тази терапия е предхождана от различно по продължителност лечение с НСПВС, съчетано с миорелаксант и/или физиотерапевтични процедури, което е било без съществено повлияване на основните им оплаквания.

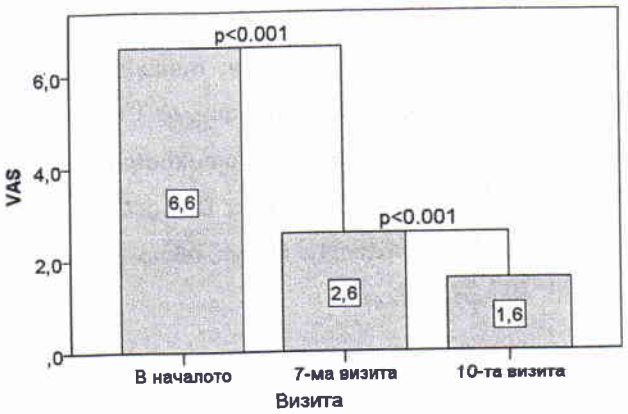
Оценката на субективните болкови прояви и на промените в неврологичния статус се осъществяваше трикратно - преди първата апликация, на седмата и на десетата процедура. В края на лечебния курс се извършваше комплексна оценка на ефективността от проведеното лечение по 5 - степенна скала: много добра, добра, задоволителна, слаба и липсваща. Поносимостта към ампулите колаген се оценяваше като: много добра, добра, задоволителна и наличие на странични нежелании реакции.

Резултати

Две от участничките не завършиха проучването. Отказът им беше съответно на 5-та и на 8-ма апликация, поради липса на лечебен ефект. При останалите 23 терапевтичната схема беше осъществена изцяло, по протокол.

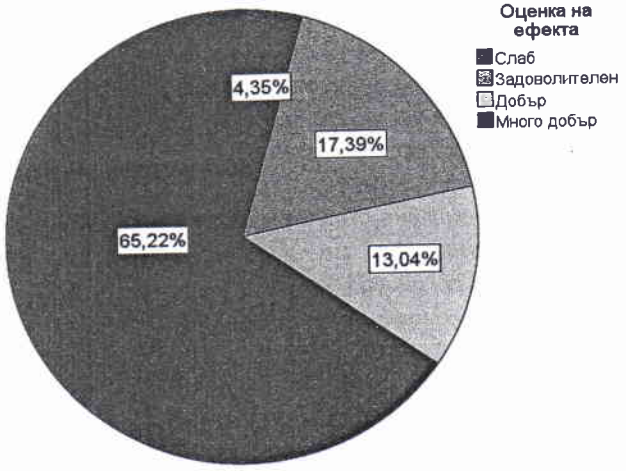
Основните субективни оплаквания на пациентите бяха от болка в лумбалната област с или без иррадиация към долните крайници. Част от болните съобщаваха за наличие на «схованост» и ограничение на движенията в кръста, изтръпване и парестезии в някой от двата крака.

Изходните стойности на лумбалгията, оценявана по VAS вариираха от 6 т. до 10 т. (средна стойности 6,6 т.). На 7-ма визита стойностите намаляват на 2,6 т. ($p < 0,001$), а на 10-та - на 1,6 т ($p < 0,001$), като при 12 пациенти (52%) VAS е = на 0 т. в края на проследяването. (**фиг.1**). Не се установи наличие на зависимост между първоначалния интензитет на болката (спонтанна и провокирана) и крайната й оценка на десетата визита. Подобряването на болковия синдром обичайно настъпваше между третата и петата апликация на GUNA MD - LUMBAR И GUNA MD - ISCHIAL. Успоредно с намаляването на интензитета на болката се отчиташе и регрес в разтежните феномени (на Ласег, на Нери и на Боне), намаляване на изразеността на вертебралния синдром и скъсяване на разстоянието "пръсти - под" (от 50 - 60 см на 0 - 10 см).



Фигура 1. Динамика на болката, оценявана по VAS

Резултатите от крайната оценка на ефекта от проведеното лечение, осъществена на десетата терапевтична процедура, са представени на **фигура 2.** При 66% (15 болни), завършили пълния лечебен курс, се отчете наличие на много добър ефект, както по отношение на субективните оплаквания, така и в обективната неврологична симптоматика. Трима пациенти (13%) оцениха ефекта като "добър"; четирима (17%) " като - задоволителен" и само 1 (4%) "като - слаб".



Фигура 2. Крайна оценка от ефекта на лечението

Поносимостта към ампулите колаген при всички 23 пациенти беше много добра, при пълна липса на странични явления и нежелани лекарствени реакции (както локални, така и общи).

Обсъждане

Колагенът е най-широко разпространеният протеин в човешкия организъм. 25% до 30% от цялата ни протеинова маса се състои от колаген (4). Той се съдържа в мускулите, сухожилията, костите, ставните капсули, серозните мембрани, кожата и в извънклетъчното пространство, изграждайки екстрацелуларния матрикс. Нарушената структура на на екстрацелуларния колагенов матрикс и недостатъчното му обновяване води до забавено функциониране на транспортните системи (3). Екстрацелуларният матрикс не е статично пространство между капилярите и клетките, а морфо-функционална система, определяща непрекъснатото взаимодействие между съдов ендотел-матрикс-мембранни рецептори. В матрикса се осъществява връзката между невропептиди, цитокини и хормони (невро-имунно-ендокринна хомеостаза). Неправилното елиминиране на отпадъчните продукти е свързано с натрупване на токсични вещества, нарушено насищане на тъканите с кислород, забавено усвояване на хранителни вещества и намалено хидратиране. Дегенерацията на диска и разкъсването на anulus fibrosus при дискова херния води до натрупване на значително количество на интрадискални деградивни ензими и химически дразнители (1, 5). В биохимичен аспект дегенерацията на диска е свързана с прогресивна загуба на гликопротеини и протеогликани в междуклетъчното пространство. Настъпват промени в глюкозаминогликаните, увеличава се кератинсулфатът и се натрупва еластин (1, 2). Нарушаването на колагеновия матрикс е свързано и с намалена възможност за задържане на водни молекули. Водното съдържание на nucleus pulposus намалява с около 30% (2). Дехидратираният диск изтънява и в него се развиват фиброзни промени. Подобни дегенеративни промени настъпват и в anulus fibrosus. Колагенните

влакна набъбват и разстоянието между тях нараства. В ламеларната структура се образуват фисури и еластичността му намалява (1,5).

Терапията с ампули колаген е един нов физиологичен подход при лечението на различни възпалителни и дегенеративни заболявания на ставно-мускулно-скелетния апарат. Локалното им приложение има укрепващ колагеновите структури ефект. Малките дози колаген действат сигнално, променяйки физиологичните условия в екстрацелуларния матрикс. В резултат на това настъпва протеазна активация и стимулиране на клетъчните функции. Инхибират се процесите на апоптоза, усилва се метаболизма, като локалните възпалителни компоненти намаляват и се укрепват колагеновите тъканни структури (3, 4). Укрепва се и обвивката на нерва, което спомага за възстановяването му при компресия. Усилването на структурите води до намаляване или премахване на болката, последвано от възстановяване на движенията в конкретния гръбначен сегмент. Стимулирането на дренажа на междуклетъчното пространство от страна на колагена, неговото положително действие върху тонуса на капилярната стена и възстановителните клетъчни процеси, правят ампулите колаген решаващ фактор при намаляване на възпалителните компоненти в меките тъкани около гръбначния стълб.

Осъщественото от нас лечение на дискогенно обусловени болки в лумбалната област с два вида ампули колаген - GUNA MD - LUMBAR И GUNA MD - ISCHIAL е технически лесно изпълнимо, ефективно и безопасно. Този вид терапия може да намери широко приложение в ежедневната неврологична практика, особено при пациенти с хронифицирана лумбалгия. Отличната поносимост и липсата на нежелани странични реакции позволяват използването на тези ампули при пациенти със съпътстващи соматични заболявания (язвена болест, лошо контролирана артериална хипертония, тежък захарен диабет, бъбречна недостатъчност и др.), при които прилагането на НСПВС и кортикостероиди е ограничено или противопоказано. В подобни случаи ампулите колаген могат да бъдат обсъждани като лечение на първи избор.

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MOVEMENT DISORDERS – Bulgaria – 10/2/2013
ORIGINAL PAPERS

EFFICACY AND SAFETY OF COMBINED TREATMENT WITH GUNA MD – LUMBAR AND GUNA – MD ISCHIAL COLLAGEN INJECTIONS IN PATIENTS WITH LUMBAR DISC HERNATION

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ABSTRACT
Collagen is the most abundant protein in the human body. The collagen reticulum (matrix) is widely spread in the intervertebral discs, ligaments, muscles and tendons, these structures are responsible for the mobility and stability of the spinal column. Structural impairments of the extracellular matrix facilitate lumbar disc herniation and collagen injections are a new physiological therapeutic approach.
GUNA MD Lumbar and GUNA MD Ischial are used as paravertebral intramuscular injections in 25 patients with lumbar disc herniation. The treatment is performed as outpatient by special protocol including 10 procedures.
64% of patients have chronic low back pain (more than 6 months duration). According to VAS, intensity of low back pain is 6.6 scores in the treatment's beginning and 1.6 scores ($p < 0.001$) at the end of observation (52% have 0 points).
79% of patients estimate efficacy s very good or good and no side effects are observed.

KEY WORDS: collagen, disc herniation, GUNA.

Low back pain is one of the most frequent complaints in routine neurological practice. It is usually a symptom of structural and degenerative alterations of the tissues surrounding and between the vertebrae and intervertebral discs, intervertebral joints, the ligaments around the vertebral column and the muscles and their tendons. Lumbar disc herniation is the cause of acute pain at waist level in around 8% to 10% of patients with lumbalgia. This percentage, however, increases to up to 40% for chronic pain in the same area (1). The intervertebral discs are cartilaginous structures that guarantee the flexibility of the vertebral column and take the pressure off the spine when walking, jumping, bending over and lifting objects of varying weights. The loadbearing component (matrix) of these cartilaginous structures is made up of collagen. The collagen reticulum forms the basis of the ligaments, muscles and tendons, whilst sheathing and delivering stability to the vertebral column. A collagen network is also found in nerve sheaths and in the soft tissues surrounding the spinal structures (intercellular space, connective tissue). Ageing and other factors cause the collagen network to become loose and break up, consequently weakening the structures it constitutes (2). This decreases the time to the onset of the first pain symptoms at waist level and of the first radiculopathy symptoms secondary to disc herniation. Pain and limited waist movement are the main symptoms of disc herniation. The phospholipase A2 enzyme releases arachidonic

acid from the cell membranes and is the main mediator of neurogenic inflammation and nerve root oedema. The pain is caused by the cytokines in the intervertebral discs (1,5).

Treatment of the acute waist pain (nociceptive or neuropathic) usually includes muscle relaxants, non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, including opiate analgesics, corticosteroids and physiotherapy. Chronic lumbalgia often has a mixed pathogenesis (nociceptive and neuropathic) and treatment therefore requires the addition of anticonvulsants to the background treatment (Gabapentin, Pregabalin) and antidepressant therapy (tricyclic and SNRI).

Therapy with ampoules containing collagen and excipients of natural origin is a new physiological approach intended to improve the quality of life of these patients (4). Unlike all the standard treatment options mentioned above, collagen for injection strengthens and reinforces the cartilaginous structures and, in turn, the intervertebral discs, as well as all structures surrounding the vertebrae – ligaments, tendons and the intercellular space of the connective tissue. Nerve sheaths are also strengthened, which facilitates recovery under compression (3).

The collagen ampoules are administered by injection, in the form of a local subcutaneous or intramuscular or intra-articular or peri-articular injection. The product's excipients carry the collagen to the desired target location. Moreover, the collagen ampoules can also be used in combination with physiotherapy equipment, such as Gunaphoresis, which utilises magnetophoresis and ferromagnetic resonance to permit deeper penetration into the tissues and joints and a high product-absorption rate (4).

The aim of this open-label post-marketing study was to establish the efficacy and tolerability of the local paravertebral or intramuscular administration of collagen ampoules (GUNA MD – Lumbar and GUNA MD – Ischial) in patients with lumbar disc herniation.

Methods and materials

25 patients were included in the study – 9 women and 16 men, aged 27 to 83 years (mean age 51.36 years) with disc herniations in the lumbar spine, as established through medical neuroimaging methods (computed tomography or MRI). In 6 cases, the disc herniation was at L4-L5, in 5 cases it was at L5-S1 and in 14 cases disc herniation was observed in two or more points (from L2-3 to L5-S1). The duration of the treatment was as follows: up to 1 month in 4 patients (16%); up to 6 months in 5 patients (20%) and over 6 months in 16 patients (64%). Some patients had had chronic relapsing pain for more than 10 years. The study was conducted according to a dedicated protocol, once subjects had signed an informed consent form. Duration of the disease, administration of previous medicinal and/or physical therapy (discontinued at least 72 hours before the treatment with collagen ampoules), pain intensity (using a ten-point visual analogue scale [VAS]), presence of growth phenomena, vertebral syndrome, and finger to floor distance were recorded.

The collagen ampoules were administered as monotherapy, locally, paravertebrally in the lumbar region at the point of maximum pain on palpation, under measured pressure. The administration regimen included a total of 10 single applications, initially on three consequent days, followed by twice-weekly injections for two weeks and one weekly administration for the subsequent three weeks. In all study subjects, therapy was preceded by NSAID treatment of varying duration, combined with a muscle relaxant and/or physiotherapy intervention, without a significant impact on the subjects' main complaints.

Subjective pain symptoms and change in neurological status were assessed at three timepoints: before the first administration and at the seventh and tenth administrations. At the end of the course of treatment, overall efficacy was assessed using a ranking scale with 5 possible outcomes: very good, good, satisfactory, poor and lack of efficacy. The tolerability of the collagen ampoules was evaluated as: very good, good, satisfactory or presence of adverse drug reactions.

Results:

Two participants did not complete the study and dropped out of the study at the 5th and 8th administrations due to lack of efficacy. The full treatment regimen was administered as per the protocol in the remaining 23 patients.

The patients' main subjective complaints were low back pain with or without radiation to the lower limbs. Some of the patients reported "stiffness" and limited movements at the waist or tingling and paraesthesia in either of the lower limbs.

The baseline lumbalgia values, assessed using the VAS, varied from 6 points to 10 points (mean value of 6.6 points). At the 7th visit, the values had dropped to 2.6 points ($p<0.001$), and at the 10^{th} visit they had dropped to 1.6 points ($p<0.001$). For 12 patients (52%), the VAS score was 0 at the end of the study. **(fig. 1).** There was no relationship between initial pain intensity (both spontaneous and induced) and its final assessment at the tenth visit. The improvement in pain syndromes most frequently occurred between the third and the fifth administration of GUNA MD – LUMBAR and GUNA MD – ISCHIAL. In addition to the decrease in pain intensity, regressions in growth phenomena (as assessed using Lasegue, Neri and Bonnet tests), decreases vertebral syndrome and decreases in the finger to floor distance (from 50 – 60 cm to 0 – 10 cm) were also observed.

Figure 1. *Changes in pain assessed by VAS*

The results of the final assessment of treatment efficacy, carried out at the tenth visit are presented in **Figure 2.** In 66% (15) of patients completing the full course of treatment, a very good effect was reported, in terms of both subjective complaints and objective neurological symptoms. Three patients (13%) judged treatment efficacy to be "good"; four (17%) judged it to be "satisfactory" and only 1 patient (4%) judged it to be "poor".

Figure 2. *Final assessment of treatment efficacy*

The tolerability of the collagen ampoules in all 23 patients was very good, with a complete absence of side effects and adverse drug reactions (both local and systemic).

Discussion

Collagen is the most abundant protein in the human body, making up 25% to 30% of our entire protein mass (4). It is contained in muscles, ligaments, bones, joint capsules, serous membranes, skin and the extracellular space, where it is present in the extracellular matrix. The impaired structure of the extracellular collagen matrix and its insufficient recovery leads to slowed functioning of the transport systems (3). The extracellular matrix (ECM) is not a static space between the capillaries and the cells, rather a morphological and functional system, defining a continuous interaction between the vascular endothelium, matrix and

membrane receptors. The connection between neuropeptides, cytokines and hormones (neuro-immuno-endocrine homeostasis) takes place in the ECM. Inappropriate waste product elimination is associated with a build-up of toxic substances, impaired oxygen saturation of the tissues, decreased intake of nutritional substances and decreased hydration. Disc degeneration and annulus fibrosus tears in disc herniation lead to the accumulation of a significant amount of degradative enzymes and chemical irritants between the disks (1, 5). From a biochemical standpoint, disc degeneration is related to a progressive loss of glycoproteins and proteoglycans in the intercellular space. Changes occur in the glycosoaminoglycans and there is an increase in keratin sulfate and a build-up of elastin (1, 2). Collagen matrix impairment is associated with a decrease in the capacity to withhold water molecules and the water content of the nucleus pulposus consequently decreases by approximately 30% (2). The dehydrated disc thins and fibrotic alterations develop within. Similar degenerative alterations also occur in the annulus fibrosus. The collagen fibres swell and the distance between them increases. Fissures form in the lamellar structure and elasticity decreases (1, 5).

Treatment with collagen ampoules is a new physiological approach to the treatment of different types of inflammatory and degenerative musculoskeletal disease and their local administration has a strengthening effect on the collagen structures. The small doses act singularly, altering the physiological conditions within the extracellular matrix. This causes protease activation and the stimulation of cell functions. Apoptotic processes are inhibited, and metabolism is boosted, whilst local inflammation decreases and the collagen tissue structures strengthen (3, 4). Nerve sheaths are also strengthened, thereby facilitating their recovery upon compression. The strengthening of the aforesaid structures leads to a decrease in or resolution of pain symptoms, followed by an improvement in the movement of the corresponding vertebral segment. The stimulation of intercellular space drainage exerted by the collagen and its positive effect on the tone of the capillary wall and cell repair process make the collagen ampoules a decisive factor in reducing inflammation in the soft tissues surrounding the vertebral column.

The treatment of discogenic pain in the lumbar region conducted with two types of collagen ampoules – GUNA MD – LUMBAR and GUNA MD – ISCHIAL is technically easy, efficacious and safe. This type of therapy can find broad application in routine neurological practice, particularly in patients with chronic low back pain. The excellent tolerability and lack of adverse drug reactions make the use of these ampoules suitable even in patients with concomitant conditions (ulcerative disease, poorly-controlled hypertension, severe diabetes mellitus, kidney impairment etc.), where the use of NSAIDs and corticosteroids is limited or contraindicated. In such cases, the collagen ampoules can be considered as the treatment of election.

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CLINICAL

E. Milano

COLLAGEN MEDICAL DEVICE LUMBAR IN THE COMBINED TREATMENT OF LUMBAR INSTABILITY-INDUCED PAIN

SUMMARY

Spondylolisthesis is a mechanical alteration in the physiological vertebral structure that is primarily characterised by the forward displacement of a part of or whole vertebra on to that below.
The L-S rachis segment is mostly interested.
There are 3 kinds of Spondylolisthesis: dysplastic, due to osteo-articular congenital alterations; isthmic, characterized by a continuous lesion of the isthmus; degenerative.

– The aim of this study is to verify if a combined treatment, Physiokinesitherapy + ultrasound-guided injection of Collagen MD (Medical Device)-Lumbar, may provide more important and durable clinical results rather than Physiokinesitherapy alone.
– 20 patients, F and M, aged between 40 and 75, have been enrolled; all of them suffering from grade 1 and 2 Spondylolisthesis.

They were randomised to 2 Groups (10 + 10 patients), a treated Group (T) and a control Group (NT).
– The clinical results, evaluated at 2, 4, 8 and 12 months with the Numeric Rating Scale, the Oswestry Disability Index, the Pain Disability Index and the use of NSAIDs (number of tablets/week), allow to state that the combined treatment Physiokinesitherapy + MD-Lumbar obtains a far better and longer-lasting improvement than Physiokinesitherapy alone.

KEY WORDS **SPONDYLOLISTHESIS, MEDICAL DEVICE LUMBAR, COLLAGEN, ARTHROSIS**

INTRODUCTION

Spondylolisthesis (SL) [from the Greek *spóndilos* (vertebra) and *ólístesis* (slipping)] is a mechanical alteration in the physiological vertebral structure that is primarily characterised by the **forward displacement** (anterolisthesis) of a part of or whole vertebra onto that below.
– Although SL can affect any segment of the spine, it is the lumbar segment that is most commonly affected.

Various authors have estimated the incidence of SL in the general population to be **3-8%**; however, it can affect up to **20%** of the individuals involved in occupational activities or sports requiring hyperlordosis (e.g. artistic gymnastics, gymnastic rings, diving, golf) or in the handling of heavy loads (e.g. weightlifting).

– Clinicians are often called on to identify the origin of spinal pain and equally frequently forget that even a moderate spinal microinstability, such as SL, may be the cause.

One particularly important anatomical point in SL is the vertebral isthmus, the element between the superior and inferior apophyses that forms a connection

between the anterior and posterior portion of the vertebra.

Undoubtedly, one of the least resistant points of the spine is the **lumbosacral junction (L5-S1)**, where the slope of the upper surface of S1 tends to cause the body of L1 to slip downwards and forwards.
– This displacement is restricted by the anatomical connections of the posterior arch of L5 and, in particular, by the isthmus.

– SL occurs when the isthmus is subject to interruption or destruction.
Furthermore, in addition to the osteoarticular structures, whose focal point are the spinal facet joints, seat to inflammatory processes developed over time driven by the pro-inflammatory cytokine network, the tendinous and ligamentous structures (e.g. the yellow ligament), the capsular structures, the intervertebral disc, the muscle structures (the multifidus muscle and the iliopsoas muscle) and the deep *fasciae* structures are also involved in the origin of SL-induced pain (mechanical low back pain).

• There are 3 main types of SL:

DYSPLASTIC

The dysplastic form is secondary to congenital osteocartilaginous alterations in the isthmus and consists of 2 main subtypes:

1) the form that is secondary to the sagittal orientation of the articular apophyses of S1 that lose contact with L5, which therefore slips forward;
2) the form that is secondary to the pathological elongation of the isthmuses of L5.

ISTHMIC

In most cases **(80%)**, idiopathic bilateral isthmic lysis involves L5 and it is characterised by a fracture of the isthmus, which causes an increase in the size of the spinal canal, as the posterior portion remains in place

The inter-articular portion (i.e. isthmus) is the point of least resistance subject to continuous microtraumas that, together with other environmental and genetic factors, reduce its mechanical resilience.

– During development, isthmic SL often occurs following a minor trauma, thus revealing the underlying malformation.
The signs and symptoms differ from those observed in adults; young patients experience mild pain without any specific topographical location, even in the presence of significant anterior displacement.
– In some cases, the only sign is hypertonia of the posterior thigh muscles, making it difficult to flex the limb at the hip with the knee extended.

DEGENERATIVE

The degenerative form is very common and is often little considered, partly due to the minimal likelihood of efficacious treatment, which constitutes the **target of this study**.

– Unlike isthmic SL, the degenerative form causes a reduction in the dimensions of the spinal canal; the favouring factors are the degeneration of the disc and of the articular apophyses, and an excessively vertical orientation of the articular apophyses.

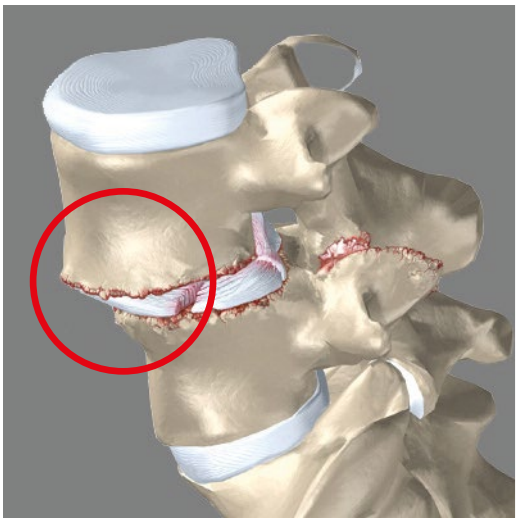
In addition to low back pain, it can also be associated with neurogenic claudication caused by spinal canal stenosis.

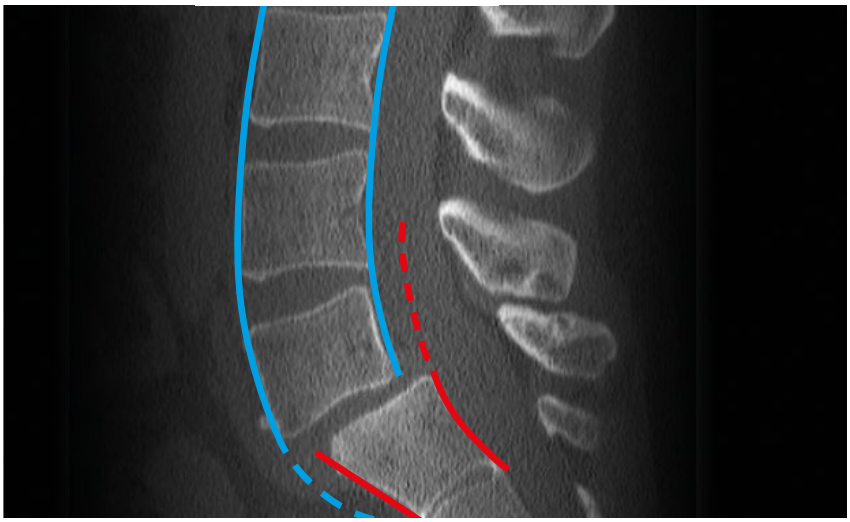
Degenerative SL affects adults; it is caused by long-standing spinal instability and by alterations secondary to the abnormal displacement of the unstable segments, i.e. **osteoarthritis** and/or **degenerative disc disease**.

This form is **4-6** times more common in **females** and affects L4 10 times more frequently; the anterior displacement can be up as much as 33%.

The degree of displacement is primarily assessed using the Meyerding Grading System, which classifies it into 4 grades:
in grade **1**, the displacement is equal to less than 25% of the upper surface of S1;
in grade **2** it is less than 50%;
in grade **3** it is less than 75%;
in grade **4**, the entity of the forward displacement can exceptionally reach 100%, with the potential displacement of L5 in the pelvis (Spondyloptosis).

– The intervertebral disc is inevitably involved; as it is no longer protected by the posterior structures, it absorbs functional overloads that exceed its anatomical characteristics, causing it to undergo a degenerative process that leads to flattening and, eventually, to herniation with an exacerbation of the pain symptoms of SL.





The nerve components are often involved with the compression of the dural sac and of the nerve roots of L5 and S1.

The severity of the SL does not often correlate with the intensity of the pain symptoms.

– The symptoms of SL are **1)** mechanical low back pain, which is made worse by movement and improves with rest;
2) irradiation of pain to the lower limbs.

– Patients often experience a worsening of the pain when changing posture (from sitting to standing).
The following symptoms are less common: discogenic low back pain that gets worse when seated and with the forward flexion of the upper body; facet joint pain that gets worse with the hyperextension of the upper body and when standing; neurogenic claudication (lower extremity asthenia when walking) caused by the spinal canal stenosis that is often present.

– Anteroposterior, laterolateral and oblique projection x-rays, in addition to a dynamic x-ray study in the position of maximum anterior flexion and maximum extension, are essential for the diagnosis of SL.
MRI is used to evaluate the possible compression of the nerve roots and any disc degeneration and/or bulging.

It is not always simple to correlate instability (such as moderate degenerative SL) with pain symptoms and it is even more arduous to identify **degenerative microinstability** at an early stage.

The real problem, however, is efficacious conservative treatment.

Most patients with SL can be treated conservatively, especially in the presence of the grade 1 and 2 degenerative forms, in which the displacement evolves in approximately **50%** of cases, depending on the case histories considered.

The conservative treatment of SL is essentially physiotherapy-rehabilitation-based: the aim is not only to strengthen the muscles of the upper body in order to stabilize the spine, but also to improve the neuromotor and proprioceptive control of the pelvic girdle muscles, antigravity muscles and respiratory muscles.

– It is, of course, essential to re-educate the patient on how to maintain a good static and dynamic posture.

In the acute phase, when the clinical situation is characterised by persistent low back pain, it is necessary to observe a suitable period of bed rest, associated with the administration of conventional and/or low-dose anti-inflammatories and muscle-relaxants, either individually or in combination.

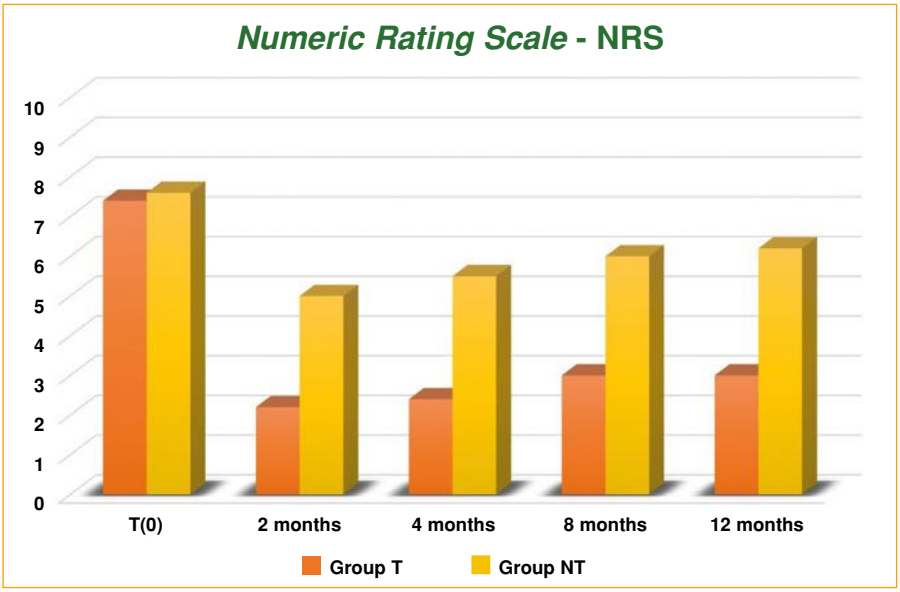
The optimisation of the conservative treatment of low back pain secondary to degenerative SL, taking into account all the anatomical structures involved in this aetiopathogenesis, allows to formulate a number of considerations.

COLLAGEN MEDICAL DEVICES

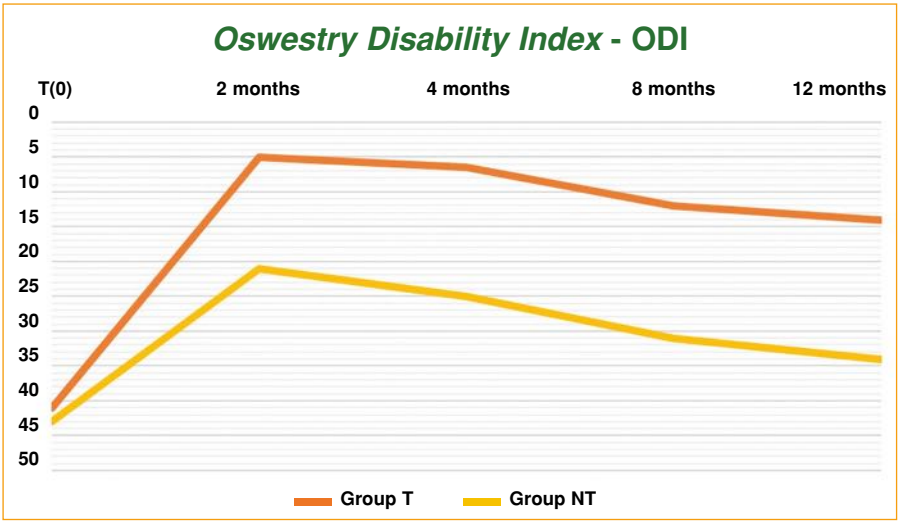
The use of injectable medical devices **(MD)** containing porcine collagen allows a more efficacious and specific *in loco* positioning of the collagen, with a carrier and stabilisation function.

– It makes it possible to replace, strengthen, structure and protect the cartilage, tendons, ligaments and joint capsules, thereby optimising the structure of the collagen fibres and of all the extra- and intra-articular structures in which it is present, thereby providing a mechanical support to the anatomical district in question.

The hypothesis of the study was that a treatment with a specific injectable Collagen MD could re-condition the anatomical structure/s impaired by SL and improve the stability of the lumbosacral spine; that a "combined" treatment would have been able to improve the functional rehabilitation outcomes and/or provide more efficacious pain control in the subacute and chronic phases; and that a combined treatment would also have been able to positively

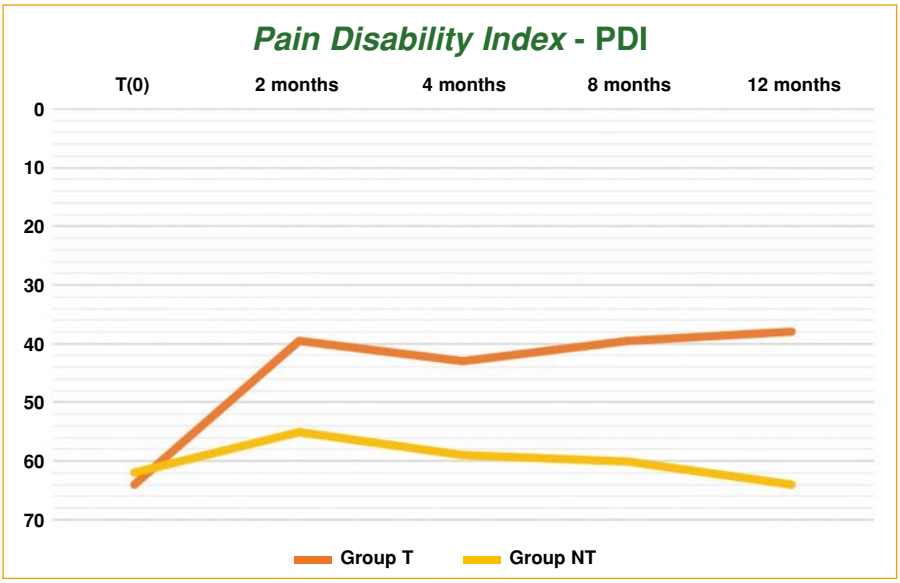


TAB. 1



TAB. 2

TAB. 3



condition the progression of SL with less frequent exacerbations.

MATERIALS AND METHODS

In order to explore this hypothesis, **20 patients** with Physical Medicine outpatient clinic appointments for low back pain were recruited and included in the study, from January 2018 to January 2019.

– The patients were randomised to 2 treatment groups [**T** Group (**Physiokinesis therapy** + ultrasound-guided injections of **MD-Lumbar**) and the **NT** Group (**Physiokinesis therapy** alone)], stratified by age and gender; the outcomes were assessed at **2**, **4**, **8** and **12 months**.

– Inclusion criteria

F and M patients aged between 40 and 75 years; clinical and instrumental diagnosis of **grade 1** and **grade 2 Spondylolisthesis**; NRS (Numeric Rating Scale) **> 5**, no use of NSAIDs, corticosteroids or opioids.

– Exclusion criteria

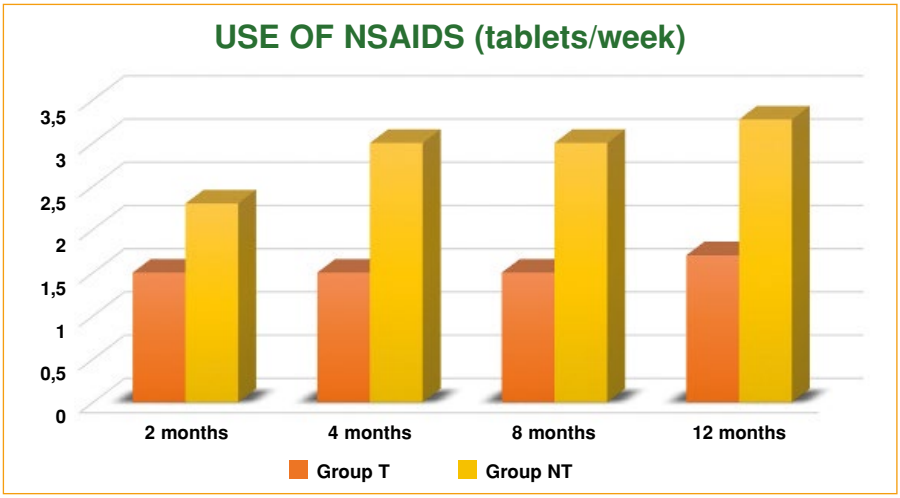
Rheumatoid arthritis, chondrocalcinosis, psoriasis, metabolic bone diseases, gout, active infections, clinical and instrumental diagnosis of grade 3 and grade 4 spondylolisthesis, spondylolysis, polyneuropathy, previous local/epidural corticosteroid injections (> 3 years), use of oral corticosteroid and/or opioid therapy in the past 6 months, use of anticoagulants, pregnancy, mental diseases.

Both the T and the NT Groups were administered the same intra-hospital rehabilitation protocol (diagnostic and therapeutic care programme) based on neuromotor treatment for the proprioceptive reconditioning of the posterior back, lumbosacral girdle and respiratory muscles.

– The protocol also included ergonomic education and occupational therapy.

The rehabilitation treatment consisted in:
daily individual motor rehabilitation treatment for a total of ten 45-minute sessions; individual assessment
by the occupational therapist at the 5th and 10th session; provision of a brochure illustrating the physiokinesis therapy exercises to be performed by patients at home and ergonomic advices; group treatment (max. 4 patients) one month after the last individual session, on 2 consecutive days, in 30-minute sessions.

• **Group T** (Treatment) also received ultrasound-guided injection therapy (Clarius Ultrasound portable system, Convex probe) according to the following protocol:
5 sessions (1/week for 4 consecutive weeks and 1 after 15 days); **2 vials** of **MD-Lumbar** per treatment.
– Half a vial (1 mL) for each facet joint; 2 joints were treated at each treatment, alternating the upper and lower facet joints; at the 5th session the 2 most impaired joints (as shown by MRI) were treated.



TAB. 4

A number of clinical and functional outcomes were investigated:
1) Numeric Rating Scale **(NRS)**
2) Oswestry Disability Index **(ODI)**
3) Pain Disability Index **(PDI)**
4) use of NSAIDs during the follow-up period (TABLES 1, 2 ,3 and 4).

CONCLUSIONS

The data obtained (TAB. 5) allow to conclude that in the treatment of grade 1 and grade 2 Spondylolisthesis combined treatment with physiokinesis therapy + injection of MD-Lumbar makes it possible to obtain a far **better** and **longer-lasting improvement**, in terms of
1) pain
2) motor function
3) impairment caused by spinal instability
4) reduced use of NSAIDs.

Furthermore, the combined treatment proposed herein, for the first time in the

OUTCOMES	T (0)		2 months		4 months		8 months		12 months	
GROUPS	**T**	**NT**	**T**	**NT**	**T**	**NT**	**T**	**NT**	**T**	**NT**
NRS *Numeric Rating Scale*	**6,9**	**7,1**	1,7	4,5	1,9	5,0	2,5	5,5	**2,5**	**5,7**
ODI *Oswestry Disability Index*	**41,0**	**42,0**	5,0	21,0	7,0	25,0	12,0	31,0	**14,0**	**34,0**
PDI *Pain Disability Index*	**64,0**	**62,0**	40,0	56,0	42,0	58,0	40,0	60,0	**38,0**	**64,0**
NSAIDs *tablets/week*			**1,3**	**2,0**	1,3	2,7	1,3	2,7	**1,4**	**3,0**

TAB. 5

From the data obtained, it emerges that:
– NRS. Group T (Physiokinesis therapy + ultrasound-guided injection therapy of MD-Lumbar) passes from 6.9 (T0) to 2.5 after 12 months (-63.8%). Group NT (Physiokinesis therapy alone) passes from 7.1 (T0) to 5.7 after 12 months (-19.7%).
– ODI. Group T passes from 41.0 (T0) to 14.0 after 12 months (-65.9%). Group NT passes from 42.0 (T0) to 34.0 after 12 months (-19.1%).
– PDI. Group T passes from 64.0 (T0) to 38.0 after 12 months (-40.6%). Group NT passes from 62.0 (T0) to 64.0 after 12 months (±0%).
– NSAIDs (tablets/week). Group T passes from 1.3 at 2 months to 1.4 at 12 months (±0%). Group NT passes from 2.0 at 2 months to 3.0 at 12 months (+50%).

treatment of Spondylolisthesis, would appear to allow a better control over disease progression and a reduction in exacerbations over time (pro-inflammatory cytokine network control).

• **MD-Lumbar** improves the stability of the lumbosacral spine and organically reconditions the impaired anatomical structures (joint capsules, yellow ligament, antigravity muscles and connective deep fascia), thereby making a considerable contribution to the promotion of neuromotor and proprioceptive capacity.

Over the next few months, we hope to be able to confirm the results obtained by expanding the study sample and, in particular, to identify the optimum timing for further injection therapy with MD-Lumbar as part of an individual maintenance rehabilitation programme. ■

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Fig. p. 40
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Fig. p. 41
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Paper presented at the 2nd INTERNATIONAL CONGRESS
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Milan, 16th November 2019

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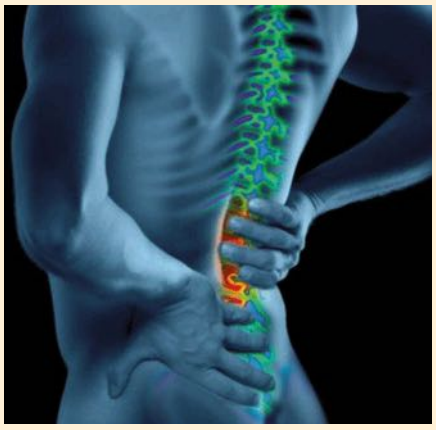
MD-LUMBAR, MD-MUSCLE AND MD-NEURAL IN THE TREATMENT OF LOW BACK PAIN

SUMMARY

– Background
There are still unmet needs in finding optimal drug for the treatment of acute LBP. One of the discussed treatment options is local injection treatment with collagen.
– Methodology
Patients: aged 20-70, suffering from acute LBP with duration < 3 months and with minimum intensity of pain ≥ 40 mm on VAS.
– Outcomes: Pain intensity of difference between the baseline and final visits (VAS). Secondary outcomes: HAQ, Oswestry questionnaire, use of rescue medication, tolerance.
– Therapy: MD-Muscle (1 ml) + MD-Lumbar (2 ml) + MD-Neural (1 ml) or 4 ml of 1 % mesocain in 8 predefined points. Rescue medication: paracetamol < 3 g/daily.
– Results
48 patients were included (36 Collagen MDs vs 12 mesocain). Pain on movement decreased from initial mean 70.1 ± 13.6 to 36.6 ± 23.5 at week 5 ($p < 0.05$) in the MD group and from 70.8 ± 11.5 to 31.9 ± 26.8 in the mesocain group ($p < 0.05$) with no statistical differences between both groups.
Pain at rest decreased from 59.6 ± 16.9 to 28.1 ± 24.1 ($p < 0.05$) in the MD group and from 57.3 ± 16.4 to 25.1 ± 26.9 ($p < 0.05$) in the mesocain group. The differences between the groups were not significant.
Consumption of analgesics tablets (paracetamol 500 mg) was numerically but not significantly lower in the MD group in comparison with the mesocain group (14.4 ± 16.2 vs. 20.4 ± 27.0 NS).
– Conclusions
MD-Lumbar, MD-Muscle, MD-Neural appear to be effective in the treatment of acute low back pain.

KEY WORDS **LOW BACK PAIN, COLLAGEN MEDICAL DEVICE**



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Acute nonspecific low back pain (**LBP**) is defined as LBP not attributed to a recognisable, known, or specific pathology (inflammation, fracture, tumor, radicular syndrome or *cauda equina* syndrome) with a duration of 6 weeks (1).

Acute LBP is usually self-limiting with a recovery rate of 90% within 6 weeks. Peak prevalence occurs between 35 and 55 years and lifetime prevalence is up to 84 %.
– The estimated lifetime prevalence of chronic LBP is about 23%.

Treatment of acute low back pain in primary care aims at: providing adequate information, providing adequate symptom control if necessary, recommending the patient to stay as much as possible active and return early to normal activities, including work (2).

The optimal solution to treat LBP is given by multidisciplinary treatment programmes which usually comprise combination of physical, vocational and behavioural components and adaptation of drug use. The following drugs are recommended for the pharmacological treatment: paracetamol and other analgesics, nonsteroidal antirheumatic drugs (NSAIDs), muscle relaxants, weak and strong opioids, and antidepressants.
– NSAID are most commonly prescribed worldwide for LBP. The administration of NSAIDs may be complicated by NSAIDS induced gastropathy and its serious complications as perforations, ulcerations, and bleeding (PUB) (3).

Introducing COX-2 selective drugs (coxibs) has improved GIT safety profile (4) but has probably increased cardiovascular risk (5); this can be true also for non-selective NSAIDS.
Because of potentially serious adverse events, NSAIDs should be used only for short periods.
There are still unmet medical needs in finding the optimal drug for the treatment of acute LBP.
One of the treatment options is the local injection treatment with collagen.

– **MD-Lumbar** (Guna Laboratories - Milan - Italy) is a medical device composed of collagen and extract of Hamamelis.
– The mechanism of action of locally applied collagen – both structural and functional – is complex.
In the affected tissues the collagen forms a bio-scaffold and long-term action is guaranteed by a patented principle of collagen injectable delivery system.
The Collagen MD replaces the lack of collagen, which is always recurrent in the inflammatory and/or degenerative diseases of the Locomotor Apparatus.
The collagen has also a barrier effect and a lubrication activity.
It is also spasmolytic, it improves function and help decreasing pain (6).

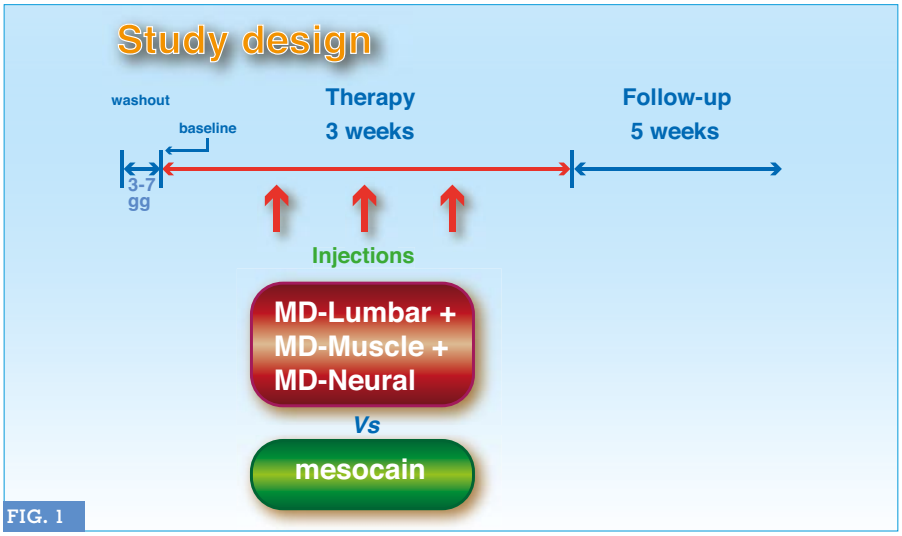

FIG. 1

The extract from Hamamelis has antioxidant and anti-inflammatory efficacy.

– **MD-Muscle** is a medical device composed also by collagen and extract of Hypericum.
This extract has anti-inflammatory, analgesic, and antidepressant activity.

– **MD-Neural** is a medical device made up of a mix of collagen and extract of Colocynthis.
It has spasmolytic and analgesic efficacy with impact on the neuropathic pain.

MD-Muscle, MD-Neural and MD-Lumbar have been tested in different painful conditions of the locomotor system, like osteoarthritis and soft tissue rheumatism including LBP.
In order to get more information about the efficacy of the mix of medical devices, we have suggested a protocol for a randomized, controlled trial to treat acute low back pain.

Collagen has been used in several experimental models of ligament lesions, where it demonstrated the ability of supporting collagen fibrillogenesis in healing collateral ligament in rabbits (7) and also in a group of 10 patients with degenerative cartilage lesions (8).

METHODOLOGY

Design of the study

This single blind, clinical study was designed to evaluate the efficacy and safety of MD-Lumbar, MD-Muscle, and MD-Neural in comparison with mesocain in subcutaneous application in patients with acute low back pain.

FIG. 1 shows the flowchart of the study. After 3-7 days washout, patients were allotted to one of the two groups according to the randomization schedule.
The study was blind for patient but not for the physician.
– The primary outcome measure occurred at week 5, two weeks after the last treatment.

Patients

Patients aged between 20 and 70 years, having signed the informed consent, were included.
They were diagnosed as having acute non-specific LBP with a duration of the disease inferior to 3 months.
The minimum intensity of pain was 40 on scale 0-100.

Main exclusion criteria were: neurologic symptoms longer than 1 month, *cauda equina* syndrome, inflammatory spinal disease, malignant diseases, compression fracture in osteoporosis, recent trauma and therapy with myorelaxants, immunosuppressive drugs and glucocorticosteroids.

– **75 patients** in the MD group; **25 patients** in the control group.

Outcomes

– The primary outcome was the comparison of the difference in pain intensity between the baseline and the final visits obtained by the two study groups.

– Secondary outcomes were functional improvement measured by HAQ, Oswestry questionnaire, comparison of the use of rescue medication and evaluation of tolerance.

Medication

In the active treatment group the patients have received injections of **MD-Muscle** (1 ml), **MD-Lumbar** (2 ml) and **MD-Neural** (1 ml) in 8 predefined points (0,5 ml per point).
– In the control group patients have been administered 4 ml of 1 % mesocain distributed in the same 8 points;

	MD	Mesocain	
Patients	**36**	**12**	
M/F	7/29	4/8	NS
Age	54.2 ± 11.4	56.2 ± 11.6	NS
VAS pain on movement	70.1 ± 13.6	70.8 ± 11.5	NS
VAS pain at rest	59.6 ± 16.9	57.3 ± 16.4	NS
Analgesic treatment before	15/21 (58.3 %)	5/7 (11.3 %)	NS

TAB. 1
General characteristics of the patients included in the 2 treatment groups.

the number of applications was 5 (2/weeks + 1).

Patients have been allowed to use paracetamol (3 g daily *max*) as rescue analgesic medication.
NSAIDs, other analgesics and local treatment with glucocorticoids were not allowed. Newly introduced physical therapy was also not allowed.
Statistical methods for assessment of consumption of analgesics, global assessment and questionnaires, parametric and non-parametric tests were used (T test, ANOVA, Manova analysis of repeated measures, Kruskall-Wallis, Wilcoxon pair test and Mann-Whitney U test).

RESULTS

Here are presented the preliminary results of the *interim* analyses.

– There were altogether **48** patients included and analysed in the study: **36** in the MD group, and **12** in the control group. There were no statistical differences between the two groups as far as sex, age, intensity of pain at rest and pain on movement and usage of analgesics before the study (TAB. 1).

The intensity of pain at baseline was high/about 70 mm on VAS scale 0-100. Pain on movement decreased from initial mean **70.1 ± 13.6** to **36.6 ± 23.5** at week 5 ($p < 0.05$) in the MD group and from **70.8 ± 11.5** to **31.9 ± 26.8** in the mesocain group ($p < 0.05$) with no statistical differences between the two groups (TAB. 2, FIG. 2).

Pain at rest decreased from **59.6 ± 16.9** to **28.1 ± 24.1** ($p < 0.05$) in the MD group and from **57.3 ± 16.4** to **25.1 ± 26.9** in the mesocain group ($p < 0.05$) at week 5. The differences between the two groups are not significant.
The consumption of analgesics tablets (paracetamol 500 mg) was numerically but not significantly lower in the MD group in comparison with the mesocain group (**14.4 ± 16.2** *vs.* **20.4 ± 27.0** NS) (TAB. 3).
The tolerance of the treatment was very good. No serious adverse event was reported in both groups.
The patients evaluated the tolerance of MD as very good in **66.7 %**, as good in **25 %**, and medium in **8.33 %**.
Tolerance of mesocain injections was evaluated as very good in **83.3 %**, good in **7.33 %** and medium in **8.33** % also (NS differences between the groups) (TAB. 4).

DISCUSSION

Management of acute but also chronic

Item	N	MD	Mesocain
VAS, Pain on movement, Visit 1	36/12	70.1 ± 13.6	70.8 ± 11.5
VAS, Pain on movement, Visit 5		46.0 ± 18.5	39.3 ± 26.6
VAS, Pain on movement, Visit 6		39.6 ± 20.5	37.6 ± 28.5
VAS, Pain on movement, Visit 7		36.6 ± 23.5	31.9 ± 26.8
VAS, Pain at rest, Visit 1	36/12	59.6 ± 16.9	57.3 ± 16.4
VAS, Pain at rest, Visit 5		37.3 ± 18.7	33.6 ± 25.8
VAS, Pain at rest, Visit 6		30.0 ± 22.4	29.5 ± 27.1
VAS, Pain at rest, Visit 7		28.1 ± 24.1	25.1 ± 26.9

TAB. 2

Analogic-visual pain scale in the 2 treatment Groups. Score decrease from Visit 1 to Visit 7 (pain on movement and at rest).

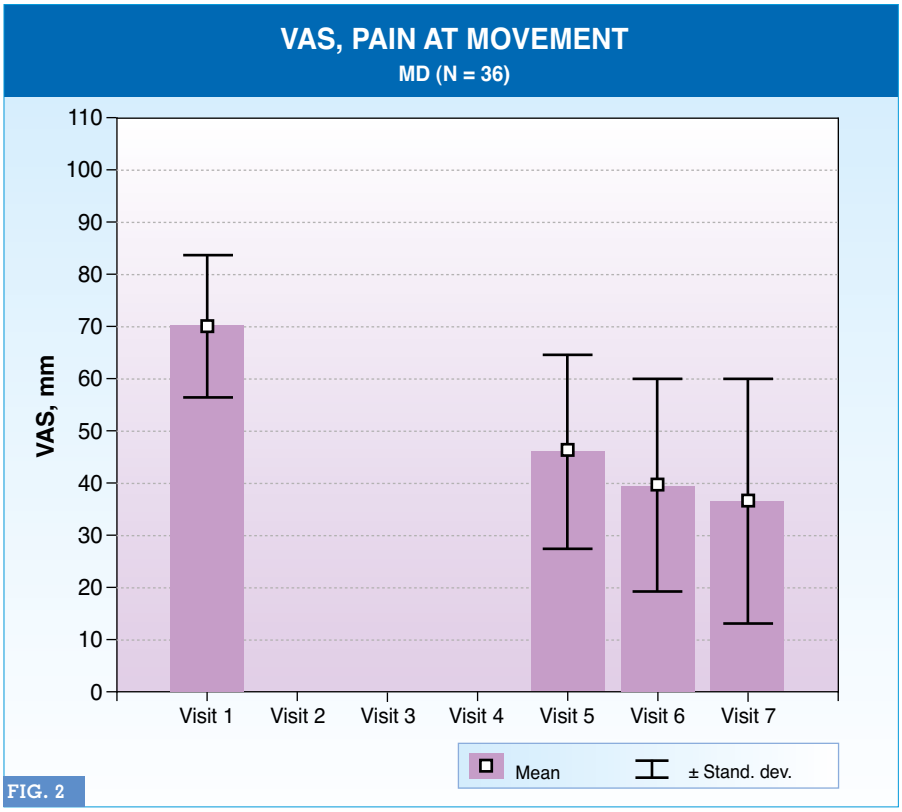

FIG. 2

back pain remains still a challenge with not yet available optimal drug.
MD local injections are new and very innovative, based on physiological regulation (Physiological Regulation Medicine).

MD injections were tested in 7 controlled trials, which has been part of submission dossier (6). Tested conditions were lumbar and neck pain, knee, hip and hand OA, sciatica, neuropathic pain, shoulder pain, wound healing.

The studies have shown good efficacy and no serious adverse events.
MD injections have also no drug interactions and can be used concomitantly with other drugs, which is of great advantage especially for old people or patients with polymorbidities.

– The results of our study suggest that the mix of the 3 tested MD is effective in the treatment of acute LBP.

Our results must be interpreted with caution, because of many limitations. Firstly, the study is still on going with aim to recruit 100 patients; here we are presenting the *interim* analysis of 48 patients.
– Nevertheless, some preliminary clinical findings can be already discussed.

The patients mean improvement of pain is around 30 mm on VAS which is definitively much more than minimal, clinically important improvement of pain, which is about 15-20 mm.
The onset of pain relief is relatively quick in less than 2 weeks.
– **Analgesic efficacy of MD seems to be at least good as of mesocain.**
Long term treatment focused on restructuralization and stabilization of connective tissue by MD injections can be achieved only by MD injections. MD injection treatment is of course much more physiological in long term therapy in comparison with local anaesthetics providing the immediate anaesthetic and analgesic effect.

The other positive point is the very good tolerance of MD local treatment and good adherence to therapy.
It is commonly accepted that generally adherence to treatment in chronic painful conditions of the Locomotor Apparatus is an important issue.

CONCLUSIONS

▶ MD-Lumbar, MD-Muscle, and MD-Neural appear to be effective in treatment of acute low back pain.
▶ MD-Lumbar, MD-Muscle, and MD-Neural are well tolerated.
▶ MDs might be effective and a safe choice in the therapy of acute back pain. ■

Item	N	MD	Mesocain	Stat. signif. of diff.
Paracetamol consumption during Visits 1 - 6 (no. of. tbl.)	36/12	**14.4 ± 16.2**	**20.4 ± 27.9**	Unpaired T-test, NS

TAB. 3
Paracetamol consumption.

Item	MD	Mesocain	Stat. signif. of diff.
Tolerance, Visit 6, Very good	24 **(66.7 %)**	10 **(83.3 %)**	Chi-square test, NS
Tolerance, Visit 6, Good	9 **(25.0 %)**	1 **(8.33 %)**	
Tolerance, Visit 6, Medium	3 **(8.33 %)**	1 **(8.33 %)**	

TAB. 4
Therapy tolerance (patients' evaluation). Evaluation took place at the end of Visit 6.

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Efficacy and Tolerability of Injectable Collagen-Containing Products in Comparison to Trimecaine in Patients With Acute Lumbar Spine Pain (Study FUTURE-MD-Back Pain)

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Summary

Low back pain (LBP) represents an important subgroup of vertebrogenic pain with estimated prevalence around 80 %. Locally acting injectable collagen for topical application has recently extended the limited range of treatment options. The aim of the study was to evaluate the efficacy and safety of injectable collagen in patients with LBP. Patients suffering from LBP (< three months) were enrolled. They were administered either collagen 4 ml or trimecaine 1 % 4 ml in the form of subcutaneous paravertebral injections into eight pre-specified points (0.5 ml per each point) in the following schedule: two administrations in the first and second week, one in the third week. The pain intensity, Thomayer distance, Oswestry disability index, Lasseque test, quality of life, consumption of rescue medication and safety were evaluated. Exertional and rest pain, evaluated by a visual analogue scale, gradually decreased in both groups. Both treatments showed a statistically significant improvement in mobility and quality of life. The consumption of paracetamol as a rescue medication was significantly lower in patients treated with collagen than in the group treated with trimecaine (p=0.048). The analgesic efficacy of locally acting injectable collagen, as well as an analgesic sparing effect when compared to local anesthetics were demonstrated.

Key words

Low back pain • Injectable collagen • Analgesics • Paracetamol • Trimecaine • Pain

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Introduction

Musculoskeletal pain including vertebrogenic pain is among the most common health complaints with significant social and economic consequences. The incidence of musculoskeletal pain increases with the rising average age of the population and decreases the quality of life of a growing number of affected people. Back pain represents an important subgroup of vertebrogenic pain. It is reported that approximately 80 % of the population in developed countries have back pain problems for which they seek medical help, at least once in a lifetime (NICE 2016).

Back pain can be classified according to its localization as neck pain (NP) or low back pain (LBP). Pain/discomfort affecting the area from the lower rib margin to the lower gluteal fold is called LBP. Lower limb pain may or may not be present at the same time. LBP can be classified by its duration as acute (back pain episodes lasting no more than three months, sometimes a subgroup of subacute pain lasting 6 to 12 weeks is also distinguished) or chronic (when pain lasts more than three months). The recurrence of problems after at least

a six-month symptom free period is known as recurrent LBP (this form must be distinguished from chronic LBP exacerbation). According to the etiology, LBP is classified as specific when the pathological process causing the pain is known (e.g. inflammatory or degenerative process, fracture, radicular syndrome, etc.) or nonspecific (when such a causative process is not apparent).

Patients with acute back pain which subsides within six weeks to three months represent the majority of the affected people. However, approximately 2-7 % of patients move to the group of chronic pain that can seriously affect not only health, but due to limited working ability, also the social and economic aspects of a patient's life. This type of chronic pain, due to back disorders, contributes to the extent of 90 % of social costs of sick leave. Concerning back pain distribution according to age groups, elderly patients are affected more often. In younger people, back pain typically arises from excessive burden to normal spinal structures. With advancing age, pathological processes (i.e. processes of degenerative nature) play an increasing role in the etiology. The symptoms and morphological findings of LBP have a very weak correlation and the pain is not always proportional to the pathological changes.

The patient's history and neurological examination play important diagnostic roles. If severe spinal pathology is suspected (specific biomedical factors or so-called "red flags", e.g. root syndromes, fractures and infections), imaging techniques are indicated to specify the cause (e.g. X-ray, magnetic resonance imaging [MRI]). Psychosocial factors (so-called "yellow flags") also play an important role and increase the risk of problem chronification. If no specific causative factors are presented, the condition is called nonspecific LBP (Nice 2016).

The problem of back pain treatment is complex due to the existence of many well-known, but also some unknown pathophysiological factors that make treatment difficult. The ranges of medical procedures include a multidisciplinary approach with conservative methods to minimally invasive interventions to surgical treatment. Conservative procedures in acute nonspecific LBP include mainly rehabilitation and medications (NICE 2016, van Tulder *et al.* 2006). These non-invasive treatment methods are effective in 80 to 90 % of patients with LBP and therefore, conservative treatment is considered the method of choice for most patients with back pain syndromes. In the treatment of acute nonspecific LBP, paracetamol is recommended as the first-line treatment and nonsteroidal anti-inflammatory drugs (NSAIDs) or muscle relaxants are recommended as the second-line treatment. In some cases, acupuncture is used; however, today it is believed to be suitable only for chronic LBP (Furlan *et al.* 2005, Itoh *et al.* 2004) or a local anesthetic is applied. Collagen-containing products intended for topical application have also recently extended the limited range of treatment options (Pavelka *et al.* 2019). Other possible therapeutic approaches have been postulated. These include (for example) newer intradiscal therapies (Charneux *et al.* 2017, Knezevic *et al.* 2017), modulation of galanin receptors (Zhang *et al.* 2019), modulation of TRPA-1 (Liu *et al.* 2019, Yamamotova *et al.* 2017), monoclonal antibody tanezumab (Webb *et al.* 2018), etc. (Bhangare *et al.* 2017).

One of the major causes of musculoskeletal pain is weakness of the internal and external joint stabilization systems. The basic component of these systems is collagen, the sufficient content and quality of, which are essential for the intact function of these structures. A lack of collagen or failure of its composition leads to weakening of the support systems and joint hypermobility, especially in non-physiological positions. This leads to premature wear of these systems and further increases the risk of progressive degeneration of structures such as cartilage. Slack hypermobile elements of the support system stimulate pain receptors and lead to muscle tension around the joints (Milani 2010, Stone *et al.* 1997). On the basis of these findings, collagen-containing products for local administration (as medical devices generally known as MD-products) have been developed. These include the MD-Lumbar, MD-Neural and MD-Muscle products (Guna, Milano, Italy) used in our study. Patients with acute lumbar spine pain were enrolled if their condition required the administration of local anesthetics or collagen-containing products. This study evaluated the efficacy and safety of the MD-Lumbar, MD-Nural and MD-Muscle products in comparison to the subcutaneously administered local anesthetic trimecaine.

Methods

Patients

Adult outpatients of both sexes who met the diagnostic criteria for acute lumbar spine pain, defined as LBP lasting no more than three months, were enrolled in

a prospective, single-blind clinical trial titled FUTURE-MD-Back Pain. A total of 97 patients were enrolled and were randomized into two groups. Randomization was performed by a generator (available from www.randomization.com) using random permuted blocks (blocks of 20 subjects), with a randomization ratio of 3:1. All patients underwent in total seven visits (V): V1 – Day 0, V2 – Day 3±2, V3 – Day 7±2, V4 – Day 11±2, V5 – Day 14±2, V6 – Day 18±2, and V7 – Day 32±2.

Materials and chemicals

The study mixture of MD-Lumbar MD, MD-Muscle and MD-Neural ("A") was administered subcutaneously to the first group of patients aged 26-70 years (n=73, including 24 males and 49 females) and Mesocaine 1 % (trimecaine hydrochloride) ("B") was subcutaneously administered to the second group aged 26-66 years (n=24, 7 men and 17 women). The combination of MD-Muscle (1 ml), MD-Lumbar (2 ml) and MD-Neural (1 ml) for a total of 4 ml per dose or Mesocaine 1 % 4 ml per dose were administered in the form of subcutaneous paravertebral injections into eight pre-specified points (0.5 ml per one application point) for a total duration of three weeks. A total of five applications were made in each patient (twice the first week, twice the second week and once the third week). If a subject not completing the study was replaced, the new subject received the same product as the patient excluded from the clinical trial.

MD-Lumbar, MD-Neural and MD-Muscle are medical devices designed to improve mobility and reduce pain in the lumbar spine area. Collagen is the primary active ingredient of these combined products. The effect of topical collagen administration is structural and functional. Collagen is directly delivered to the area where it is lacking to strengthen, give structure and protect joint cartilage, tendons, ligaments and joint capsules by creating an adhesive barrier (Milani 2010). The transport of collagen along with the other ingredients to the local destination is based on a patented "collagen delivery system". When using this system, a temporary porous collagen matrix forms in the tissue where the product is applied, and gradually releases the active substances into the targeted area at a defined speed (depending on the porosity of the matrix), thus ensuring prolonged activity. The main therapeutic functions of collagen include the barrier effect, lubricating activity and support of potential concomitant analgesic medication. Collagen helps to improve the functionality of the joints, improves the profile of the collagen fibres and, consequently, all the anatomical collagen-containing structures. When strengthening the joint stabilization systems with locally administered collagen, an analgesic effect is achieved in addition to a structural recovery (creating biological support, so-called bioscaffold). The locally administered collagen in these products helps to relieve painful muscle tension in the region and restore its physiological function. Therefore, it helps to eliminate the cause of pain and to normalize the function of the affected joint and its supporting apparatus. The other ingredients of individual collagen-containing products differ (Randelli *et al.* 2018).

In addition to collagen, MD-Lumbar contains an extract from the bark and roots of the medicinal plant *Hamamelis virginiana*. The active ingredients of this extract are tannins, organic acids and essential oils; the extract has anti-inflammatory and antioxidant effects. It protects tissues at the injection site from the development of the inflammatory process that occur secondary to degenerative changes of the connective tissue; this inflammation further damages the tissues affected by degeneration. The anti-inflammatory effect of the extract from *Hamamelis virginiana* thus contributes to the effect of collagen. The extract, in addition to its antioxidative action, protects the integrity of tissues at the application site from the effects of harmful oxygen radicals.

MD-Neural is a medical device designed primarily to suppress neuropathic pain in different locations *via* its effect on the collagen component of the perineurium. In addition to collagen, it contains an extract from the medicinal plant *Citrullus colocynthis*. The extract from this plant is used in low concentration dilution in traditional medicine as a spasmolytic and analgesic. The analgesic effects of the ingredients (e.g. bitter compounds, triterpenes, and resins) are used in neuropathic pain, i.e. the stabbing pain typical for lumbago and sciatica.

MD-Muscle is a medical device which acts as an analgesic due to its effect on muscle tissue. In addition to collagen, it contains an extract from the medicinal plant *Hypericum perforatum.* Besides showing antidepressant action, this extract has anti-inflammatory and analgesic effects. It contains the full spectrum of active ingredients (e.g. hypericin, hyperforin, tannins, flavonoids) with anti-inflammatory, analgesic and regenerative effects. Its analgesic effects can be useful in cases of neuropathic and muscle pain.

Trimecaine (product Mesocaine 1 %) belongs to

the group of medicines that produce local tissue anesthesia. It is an amide local anesthetic with a moderately long effect, which is rapidly and well absorbed. It inhibits genesis and conduction of painful stimuli and other centripetal impulses generated by pressure, tension, heat, etc. The anesthetic effect occurs within 15 min after administration and lasts for 60-90 min.

Evaluation of effectiveness

Both exertional and rest pain were measured by visual analogue scale (VAS) at each visit. Additionally, both Thomayer distance (expressed in cm) and Lassegue test were evaluated on V1, V3, V6, and V7. A quality of life questionnaire (EuroQol) and Oswestry Disability Index were measured on V2, V6, and V7. During the whole treatment period (i.e. V1-V6), the total paracetamol consumption was evaluated. Finally, the tolerability of both treatments was assessed by the patients during V6 and V7.

Statistical analysis

Thomayer distance, Oswestry Disability index, EuroQol and VAS were evaluated using repeated measures analysis and *post hoc* Fisher's LSD (Least Significant Difference) test. Paracetamol consumption was evaluated using a one-tailed T-test. Treatment tolerability was assessed using the chi-square test.

Results

Patients were recruited for a total of about six weeks and a three day wash-out period was carried out, during which all analgesic and anti-inflammatory treatments were discontinued and patients were only allowed to use paracetamol. After the baseline examination, the evaluated products were administered for three weeks followed by a two week follow-up (for a total of 7 visits). The efficacy of the treatment was evaluated at individual visits. The tolerability of the treatment was assessed at the same time, both by the patient and by the attending physician. The current intensity of lumbar spine pain was measured by means of a horizontal visual analogue scale (VAS). The efficacy was also evaluated by identifying trigger points, evaluation of back muscle spasms, examination of the Thomayer distance and the Lassegue test. In addition, the EuroQol questionnaire (characterizing the quality of life of the patient) and the Oswestry questionnaire (Oswestry Disability Index) were also used for evaluation. The Oswestry questionnaire, which was completed at V2 and V6, quantifies the restriction of daily activities due to LBP, quantifies the subjective complaints of the patient and expresses the degree of disability, i.e. it reflects also the quality of life of the patient. The final examination was performed two weeks after the last treatment administration. The final examination (follow-up) included, besides the clinical examination, the overall efficacy of the treatment assessed by the physician and by the patient, as well as the patient's functional status. The patients again completed the final EuroQol and Oswestry questionnaires. The schematic design of the study is given in Table 1a.

Table 1a. Clinical study design.

Examination	Visit 1 Day 0 Week 0	Visit 2 Day 3±2 Week 1a	Visit 3 Day 7±2 Week 1b	Visit 4 Day 11±2 Week 2a	Visit 5 Day 14±2 Week 2b	Visit 6 Day 18±2 Week 3	Visit 7 (follow-up) Day 32±2 Week 5
Baseline examinations	+	-	-	-	-	-	-
Medical history	+	-	-	-	-	-	-
Clinical examination	+	+	+	+	+	+	+
Laboratory assessments	+	-	-	-	-	-	-
BP	+	+	+	+	+	+	+
Current treatment	+	+	+	+	+	+	+
Product administration	-	+	+	+	+	+	-
VAS – evaluation of efficacy by the patient, by the physician	+	+	+	+	+	+	+
EuroQol questionnaire	-	+	-	-	-	+	+

Table 1b. Characteristics of the population.

Item	MD inj.	Mesocaine inj.
Number of patients		
- men	24	7
- women	49	17
- total	73	24
Patient age (years)		
- men	48.1 ± 12.8	46.4 ± 13.6
- women	55.0 ± 10.7	56.6 ± 10.0
Analgesic treatment before the YES/NO	42/31 (57.5 %)	14/10 (58.3 %)

* – statistically significant difference from baseline $p<0.05$ (MANOVA and *post hoc* Fisher´s LSD test). The difference between the groups was not significant.

Both evaluated populations were comparable in their composition. In terms of median age, and in terms of the proportion of patients previously taking analgesics, there were no statistically significant differences between the populations. The characteristics of the population are schematically shown in Table 1b, which shows the number of patients with/or without analgesic treatment before entering the clinical trial.

Regarding the assessment of mobility by the measurement of the Thomayer distance (Table 2a), both treatments showed improvement in mobility (statistically significant reduction of the distance) during the treatment. This improvement was statistically significant from the baseline in both groups and there were no statistically significant differences between the treatment groups, although slightly better results were achieved in the group with the MD applications. No progress was observed regarding the Lassegue test values (also presented in Table 2b) during the treatment.

Table 2a. Thomayer distance.

Item	n (MD inj./Mesocaine inj.)	MD inj.	Mesocaine inj.
Thomayer distance (cm), Visit 1	73/24	12.2 ± 10.0	13.1 ± 9.16
Thomayer distance (cm), Visit 3		11.3 ± 9.64	11.0 ± 6.86
Thomayer distance (cm), Visit 6		8.07 ± 9.50*	9.42 ± 8.29*
Thomayer distance (cm), Visit 7			10.0 ± 7.52*

* – statistically significant difference from baseline $p<0.05$ (MANOVA and *post hoc* Fisher´s LSD test). The difference between the groups was not significant.

Table 2b. Lassegue test.

Item	n (MD inj./Mesocaine inj.)	MD inj.	Mesocaine inj.
Lassegue test ≤ 45°, Visit 1	73/24	Negative 73 times	Positive 1 time
Lassegue test ≤ 45°, Visit 3		Negative 73 times	Negative 23 times
Lassegue test ≤ 45°, Visit 6		Negative 73 times	Negative 24 times
Lassegue test ≤ 45°, Visit 7		Negative 73 times	Negative 24 times

The principal endpoints of the study included back pain assessed by patients using a visual analogue scale (VAS) (Tables 3a and 3b). Exertional and rest pain gradually decreased. There was no statistically significant difference between the study groups regarding the pain relief and its outcome. A statistically significant decrease in exercise-induced pain from baseline was achieved in both groups from Visit 3 and statistically significant difference in rest pain was also recorded in the group treated with MD products from Visit 3 and in the group of patients treated with trimecaine from Visit 4. The difference between the treatment groups could be

attributed to the rather low number of patients treated in the trimecaine group. Another evaluated parameter was the consumption of the auxiliary analgesic (paracetamol) in the reference period (Table 4). As shown by the results, the consumption of paracetamol was significantly lower in the group treated with MD preparations (approximately half) than in the group treated with Mesocaine. The difference is statistically and clinically significant (p=0.0485) in favor of MD injections.

Table 3a. Visual analogue scale for exertional pain (VAS), absolute values (cm), assessed by the patient.

Item	n (MD inj./Mesocaine inj.)	MD inj.	Stat.	Mesocaine inj.
VAS, Exertional pain, Visit 1		67.0 ± 12.6	NS	70.5 ± 12.3
VAS, Exertional pain, Visit 2		63.8 ± 12.1	NS	68.2 ± 17.3
VAS, Exertional pain, Visit 3		58.4 ± 15.1*	NS	62.0 ± 20.4*
VAS, Exertional pain, Visit 4	73/24	53.7 ± 18.0*	NS	55.2 ± 24.4*
VAS, Exertional pain, Visit 5		43.5 ± 20.1*	NS	42.9 ± 26.1*
VAS, Exertional pain, Visit 6		37.9 ± 22.3*	NS	39.3 ± 26.1*
VAS, Exertional pain, Visit 7		34.1 ± 22.1*	NS	37.3 ± 29.0*

* – statistically significant difference from baseline p<0.05 (MANOVA and *post hoc* Fisher´s LSD test). The differences between groups were not statistically significant.

Table 3b. Visual analogue scale for rest pain (VAS), absolute values (cm), assessed by the patient.

Item	n (MD inj./Mesocaine inj.)	MD inj.	Stat.	Mesocaine inj.
VAS, Rest pain, Visit 1		59.0 ± 14.7	NS	59.2 ± 15.1
VAS, Rest pain, Visit 2		59.2 ± 15.2	NS	62.9 ± 18.8
VAS, Rest pain, Visit 3		52.3 ± 19.0*	NS	51.1 ± 19.4
VAS, Rest pain, Visit 4	73/24	45.7 ± 19.2*	NS	46.2 ± 22.2*
VAS, Rest pain, Visit 5		36.1 ± 20.2*	NS	33.3 ± 24.1*
VAS, Rest pain, Visit 6		31.5 ± 23.1*	NS	31.7 ± 25.2*
VAS, Rest pain, Visit 7		27.1 ± 21.9*	NS	30.8 ± 30.0*

* – statistically significant difference from baseline p<0.05 (MANOVA and *post hoc* Fisher´s LSD test). The differences between groups were not statistically significant.

Table 4. Paracetamol consumption during Visits 1-6 (number of tablets).

MD inj. (n=73)	Mesocaine inj. (n=24)	p
13.7 ± 20.7	24.5 ± 28.9	One-tailed T-test * (p=0.0485)

* – statistically significant difference between groups.

Tables 5a and 5b show treatment tolerability assessed by the patients (evaluation during Visits 6 and 7). Assessments of "very good tolerability" and "good tolerability" prevailed in both groups, in both intervals. The patients in both groups rated the tolerability of the treatment similarly at Visit 6; patients treated with MD products assessed the treatment tolerability slightly better at Visit 7. The assessment of tolerability decreased at Visit 7, whereas in the group treated with trimecaine tolerability decreased at Visit 6.

Table 6 shows the assessment of quality of life using the EuroQol questionnaire (the patient's previous health condition versus "today's" health condition at the reference control examination). The condition

Table 5a. Treatment tolerability (assessed by the patient) during Visit 6.

Category	MD inj.	Mesocaine inj.
Very good	50 (68.5 %)	17 (70.8 %)
Good	15 (20.5 %)	4 (16.7 %)
Medium	8 (11.0 %)	3 (12.5 %)
Poor	0	0

Table 5b. Treatment tolerability (assessed by patients) during Visit 7.

Item	MD inj.	Mesocaine inj.
Very good	51 (69.9 %)	14 (58.3 %)
Good	17 (23.3 %)	8 (33.3 %)
Medium	4 (5.48 %)	2 (8.33 %)
Poor	1 (1.37 %)	0

improvement from baseline is evident in both groups, with no statistically significant differences between the groups found.

Table 7 shows the selected results of the OSWESTRY questionnaire assessment, which expresses the degree of disability. The table shows improvement of the patients' condition in both groups during the treatment with a slight tendency toward better results in the group with MD injections (mostly without a statistically significant difference between treatment groups).

Table 6. Quality of life questionnaire (EuroQol).

In comparison with the health condition in the last 12 months, my health condition today is:	Treatment	n (MD inj./ Mesocaine inj.)	2nd Visit (Frequency, %)	p	6th Visit (Frequency, %)	p	7th Visit (Frequency, %)	p
Better	MD inj.	73/24	3 (4.11 %)	n. s.	43 (58.9 %)	n. s.	44 (60.3 %)	n. s.
	Mesocaine inj.		2 (8.33 %)		13 (54.2 %)		15 (62.5 %)	
Nearly the same	MD inj.		39 (53.4 %)		23 (31.5 %)		23 (31.5 %)	
	Mesocaine inj.		9 (37.5 %)		9 (37.5 %)		6 (25.0 %)	
Worse	MD inj.		31 (42.5 %)		7 (9.59 %)		6 (8.22 %)	
	Mesocaine inj.		13 (54.2 %)		2 (8.33 %)		3 (12.5 %)	

Table 7. OSWESTRY questionnaire (Oswestry Disability Index).

Item	Treatment	n (MD inj./ Mesocaine inj.)	2nd Visit	p	6th Visit	p	7th Visit	p
Disability (%)	MD inj.	73/24	27.5 ± 13.5	0.217	19.0 ± 13.9	0.214*	17.6 ± 13.5	0.310*
	Mesocaine inj.		34.5 ± 17.0		26.0 ± 19.3		23.3 ± 19.5	

Statistical significance of the difference, parametric and non-parametric evaluations. Parametric evaluation – the statistical significance of the difference between both drugs in a given interval for each item (MANOVA and *post hoc* Fisher´s LSD test, MF). Non-parametric evaluation – in the type of disability according to the percent, the difference between the drugs is evaluated by chi-square test (* – statistical significance, $p<0.05$).

Discussion

In our study, we evaluated the efficacy and safety of combined products containing collagen which were subcutaneously administered (MD-Lumbar, MD-Neural, MD-Muscle, Guna, Milano, Italy) for the treatment of patients with acute non-specific back pain. These MD-products represent a new concept in the

treatment of pain, based on strengthening the collagen matrix underlying the musculoskeletal system structures (the so called bioscaffold) and on the analgesic and antioxidative effects of these products. We compared the effects of the MD products with standard medicine, used for this indication, trimecaine (product Mesocaine 1 %) also in subcutaneous application. When the MD product is applied, a temporary porous collagen matrix forms in the tissue and the active substances are gradually released into the target area at a defined speed, thus ensuring their prolonged activity.

Collagen is the primary active ingredient of the MD products. The effect of locally applied collagen administration is structural and functional. The collagen is delivered directly to the areas where it is lacking and by creating so called adhesive barrier, it strengthens, gives structure and protects muscles, tendons and ligaments. It improves the profile of the collagen fibres and consequently, all collagen-containing anatomical structures. In addition, locally administered collagen helps to release painful muscle tension in the region and to restore its physiological function. Although the prompt analgesic activity of the MD products was not primarily expected, their administration removed the cause of pain. This may explain why their efficacy is comparable to other analgesic medications, although their analgesic effect is achieved by non-pharmacological means.

This study also has its limitations. The most important limitation is the absence of a placebo group in the study. This may be particularly important in diseases such as acute LBP, which usually have a limited duration (self-limited). However, the administration of placebo in this case also presents ethical problems.

There is lack of published data on injectable collagen in the treatment of back pain. Nevertheless, there is one randomized clinical study (Nitecka-Buchta *et al.* 2018) demonstrating the effectiveness of intramuscularly administered collagen in patients suffering from myofascial pain. The use of collagen was even superior to intramuscular administration of lidocaine. Additionally, the intraarticular injection of MD-preparations containing collagen exerted similar clinical effects as sodium hyaluronate in patients with knee osteoarthritis (Martin Martin *et al.* 2016).

Importantly, even the effectiveness of common clinically used injections with local anesthetics, either alone or in combination with corticosteroids remains disputable (Manchikanti *et al.* 2016) and is mostly based on empirical data. Some authors also mention the so-called "needle effect", i.e. an observable beneficial effect caused by puncture with a needle only. Hence, the recorded effect in our study might be at least partially attributed to needle stimulation of some dermal/subdermal structures as previously reported in a meta-analysis by Manheimer *et al.* (2007). They concluded that acupuncture seems to have a genuine biological effect, as suggested by the small short-term improvements in pain and function compared to placebo in the treatment of osteoarthritis of the knee. On the contrary, the effectiveness of acupuncture alone in the treatment of LBP has recently been the subject of re-evaluation by NICE (2016) who have reported that acupuncture is no longer recommended for the management of LBP with or without sciatica. Therefore, the beneficial effects of the active pharmaceutical ingredients in the MD injections have been suggested as the principal explanation of the recorded effects.

Importantly, the good safety profile of the MD products are very valuable, especially in comparison to the commonly used NSAIDs, which possess a huge risk of gastrotoxicity, hepatotoxicity, cardiotoxicity and nephrotoxicity, namely after long-term use and/or the use of high daily doses. Therefore, locally applied treatment with collagen products represents a safer treatment option.

Conclusions

The study results showed that in most evaluated efficacy parameters (e.g. pain assessed by visual analogue scale, functional parameters, questionnaires focusing on disability and quality of life):

- the efficacy of both treatments is comparable both in terms of quantification of the effect and its time course;
- the MD products are relatively without any risk of adverse effects;
- the MD product analgesic effect persisted even through follow-up examinations;
- a statistically and clinically significant difference in the consumption of paracetamol (as a system analgesic) was observed – approximately twice in treatment group B (trimecaine) compared to treatment group A (MD products), i.e. to achieve the same effect, significantly more rescue medications were consumed;
- the tolerability was very good or good in both groups, but was statistically better in the MD products group.

Finally, the study results can be assessed by noting that in patients with acute nonspecific back pain, collagen-containing combination products (i.e. MD-Lumbar, MD-Neural, MD-Muscle) have a comparable efficacy with the standardly used trimecaine; the advantages of these products include lower consumption of supplemental analgesics and better tolerability. According to the results of this study, these products could properly extend the current relatively limited range of treatment methods available for acute non-specific back pain.

Conflict of Interest

There is no conflict of interest.

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C. Massullo

INJECTABLE GUNA COLLAGEN MEDICAL DEVICES IN FUNCTIONAL RECOVERY FROM SPORT TRAUMATOLOGY. CASE REPORTS

SUMMARY

Low back pain is one of the most frequent diseases of our time and, due to the multiplicity of causative factors and concomitant causes, it represents one of the most controversial issues of medicine; numerous studies have shown that 60-80% of humans are affected at least once in their lifetime by a low back pain episode that may recur in 90% of cases.

– The most affected age group is the one ranging between 30 and 50 years. Nevertheless, as it is well known in Sports Medicine, a substantial percentage affects individuals under 20. The most frequent occurrence in Sports Medicine is represented by prevailing irritative forms of the *annulus fibrosus* whose etiology should be sought in the particular biomechanics of the lumbar spine.
If analysed carefully, it can be understood that the intervertebral disc can be damaged more easily not by compressive forces, but by the combined stress of lateral bend and rotation, because the lumbar vertebrae have no anatomic features to bear this kind of stress, which is typical of the athletic gestures. The force and speed that characterize sports activities may thus damage the *annulus fibrosus* formed by concentric layers of collagen fibers type 1, oriented at an angle of 30° on a horizontal axis and at an angle of 120° with the adjacent fibers. As the disc damage is represented by the collagen fibers lesion of the *annulus fibrosus*, the possibility of using Guna Collagen Medical Devices – which are specific, injectable, and replace the lack of collagen – gives an innovative and practical tool for the prevention, repair and treatment of the aging process of the intra-articular and periarticular structures as well as supporting the neighbouring mesodermal tissues.

In this article are presented two clinical cases from the author's outpatient practice, as examples of treatment protocols.

KEY WORDS

ATHLETE, DISC LESION, VERTEBRAL BIOMECHANICS, OSTEOPATHY, GUNA COLLAGEN MEDICAL DEVICES

In the whole population backache is, after common cold, the most frequent human disease.
Almost 80% of the population is destined to experience low back pain during the course of their lives.
Most of the scientific studies on this topic show an annual presence of symptoms in 50% of adults in their working age. 15-20% of these people use medical or pharmacological treatments.

Low back pain equally affects men and women and the onset is more frequent between 30 and 50 years of age, but, by virtue of the socio-cultural changes that are characterizing the industrialized countries, the onset tends to affect people in a younger age.
Backache involves high individual and social costs in terms of imaging techniques and treatments, reduced productivity and decreased ability to perform activities of daily living.
For people under 45 years of age, low back pain and neck pain are the most common cause of disability.
Despite technology and information have improved working conditions, and although Medicine has greatly developed diagnostic and therapeutic opportunities, the inability to work caused by back pain is constantly increasing.
Therefore, we can consider that Medicine, especially preventive Medicine, has not taken appropriate action on this issue.

Medical science had thought that mechanization could greatly reduce the chances of damaging the osteoarticular structure, especially the spine.
Nevertheless, results have refuted these expectations.
Medical science has then concluded that the problem could lie in reduced muscle strength, and therefore athletes, with their athleticism, could run less risk of being affected by spinal diseases.
But the number of cases in the field of sports medicine is not different.
In fact, a large percentage of cases involve subjects aged under 20 years (Candela *and* Dragoni, 1998).

So, the answer of medical doctors to the question *"What can I do for my back pain?"* has been for a long time *"perform physical activity"*, or *"go swimming"*.

The results, however, have not been encouraging, so that in doubtful cases we continue to recommend "rest" to athletes and "physical activity" to sedentary people.

– Therefore, one wonders why both athletes and sedentary people may suffer from low back pain.

Actually, sport has contradictory effects on the lumbar spine: it strengthens the muscles with protective effect on discs structures, but the microtrauma caused by repetitive stress typical of sports activities can be harmful (Danowki and Chanussot, 1998).

The sports that most often involve lumbar spine problems are: **gymnastics**, **football**, **canoeing**, **rowing**, **wrestling**, **weightlifting**, **tennis** and **golf**.
– Reading an NMR which shows essentially the presence of disc protrusions is the most frequent event in Sports Medicine.
This confirms the hypothesis based on clinical experience that common irritation of *annulus fibrosus*, muscle groups, tendons and ligaments of the low back pain due to sport is a sign of a functional disorder of the lumbar spine.

The arthritic degenerative forms or herniated disc are much more rare (Candela *and* Dragoni, 1998).
The most common source of low back pain due to sport is pain-disc lesion that affects L4-L5 or L5-S1.
We can distinguish:
1) herniated low back pain, in which the disc lesion is directly responsible for pain;
2) low back pain due to segmental instability, in which the disc degeneration and the consequent instability turn out to be the cause.
In this case, the posterior joints and the interspinous ligament are also involved and become a further source of pain, as they are highly innervated structures.

To understand the cause of the degeneration of the lumbar intervertebral disc we should recall some aspects of spinal biomechanics. An important biomechanical property of the spine is viscoelasticity, which determines a continuous deformation of the tissues of this structure, provided that the applied force is slow and progressive (Bersi, 1995).
This situation is rarely found in sports where, by definition, gestures are always the ultimate expression of joint speed and mobility.

Schematically, from a biomechanical point of view, there are two different tissues in the spine: bone and soft tissue structures (disc, ligaments, muscles).
The bone strength capacities are more important under compression (load resistance) (Bersi, 1995) **(Figure 1)**.
The soft tissue resistance, as the complex disc (*nucleus pulposus* + *annulus fibrosus* + ligaments) are more important under strain (resistance to stretching) (Bersi, 1995) **(Figure 1)**.
In order to fulfill these functions the intervertebral disc has a very complex functional anatomy: the *annulus fibrosus* consists of collagen type I fibers oriented at 30 degrees on a horizontal axis and 120° with respect to the neighboring fibers **(Figure 2)**.
Such fibers are capable of withstanding only the tension forces (Antoniou *et* Al., 1996; Hayes *et* Al., 2001).
The *nucleus pulposus* is less rich in collagen fibers (type II), but consists mainly of proteoglycans (hydrophilic) (Adams *et* Al., 1977; Hayes *et* Al., 2001; Cs-Szabo *et* Al., 2002; Sztrolovics *et* Al., 2002): the whole structure appears as an incompressible gel.

The risks of stress of the *annulus fibrosus* under tension beyond the physiological limits are much higher in combined stresses during flexion-rotation, and these are the most common stresses in sports gestures that, moreover, are made at very high speeds **(Figure 3)**.
These movements cannot be separated or governed by specific laws described by Fryette (Harrison H. Fryette, 1878-1960) as follows:

First Law: when a vertebra or a vertebral segment is in easy flexion (or neutral bending), any lateral inclination automatically results in an opposite rotation of the vertebral bodies, towards the convexity.

Second Law: when a vertebra is in forced flexion or extension, to make a lateral flexion, is obliged to first make a rotation on the same side, towards the concavity.
The rotation movements, which are of

course unavoidable, jeopardize the integrity of the lumbar spine.
We usually consider the lumbar vertebrae as extremely open in rotations, because their structures **do not** hinder movement, as it happens with the dorsal vertebrae.
The facet joints of the lumbar vertebrae ensure that the rotational movement takes place around an axis that does not correspond to the center of the vertebral end plates, but which is located at the base of the spinous process (Kapandji, 2002) (Figure 4).

Therefore, when a vertebra rotates upon another vertebra, this movement is necessarily accompanied by a lateral sliding of the vertebral body stressed in torsion. This results in a tensioning of the *annulus fibrosus* fibers that, due to typically extreme sports movements, may overcome the resistance of the structure concerned. All this may result in a progressive, anatomical damage due to failure of the collagen fibers.

We should emphasize that, in outpatient cases, pain or lumbar disk lesions are almost always localized in the vertebrae L4-L5 and L5-S1. This is conceivably due to the fact that L4 and L5 are the only two vertebrae to be connected to the pelvis by the ilio-lumbar ligament (Figure 5), and that may be affected by stresses radiating from the lower limbs that, in case of stiffness or of strong stresses, as it happens in sports gestures,

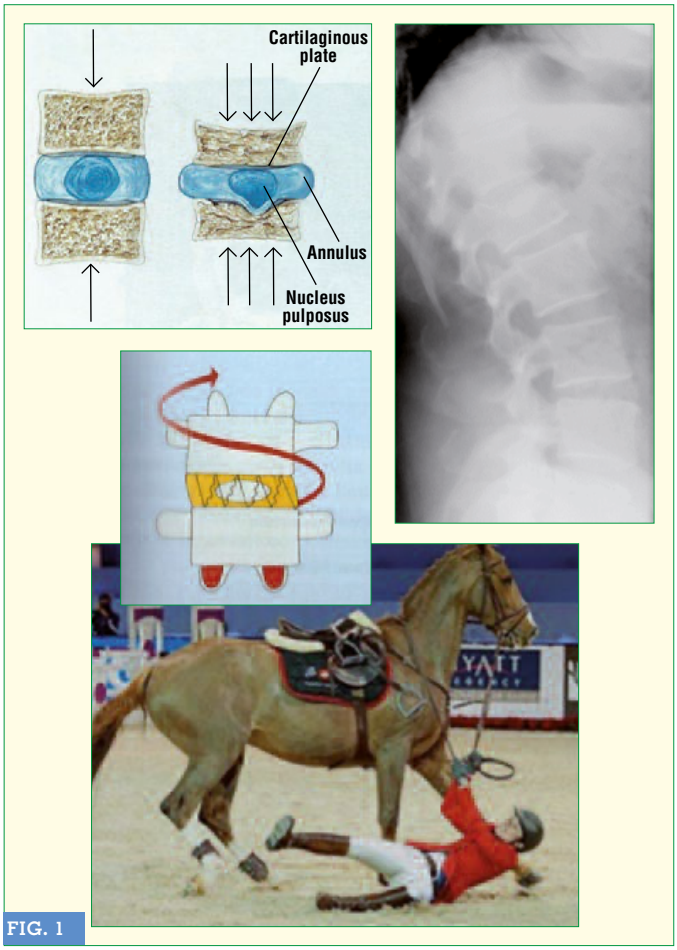


FIG. 1

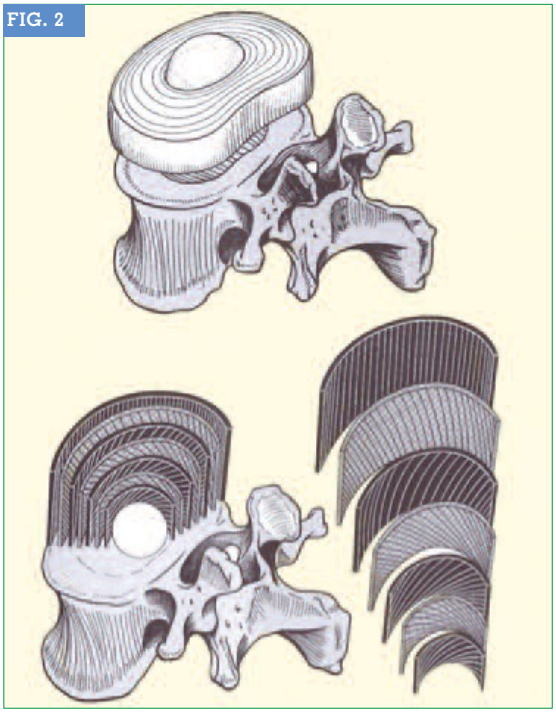


FIG. 2

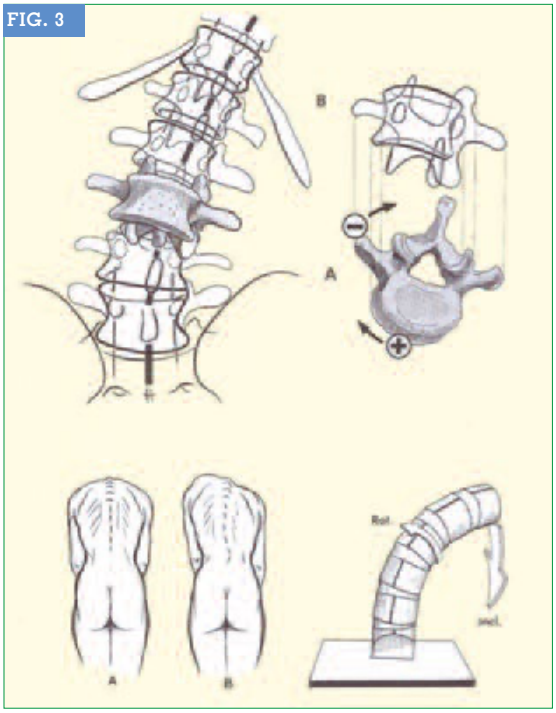


FIG. 3

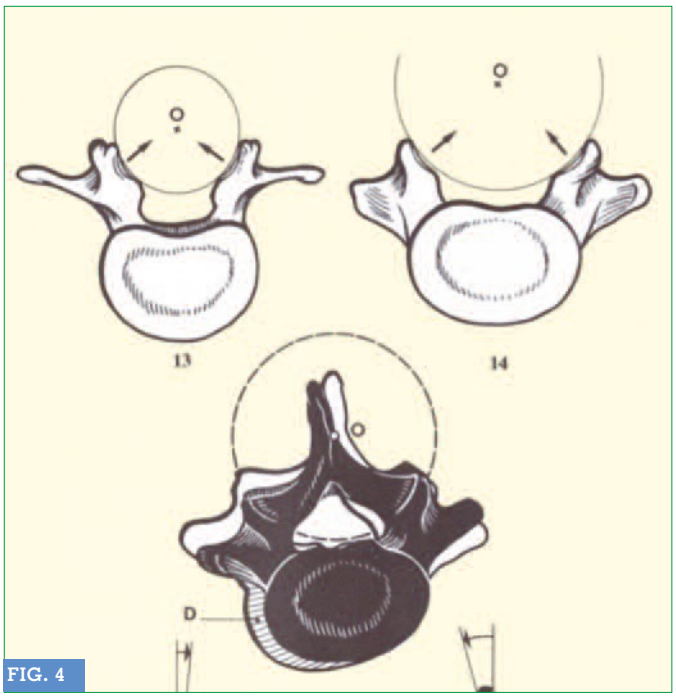


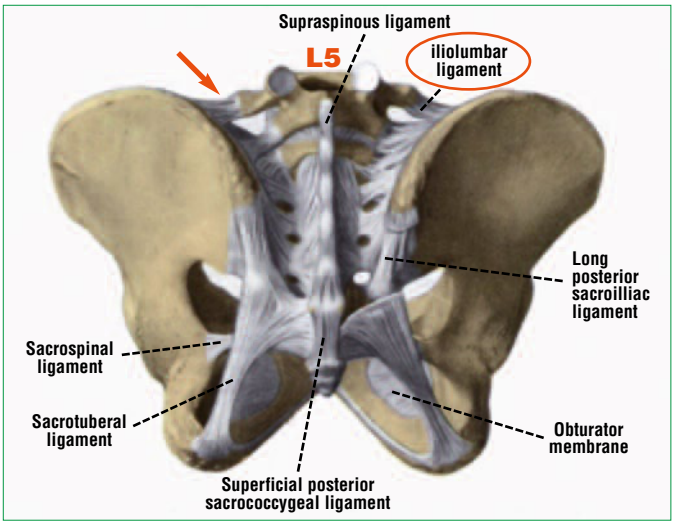
FIG. 4

can lead the spinal rotational movement beyond the physiological limits.
So, contrary to common opinion, the disc damage cannot be primarily ascribed to compressive stresses, such as those of the bounces of a race, but to a number of causes, such as:
– strong tractions that the muscles of the lower limbs exert on the pelvis;
– pelvis that causes rotation of the vertebral bodies of L4 and L5 through the ileo-lumbar ligaments;
– joint facets of the lumbar vertebrae that do not facilitate rotation;
– translation of the vertebral body.

This is the series of events that may induce the progressive lesion of the collagen fibers of the *annulus fibrosus* leading to the herniation of the *nucleus pulposus*.
The disc damage is due to a lesion of the *annulus fibrosus* collagen fibers.
Therefore, the availability in the current medical practice of **Guna Collagen Medical Devices** – specific injectable devices that replace the collagen degradation – can be seen as an innovative and practical tool for prevention, repair and treatment of the aging process of **intra-articular** and **periarticular structures**, and of the neighboring mesodermal support tissues.

FIG. 5

From Netter F.H. – Atlas of human anatomy. EDRA Ed. 2014 (see References).



– In my personal medical practice of Sports Medicine and Osteopathy, I daily assist athletes affected by bone, joint and myofascial disorders, using manual medicine with excellent results.
– The combined treatment with Collagen MDs has speeded up the healing process, further reducing the athlete's recovery time, and has ensured a more permanent damage repair, especially in cases of tendency to relapses.

CASE REPORTS

43 professional athletes were treated between January 2014 and December 2015. Amateur athletes were excluded.
– All athletes were treated for acute low back pain (or relapses) resulting from pain or disc lesion without disc herniation diagnosed via NMR.
The athletes, aged between 19 and 32 years, were practicing the following sports: Karate (**2**), Fencing (**3**), Rowing (**5**), Triathlon (**5**), Horse riding, Show Jumping (**6**), Volleyball (**6**), Athletics, Race (**7**) and Football (**9**).
Treatment: manual + injectable therapy with **Guna MD-Lumbar** + **Guna MD-Muscle** and **Guna MD-Matrix**, 4-5 cm lateral to the spinous processes of L4, L5, S1 with 30G, 13mm needle.
– We hereby present two emblematic examples of the treatment protocol, using the rapid return to sports as an indicator of treatment efficacy.

CLINICAL CASE 1

Female, 26 years old, practicing riding, show jumping discipline, professional athlete.

– In June 2014 she fell during a jump, because of a technical error. This athlete experienced strong back pain at that time, which worsened some days later, until discontinuance of sports activity.
NMR negative for herniated discs.
Treated with manual therapy: muscle stretching for hamstrings, intra and external rotators, iliopsoas; manipulations of sacroiliac joints and lower back.

She went back to training after only two sessions of manual therapy, because of fear of injections. A slight discomfort still persisted after one month.
The athlete understood the necessity of an injection treatment with Guna Collagen Medical Devices with the following protocol: 2 sessions/week for 2 weeks; then 1 session/week for 6 weeks.
MD-Lumbar + MD-Matrix, 4-5 cm lateral to the spinous processes L4, L5, S1 with 30G 13 mm needle. After 3 sessions, full remission of pain. Anyway, the patient completed the course of therapy.

Comments
Certainly, at the beginning, the fact that it was impossible to fully discontinue physical activity (you have to train the horse, especially) has not facilitated an optimal repair of the lesion. The locoregional injection of **MD-Lumbar** (specific for the skeletal structure) and **MD-Matrix** (specific for the extracellular matrix), has probably supported the deposition of neo-synthesized collagen fibers in the damaged region, helping the patient to fully recover.

CLINICAL CASE 2

Male, 28 year old, professional football player, striker.

– In September 2014 acute lumbar joint block after an athletic training session in the gym, which caused immediate discontinuation of sport activity.
The athlete was treated with NSAIDs for 5 days by the team doctor. Then he was treated by the team osteopath for three times + 8 Tecar therapy sessions.
The football player resumed training sessions after 15 days, but did not completely recover. After new worsening symptoms, the athlete came to my clinical practice.
Results of NMR: *"Slight disk protrusion in the back median area between L4-L5 and L5-S1. There are no herniated disks"*.
Treatment with manual therapy: muscle stretching for hamstrings, intra and external rotator muscles of the hip, iliopsoas + injection treatment with Collagen as follows: 3 sessions/week for 1 week; 2 sessions/week for 2 weeks; 1 session/week for 5 weeks.
The treatment included **Guna MD-Lumbar + Guna MD-Matrix + Guna MD-Muscle** (in the long run analgesic muscle contractures appear); 4-5 cm lateral to the spinous processes of L4, L5, S1 with 30G 13mm needle.
After 3 sessions the patient has gradually resumed his training sessions; after 7 sessions (3 weeks) he played a full game. Some discomfort persisted in the movements early in the morning until session n. 9.

Comments
This patient showed marked stiffness of the muscles of the posterior kinetic chain of the lower limbs.
So, the only spinal manipulative therapy could not remove the actual triggering cause, resulting in the worsening of the lesion.
The stretching treatment was useful to restore a more correct spinal biomechanics, and the injection therapy with MD-Lumbar (specific for the skeletal structure), MD-Matrix (specific for the extracellular matrix) and MD-Muscle (specific for the muscle tissues) allowed to neutralize the inflammatory-degenerative disk overlap. ■

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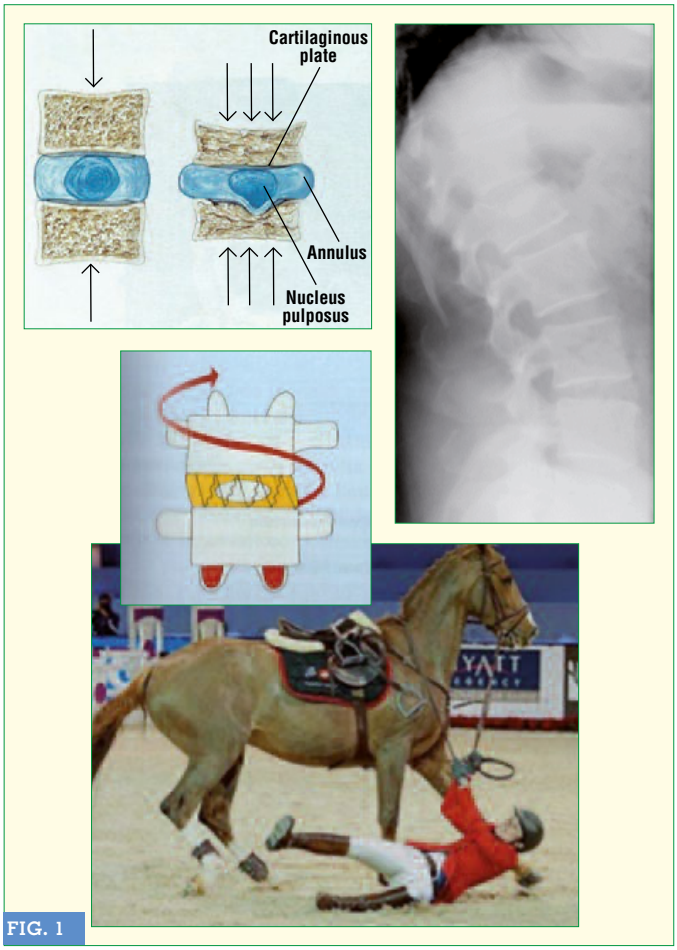


FIG. 1

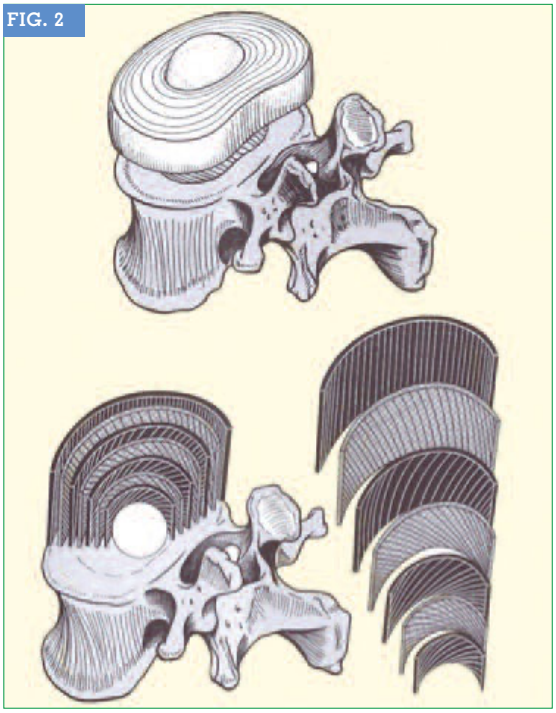


FIG. 2

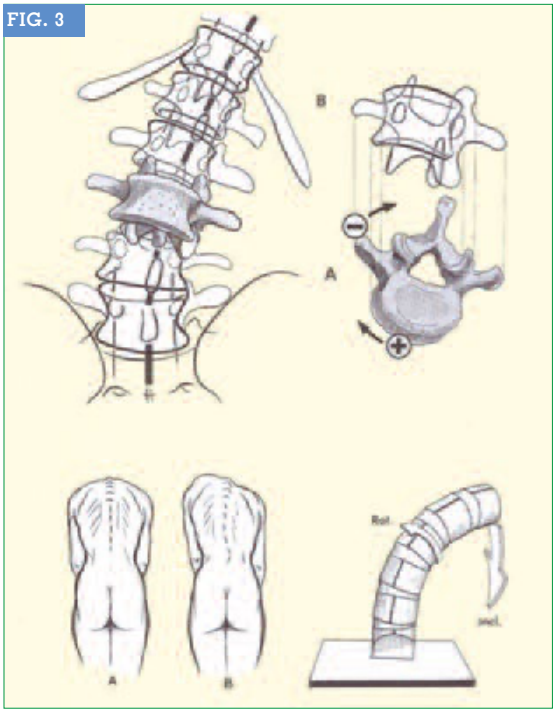


FIG. 3

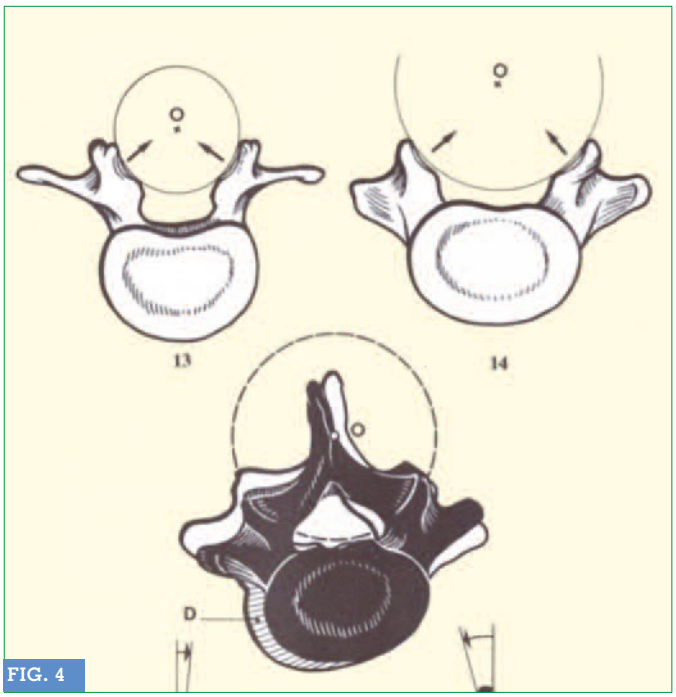


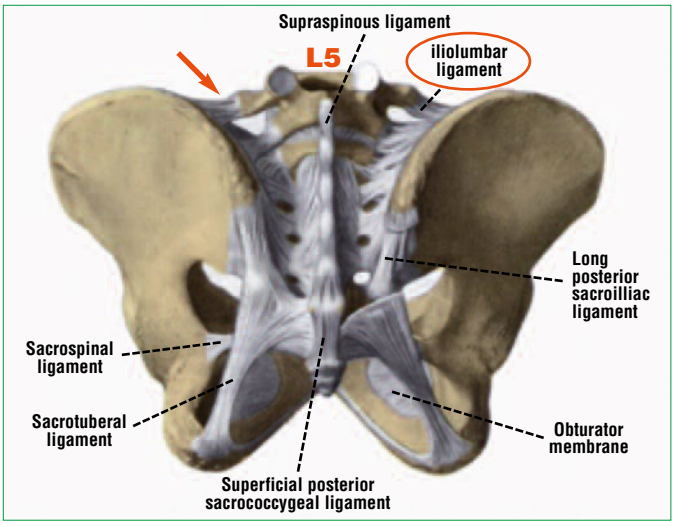
FIG. 4

can lead the spinal rotational movement beyond the physiological limits.
So, contrary to common opinion, the disc damage cannot be primarily ascribed to compressive stresses, such as those of the bounces of a race, but to a number of causes, such as:
– strong tractions that the muscles of the lower limbs exert on the pelvis;
– pelvis that causes rotation of the vertebral bodies of L4 and L5 through the ileo-lumbar ligaments;
– joint facets of the lumbar vertebrae that do not facilitate rotation;
– translation of the vertebral body.

This is the series of events that may induce the progressive lesion of the collagen fibers of the *annulus fibrosus* leading to the herniation of the *nucleus pulposus*.
The disc damage is due to a lesion of the *annulus fibrosus* collagen fibers.
Therefore, the availability in the current medical practice of **Guna Collagen Medical Devices** – specific injectable devices that replace the collagen degradation – can be seen as an innovative and practical tool for prevention, repair and treatment of the aging process of **intra-articular** and **periarticular structures**, and of the neighboring mesodermal support tissues.

FIG. 5

From Netter F.H. – Atlas of human anatomy. EDRA Ed. 2014 (see References).



– In my personal medical practice of Sports Medicine and Osteopathy, I daily assist athletes affected by bone, joint and myofascial disorders, using manual medicine with excellent results.
– The combined treatment with Collagen MDs has speeded up the healing process, further reducing the athlete's recovery time, and has ensured a more permanent damage repair, especially in cases of tendency to relapses.

CASE REPORTS

43 professional athletes were treated between January 2014 and December 2015. Amateur athletes were excluded.
– All athletes were treated for acute low back pain (or relapses) resulting from pain or disc lesion without disc herniation diagnosed via NMR.
The athletes, aged between 19 and 32 years, were practicing the following sports: Karate (**2**), Fencing (**3**), Rowing (**5**), Triathlon (**5**), Horse riding, Show Jumping (**6**), Volleyball (**6**), Athletics, Race (**7**) and Football (**9**).
Treatment: manual + injectable therapy with **Guna MD-Lumbar** + **Guna MD-Muscle** and **Guna MD-Matrix**, 4-5 cm lateral to the spinous processes of L4, L5, S1 with 30G, 13mm needle.
– We hereby present two emblematic examples of the treatment protocol, using the rapid return to sports as an indicator of treatment efficacy.

CLINICAL CASE 1

Female, 26 years old, practicing riding, show jumping discipline, professional athlete.

– In June 2014 she fell during a jump, because of a technical error. This athlete experienced strong back pain at that time, which worsened some days later, until discontinuance of sports activity.
NMR negative for herniated discs.
Treated with manual therapy: muscle stretching for hamstrings, intra and external rotators, iliopsoas; manipulations of sacroiliac joints and lower back.

She went back to training after only two sessions of manual therapy, because of fear of injections. A slight discomfort still persisted after one month.
The athlete understood the necessity of an injection treatment with Guna Collagen Medical Devices with the following protocol: 2 sessions/week for 2 weeks; then 1 session/week for 6 weeks.
MD-Lumbar + MD-Matrix, 4-5 cm lateral to the spinous processes L4, L5, S1 with 30G 13 mm needle. After 3 sessions, full remission of pain. Anyway, the patient completed the course of therapy.

Comments
Certainly, at the beginning, the fact that it was impossible to fully discontinue physical activity (you have to train the horse, especially) has not facilitated an optimal repair of the lesion. The locoregional injection of **MD-Lumbar** (specific for the skeletal structure) and **MD-Matrix** (specific for the extracellular matrix), has probably supported the deposition of neo-synthesized collagen fibers in the damaged region, helping the patient to fully recover.

CLINICAL CASE 2

Male, 28 year old, professional football player, striker.

– In September 2014 acute lumbar joint block after an athletic training session in the gym, which caused immediate discontinuation of sport activity.
The athlete was treated with NSAIDs for 5 days by the team doctor. Then he was treated by the team osteopath for three times + 8 Tecar therapy sessions.
The football player resumed training sessions after 15 days, but did not completely recover. After new worsening symptoms, the athlete came to my clinical practice.
Results of NMR: *"Slight disk protrusion in the back median area between L4-L5 and L5-S1. There are no herniated disks"*.
Treatment with manual therapy: muscle stretching for hamstrings, intra and external rotator muscles of the hip, iliopsoas + injection treatment with Collagen as follows: 3 sessions/week for 1 week; 2 sessions/week for 2 weeks; 1 session/week for 5 weeks.
The treatment included **Guna MD-Lumbar + Guna MD-Matrix + Guna MD-Muscle** (in the long run analgesic muscle contractures appear); 4-5 cm lateral to the spinous processes of L4, L5, S1 with 30G 13mm needle.
After 3 sessions the patient has gradually resumed his training sessions; after 7 sessions (3 weeks) he played a full game. Some discomfort persisted in the movements early in the morning until session n. 9.

Comments
This patient showed marked stiffness of the muscles of the posterior kinetic chain of the lower limbs.
So, the only spinal manipulative therapy could not remove the actual triggering cause, resulting in the worsening of the lesion.
The stretching treatment was useful to restore a more correct spinal biomechanics, and the injection therapy with MD-Lumbar (specific for the skeletal structure), MD-Matrix (specific for the extracellular matrix) and MD-Muscle (specific for the muscle tissues) allowed to neutralize the inflammatory-degenerative disk overlap. ■

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Paper presented in the 1st International Congress - Collagen in musculoskeletal System disorders. A journey through pain relief, tissue repair, and functional recovery. Milan, 19th November 2016.

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THERAPEUTICS

L. Milani

A NEW AND REFINED INJECTABLE TREATMENT FOR MUSCULOSKELETAL DISORDERS

– BIOSCAFFOLD PROPERTIES OF COLLAGEN AND ITS CLINICAL USE

SUMMARY

Connective tissue and collagen in particular – a real protein-tissue – progressively degrade and reveal to be inadequate to perform the functions they are to accomplish in each organism. This is due to aging, sedentarity, intense physical activity or inadequate sports activity, postural alteration, alimentary disequilibrium, and PNEI-axis alteration. Specific injectable Medical Devices (MD) (both distrectual and tissular) represent a new and refined tool in prevention and therapy to treat the ageing of articular structures, as well as periarticular ones and those concerning mesodermic supporting tissues. These MDs replace the lack of collagen, which is always recurrent in the inflammatory and/or degenerative diseases of the locomotor Apparatus and other anatomical structures of mesodermic origin; they are natural, free from negative side effects (excellent safety); they can be associated with homotoxicological therapies as well as allopathic ones that are being applied or that will be scheduled; moreover, they can be associated with physical therapies. Non-invasiveness of injections using Guna MDs – which are the first to highlight quality therapeutic results in 7 controlled clinical trials [Registration Dossier c/o Istituto Superiore di Sanità (Italian Superior Health Institute)] – together with other characteristics such as effectiveness, tolerability, absence of allergic reactions and their natural origin make them a valuable tool in standard procedures (both in treatments by specialists or general practictioners) and in processes aimed at improving the patients' quality of life, which could otherwise worsen or become further chronic.

KEY WORDS **COLLAGEN, MEDICAL DEVICE, ANCILLARY SUBSTANCE, GUNA MEDICAL DEVICE, PAIN, OSTEO-ARTHRO-MYO-FASCIAL PATHOLOGIES**

COLLAGEN – COMPOSITION AND ACTION

Collagen is the most abundant protein (structural protein – tissue; molecular weight 300KDa) in mammalians' organism – accounting for about 5-6% of an adult's body weight (Van der Rest *et* Al., 1991); one third (Trentham *et* Al., 1977) or one fourth (Lynsenmeyer, 1991) of the whole protein mass of higher animals is composed of collagen: bones and tendons, joint capsules and muscles, ligaments and fascia, teeth and serous membranes, the skin and the extracellular matrix (ECM).

– According to some hypotheses, the ancestral gene that synthesizes collagen has evolved to its present form due to further mutations starting from one single unit composed of only 54 base pairs of DNA.

At present the alpha 2 collagen gene is composed of about 38.000 base pairs.

– The basic difference between **functional proteins**, which are involved in biochemical, enzymatic, immune, membrane and/or transmembrane receptor processes, and **structural proteins**, which play an important role in building the scaffold of higher organisms (connective tissue in a wider sense and more specifically – fibrous tissue) is not considered so important for collagen.

For example, collagen VI plays an essential role in the processes of cell adhesion, replication and survival through its interaction (*cross-talk*) with integrins and/or other transmembrane receptors (Pfaff *et* Al., 1993; Jan *et* Al., 2004), showing both roles: the genetic absence of Collagen VI causes severe morpho-functional alterations of muscle fibres and apoptosis by acting directly on the mitochondrion (Rizzuto, 2003) due to a failure to regulate cell permeability (last author mentioned).

– **Collagen "health"** is ultimately the **individual's health**: man's peak of collagen biosynthesis occurs between 45 and 60 years of age (Heine, 2009): after that age there is a rapid decrease of collagen that is also accompanied by a rapid decrease of elastin and proteoglycans (Milani, 2004 *a*) (FIG. 1).

An insufficient renewal of the ECM brings about a sluggish function of the

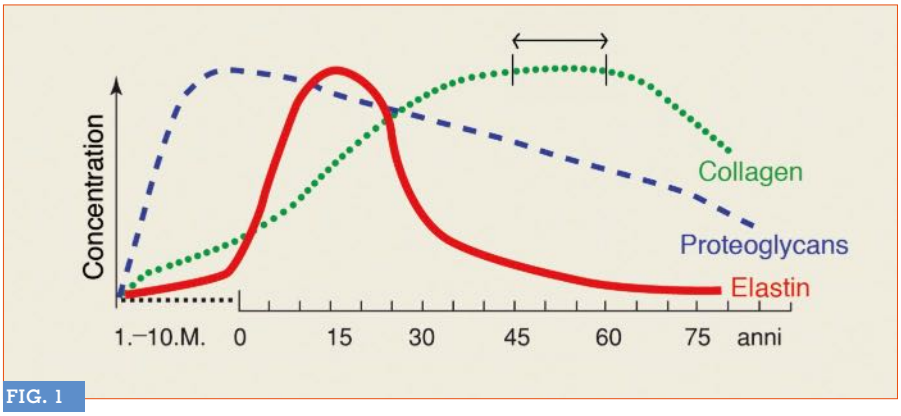


FIG. 1

Life curve of the most important macromolecules of the extracellular matrix (*in* Heine, 2009).

Transit System (Pischinger, 1983). Faulty routing of waste will cause the accumulation of toxins usually directed by the cells in the microvessels of the lymphatic system; this impacts oxygenation of tissues, nutrient assimilation and hydration. Fragility and sclerosis are silent symptoms preceding degeneration and possible tissue dedifferentiation (disease evolution according to Reckeweg).

The base unit of collagen is **tropocollagen** (FIG. 2), a glycoprotein composed of three left-handed helices of polypeptide units carrying glucose and galactose molecules that are attached **only** to the molecule of the amino acid hydroxylysine (Hyl), one of the only four amino acids that form tropocollagen with Glycine (Gly), Proline (Pro) and 4-Hydroxyproline (Hyp).

Tropocollagen has some interesting structural "anomalies" compared to other proteins:
– In the molecule:

1) Every triplet of amino acids always starts with Glycine (**Gly**-A-B);
2) The amino acid sequence is often represented by the triplet Gly-Pro-Hyp;
3) These triplets cannot usually be found in other proteins and have to be considered unique and special;
4) Proline determines the twisting, the "change of direction" along the axis of the protein strand; that's why it is absolutely absent in globular proteins;
5) Many residues of Hyp have two sugar residues.
   Therefore, collagen is a glycoprotein (great amount of protein – small amount of sugar) and not a proteoglycan (PG) (great amount of sugar – small amount of protein);
   The collagen imbalance of sugar/protein ratio balances that of PGs.
6) Axial periodicity (text, *see after*: FIG. 6), a true metamerism that is visible only with the electron microscope.

These "anomalies" guarantee a perfect strength and function of the molecule: when the three polypeptide units are intertwined in a tight triple helix, stabilized between hydroxylated amino acids (*crosslinks*) by weak H^+ bonds, they give basic and special characteristics to collagen 2: structural **strength** and organoleptic **rigidity**. The spatial configuration of tropocollagen is a cylindrical braid composed of three rods wrapped in an helix. This gives the molecule great **resistance** and **flexibility**: to break a 1 mm diameter collagen fiber an 11 kg weight must be applied to each end.
The hydrogen bond is a weak, non-covalent bond: it is the number of atoms that gives it its strength, as it occurs with fibroin, the structural protein of silk.
The hydroxylation of Pro and Hyp and the hydroxylation of Lys and Hyl occur thanks to the cofactor ascorbic acid (Vitamin C) and to the substrate acidum α-ketoglutaricum, one of the three-carboxylic acids of Krebs' Cycle. A deficit of one of these metabolic boosters will cause severe alterations of the connective tissue which can manifest as scurvy and cancer cachexia.
A failed hydroxylation to Hyp and Hyl leads to the formation of a collagen fibril that is structurally and functionally impaired.

According to the different types of collagen involved some severe genetic cases of *Osteogenesis imperfecta*, Bethlem myopathy, Ulrich's scleroatonic muscular dystrophy, mitochondrial myopathy may occur, just to mention a few that illustrate the truth behind Garrod's "old" theory (1902) – "*one gene, one enzyme*" which still applies today.

▶ The diseases due to an acquired collagen deficiency are also thought to have their pathogenesis in a faulty synthesis and use of collagen (TAB. 1).
– I would like to remind that Lys, precursor of tropocollagen 5-Hyl is an **essential amino acid** that must be sourced from food and/or from supplementation.
– Collagen biosynthesis is carried out by different cell lines (fibroblasts in the loose and fibrous fibrillar connective tissue, osteoblasts in bones, chondroblasts in cartilage, etc.)
After the amino acids interlock, the **globular procollagen** is produced at an intracellular level and is pushed outwards through the Golgi apparatus (Olsen, 1983) (FIG. 3). Here, thanks to the shortening of the 2 telomeres (one N-terminal, the other C-terminal), the procollagen turns into **protocollagen**; as soon as protocollagen is being formed, this produces a negative feedback on the collagenous-genetic cell, by inhibiting a further synthesis.
– The procollagen microfibrils are therefore polymerized **outside** the collagenous-genetic cell.
The single units of protocollagen are staggered thanks to Lysyl-oxidase, linearly and in parallel array to gradually form one microfibril, one subfibril, and

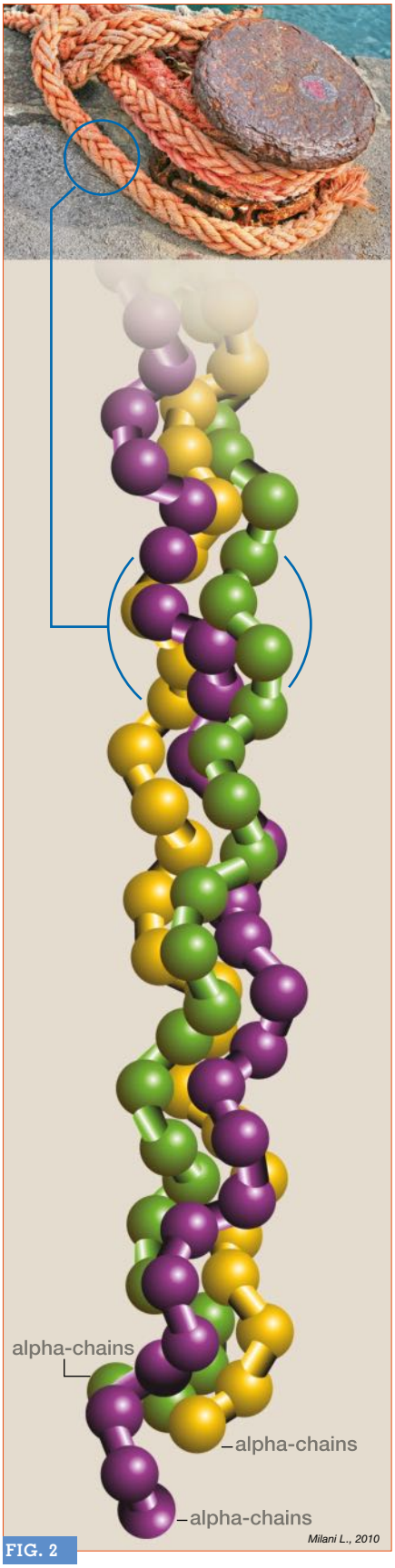


FIG. 2

The triple helix (three alpha-chains) **of tropocollagen, the basic unit of mature collagen.**
- The molecule is stabilized by the presence in the alpha chains of hydroxylated amino acids whose H^+ bonds give it strength and rigidity.

TAB. 1

SOME OF THE MOST IMPORTANT AND FREQUENT ACQUIRED COLLAGENOPATHIES
– PRIMARY CHRONIC POLYARTHRITIS (RHEUMATOID ARTHRITIS)
– STILL'S SYNDROME
– FELTY'S SYNDROME
– ANCYLOSING SPONDYLITIS (STRÜMPELL-BECHTEREW-MARIE DISEASE)
– REITER'S SYNDROME
– SCLERODERMIA
– SLE
– DERMATOMYOSITIS
– POLYMYOSITIS
– KUSSMAUL PANARTHRITIS
– HORTON'S TEMPORAL ARTHERITIS
– MOSKOWITZ PURPURA
– GOODPASTURE'S SYNDROME
– MOYAMOYA DISEASE
– TAKAYASU'S SYNDROME
– SHARP'S SYNDROME (mixed connective tissue disease)

Milani L., 2010

one **collagen fibril**. (FIG. 4).
Several collagen fibrils constitute a **collagen fibre**.

– This process is thought to occur, at least partly, via an *autocatalytic* route (Prockop, 2004; Cisneros *et* Al., 2006).
In some rare moments biology by-passes the rigid genetic determinism and the most flexible epigenetic possibilism and shows great adaptability supported by autocatalysis with more flexibility and adaptability (Lima de Faria, 2003).

This undermines deeply the Darwinian and post-Darwinian pure evolutionary theory (Milani, 2009).

– The fibrils are characterized by a periodicity: they show small structural units along their own course which repeat every 670 Amstrong [FIGG. 5 (1, 2), 6].
– The reason for this periodicity (a true structural form), which has been sought for a long time, is simple: as both fibrils and the collagen fibres are

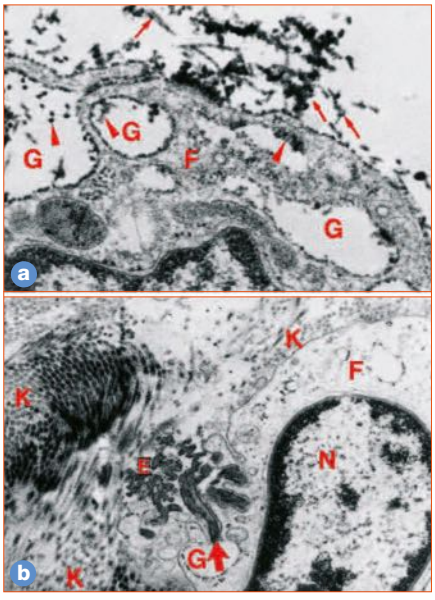


FIG. 3

Synthesis and extracellular cross link of collagen and elastin;
F = fibroblast; G = Golgi (vesicles)**;**
K = Collagen, E = Elastin, N = Cell nucleus.
a After the release and the "cutting" of telopeptides, tropocollagen molecules are formed (→) these bind to collagen fibrils (2.400X)**;**
b Release of elastin precursors (tropoelastin) from a Golgi vesicle and neosynthesis of elastin (→) (2.400X)**.**

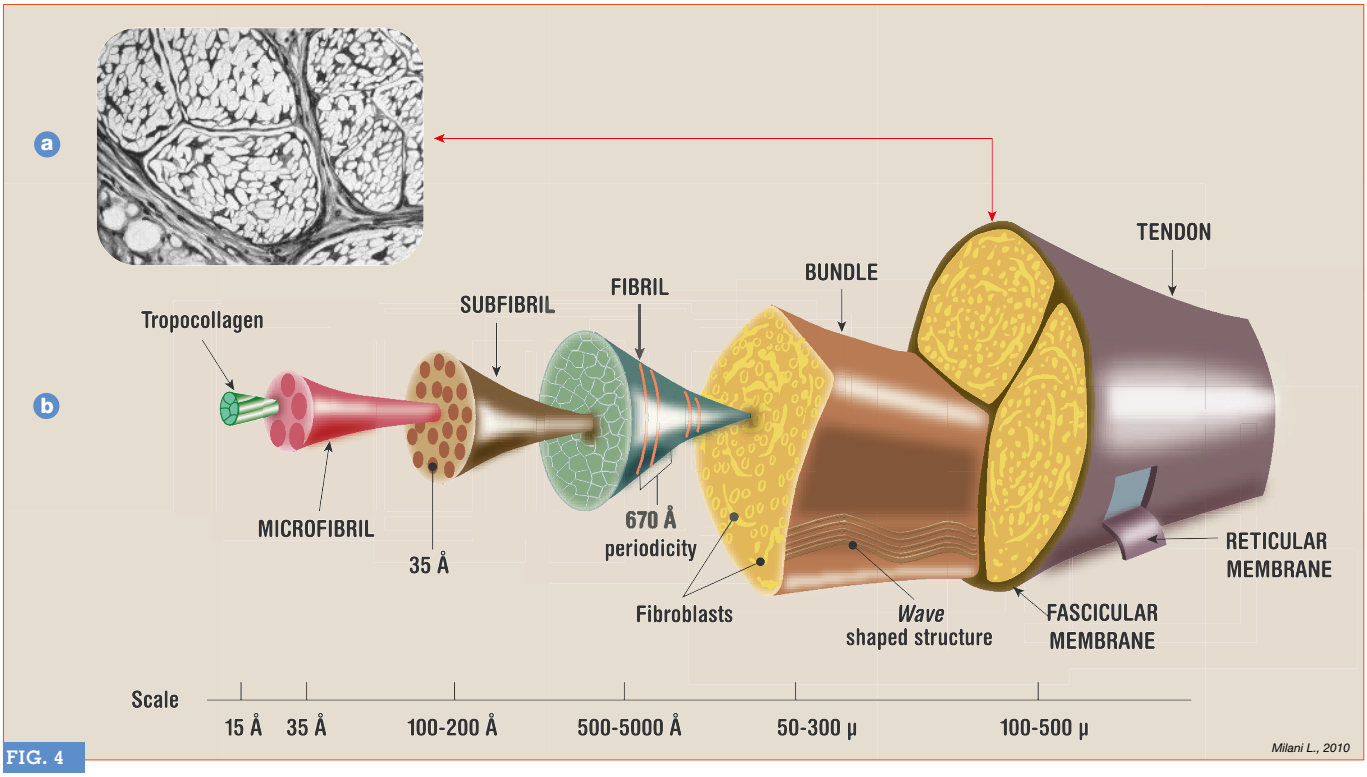


FIG. 4

a Tendon in cross-section [350X magnification (Chèvremont)]**. The collagen fibers are grouped in sepimented bundles of different levels.**
b Hierarchical structure of the tendon acc. to Kastelic *et* Al., 1978 (reconstructed, updated by the author).

much longer than the maximum diameter of the cells that synthesize them, the basic collagen molecules must be small enough to be secreted and polymerized afterwards.

If a tropocollagen fibre is 2,800 Amstrong long, how can we justify a 670 Amstrong axial periodicity? This is possible **only if** the underlying fibrils are out of phase of one quarter compared to the overlapping fibrils (Hodge *and* Petruska model, 1964) and **if** these do not relate by the ends but rather line up in a way that there is a half length period between their own extremities (1 *dark* segment + 1 *light* segment = 1 period).

Each molecule of tropocollagen is composed of 5 *light* segments spaced out by 4 *dark* segments. Thanks to the use of Conventional Amplitude Modulation (AC Imaging) structural models have been recently proposed, different from the traditional model that is recognized by the scientific community (Bozel *et* Al., 2007), even if a new convincing molecular scheme has not yet been defined (Jiang *et* Al., 2009).

▶ Such arrangement of the fibrils in the formation of collagen fibres guarantees a great strength in terms of:

– **RESISTANCE**
– **NON-EXTENSIBILITY**
– **NON-COMPRESSIBILITY,**

but also

– **PLASTICITY**
– **FLEXIBILITY**
– **LOAD RESISTANCE**
– **TORSION RESISTANCE**

These characteristics make collagen an extremely versatile "structure" that Nature has been selecting during hundreds of millions of years and upheld as the best means to fulfil its many functions.

Besides these characteristics, collagen is the prerequisite for the activation of the repair process of all the body tissues.

- Before concluding this section, I would like to point out a further characteristic of collagen that is little known, but extraordinary: **piezoelectricity**, an electric charge generated by pressure, traction, torsion (Athenstedt, 1974).

Thanks to its helical structure, collagen, an out-and-out electric dipole, can **oscillate** thus piloting the growth and the orientation of the neo-fibrils.

From this point of view, a special electromagnetic activity is ascribed to the large trabeculations of the connective tissue that are located between the big muscular bundles and their tendons of origin and insertion.

Heine (2009), resuming the work by Bergsmann *and* Bergsmann (1997), suggests that the large connective *trabeculae* clearly correspond to the Chinese Acupuncture Meridians.

– In any case, they can be found more frequently between antagonistic muscle groups (Milani, 2004 *b*), which raises the real possibility to intervene therapeutically with injections of collagen in these points/areas in cases of osteo-arthritis and local myo-fascial interstitial pathologies.

THE ARTICULAR STABILIZATION SYSTEMS – THE COLLAGEN REIGNS

The restraint and stabilization function of each joint must ensure two principles in apparent opposition: **stability** and **locomotion**.
Later we are going to explain how the anatomical alterations that cause changes in one or both of these functions, cause dysfunctions and pathologies of the skeletal muscle, with resulting motor deficit.
The stabilization systems are represented by stabilizing structures that cooperate at different levels for an optimal articular functionality.

1 – EXTRA - ARTICULAR COMPARTMENT

(FIG. 7)

– LIGAMENTS

Intra-articular (only big joints) and extra-articular elements consisting of a parallel system of collagen bundles.
By examining the conditions under which the ligaments are put under tension-traction, it easy to determine the reason why they can be blocked or prevented from movement.

– INTRA ARTICULAR CAPSULE

The covering element for protection and reinforcement of the joint, is fixed on the two elements of the adjacent bones. In smaller joints, the line of intersection is located along the edge of the articular cartilage. The capsule consists of interwoven heavily and closely staggered bundles of collagen, zones of less dense fibrillar tissue and adipose lobules.
The collagen bundles that form the joint capsule are never arranged longitudinally between the two articular heads, but rather obliqually following the interwined trajectories thus forming a strong and rigid capsule.

– TENDONS

The long tendons connecting one section with the other of the locomotor system are provided with restraint elements that keep the two sections in contact with the bone axis during the joint movement.
The tendons are strengthened and protected by mucous sheaths, in some cases along the whole stretch of sliding.
Between tendon and sheath there is a lubricant liquid, similar to the synovial fluid, which facilitates the tendon sliding.

– MUSCLES

Also the muscles are involved in the articular resistance through their surface coating bundles (coating aponeurosis), deep fascia, connective tissue which sometimes acts as an individualized *lamina*, and intermuscular *septa*.
If the restraining function of the muscles is insufficient, only the capsule and ligaments ensure this function: their resistance is below the threshold of effort, and the joint is exposed to not sustainable risks.
– Many cases of mild to medium severity of hip dysplasia can be controlled by inducing hypertrophy of the surrounding muscles by means of specific physical exercises and nutritional sup-

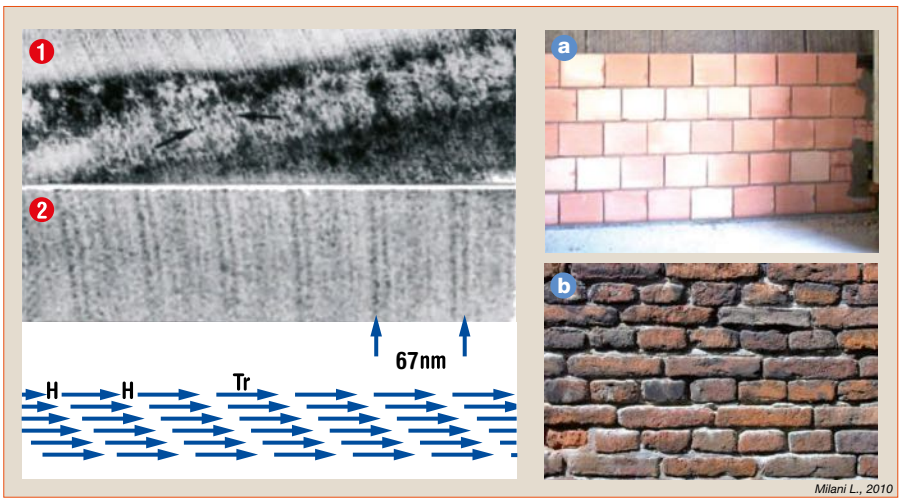


FIG. 5

1: Sugars linked to collagen (ruthenium red colour)**. Correlation of sugar** (black precipitations) **to the periodicity of collagen fibrils** (ME 112.000X)**;**
2: Section of a collagen fibril (ME 240.000X)**. A cycle of 67 nm** (670 A) **is formed on the basis of collagen molecules each time slipped of one-quarter of their length.**
a This placement of bricks responds well to the pressure from above, not to the tangential one.
b This placement of bricks responds well to the pressure from above, and to the tangential forces: this provision shows a displacement of many bricks compared to the overlying ones of ca. one quarter of the length of the single element (author, 2010)**.**

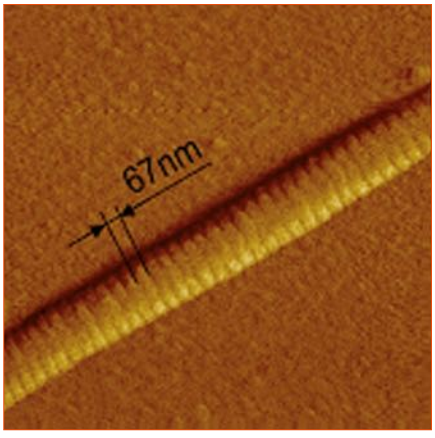


FIG. 6

Ultrastructure of the collagen. Native collagen fibril type I (AFM images)**.**
– The most recent ultrastructural measurements show a period of 67 nm (670A) **and not of 64 nm, as previously reported by various Authors and frequently even by scientific literature and in medical textbooks.**
– Collagen shows a clear and defined "metameric" structure with a simple or elementary recurrent base scaffold.

plementation with MAP-Son Formula *(personal observations)*.
Even after many years the situation of X-ray shows only minimal endoarticular alterations that are compatible with normal mobility and quality of life.

2 – INTRA-ARTICULAR COMPARTMENT

– LIGAMENTS

Intra-articular ligaments of the big joints (FIG. 8).

– ARTICULAR CARTILAGE

The great Italian anatomist R. Amprino (Anatomical Institute, University of Turin), had the merit to carry out the early studies on the mechanical function of the collagen fibrils of the hyaline cartilage in man (Amprino, 1938).
The collagen fibrils are arranged in vertical bundles in the fundamental substance of the deep layer while they are arranged tangentially on the surface layer.
Overall, the fibrillar arches form a structure similar to a Romanesque arch (FIG. 9); this is an optimal architectural solution for well withstanding the pressure from above and tangential forces exerted during the joint movement.

All extra-and intra-articular structures consist basically of collagen.

– The (rare) genetic-metabolic alterations, mechanical alterations (recurring microtrauma, trauma), abnormal posture, age (chrono-aging) acquired collagenopathies, chronic inflammatory diseases and cancers **damage the integrity of collagen fibers** and - consequently - of the support system as well as the mechanical function of the whole organism.
Some studies carried out by Ozaki *et* Al., (1988) and Riley *et* Al., (1994) show - in autopsy reports – flagrant changes in the composition of collagen in rotator cuff tendinitis and how the body triggers the collagen neosynthesis in an attempt to remodel the micro-damage and repair the tendons involved, also in elderly.
The electron microscope photographs shown in Provenzano *et* Al., (2001) on the ultrastructure of the repair process of medial collateral ligament injuries of the knee, are very exhaustive (FIG. 10).

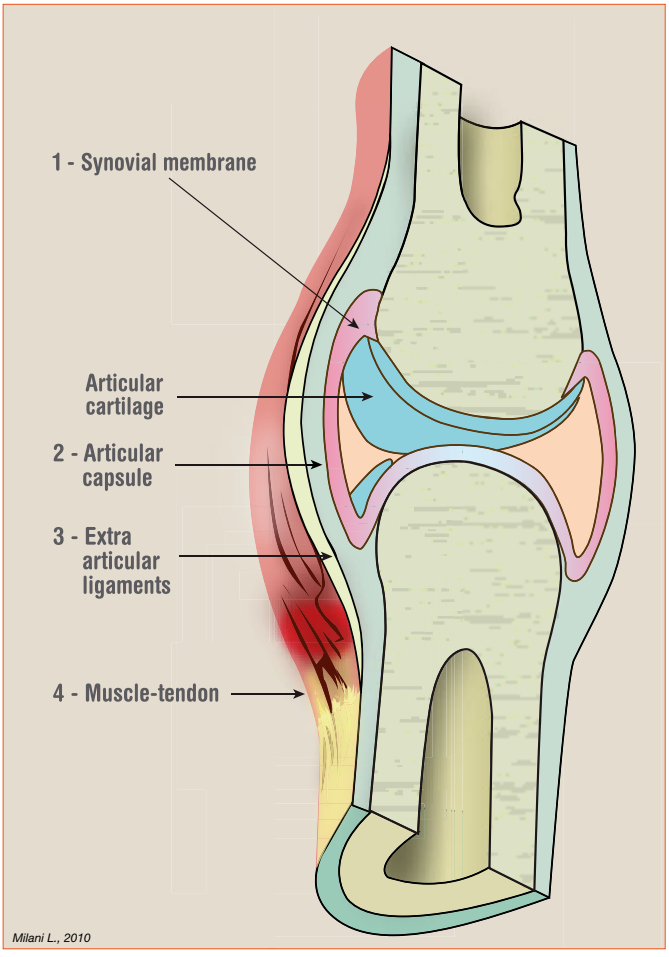
– Gronemann *et* Al., (2004) show that patients affected with fibromyalgia in non-tender (non-trigger) points have lower levels of Hyp compared with healthy controls and - in general - a lower total concentration of amino acids in collagen.
The amount of total protein and myosin are within normal range.
Electron microscopy shows atrophic muscle fibrils **only** in cases of fibromyalgia.
The above mentioned Authors conclude that fibromyalgic patients have significantly reduced collagen amount in the muscles and this could lower the threshold for muscle microtrauma (FIG. 11).
The results of these studies confirm those of Yunus *et* Al., (1986), Savolainen *et* Al (1987), and Mackey *et* Al., (2002).
– Xu *and* Shen (2007) show that the oral administration of collagen reduces the degeneration of articular cartilage and the levels of intracartilage MMP-13, MMP-9, and cathepsin K.

The study of Handson *and* Teller (2010) confirmed those of Garcia *et* Al., (1999) and Xu *and* Shen (2007).
– The effects of collagen administration (of different origin) in the prevention and therapy, are shown in TAB. 2 (author, 2010).

Trentham *et* Al., (1993) report successful results obtained with the administration of collagen in cases of active rheumatoid arthritis in a randomized, double-blind, placebo controlled trial carried out on a high number of cases (among which 4 complete resolutions), as well as the more recent trial by

FIG. 7

Extra-articular restraint apparatus. - Four reinforcing overlapped structures (1, 2, 3, 4) **cooperate with the good articular resistance, providing coaxial articular function or articular function according to the physiological slipping axes.**



Bagchi (2002) on non-rheumatoid arthritic diseases.

The use of hydroxyapatite-collagen nanocomposites (implants) has produced interesting results in serious deforming pathologies of the the cervical spine (Itoh *et* Al., 2004).
- However, the method is highly complicated and impractical as it involves fixing and removal interventions.

GUNA MEDICAL DEVICES FOR THE INJECTIVE TREATMENT OF DYSFUNCTIONAL AND PAINFUL ARTHRO MYOFASCIAL PATHOLOGIES

A new substantial and refined approach to the painful dysfunctional pathologies of the musculoskeletal system and of the related motor functions is now offered by **Guna Medical Devices** for use in clinical practice and in specialist facilities.

The **13 Guna Medical Devices (MD) contain collagen** and **ancillary substances of natural origin** (TAB. 3).
The ancillary substances allow a more effective and specific placement of collagen and have the function of conveying and stabilization.
▶ **Eight** of these MD are specific of the individual anatomical skeletal areas and of the disorders connected with them: **MD-NECK**, **MD-THORACIC**, **MD-LUMBAR**, **MD-SHOULDER**, **MD-HIP**, **MD-KNEE**, **MD-SMALL JOINTS**, **MD-POLY** (multi-articular)]; **one** is specific for the sciatic nerve [**MD-ISCHIAL**], and **four** others that are specific for tissue diseases, derived predominantly from mesodermal tissue: **MD-MUSCLE**, **MD-NEURAL**, **MD-MATRIX** (Extra Cellular Matrix), **MD-TISSUE** (soft tissues) (TAB. 3; FIG. 12).

All 13 Guna MD contain, in addition to the carrier excipient (ancillary), collagen of porcine origin.
–The swine tissues have a **very high** average content of collagen (22.8% =

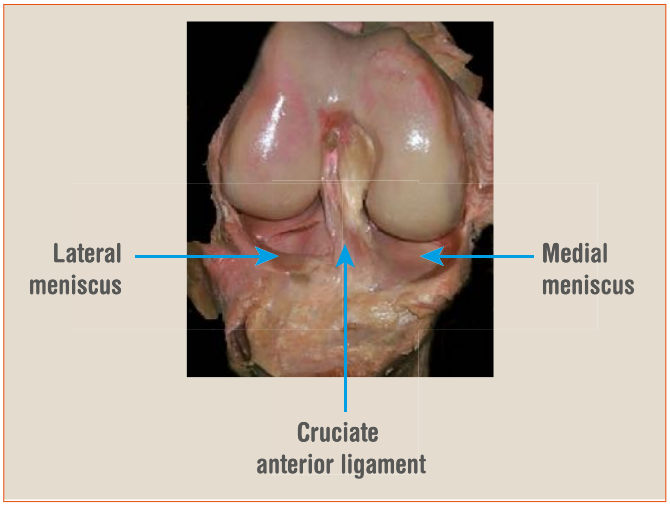


FIG. 8

Knee joint.
- Intra-articular structures; the posterior cruciate ligament is not visible, the synovium is removed.

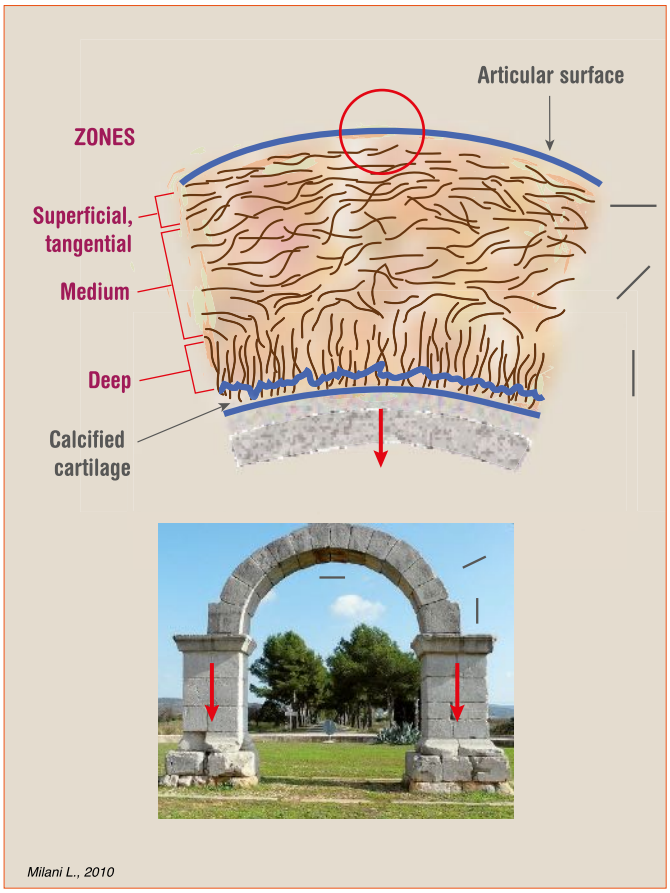


FIG. 9

a Schematic representation of the 3 different directions (superficial, medium, deep) of the collagen fibers in the articular cartilage.
b Structural equivalence between the orientations of the collagen fibers of the articular cartilage and the positioning of the stone blocks for the construction of a Romanesque arch (author, 2010).
– The *stone of the arch* has its biological equivalent in the shorter length and larger thickening of collagen fibers in the area of maximum curvature of the cartilage (red circle).

Glycine, Proline = 13.8%; Hydroxy-Proline = 13%).
The average content of the other amino acids is only 3% (*max* Glutamic acid = 9.5%; *min* Tyrosine = 0.4%): the **50%** is then made up of collagen.

Thanks to the particular process of tangential filtration, sterilization and control of molecular weight, a pure product (without contaminants) is obtained, that has the standard chemical and physical characteristics of a good and clinical safety.
The purpose of the local administration of this biomaterial "where it is needed" is structural: to replace, strengthen, structure and protect (adhesion barrier) the cartilage, the tendons, the ligaments, the joint capsules, etc.; to improve the structure of collagen fibers and - consequently - of all anatomical structures in which it is present; to provide mechanical support to the district concerned.

– One of the most important causes of district joint pain is the **laxity of the intra-and extra-articular stabilization structures**; the loose restraint systems determine joint hypermobility, especially in not physiological directions and angles that wear and tear early the restraint systems themselves and act towards a progressive degeneration of the cartilage.

The **mechanical support** provided by the collagen is an effective natural support scaffold (bio-scaffold).

The infiltration of collagen and the single ancillary ingredients, is perfectly tolerated by the patient and devoid of adverse reactions. It is physiological, compatible and does not cause micro-inflammation with subsequent fibrotic retraction, as in prolotherapy, which covers basically the same purpose: the stabilization of periartricular structures.

– The proteoglycans (PGs) of the Extracellular Matrix (ECM) cementing the collagen fibers improve the viscoelastic properties of the endoarticular fluid, which does not happen in prolotherapy.

The loose musculoskeletal components and hypermobile joints stimulate local nociceptors and cause tension and excessive stress to localized areas.
By reinforcing these areas, **regeneration** and **analgesic** effects occur.

The Guna MD improve physiological joint mobility, promote localized muscle distention, relieve localized pain or pain caused by joint movement or faulty posture.

Guna MD are **2ml injectable ampoules** for **subcutaneous, intradermal, periarticular, intraarticular** and **intramuscular** (local muscles) **use**.

▶ Guna MD can be used by themselves or along with in different associations (up to 2 ampoules per MD) according to the specific needs of the patient, or mixed with PRM injectable ampoules for Pain Therapy (ex. **MD-NECK + MD-MUSCLE + GUNA-NECK + GUNA-MUSCLE**) or as a complement to Homotoxicology (ex. Zeel T, Arnica comp.-Heel) or even conventional or local anesthetic injectable treatment.

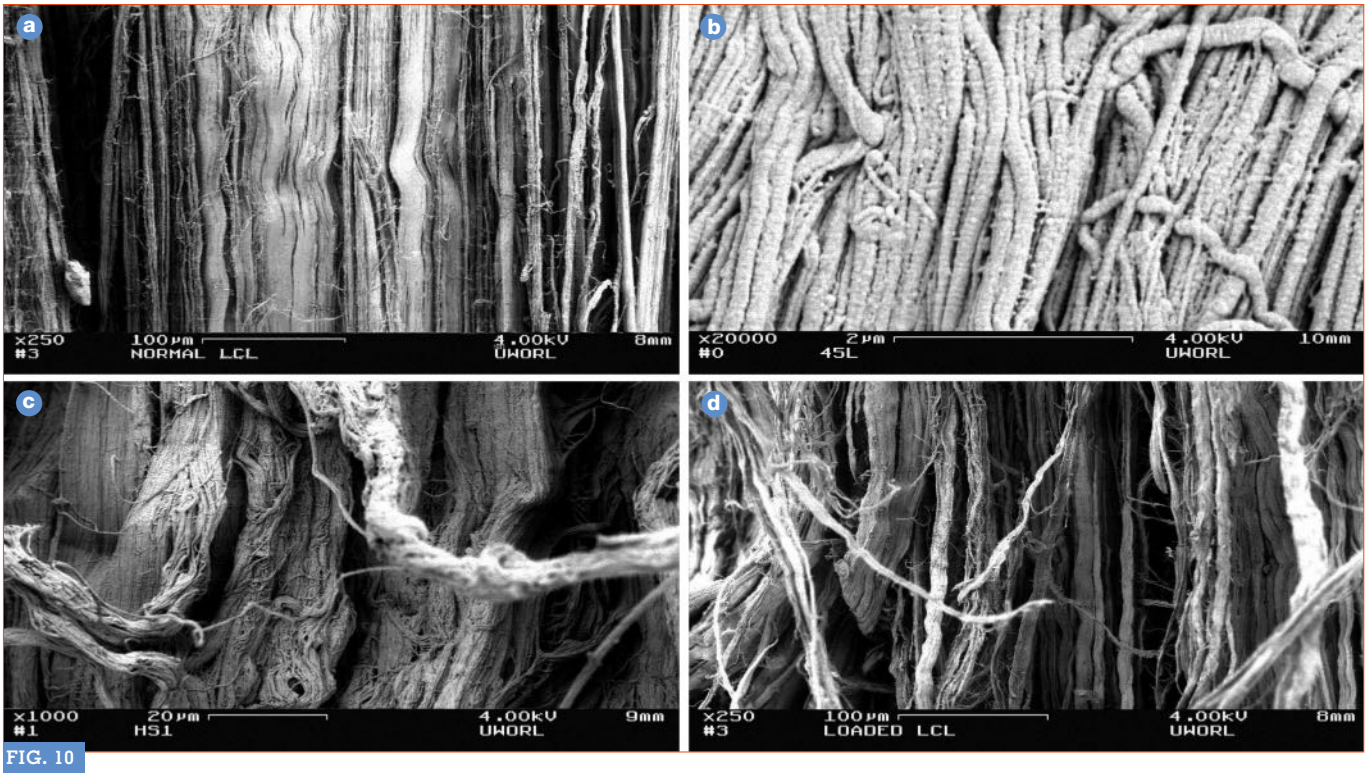


FIG. 10

Medial collateral ligament: a normal; b fork-fusion of collagen fibrils; c wound healing process; d microstructural damage due to overload (not breakage)**.**

– Photomicrographs *in* P. Provenzano, Hurschler C., R. Vanderby Jr. - Connective Tissue Research, 42, 123-133, 2001.

Guna MD can also be used when the patient is treated with cortisone, NSAIDs and / or chondroprotective drugs without contraindications - and - as already mentioned - if the patient receives – during the treatment - manipulative therapy or other physical therapeutic methods (acupuncture, electroacupuncture, shiatsu, phyisiokinesitherapy), instrumental methods (magnetic therapy, ultrasound, laser therapy, electrotherapy, etc.) or thermal therapy.

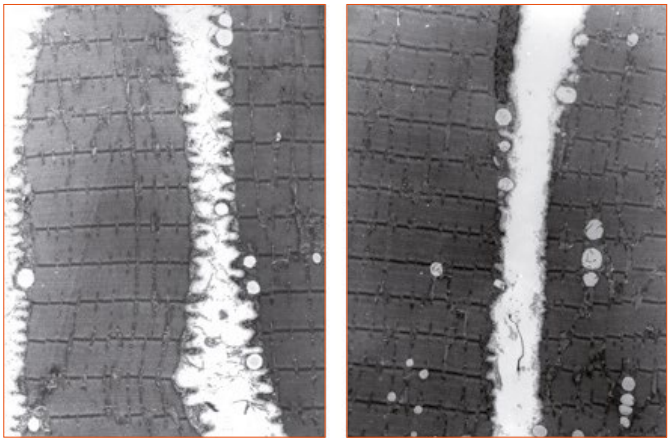


FIG. 11

Photomicrographs (ME 3.000X) **of muscle tissue of a fibromyalgic patients** (left) **and normal control** (right)**.**
– In the fibromyalgic tissue significant changes in the collagen structure can be observed (*moth-eaten*)**.**

EFFECTS OF COLLAGEN ADMNISTRATION

PREVENTION	Author/s Chronological order
1 **Inhibition of collagenasis**	Scutli, **1994** Walker, **1994** Wilson-Townsend, **1994** *Kriegel,* **1995**
2 **Inhibition of matrix metalloproteasis (MMPs)**	Lee *and* Langer, **1983** Lee, **1984** Moses, **1990** Moses, **1993**
THERAPY	
1 **Wounds healing**	Lansman *et* Al., **2009**
2 **Repair of Articular cartilage**	Stone *et* Al., **1997** Cook *et* Al., **2006**
3 **Repair of tendons** (acute and chronic pathologies)	Chenet *et* Al., **2007** Karaoglu *et* Al., **2007** Perry *et* Al., **2009**
4 **Repair of ligaments**	Nijbizi *et* Al., **2000** Musahl *et* Al., **2006** Woo *et* Al., **2006** Liang *et* Al., **2006** Liang *et* Al., **2008**

Milani L., 2010

TAB. 2

MAIN INDICATIONS OF GUNA MEDICAL DEVICES

MD-NECK

- Cervical pain secondary to cartilage degeneration of the cervical spine segments (cervical osteoarthrosis) (in association with **MD-POLY**)
- Cervical pain secondary to muscle trigger point (in association with **MD-MUSCLE**)
- Stiff neck (in association with **MD-MUSCLE** and **MD-NEURAL**)
- Muscle tension cervical pain (in association with **MD-NEURAL** and **MD-MUSCLE**)
- Whiplash (in association with **MD-NEURAL** and **MD-MUSCLE**)
- Cervical pain due to postural defects (in association with **MD-NEURAL** and **MD-MUSCLE**)
- Alterations of the cervical axis (articular facet syndrome) (in association with **MD-NEURAL**)
- Cervical spinal ligaments syndrome (in association with **MD-NEURAL** and **MD-MATRIX**)
- Cervical radicular neuritis (in association with **MD-NEURAL**).

MD-THORACIC

- Back pain secondary to degenerative disorders of the cartilage of the dorsal spine segments (spinal osteoarthritis) (in association with **MD-POLY**)
- Back pain secondary to scoliosis (in association with **MD-MUSCLE** and **MD-NEURAL**)
- Back pain secondary to trigger point of the dorsal muscles (in association with **MD-MUSCLE**)
- Pain secondary to osteophytosis of the dorsal spine (in association with **MD-NEURAL** and **MD-MATRIX**)
- Back pain secondary to osteoporosis (in association with **MD-NEURAL**, **MD-MUSCLE**, and **MD-TISSUE**)
- Alterations of the dorsal axis (articular spinal costal facet syndrome) (in association with **MD-NEURAL** and **MD-MATRIX**)
- Syndrome of spinal dorsal ligaments (in association with **MD-NEURAL**)
- Radicular neuritis of the dorsal spinal nerves (in association with **MD-NEURAL**).

TAB. 3

	GUNA Medical Device	COMPOSITIONS
SPECIFIC LOCAL MDs	MD-NECK	Collagen + Silica
	MD-THORACIC	Collagen + *Cimicifuga racemosa*
	MD-LUMBAR	Collagen + *Hamamelis virginiana*
	MD-SHOULDER	Collagen + *Iris versicolor*
	MD-HIP	Collagen + Calcium phosphate
	MD-KNEE	Collagen + *Arnica montana*
	MD-SMALL JOINTS	Collagen + *Viola odorata*
	MD-POLY	Collagen + *Drosera rotundifolia*
	MD-ISCHIAL	Collagen + *Rhododendron chrysanthum*
SPECIFIC TISSUE MDs	MD-MUSCLE	Collagen + *Hypericum perforatum*
	MD-NEURAL	Collagen + *Citrullus colocynthis*
	MD-MATRIX	Collagen + Citric Acid, Nicotinamide
	MD-TISSUE	Collagen + Ascorbic Acid, Magnesium Gluconate, Pyridoxine chlorhydrate, Riboflavin, Thiamine chlorhydrate

MD-LUMBAR

- Low back pain secondary to lumbar cartilage degeneration (low back pain and lumbar osteoarthritis)
- Osteophytosis of the lumbar spine segments (in association with **MD-NEURAL** and **MD-MATRIX**)
- Low back pain secondary to muscle-tendon trigger points (in association with **MD-MUSCLE**)
- Low back pain from postural defects (in association with **MD-NEURAL**, **MD-MUSCLE**, and **MD-TISSUE**)
- Mechanical alterations of the lumbar and lumbosacral axis (in association with **MD-NEURAL**)
- Syndrome of lumbar and lumbosacral spinal ligaments (in association with **MD-MATRIX**)
- Sacroiliac joint syndrome (in association with **MD-NEURAL**)
- Radicular neuritis of the lumbar and lumbosacral spinal nerves (in association with **MD-NEURAL** and **MD-ISCHIAL**).

MD-SHOULDER

- Humero-scapular periarthritis (in association with **MD-POLY**)
- Rotator cuff syndrome (in association with **MD-MUSCLE** and **MD-TISSUE**)
- Shoulder-arm syndrome (in association with **MD-NEURAL** and **MD-MUSCLE**)
- Frozen shoulder (in association with **MD-MUSCLE**)
- Shoulder pain secondary to dislocation (pre-therapy and post-reduction, in association with **MD-NEURAL**)
- Epicondylitis (in association with **MD-NEURAL** and **MD-POLY**).

MD-HIP

- Coxarthrosis
- Inflammation of the hip joint capsule (in association with **MD-MATRIX**)
- Coxarthrosis in case of rheumatoid arthritis (in association with **MD-POLY**)
- Coxalgia of muscular origin (in association with **MD-MUSCLE**)
- Coxalgia of nervous origin (burning hip) (in association with **MD-NEURAL**)
- Coxalgia due to prolonged bed rest (in association with **MD-MATRIX** and **MD-TISSUE**).

MD-KNEE

- Gonarthrosis (in association with **MD-POLY**)
- Knee pain secondary to rheumatoid arthritis or other autoimmune diseases (in association with **MD-POLY**)
- Acute and chronic arthrosynovitis secondary to trauma, arthrosis and rheumatoid arthritis (in combination with **MD-POLY**)
- Arthrosynovitis post-traumatic and post-surgical acute and chronic
- Traumatic injuries or collateral ligament of the knee
- Meniscus pain (in association with **MD-POLY**)
- Preparation of meniscectomy surgery (in association with **MD-MUSCLE**)
- Maintenance therapy after knee surgery (in association with **MD-MUSCLE-NEURAL**).

MD-SMALL JOINTS

- Osteoarthritis of the hand fingers
- Rhizoarthrosis of the thumb (Forestier's disease)
- Arthralgia caused bunion
- Carpal tunnel syndrome (in associ-

ation with **MD-NEURAL**)
- De Quervain's disease (in association with **MD-NEURAL**)
- Simple metatarsalgia
- Metatarsalgia associated with Morton's neuroma (in association with **MD-NEURAL**)
- Rheumatoid arthritis of the hand and foot (in association with **MD-POLY**)
- Hand and foot tendinopathy secondary to prolonged immobilization (in association with **MD-MATRIX**).

MD-ISCHIAL

- Sciatica
- Lumbar-sciatic pain (in association with **MD-LUMBAR** and **MD-NEURAL**)
- Lumbar neuralgia (in association with **MD-MUSCLE**)
- Sciatica after surgery for herniated disc L4-L5, L5-S1 (in association with **MD-NEURAL**)
- Morton's neuroma (in association with **MD-NEURAL**).

MD-POLY

- Nonspecific diffuse pain (in association with **MD-NECK** or **MD-THORACIC** or **MD-LUMBAR**, and **MD-NEURAL**)
- Costal sternal syndrome (in association with **MD-NEURAL**)
- Chronic polyarthritis secondary to autoimmune disease (eg, Systemic Lupus Erythematosus) (if the neuralgic symptoms prevail: in association with **MD-NEURAL**; if muscle symptoms prevail: in association with **MD-MUSCLE**)
- Syndrome of "the broken bones" (if the neuralgic symptoms prevail: in association with **MD-NEURAL**; if muscle symptoms prevail: in association with **MD-MUSCLE**)
- Joint pain secondary to viral disease (in association with other specific Guna MD)
- Joint pain secondary to cancer (eg, chronic leukemia, multiple myeloma) (in association with other specific district Guna MD).

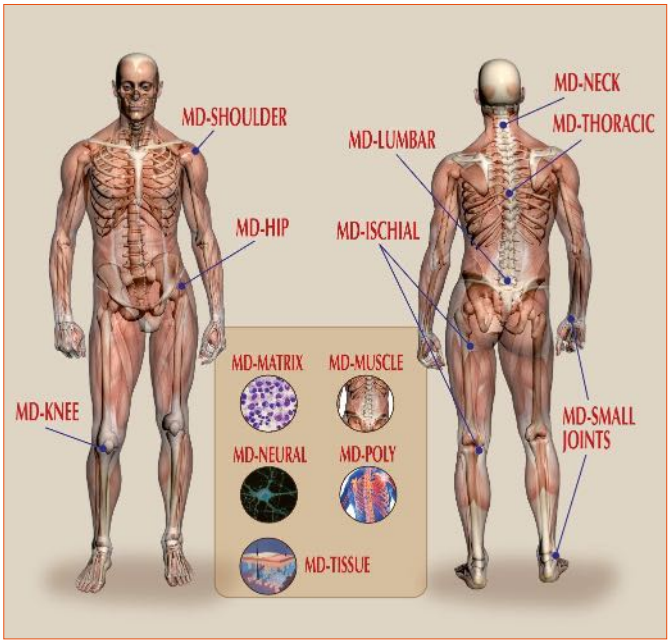


FIG. 12

Synopsis of the 13 injectable Guna Medical Devices.

MD-MUSCLE

- Treatment of acute, subacute, chronic myofascial pain
- Treatment of trigger points (in association with **MD-NEURAL**)
- Treatment of referred pain areas (in association with **MD-NEURAL**)
- Fibromyalgia (in association with **MD-NEURAL** and **MD-MATRIX**)
- Dermatomyositis.

MD-NEURAL

- Brachial nerve neuralgia secondary to cervical entrapment syndrome (in association with **MD-NECK**)
- Persistent intercostal neuralgia (in association with **MD-THORACIC**)
- Postherpetic neuralgia (in association with **MD-THORACIC** or **MD-LUMBAR**)
- Atypical facial neuralgia (in association with **MD-NECK** and **MD-TISSUE**)
- Trigeminal neuralgia (in association with **MD-NECK** and **MD-MATRIX**)
- Pain of the temporomandibular joint (in association with **MD-NECK**)
- Radicular neuritis of the cervical dorsal, lumbar, sacral spinal nerves, (respectively in association with **MD-NECK**, **MD-THORACIC**, **MD-LUMBAR**, and **MD-ISCHIAL**).

MD-MATRIX

MD-MATRIX can be used alone or combined with any other MD of the same line, in order to create a personalized treatment based on the individual clinical picture.

▶ **MD-MATRIX can also be used in patients who need anti-aging topical treatment.**

MD-TISSUE

Also MD-TISSUE may be used alone or combined with any other MD of the same line, according to the individual clinical picture.

▶ **MD-TISSUE can also be used in patients who need anti-aging topical treatment.**

CONCLUSIONS

With increasing age (Mays *et* Al., 1988), physical inactivity, intense physical activity or inadequate sports activity (Adam *et* Al., 1984), postural alterations, nutrient imbalances, changes of the PNEI axis, the connective tissue and the collagen in particular (real tissue protein) gradually dete-

riorate and become inadequate at fulfilling their many specific functions.

– The possibility to use in the praxis specific injections of **Medical Devices** (district and tissue MD) that replace the collagen deficiency always detectable in inflammatory and/or degenerative diseases of the locomotor apparatus and of other structures of mesodermal origin, injections that are easy to apply, natural, with no negative side effects, that can be associated with PRM (Physiological Regulating Medicine) therapies or homotoxicological or conventional local or systemic injective therapies in progress or planned and/or any physical therapy, provides an innovative and sophisticated tool for the prevention and treatment of the aging process of intra-articular and periarticular structures as well as structures of the nearby mesodermal support tissues.

– The non-invasiveness of the injections with Guna MD, the first ones in this field having reported therapeutic results in 7 controlled clinical trials (Registration report at the High Institute of Health - Italy), as well as their other characteristics such as efficacy, tolerability, absence of allergic and natural reactions, makes this a unique and valuable tool in the specialistic and non specialistic praxis in improving the quality of life of patients who were intended - otherwise - to get worse or become chronic. ■

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including the items shown in Figures and Tables

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Hippokrates Verlag and Guna Editore for the reproduction of the images in **Figs. 1** (amended), **3**, **5** (only 1, 2) from H. Heine - Manuale di Medicina Biologica. Regolazione di base e matrice extracellulare. 3rd edition, completely revised, **2009**, and the Editors of the websites from which the images were taken:

Figure 2 (only on the top):
http://farm1.static.flickr.com/160/405756871_794fca5e86.jpg
Fig. 6: http://www.helmholtz-muenchen.de/uploads/pics/fig4-2_textmedium.png
Fig. 10:
a: http://silver.neep.wisc.edu/~lakes/slideTissue.dir/LigFig3.jpg
b: http://silver.neep.wisc.edu/~lakes/slideTissue.dir/LigFig4A.jpg
c: http://silver.neep.wisc.edu/~lakes/slideTissue.dir/LigFig2.jpg
d: http://silver.neep.wisc.edu/~lakes/slideTissue.dir/LigFig4B.jpg
Fig. 11: http://rheumatology.oxfordjournals.org/cgi/content/ful/43/1/27

Figs. **2**, **4** (amended), **5**, **7**, **9** and Tabb. **1**, **2**, **3** belong to the author.

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cells

MDPI

Article

The Collagen-Based Medical Device MD-Tissue Acts as a Mechanical Scaffold Influencing Morpho-Functional Properties of Cultured Human Tenocytes

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Abstract: Mechanotransduction is the ability of cells to translate mechanical stimuli into biochemical signals that can ultimately influence gene expression, cell morphology and cell fate. Tenocytes are responsible for tendon mechanical adaptation converting mechanical stimuli imposed during mechanical loading, thus affecting extracellular matrix homeostasis. Since we previously demonstrated that MD-Tissue, an injectable collagen-based medical compound containing swine-derived collagen as the main component, is able to affect tenocyte properties, the aim of this study was to analyze whether the effects triggered by MD-Tissue were based on mechanotransduction-related mechanisms. For this purpose, MD-Tissue was used to coat Petri dishes and cytochalasin B was used to deprive tenocytes of mechanical stimulation mediated by the actin cytoskeleton. Cell morphology, migration, collagen turnover pathways and the expression of key mechanosensors were analyzed by morphological and molecular methods. Our findings confirm that MD-Tissue affects collagen turnover pathways and favors cell migration and show that the MD-Tissue-induced effect represents a mechanical input involving the mechanotransduction machinery. Overall, MD-Tissue, acting as a mechanical scaffold, could represent an effective medical device for a novel therapeutic, regenerative and rehabilitative approach to favor tendon healing in tendinopathies.

Keywords: tendon; tenocytes; tendinopathy; collagen turnover; mechanotransduction; actin cytoskeleton; YAP/TAZ; medical device

1. Introduction

Tendinopathy is a chronic and painful condition affecting tendons, characterized by histological modifications such as hypercellularity, neovascularization, loss of collagen fibril organization, increased proteoglycan and glycosaminoglycan contents and increased non-collagen extracellular matrix components [1,2]. The therapeutic approach for tendinopathy includes rest, ice-packs, non-steroidal anti-inflammatory drugs (NSAIDs), physiotherapy, local corticosteroid injections or biological and regenerative therapies using platelet-rich plasma (PRP) or hyaluronic acid [3]. However,

treatment of tendinopathy remains a clinical unmet need, since the available treatments did not show to have a strong efficacy and no long-term benefits were reported [2,4,5]. Therapeutic strategies are also needed in veterinary medicine to especially treat equine tendon lesions and musculoskeletal disorders [6–8]. MD-Tissue (MD) is an injectable collagen-based medical compound containing swine-derived collagen as the main component. Swine collagen has high biocompatibility with human collagen, with a very low risk of adverse effects when used in different medical applications, and it was also used to prepare collagen-based skin-like scaffolds [9]. Indeed, clinical studies reported that MD-Knee, a collagen-based medical compound very similar in terms of composition to MD, is well tolerated, and no systemic adverse events or septic complications were observed when utilized on patients [10,11]. Therefore, MD may have the potential to be used to treat tendinopathy. Moreover, since it can be utilized alone or in association with other therapeutic agents, and the lower cost compared to hyaluronic acid could favor its wider use, it may offer some advantages compared to other biological agents.

Tenocytes are specialized fibroblasts in tendon connective tissue, responsible for tendon extracellular matrix (ECM) remodeling by influencing the turnover pathways of type I collagen (COL-I), the main component of tendon ECM [12–14]. Tendons are interposed between muscles and bones and transfer forces generated by muscle contraction to the skeleton. Mechanical forces acting on tendons influence their metabolic activity and the expression of genes and proteins involved in ECM remodeling of tenocytes that play key roles acting as mechanosensors [13,15,16].

Mechanotransduction is the ability of cells to translate mechanical stimuli into biochemical signals that can ultimately influence gene expression, cell morphology and cell fate. Mechanotransduction allows cells to respond to external forces and to interpret the mechanical characteristics of the ECM. In this way, tenocytes can timely adapt to the continuous dynamic modifications of the ECM by remodeling it [17,18]. Recently, we analyzed the in vitro effect of MD on human tenocytes [19]. We focused our attention on collagen turnover pathways, in order to describe the molecular mechanisms triggered by this medical compound and to understand how it can affect tenocytes' biological properties to favor tendon homeostasis and repair [19]. In fact, in that study, we reported that MD was able to stimulate COL-I biosynthesis, secretion and maturation and to induce tenocyte proliferation and migration. Since tenocytes act as mechanosensors and it was demonstrated that MD is able to affect collagen turnover pathways and cell migration, the aim of this study was to analyze whether the effects triggered by MD were based on mechanotransduction-related mechanisms.

2. Materials and Methods

2.1. Samples

Fragments from the human Gluteus Minimus tendon were obtained from 4 patients (mean age 62.25 ± 4.57 years, 2 males and 2 females) undergoing total hip replacement through an anterior approach but without any gluteal tendon pathology (Figure 1). Patients diagnosed with great trochanter tendinopathy, affected by genetic collagen disorders, or patients diagnosed with spondyloarthritis with involvement of the affected hip or affected by psoriatic arthritis were excluded from the study, as well as drug- and alcohol-addicted patients, pregnant or breastfeeding women and patients affected by diabetes mellitus or who had taken fluoroquinolones within 30 days before the surgery.

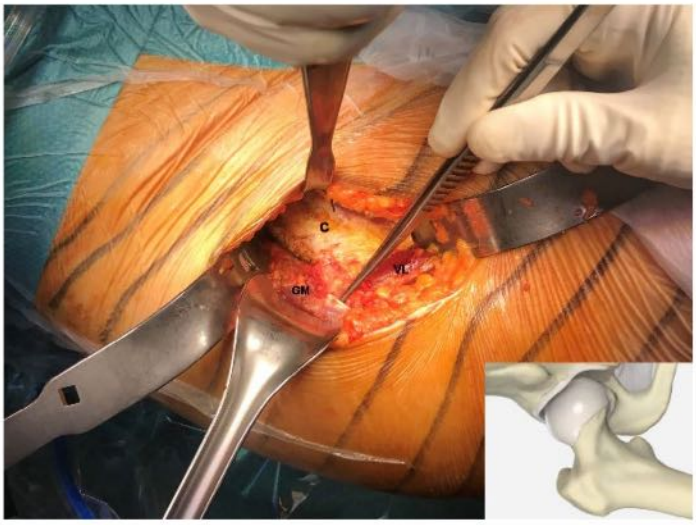

Figure 1. Harvesting a small fragment from the Gluteus Minimus (GM) tendon, indicated by the surgical forceps, during a total hip replacement through an anterior approach. The small fragment is collected at the mid-tendon substance, the white region with the typical structure of the dense regular connective tissue. The hip capsule (C) has been isolated and the Vastus Lateralis (VS) is visible at the bottom of the surgical field.

For each collected tendon, the mid-substance, the region with the typical structure of the dense regular connective tissue, was isolated and analyzed.

All subjects gave their informed consent for inclusion in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the local ethics committee (San Raffaele Hospital Ethical Committee, Milan, Italy) of the coordinating institution (IRCCS Policlinico San Donato, Milan, Italy) (63/INT/2017).

2.2. Cell Cultures

Tendon fragments were collected and immediately washed in sterile PBS. They were plated in T25 flasks and incubated in Dulbecco's Modified Eagle Medium (DMEM) (Euroclone, Pero, Milan, Italy) supplemented with 10% heat-inactivated fetal bovine serum (FBS) (Gibco, Life Technologies, Monza, Italy) and antibiotics (100 U/mL penicillin, 0.1 mg/mL streptomycin) (Euroclone), at 37 °C in a humidified atmosphere containing 5% CO_2. When tenocytes grew out from the explant, they were harvested and subcultured in T75 flasks. Human tenocytes derived for each subject were cultured in duplicate. For morphological, functional and molecular evaluations, confluent tenocytes were cultured in 6-well multi-well plates at the fifth passage, adding ascorbic acid (200 μM) to DMEM to preserve collagen synthesis, and harvested after 48 h. A diagram summarizing the experimental design of the study is shown in Figure 2.

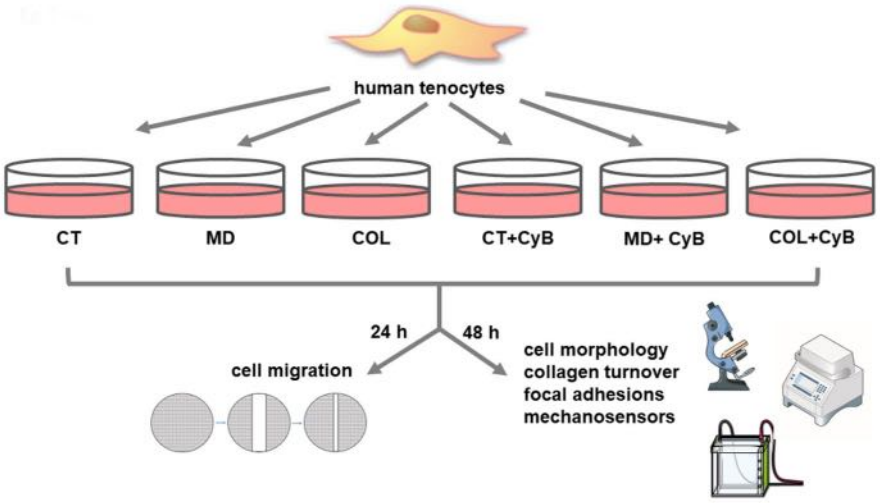

Figure 2. Diagram summarizing the experimental groups and the experimental design used in this study.

2.3. Coating with MD-Tissue or Collagen

MD (100 µg/2 mL ampoules) and collagen (COL) were kindly provided by Guna (Milan, Italy). COL is the collagen of swine origin, the principal constituent of MD, that also contains ascorbic acid, magnesium gluconate, pyridoxin hydrochloride, riboflavin, thiamine hydrochloride, NaCl and water as excipients. MD or COL (50 µg/mL) were used to obtain a thin coating on 6-well multi-well plates as previously described [19]. After an incubation of at least 3–4 h at room temperature to obtain collagen adhesion to the plastic, excess fluid was removed from the coated surface and the multi-well plate was dried under the laminar flux hood. Coated plastic was immediately used or stored at 4 °C. Cells cultured on MD-Tissue or COL were compared with cells grown on uncoated cell culture plastic, used as untreated controls (CT).

2.4. Cytochalasin Administration

To understand if MD exerts its effect on tenocytes by a mechanical stimulation, cells were treated with 10 µM cytochalasin B (CyB) (Santa Cruz Biotechnology, Heidelberg, Germany) which inhibits actin filaments polymerization. The dose of CyB used to treat tenocytes was chosen according to the literature [20]. Moreover, different doses were tested to evaluate the possible microfilament modifications leading to cytoskeleton injury.

2.5. Scanning Electron Microscopy

The coating containing MD and COL was observed with a scanning electron microscope (SEM) to detect the presence of collagen fibrils/fibers and their alignment. For this purpose, the samples were fixed with 2% glutaraldehyde and 2% paraformaldehyde buffered with 0.1 M sodium cacodylate (pH 7.3) for 1 h at room temperature. After fixation, they were rinsed three times with 0.2 M sodium cacodylate buffer (pH 7.3) for 10 min and post-fixed with 1% osmium tetroxide (OsO4) in the same buffer for 1 h on ice. Samples were rinsed twice with bi-distilled water and gradually dehydrated by consecutive 10-min incubations in 20%, 30%, 40%, 50%, 70%, 80%, 90% and 100% ethanol, followed by chemical drying with 50% (*v*/*v*) ethanol-hexamethyldisilazane (HMDS) and 100% HMDS that was air-dried overnight at room temperature. All the reagents were purchased from Electron Microscopy Sciences (Hatfield, PA, USA). Before SEM imaging, samples were mounted on 12-mm specimen stubs using double-sided carbon tape and gold coated with a 20 nm-thick film using a Polaron E5100 sputter coater. The SEM imaging was performed by a JEOL JSM-840A (Tokyo, Japan), operating at 15 kV and acquiring the secondary electron signal by an Everhart-Thornley (ET) in-chamber detector.

2.6. Raman Spectroscopy

Raman spectroscopy was used to analyze the coating containing MD or COL. Raman spectra were acquired using an Aramis Raman microscope (Horiba Jobin Yvon, France) equipped with a laser source operating at 532 nm. All the materials were analyzed in the 400–1800 cm^{-1} range, with a spectral resolution of 0.8 cm^{-1} and accumulation time of 30 s repeated on the same point for 2 accumulations. The acquisition delay time was maintained at 2 s in order to prevent the formation of artifact spectra. Before each analysis, the instrument was calibrated on the reference band of silicon at 520.7 cm^{-1}. All the samples were analyzed using a line-focused map (at least 25 points) centered using 10x, 50x and 100x objectives (Olympus, Tokyo, Japan). A laser grating of 1800, with hole at 400 and slit at 200, was used. Sample preparation was conducted depositing a 5 µL drop on a Calcium Fluoride ($CaFl_2$) disk, dried overnight at room temperature. The data processing procedure was performed following and adapting the protocol reported by Carlomagno et al. [21]. Briefly, all the spectra were fit with a third-degree polynomial baseline, considering 68 baseline points, and consecutively normalized by a unit vector. A second-degree Savitzky–Golay smoothing was applied in order to reduce noise and non-informative spikes present in the resultant spectra. All the procedures described were performed using the Raman integrated software LabSpec6 (Horiba Jobin Yvon, France) and Origin2018 (OriginLab, Northampton, MA, USA).

2.7. Immunofluorescence Analysis

For fluorescence microscopy, tenocytes were cultured on 12-mm diameter round coverslips uncoated or coated with MD or COL into 24-well culture plates, with or without CyB, as previously described [22]. For vinculin detection, cells were incubated for 1 h at room temperature with the mouse monoclonal antibody anti-vinculin (1:500 in PBS, clone VIN-11-5, Biotechne, Milan, Italy) and with the secondary antibody anti-mouse/Alexa488 (1:500, Life Technologies, Carlsbad, CA, USA). In order to analyze the actin cytoskeleton, cells were incubated with 50 µM rhodamine-phalloidin (Sigma-Aldrich, St. Louis, MO, USA).

To assess YAP/TAZ nuclear or cytoplasmic localization, cells were incubated with a rabbit anti-YAP/TAZ antibody (D24E4, 1:400, Cell Signaling, Danvers, MA, USA) and an anti-rabbit/Alexa488 (1:500, Cell Signaling, Danvers, MA, USA).

Finally, cells on coverslips were incubated with DAPI (1:100.000, Sigma Aldrich) for 15 min and mounted onto glass slides using Mowiol. Cells were analyzed and imaged by a WD THUNDER Imager Tissue 3D (Leica Microsystems CMS GmbH, Wetzlar, Germany).

2.8. Real-Time PCR

Cells were harvested and total RNA was isolated (Tri-Reagent, Sigma, Italy). One µg of total RNA was reverse-transcribed in 20 µL final volume of reaction mix (Biorad, Segrate, Milan, Italy). Gene expression for long lysyl hydroxylase 2 (LH2b), tissue inhibitor of matrix metalloproteinase 1 (TIMP-1), focal adhesion kinase (FAK) and paxillin (PAX) was analyzed by real-time RT-PCR in samples run in triplicate. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as endogenous control to normalize the differences in the amount of total RNA in each sample. The primers sequences were the following: GAPDH: sense CCCTTCATTGACCTCAACTACATG, antisense TGGGATTTCCATTGATGACAAGC; LH2b: sense CCGGAAACATTCCAAATGCTCAG, antisense GCCAGAGGTCATTGTTATAATGGG; TIMP-1: sense GGCTTCTGGCATCCTGTTGTTG, antisense AAGGTGGTCTGGTTGACTTCTGG; FAK: sense GTCTGCCTTCGCTTCACG, antisense GAATTTGTAACTGGAAGATGCAAG; and PAX: sense CAGCAGACACGCATCTCG, antisense GAGCTGCTCCCTGTCTTCC. Each sample was analyzed in triplicate in a Bioer LineGene 9600 thermal cycler (Bioer, Hangzhou, China). The cycle threshold (Ct) was determined and gene expression levels relative to that of GAPDH were calculated using the ΔC_T method.

2.9. Slot Blot

Collagen type I (COL-I) and matrix metalloproteinase (MMP)-1 protein levels secreted by tenocytes in serum-free cell supernatants were analyzed by slot blot analysis, as previously detailed [18]. Membranes were incubated for 1 h at room temperature with primary monoclonal antibodies to COL-I (1:1000 in TBST) (Sigma-Aldrich, Milan, Italy) or MMP-1 (1 µg/mL in TBST) (Millipore, Milan, Italy). Immunoreactive bands were revealed by the Amplified Opti-4CN substrate (Amplified Opti-4CN, Bio Rad, Segrate, Milan, Italy) and quantification was obtained after densitometric scanning of immunoreactive bands (UVBand, Eppendorf, Italy).

2.10. Western Blot

Cells were harvested and lysed in Tris-HCl 50 mM pH 7.6, 150 mM NaCl, 1% Triton X-100, 5 mM EDTA, 1% Sodium Dodecyl Sulphate (SDS), proteases inhibitors and 1 mM sodium orthovanadate. After a 30-min incubation in ice, lysates were centrifuged at 14,000× *g* for 10 min at 4 °C. Cell lysates (15 µg of total proteins) were run on 10% SDS–polyacrylamide gel, separated under reducing and denaturing conditions at 80 V according to Laemmli and transferred at 90 V for 90 min to a nitrocellulose membrane in 0.025 M Tris, 192 mM glycine and 20% methanol, pH 8.3. For VNC analysis, membranes were incubated for 1 h at room temperature with the monoclonal antibody anti-VNC (1:2000) (clone VIN-11-5, Biotechne, Milan, Italy) and, after washing, in horseradish peroxidase (HRP)-conjugated rabbit anti-mouse antibody (1:6000 dilution, Sigma Aldrich). Immunoreactive bands were revealed using the Opti-4CN substrate (Bio Rad).

For YAP/TAZ evaluation, membranes were incubated with the following antibodies (Cell Signaling Technology, USA): YAP (D8H1X) XP® Rabbit mAb, p-YAP (S109) Rabbit Ab, TAZ (D3I6D) Rabbit mAb and p-TAZ (S89) (E1X9C) Rabbit mAb. After the incubation with a horseradish peroxidase (HRP)-conjugated goat anti-rabbit antibody (1:20000 dilution, Cell Signaling), immunoreactive bands were revealed using the Amplified Opti-4CN (Bio Rad).

To confirm equal loading, membranes were reprobed by a monoclonal antibody to α-tubulin (1:2000 dilution, Sigma Aldrich).

2.11. SDS-Zymography

MMP-2 levels and activity were analyzed in serum-free culture supernatants (5 µg of total protein per sample) in tenocytes cultured for 48 h by SDS-zymography on 10% polyacrylamide gels co-polymerized with 1 mg/mL type I gelatin. The gels were run at 4 °C and, after SDS-PAGE, they were washed twice in 2.5% Triton X-100 for 30 min each and incubated overnight in a substrate buffer at 37 °C (Tris-HCl 50 mM, $CaCl_2$ 5 mM, NaN_3 0.02%, pH 7.5). After staining and destaining the gels, MMP gelatinolytic activity was detected as clear bands on a blue background after staining the gels with Coomassie brilliant blue R250. Clear bands were quantified by densitometric scanning (UVBand, Eppendorf, Italy).

2.12. Wound Healing Assay

Cell migration of tenocytes was analyzed by a wound healing assay [23] in CT-, MD- or COL-coated 6-well multi-well plates. The "scratch" was obtained in confluent tenocytes using a p 200 pipet tip. After washing with DMEM to remove cell debris, multi-well plates were incubated in serum-free DMEM at 37 °C and observed under an inverted microscope. Migration was evaluated by measuring the closure of the wound at 0 and 24 h.

Digital images were captured by a digital camera at different time points (0 and 24 h), and the size of the "scratch" was measured to assess the migration potential, expressed as a % compared with the 0 h time point.

2.13. Statistical Analysis

Data were obtained from two replicate experiments for each of the subjects-derived cell lines cultured in duplicate and were expressed as mean ± standard deviation (SD). Statistical analysis was performed by *t*-test to compare untreated vs. CyB-treated samples cultured on the same substrate and ANOVA followed by Tukey's multiple comparisons test using GraphPad Prism v 5.0 software (GraphPad Software Inc., San Diego, CA 92108, USA). Differences associated with *p* values lower than 5% were considered statistically significant.

3. Results

3.1. Analysis and Characterization of the Coating

The presence and the characteristics of the coating obtained using MD or COL were analyzed by scanning electron microscopy (SEM). We did not detect collagen fibrils in Petri dishes coated with MD or COL (Figure 3), compared to CT. As a control, we compared MD- and COL-coated Petri dishes with a commercially available Petri dish coated with Type I collagen (CELLCOAT Type I Collagen—Greiner bio-one cod.628950), in which the presence of the coating resulted undetectable at SEM as well (Figure 3).

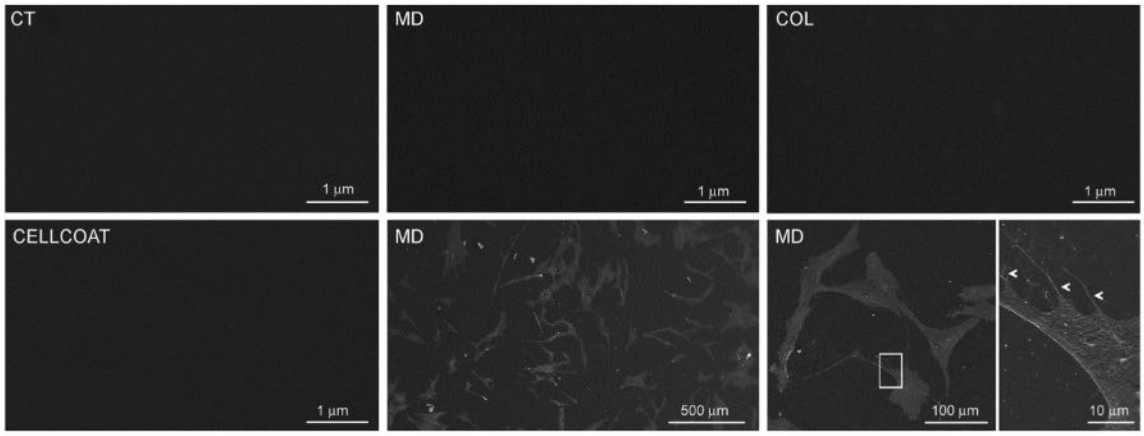

Figure 3. Scanning electron microscopy (SEM) images of Petri dish uncoated (CT) or coated with MD-Tissue (MD) or collagen (COL) solution. An SEM image of a commercial Petri dish coated with Type I collagen (CELLCOAT Type I Collagen—Greiner bio-one cod.628950) is also shown. SEM images of human tenocytes cultured on an MD Tissue-coated Petri dish at low (left) and high magnification (right); in the inset at higher magnification, the thin flattened processes extending from the cell body (arrowheads) are visible. The scale bar is shown in the bottom right corner of each image.

To understand if the coating influences cell alignment, cells were grown on 12-mm diameter coverslips coated with MD: SEM analysis confirmed that collagen fibrils are undetectable and that the coating does not induce cell alignment. Indeed, cells were arranged without any preferential direction (Figure 3).

Since the morphological analysis was not able to reveal the presence of the coating, we analyzed coated specimens by Raman spectroscopy. As described in the Materials and Methods section, MD and COL were deposited on a calcium fluoride slide and dried overnight [24]. The microscopic analysis revealed two separated regions in MD, characterized by a crystal formation and a fibrillary dispersion (Figure 4a–c). The Raman analysis was focused on these two regions (Figure 4d,e).

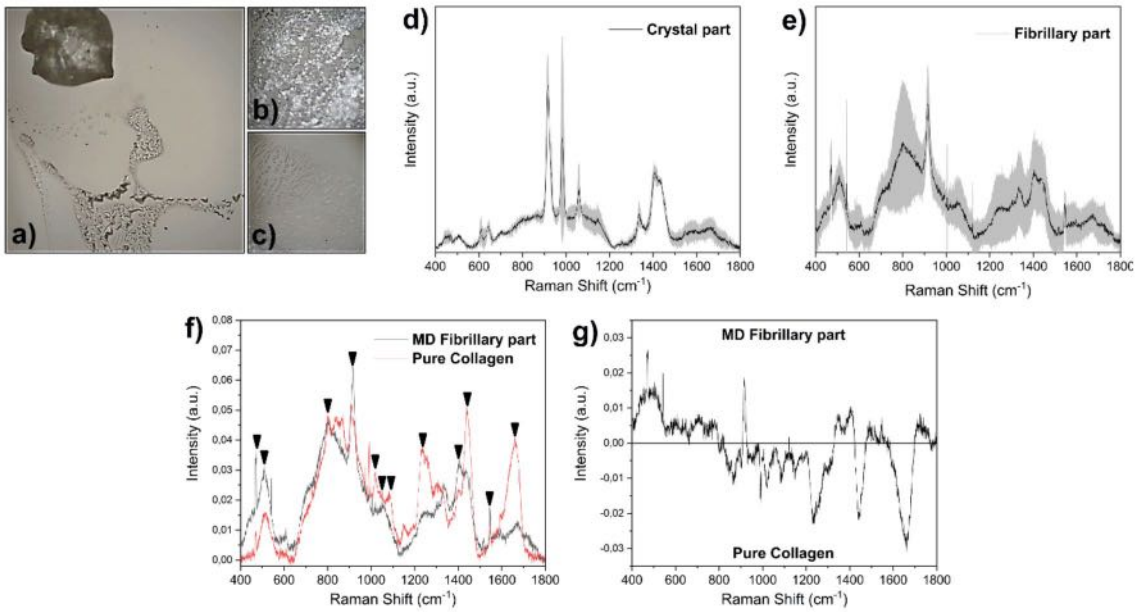

Figure 4. (**a**) Light microscopy micrograph of MD on calcium fluoride (original magnification 50×). In the insets, the crystal (**b**) and fibrillary parts (**c**) at higher magnification (100×) are shown. Raman signals collected from the (**d**) crystal and (**e**) fibrillary parts. The gray bands represent the associated standard deviation. (**f**) Comparison between pure collagen and MD fibrillary part, with peaks of interest highlighted by the black arrows. (**g**) Subtraction spectrum of MD fibrillary part and pure collagen obtained with the error propagation.

The crystal part presents the typical sharp peaks of crystal structures, with peaks attributable to the characteristic signals of riboflavin (750, 1345, 1410 cm^{-1}) and ascorbic acid (605 and 632 cm^{-1}) (Figure 4d), both present in the MD product [25,26]. The fibrillary part was mainly composed of collagen due to the presence of characteristic peaks at 536, 858, 919, 1065, 1343, 1454 and 1674 cm^{-1} (Figure 4e) [27].

The comparison between COL and the MD fibrillary part (Figure 4f) reveals common peaks at 500, 580, 829, 1248, 1430 and 1650 cm^{-1} with a partial difference in the global spectral shape. A potential explanation can be found in the presence of MD in dissolved salts in the product solution that can alter and modify the conformation, interaction with the environment and structure of the protein. As a consequence, the detected Raman signal is altered, but still consistent with the presence of collagen. The potential attribution of the main peaks (Figure 4f) is reported in Table 1. The main differences between COL and the MD fibrillary part are highlighted by the subtraction spectrum in Figure 4g. The alteration of peaks at 1235 and 1665 cm^{-1} due to the Amide I and III bands and at 1443 cm^{-1} due to the CH3 skeletal deformation indicates a change in the collagen fundamental structure of MD.

Table 1. Potential peaks attribution, based according to Carcamo et al. [23].

Raman Shift (cm^{-1})	Attribution
475	Skeletal deformations
508	Skeletal deformations
800	Skeletal C-C vibrations
920	C-COO^{-} vibrations
992	Phenylalanine
1015	Vibration of Proline C-N
1055	Distortion of Proline N-C-H
1235	Amide III

Table 1. *Cont.*

Raman Shift (cm^{-1})	Attribution
1403	Deformation of CH_3
1443	Deformation of CH_3
1544	Deformation of NH_3^+
1665	Amide I

3.2. Cell Morphology

Before analyzing the effect of MD and COL on tenocytes, we first observed the actin cytoskeleton in cells treated with different doses of CyB. Tenocytes possess long microfilaments mostly arranged in longitudinal arrays parallel to the long axis of the cells. At the concentration of 10 µM, CyB is able to block the dynamic instability of the actin cytoskeleton in order to deprive tenocytes of the mechanical stimulation mediated by actin microfilaments. At this concentration, filaments preserved their integrity and their distribution, without any evident morphological modification and without significantly damaging the mechanosensory apparatus. Higher doses strongly induce actin filaments loss, becoming progressively more evident when increasing the dose (Figure 5a). Phase contrast microscopy analysis revealed that cell morphology was unaffected in cells grown on MD and COL, compared to CT. However, when cells are treated with CyB, tenocytes cultured on MD and COL do not change their morphology, while CT cells become less flattened and more rounded (Figure 5b), suggesting that they are less attached to the substrate.

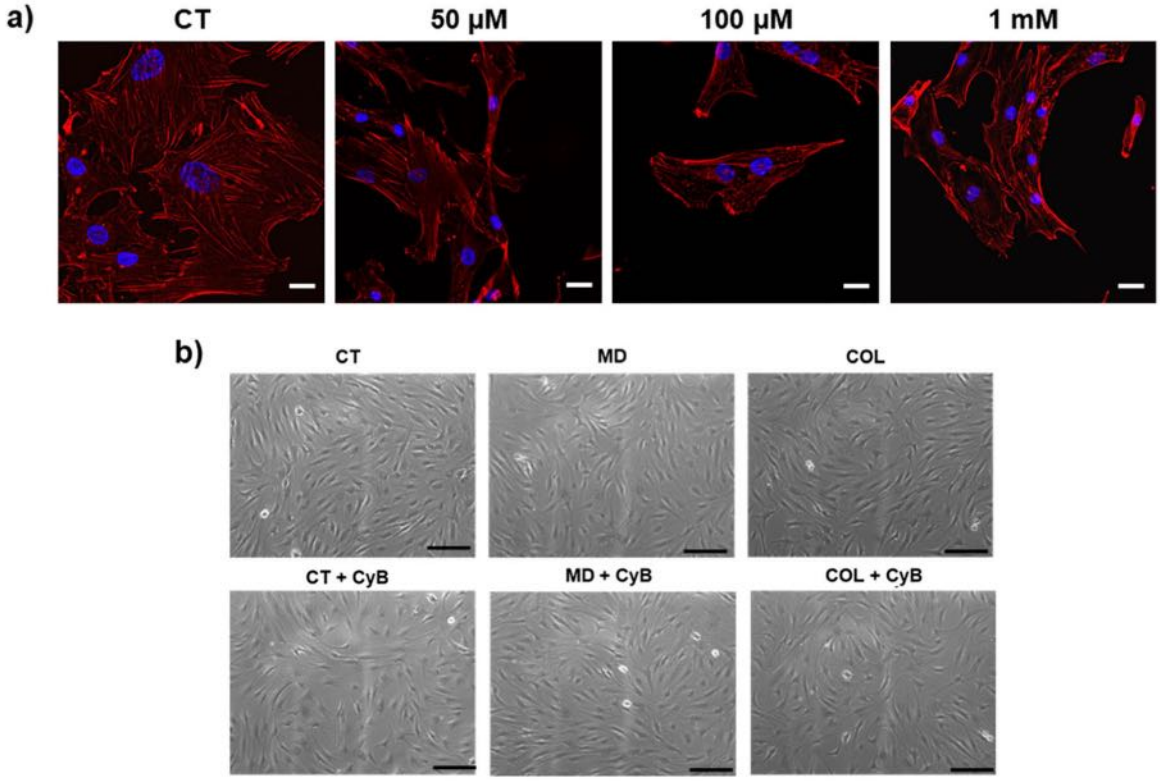

Figure 5. (**a**) Micrographs showing actin filaments detected by rodhamine-phalloidin by THUNDER in control cells (CT) and after administration of CyB at the indicated doses. After 50 µM CyB, actin filaments become shorter and more evident, indicating that the cytoskeleton is not preserved after CyB. (**b**) Representative phase contrast microscopy micrographs showing cell morphology of cells grown on MD and COL, compared to CT. After CyB, CT cells become less flattened and more rounded (Figure 4b). Scale bar 200 µm (**a**) and 20 µm (**b**).

3.3. Expression of Genes and Proteins Related to Collagen Turnover

COL-I protein levels secreted by tenocytes in cell supernatants were analyzed by slot blot. The statistical analysis using the t-test revealed a significantly increased COL-I secretion in cells cultured on MD ($p = 0.033$) and a trend of increase in cells cultured on COL ($p = 0.08$), compared to CT. CyB administration did not influence COL-I secretion by tenocytes (Figure 6a). The AVOVA p-value was statistically significant ($p = 0.0056$) and the post-test showed a significant increase in COL-I in COL vs. CT ($p = 0.041$), in COL vs. CT+CyB ($p = 0.011$) and in COL+CyB vs. CT+CyB ($p = 0.022$).

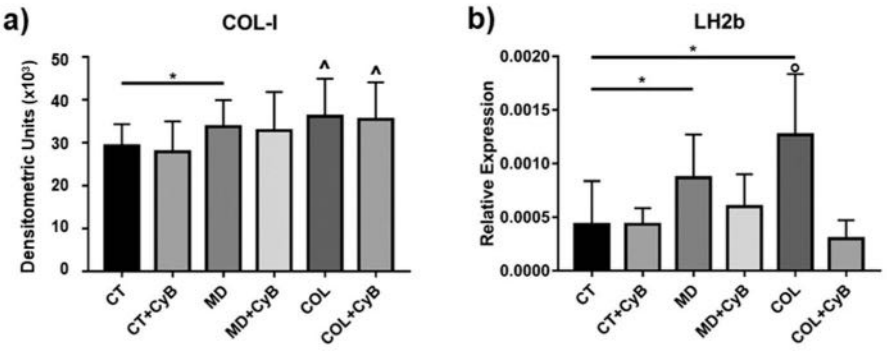

Figure 6. (**a**) Bar graphs showing COL-I protein levels obtained using slot blot after densitometric scanning of immunoreactive bands in the considered experimental conditions. Data are expressed as mean ± SD. (**b**) mRNA levels for Long lysyl hydroxylase 2 (LH2b) in CT and tenocytes cultured on MD and COL with or without CyB treatment assessed by real-time PCR. Data were normalized on GAPDH gene expression and are expressed as mean ± SD for at least two independent experiments. * $p < 0.05$ using t-test. ^ $p < 0.05$ vs. CT, CT+CyB, COL+CyB vs. CT+CyB; ° $p < 0.05$ vs. CT and COL+CyB using ANOVA.

Collagen maturation was analyzed by assessing the mRNA levels for LH2b, involved in the cross-linking of newly synthetized collagen, by real-time PCR. LH2b mRNA levels were significantly higher in tenocytes cultured on MD and COL ($p = 0.039$ and 0.020, respectively), compared to CT. CyB administration reduced LH2b gene expression in cells cultured on MD and COL ($p = 0.053$ for COL vs. COL+CyB), but not in CT (Figure 6b): this finding suggests that LH2b up-regulation induced by the coating is triggered by a mechanical stimulation mediated by the actin cytoskeleton. The ANOVA p value was 0.0095 and the post-test confirmed the induction of LH2b in COL compared with CT ($p = 0.025$) and revealed a significant decrease in COL+CyB vs. COL (p=0.025).

Interstitial collagen degradation is driven by MMP-1. Slot blot analysis of MMP-1 levels in cell culture supernatants revealed that this collagenase remained unaffected in tenocytes cultured on MD and COL, compared to CT, as well as after CyB administration (Figure 7a,c). A similar pattern of expression was observed for MMP-2 gelatinolytic activity, assessed by SDS-zymography (Figure 7b,d). A similar pattern was also observed for TIMP-1, the main inhibitor of MMP-1, analyzed at the gene expression level by real-time PCR. TIMP-1 mRNA levels revealed wide interindividual differences and were similarly modified by CyB in all the experimental groups (Figure 7e).

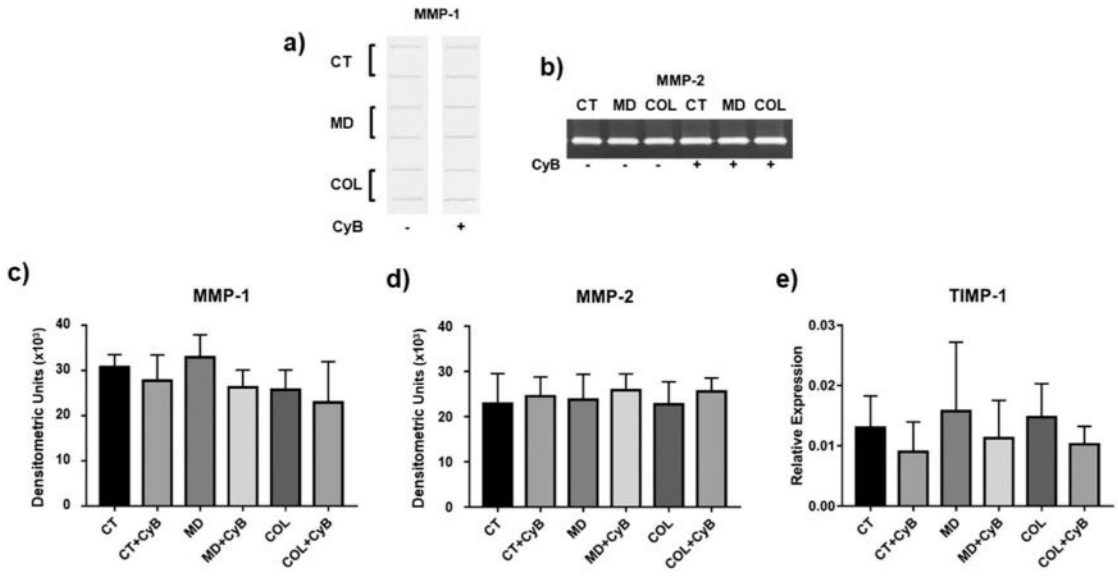

Figure 7. Representative slot blot for matrix metalloproteinase-1 (MMP-1) levels (**a**) and representative SDS-zymography showing MMP-2 activity (**b**) assayed in serum-free cell supernatants of tenocytes cultured in the considered experimental settings. Bar graphs showing MMP-1 protein levels (**c**) and MMP-2 activity (**d**) after densitometric analysis of immunoreactive and lytic bands, respectively. Data are expressed as means ± SD for at least two independent experiments. (**c**,**e**) Bar graphs showing TIMP-1 gene expression after normalization on GAPDH mRNA levels. Data are expressed as mean ± SD for at least two independent experiments.

3.4. Cytoskeleton Arrangement and Vinculin Expression in Focal Adhesions

In order to understand whether MD or COL may represent a mechanical stimulation able to influence the ability of tenocytes to form focal adhesions, we analyzed the expression of VNC, a key protein involved in the formation of the adhesion plaque, by morphological and molecular methods. Western blot analysis showed that VNC protein levels were significantly up-regulated in cells grown on MD (MD vs. CT, $p = 0.033$) and tended to increase also in cells cultured on COL. In this experimental group, VNC was significantly decreased by CyB treatment (COL vs. COL+CyB, $p = 0.040$) (Figure 8a,b). The effects of the presence of the scaffold and of CyB administration were more evident using morphological analysis by immunofluorescence. Indeed, VNC immunoreactivity, localized at the extremities of actin filaments in correspondence with focal adhesion formation on the substrate, was found to be stronger and wider in tenocytes grown on MD and COL, compared to CT (Figure 8c). After CyB administration, the VNC immunofluorescence signal and the regions corresponding to the presence of the focal adhesion seemed less evident and smaller only in cells grown on MD and COL, but not in CT, becoming similar to CT (Figure 8c, arrows).

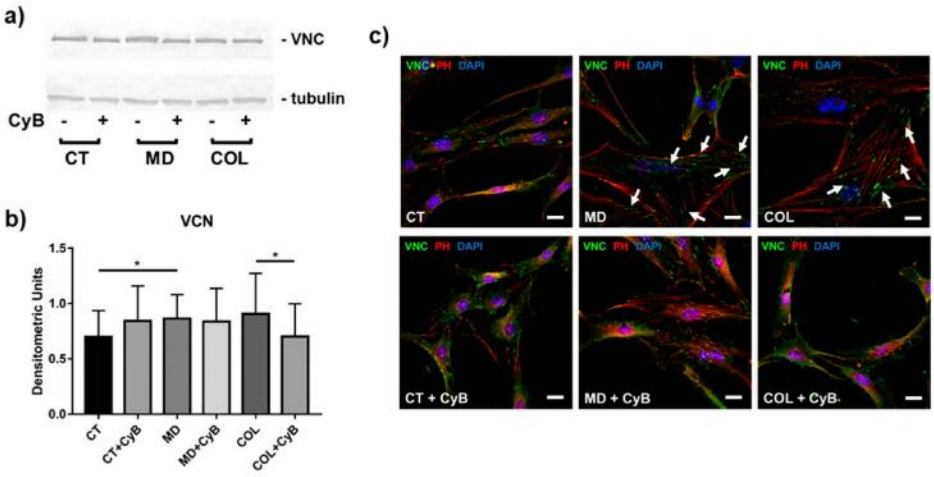

Figure 8. (**a**) Representative Western blot for VNC quantification in cell lysates obtained from tenocytes cultured on MD and COL, compared to CT, with or without CyB treatment. VNC expression was normalized on tubulin. (**b**) Bar graphs showing VCN expression after densitometric analysis of immunoreactive bands. Data are mean ± SD for at least two independent experiments. (**c**). Immunofluorescence analysis for VNC (green) in tenocytes cultured on MD and COL, compared to CT, before and after CyB treatment. Actin filaments are stained using rhodamine-phalloidin labeling. Nuclei are stained in blue by DAPI. Original magnification: 60×. White arrows point to larger and more evident VNC-containing focal adhesions observed in MD and COL samples, compared to the same samples treated with CyB. CyB modified the size of VCN-containing focal adhesions similarly to CT. VNC: vinculin; PH: phalloidin. Scale bar: 20 μm. * $p < 0.05$ using *t*-test.

3.5. Wound Healing Assay

Cell migration, playing a key role during tendon healing, was assessed by a wound healing assay in tenocytes grown on CT, MD and COL with or without CyB administration. The quantification of the scratch size revealed that cell migration is significantly increased in tenocytes cultured on MD and COL, compared to CT ($p = 0.023$ and $p = 0.032$, respectively). Conversely, cell migration remained unaffected by CyB treatment in CT, but was strongly reduced in MD (MD vs. MD+CyB, $p = 0.040$) and, although not statistically significant, in COL tenocytes (COL vs. COL+CyB, $p = 0.07$) (Figure 9a,b). The ANOVA p value was 0.001 and the post-test confirmed the increased migration induced by COL compared to CT ($p = 0.015$) and revealed a significant increase in the migration of cells cultured on MD or COL compared to CT+CyB ($p = 0.009$ and $p = 0.001$, respectively).

3.6. Expression of FAK, PAX and YAP/TAZ as Mechanosensors

To understand if the scaffold containing MD and COL affects tenocytes biology by a mechanical stimulation, the expression of key proteins playing a role as mechanosensors was analyzed.

FAK and PAX are proteins in the adhesion plaque that also act as mechanosensors. Their mRNA levels tended to be up-regulated in tenocytes cultured on MD and COL compared to CT, although not reaching the statistical significance ($p = 0.09$). CyB treatment did not affect FAK in CT but had an impact on its expression in cells cultured on MD ($p = 0.09$) and COL, determining its reduction (Figure 10a). The ANOVA revealed that FAK mRNA levels are up-regulated in MD vs. CT ($p = 0.017$) and vs. CT+CyB ($p = 0.020$) and that they are decreased in MD vs. MD+CyB ($p = 0.013$) and COL+CyB ($p = 0.018$). A similar pattern was observed for PAX: its expression was higher in MD ($p = 0.075$) and COL, compared with CT, and was reduced by CyB only in cells cultured on the scaffold ($p = 0.07$ for MD vs. MD+CyB and $p < 0.05$ for COL vs. COL+CyB), whilst it remained unchanged in CT (Figure 10b). The analysis of PAX gene expression by ANOVA showed that its expression was significantly increased in MD vs. CT and vs. CT+CyB ($p = 0.0059$ and $p = 0.052$, respectively), while it was reduced in MD+CyB ($p = 0.003$) and COL+CyB ($p = 0.007$) compared to MD.

Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) are mechanosensors whose activity is regulated by phosphorylation, leading to protein inactivation and cytoplasmic translocation. YAP/TAZ were first analyzed by Western blot using antibodies to detect both the unphosphorylated (active) and phosphorylated (inactive) proteins. YAP and p-YAP resulted in being similarly expressed in cell lysates obtained from CT, MD and COL tenocytes, although a significant down-regulation was observed after CyB administration in cells cultured on MD ($p = 0.044$) (Figure 10c). p-YAP resulted in being similar in all the experimental conditions (Figure 10d) as well as the YAP/p-YAP ratio (Figure 10e). A similar pattern was observed for TAZ and p-TAZ (data not shown).

In order to understand whether MD or COL were able to trigger a mechanical stimulation in tenocytes, YAP/TAZ activation induced by the scaffold was investigated by analyzing their localization by immunofluorescence analysis. YAP/TAZ were expressed both in nuclei and the cytoplasm. We observed a stronger nuclear immunoreactivity in tenocytes cultured on MD and COL, compared to CT. In CT, CyB did not significantly modify this pattern of expression, whilst in tenocytes cultured on MD and COL, CyB strongly increased the number of nuclei having a less intense YAP/TAZ labeling (Figure 11): this finding suggests that mechanical stimulus deprivation following CyB administration inactivated YAP/TAZ and induced their translocation from the nucleus to the cytoplasm.

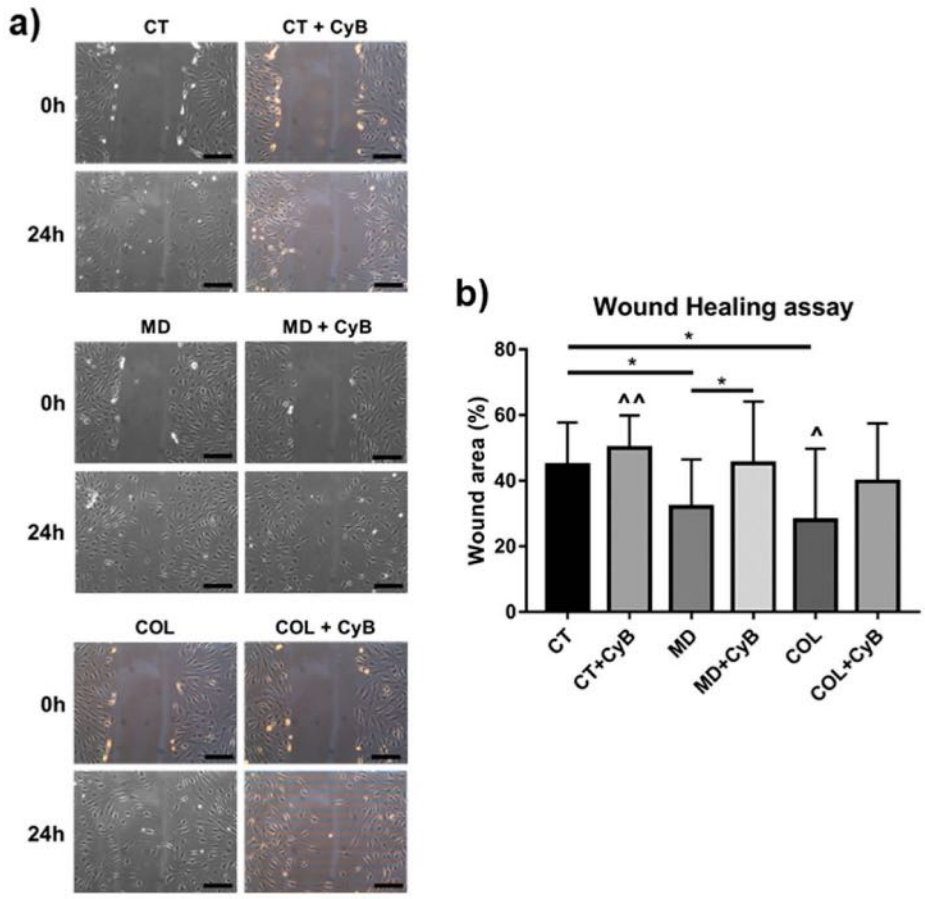

Figure 9. (**a**) Representative phase contrast micrographs showing the results of the wound healing assay in control tenocytes (CT) and tenocytes grown on MD and COL at 0 and 24 h after the scratch, with or without CyB administration. Original magnification: 10×. (**b**) Bar graphs showing the area of wound closure after 24 h, expressed as a % of the area at 0 h, in cultured tenocytes in the different experimental conditions. Data are mean ± SD for at least two independent experiments. * $p < 0.05$ for *t*-test; ^ $p < 0.05$ vs. CT; ^^ $p < 0.01$ vs. MD and COL using ANOVA.

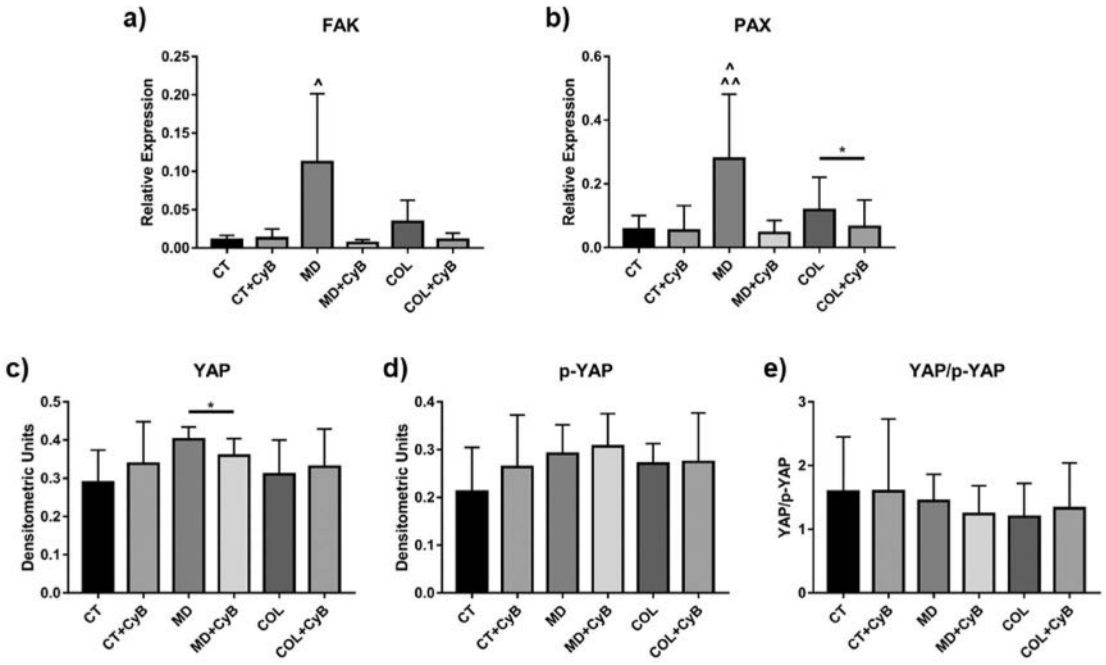

Figure 10. Bar graphs showing FAK (**a**) and PAX (**b**) mRNA levels after normalization on GAPDH gene expression. Data are means ± SD for at least two independent experiments. For YAP expression, the active-form YAP (**c**), the inactive phosphorylated form (**d**) and the YAP/p-YAP ratio (**e**) were assessed by Western blot and represented by the histograms showing mean ± SD for at least two independent experiments for the considered experimental groups. * $p < 0.05$ for *t*-test; ^ $p < 0.05$ vs. CT, CT+CyB, MD+CyB, COL+CyB; ^^ $p < 0.01$ vs. MD+CyB and COL+CyB using ANOVA.

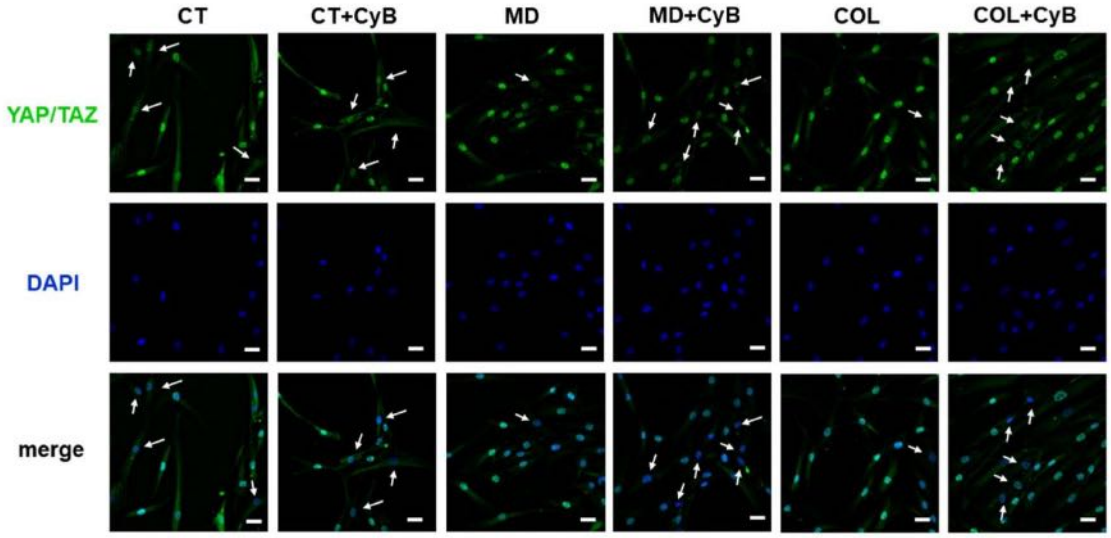

Figure 11. Immunofluorescence analysis for YAP/TAZ (green) in tenocytes cultured on MD and COL, compared to CT, before and after CyB treatment. The merged micrographs show that in tenocytes cultured on MD and COL, immunoreactivity is more evident in the nucleus, while, after CyB treatment and in CT, immunoreactivity is mostly in the cytoplasm and nuclei are more blue, suggesting that the presence of MD and COL induces YAP/TAZ activation, while mechanical stress deprivation induces a phenotype more similar to CT cells. Original magnification: 60×. Scale bar: 20 µm.

4. Discussion

The mechanobiology of tenocytes is vital to preserve tendon homeostasis [28–31]. Tenocytes are able to sense mechanical stimuli imposed on tendons during mechanical loading and can adapt their metabolism in an anabolic or catabolic manner in order to remodel the ECM according to the applied loads [32–34]. Therefore, tenocytes are responsible for tendon mechanical adaptation: they convert mechanical stimuli into biochemical signals that ultimately influence tendon adaptive physiological or pathological changes, thus affecting its biomechanical properties [13,15,16]. In fact, it was reported that physiological mechanical loading increases collagen synthesis [14,35], while reduced loading leads to MMP-1 up-regulation [36].

Tensile loading acting on tendons is transduced into intracellular biochemical responses by various sensors and pathways, and the propagation of extracellular-generated forces rely on the actin cytoskeleton [37]. Actin filaments mediate the modification and deformation of the ECM and contribute to the propagation of mechanical stimulation to the nucleus, where gene expression for ECM components can be accordingly affected [38]. It has been demonstrated that the deprivation of mechanical stimulation on tendons mediated by the actin cytoskeleton can be obtained by CyB treatment [36]. Therefore, in order to understand if MD acts as a mechanical scaffold, we utilized CyB to analyze if the effects elicited by MD or COL on tenocytes behavior are affected by mechanical loading deprivation.

For this purpose, we first analyzed the scaffold containing MD and COL at SEM to evaluate if the substrate arrangement could influence cell alignment. The observation at SEM of Petri dishes coated with MD or COL did not reveal the presence of collagen fibrils, possibly due to a fragmentation into small fragments of the collagen contained in the device. As a consequence, when cultured on the scaffold, cells were not influenced in their arrangement and grew without any specific distribution. To support our findings, a further SEM analysis conducted on a commercial Petri dish coated with type I collagen confirmed that collagen fibrils are undetectable. Since, in our previous study, we showed that MD was able to modify some biological activities of tenocytes [19], we tried to demonstrate the presence of the scaffold using a different approach such as Raman spectroscopy. Using this technique, we were able to assess the presence of mainly type I collagen in MD prepared to culture tenocytes.

After demonstrating the presence of the scaffold, we investigated collagen turnover, since COL-I is the main component of the tendon ECM. Its content is regulated by a finely balanced turnover controlled by tenocytes acting at the level of collagen synthesis, maturation and degradation. Collagen turnover, therefore, plays a key role in determining the tendon ability to resist mechanical forces and repair in response to injury [9]. We previously demonstrated that MD favors COL-I secretion [19], suggesting that this medical compound is able to trigger the anabolic phenotype of tenocytes. In the present study, our results confirm the increase in COL-I protein levels in the supernatant of tenocytes cultured on MD and COL, compared to CT. Since CyB administration had no effect on collagen expression in all experimental groups, there is not a clear demonstration that the effect of the scaffold on COL-I expression is mechanically induced and mediated by the actin cytoskeleton.

Maturation of newly synthesized collagen is needed to provide collagen fibril stabilization and tendon tensile strength and is obtained by the cross-linking of newly secreted collagen by enzymes such as LH2b [39,40]. Our results show that LH2b is up-regulated by MD, and also by COL, in tenocytes cultured for 48 h, as previously demonstrated [19]. Interestingly, this effect was lost after CyB administration only in tenocytes cultured on MD and COL, but not in CT, pointing to a mechanical mechanism exerted by MD to trigger collagen maturation to improve collagen stability.

Collagen turnover pathways include collagen breakdown played by MMP-1, which cleaves the intact collagen triple helix, followed by other proteases such as MMP-2 [41,42]. The key role of MMP-1 in tendon ECM homeostasis is based on the previously demonstrated inverse correlation between MMP-1 expression at the gene and protein levels and the amplitude of tensile mechanical load acting on tendons. In fact, low levels of MMP-1 induced by mechanical loading are related to a more stable tendon structure [36]. Here, we show that MMP-1 and MMP-2 levels are not affected by MD and

COL, and they remain unchanged by CyB administration. When investigating collagen degradation, TIMPs expression should be also analyzed. TIMP-1 is the main inhibitor of MMP-1, binding MMP-1 in a 1:1 stoichiometric ratio and inhibiting its activation and activity [43,44]. TIMP-1 mRNA levels slightly increased in tenocytes cultured for 48 h on MD and COL, compared to CT, as previously reported [19], and were reduced after CyB administration in all the considered experimental groups. This finding suggests that, in our experimental conditions, TIMP-1 levels are not under specific mechanical control mediated by the actin cytoskeleton. Overall, collagen turnover mechanisms involving the activity of MMP-1, MMP-2 and TIMP-1 seem to be unaffected by CyB.

ECM remodeling and homeostasis are influenced by mechanical stimuli acting on tendons and tenocytes are mechanoresponsive cells: they play a key role as the effectors since they are able to sense mechanical signals and convert them into biological responses [45,46]. This activity of tenocytes is based on their actin microfilaments that represent a mechanotransduction system allowing to adapt tenocyte metabolism in response to different mechanical forces acting on tendons [36]. CyB is known to modify the dynamic instability of actin filaments. However, as shown in Figure 8, the dose of CyB used in this study did not injure microfilaments and tenocytes preserved their structural integrity.

The actin cytoskeleton also plays a key role during cell migration. Since tenocytes migration is needed during tendon healing [47], we investigated, by a wound healing assay, if MD and COL affect cell migration and if their effect relies on a mechanoresponsive mechanism influenced by CyB treatment. We found that MD favors cell migration, as previously reported [19], as well as COL, confirming that the therapeutic activity of this medical device could be related to this effect. To demonstrate that MD-induced cell migration is triggered by a mechanotransduction system, the wound area was measured after CyB administration. Interestingly, CyB was able to decrease cell migration in tenocytes cultured on MD and COL, but not in CT, strongly suggesting that the stimulation of cell migration induced by MD is mediated by a mechanical effect.

During the dynamic process of cell migration, cells undergo a repeated cycle of attachment to the ECM and subsequent detachment of the cell from the matrix. Transmembrane proteins, the integrins, mediate the attachment of tenocytes to the ECM and bridge the inside and outside of the cells. To do this, they link their cytoplasmic domain to the focal adhesion complexes at the leading edge of the cell, including many different proteins such as VNC, a cytoplasmic actin-binding protein enriched in focal adhesions [48–50]. Interestingly, the presence of VNC at adhesion complexes is force-dependent [50]. Western blot analysis of VNC revealed some significant modifications induced by the medical device before and after CyB treatment. However, more interesting findings were obtained by morphological analysis using immunofluorescence, which revealed some qualitative differences in cells cultured on MD and COL, compared to CT. In fact, VNC immunoreactivity detectable at the extremity of microfilaments and the size of focal adhesions containing VNC seem more evident and larger in cells grown on the medical device, compared to CT. This observation suggests the hypothesis that VNC expression can be affected by MD and COL, and that the medical devices could improve the attachment of tenocytes to ECM components and, therefore, their ability to form more efficient focal adhesions to favor cell migration. This hypothesis is supported by the observation that, after CyB administration, focal adhesions of cells cultured on MD and COL are similar to those observed in CT. Accordingly, it was reported that VNC recruitment is enhanced when tension increases, while, when tension decreases, focal adhesions are disassembled in response to decreased tension [50]. Moreover, the analysis with the phase contrast microscope revealed that cell morphology was similar in tenocytes grown on CT, MD and COL. By contrast, CyB induced a less flattened morphology in CT, confirming the hypothesis that the medical device is able to favor cell adhesion and thus cell migration.

To finally demonstrate that MD affects tenocyte behavior representing a mechanical stimulus acting on mechanotransduction mechanisms, we analyzed the effect of the medical device on the expression of key mechanosensors such as FAK, PAX and YAP/TAZ. FAK and PAX are components of the adhesion plaque complex. They are involved in the formation of focal adhesions needed for cell migration but they also play a key role acting as mechanosensors [51–53]. Our data show that FAK

and PAX gene expression is strongly influenced by MD as well as by COL, compared to CT. When CyB is added to the cell culture medium for 48 h, FAK and PAX mRNA levels are down-regulated only in tenocytes grown on MD and COL, and not in CT. This finding suggests that their induction is dependent on the mechanical stimulus exerted by the medical device used as a scaffold. Moreover, this effect is lost when the transmission of the mechanical stimulus on tenocytes is blocked when cells are deprived of their mechanotransduction apparatus. To strengthen this hypothesis, we analyzed the expression of the transcriptional regulators YAP/TAZ, which are regulated by mechanical inputs in a variety of cellular settings, thus impacting many different cell activities [51]. YAP and TAZ act as mechanosensors primarily regulated by the substrate on which cells adhere, which, in turn, influences YAP/TAZ activity stimulating the actin cytoskeleton. The integrity of microfilaments is pivotal on YAP/TAZ activity. In fact, treatment of cells with Latrunculin A, an inhibitor of actin polymerization, results in phosphorylation of YAP and cytosolic localization of YAP/TAZ [51]. In this study, we used CyB to inhibit actin polymerization and to block its dynamic instability in order to analyze YAP/TAZ expression in tenocytes cultured on MD and COL, compared to CT, to demonstrate that the medical device represents a mechanical stimulus to affect cell behavior.

Western blot analysis of YAP/TAZ did not reveal important differences as well as in the YAP/p-YAP ratio. However, our data suggest that MD and COL represent a mechanical input for tenocytes since immunofluorescence analysis demonstrated that YAP/TAZ expression is more nuclear in cells cultured on MD and COL, compared to CT. This suggestion is further supported by the observation that after CyB administration, depriving cells of the mechanical input mediated by the cytoskeleton, YAP/TAZ immunoreactivity becomes less nuclear and more cytoplasmic only in cells grown on MD and COL, and not in CT. This suggestion is consistent with previous studies demonstrating that, since YAP/TAZ serve as mechanotransducers and mechanosensors, their subcellular localization and activity are tightly regulated by cell substrate rigidity and tensile inputs from the ECM [53–55], and that cytoskeletal tension is required for YAP/TAZ nuclear localization [53].

5. Conclusions

Considered as a whole, these in vitro findings suggest that MD and COL trigger similar responses in tenocytes and that their effect on tenocytes behavior represents a mechanical input involving the mechanotransduction machinery. In particular, we showed that MD-Tissue influences some tenocytes activity involved in ECM homeostasis and improves focal adhesion formation and migration ability. Overall, we confirm that MD-Tissue, acting as a mechanical scaffold, could be an effective medical device used as a novel therapeutic, regenerative and rehabilitative approach to favor tendon healing in tendinopathies.

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Collagen and PRP in Partial Thickness Rotator Cuff Injuries. Friends or Only Indifferent Neighbours? Randomized Controlled Trial

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Abstract

INTRODUCTION: Partial thickness rotator cuff injuries (PTRCI) is the sum of degenerative, overload and microtrauma processes, external supply of collagen and platelet-rich plasma (PRP) could potentially counteract deterioration of degenerative tendinopathy.

AIM: Comparison of the effectiveness: collagen with PRP, PRP alone, collagen alone in the treatment of PTRCI.

METHODS: Ninety patients with PTRCI treated with US–guided injections into the shoulder bursa every consecutive week: Group A - collagen with PRP (n=30), B - collagen alone (n=30), C - PRP alone (n=30). Primary outcomes: numeric rating scale (NRS), QuickDash and EQ-5D-5L questionnaires in control points: IA (initial assessment), T1, T2, T3 – after 6, 12 and 24 weeks, respectively. Secondary outcomes: number of patients with loss of RC continuity, number of regenerated RC between IA and T3.

RESULTS: No statistical difference between groups in primary outcomes, tendency for further improvement in A and C group (opposite to group B) between T2 and T3. The RC discontinuity (n = 3, one case in each group) and RC regeneration (n = 65; 73%, 67% and 77%, in group A, B and C, respectively).

CONCLUSIONS: Combined therapy of collagen and PRP in PTRCI is not more effective than monotherapies with collagen or PRP.

(clinicaltrials.gov - NCT04492748)

Introduction

Rotator cuff injuries (RCI) ranks third in the population prevalence among musculoskeletal system pathologies (16%) after lumbar spine pain (25%) and knee pain (19%). Depending on the source, the prevalence of RCI is from 5 to 39%. It increases very clearly with age and in patients over 60 years of age reaches over 30%, with a great majority being described as rotator cuff tendinopathy (RCT), mostly in the form of partial thickness RCI (PTRCI) as an emanation of the degenerative process [1].

Over 85% of the dry mass of the rotator cuff tendons is type I collagen. Damage, disorganization of collagen fibers and a negative metabolic balance of collagen underlie the macroscopic lesions visible in ultrasound (US) or resonance imaging (RI) [2].

Most often, the PTRCI concerns the supraspinatus tendon (SSP), which is the crucial factor in centering of the humeral head in joint glenoid during the act of upper limb elevation. In traumatic cases also subscapularis (SSC) and infraspinatus (ISP) tendons are affected often with long head biceps (LHB) instability. There are several reasons for the degenerative process leading initially to edema, micro-perforations and then full thickness tendon lesions: 1) natural age-related weakening of blood supply near the SSP insertion, 2) concomitant degenerative spurs of acromioclavicular joint or acromion shape as a direct cause of the subacromial impingement, 3) disturbed muscle timing between RC and deltoid

usually associated with cervical spondylosis (scapular dyskinesis), 4) shoulder joint multidirectional instability as a result of capsule-ligamentous elements laxity and disturbed contact of joint surfaces with RC posterior impingement. The consequences of RCI are further destabilization of the shoulder, scapular dyskinesis, upper and anterior migration of humeral head followed by subacromial bursitis. The clinical picture of PTRCI includes shoulder pain radiating to the deltoid area and even to the elbow both at rest and at strain, weakening of muscular strength, impaired limb function and disability of self-service. Due to the risk of surgical treatment, reduced strength of RC tendons affected by the degenerative process and a significant risk of injury recurrence, conservative treatment of PTRCI is the first choice, especially for inactive patients over the age of 60 years. It assumes the alleviation of inflammatory symptoms (physical therapy, general and local pharmacotherapy - most often steroid injections), attempts of regenerative treatment as: Platelet Rich Plasma (PRP), collagen injections, autologous conditioned serum (ACS) and rehabilitation (muscular centering of the humeral head, developing compensatory movement patterns).

Reports on PRP show its positive effects, both alleviating symptoms and slowing down the process of further degeneration of the tendon, demonstrating its advantage over steroid administration or prolotherapy [3, 4, 5].

Another form of therapy aimed at suppressing the negative balance of collagen metabolism is to supply collagen in the form of an injection in the vicinity of the injured tissue (into the tendon itself or into the subacromial bursa). The premises for this type of injection are reports showing a reduction in pain after collagen injections compared to steroid injections and a significant acceleration of the proliferation and migration of tenocytes cultured in an exogenous collagen environment in vitro [6, 7]. The same is true for synergic effects of collagen and PRP confirmed in multiple studies utilized tendon-like cell models, where increased cell proliferation was observed with the addition of various PRP products. This suggests that PRP products have a positive effect on the cell's mitogenic activity, collagen production and optimization of the collagen I/III ratio [8].

These positive effects and their consequences for clinical significance have not yet been demonstrated in clinical studies and it was our main premise to initiate comparative study about the effectiveness of three treatment concepts: collagen with PRP, collagen alone, PRP alone, in the treatment of PTRCI.

Material And Methods

The study design was single center open randomized controlled trial. The protocol of the trial was approved by the Bioethics Committee at the Faculty of Health Sciences of the Jan Kochanowski University in Kielce (Reference No. 15/2020, May 18, 2020). All experiments were performed in accordance with and following the Declaration of Helsinki Principles. All methods were performed in accordance with the relevant guideline and regulations. Written informed consent was obtained from all participants prior to injections and the publication of their individual data. The study was performed in Sutherland Medical Center (SMC), Warsaw, Poland. The trial was registered in Clinicaltrials.gov

(NCT04492748) on 20/07/2020 (Initial Release), last update 03/10/2021. Unique Protocol ID: SMC2020001. Brief title: Rotator Cuff Tendinopathy Conservative Treatment With Collagen, PRP or Both (RCCT).

Inclusion criteria:

- clinical signs and symptoms of rotator cuff pathology
- an adult person consenting to injections
- partial thickness rotator cuff injury confirmed by ultrasound examination without coexisting severe pathologies (systemic inflammatory disease, malignancy, severe stage of osteoarthritis)
- no traumatic event

Exclusion criteria:

- full thickness rotator cuff injury
- acute, traumatic injuries requiring surgical treatment
- coexisting injuries of the shoulder joint requiring other intervention
- severe pathologies of the shoulder of another origin (systemic inflammatory disease, malignancy, severe stage of osteoarthritis)
- no consent

Three groups of patients, each containing 30 participants, were enrolled in the study. Patients meeting the inclusion criteria were allocated randomly according to the computer-generated randomization list (block randomization; block size = 6). No changes of allocation and no changes in the methodology of the study took place throughout the study.

All data were collected at SMC Clinic.During the Initial Assessment (IA), patients were asked to evaluate intensity of the pain (Numeric Rating Scale, NRS, range from 0 (no pain) to 10 (extreme pain) and to complete widely used, validated questionnaires:QuickDash (0-50) and theEQ-5D-5L (descriptive part and EQ-VAS 0-100).US-examination of the shoulder was performed with the usage of Alpinion E-CUBE 12 device, linear transducer L3-12H (3-12 MHz).

SSP tendon width (cross-section in mm) was measured in the internal rotation position of the arm. We distinguished following ultrasound patterns of PTRCI: bursa- sided (BS), joint – sided (JS), intra-tendon (IT) and oblique or focal (OF). The measurement in BS and JS types was performed in the narrowest point (follow- up measure estimates tendency for increase of the RC width as a sign of regeneration). In

IT or OF type of injury the measurement was performed at the thickest point of RC (follow- up measure estimates tendency for reduction of inflammatory and oedematous overgrowth of the RC as a sign of regeneration).

Each group was treated by three US-guided injections into the subacromial bursa using the in-plane technique. Injections were performed every consecutive week by the same physician (P.G.). Group A - collagen (3 vials of Collagen MD Shoulder – total 6 cc) simultaneously with PRP GLOFINN (10 cc whole blood, double centrifugate, leukocyte rich PRP, volume of PRP – 2 cc); Group B - collagen alone (3 vials of Collagen MD Shoulder); Group C - PRP GLOFINN alone.

All patients were allowed to continue a rehabilitation protocol with preservation of safe, pain-free range of motion, postural exercises, scapular stabilization exercises. Prohibited were any exercises with resistance which would compromise the healing process of RC.

Primary outcomesincludedNumeric Rating Scale, NRS (0-10; 0-no pain, 10-maximal pain), QuickDash questionnaire (0-50; 0-no disability, 50 maximal disability), EQ-5D-5L questionnaire (five dimensions: MO-mobility, SC-self-care, UA-usual activities, PD-pain and discomfort, AD- anxiety and depression; each dimension with five levels of limitations: 1-no limitation, 5-maximal limitation; visual analogue scale EQ-VAS 0-100; 0 – the worst health status, 100-optimal heath status). Follow-up schedule for primary outcomes: Initial assessment (IA), 6, 12 and 24 weeks after last injection.

Secondary outcomes included percentage of patients in each group where the RC continuity was preserved with desired evolution of RC cross-section width and percentage of patients who had US signs of RC regeneration. Secondary outcomes were assessed at IA and T3.

The power of the test was set at 0.8 and the significance level at 0.05, assuming that the effect size was f = 0.35. This allowed us to establish that the research sample for the three compared groups should not be smaller than 90 subjects (each group with 30 participants).

Descriptive statistics for demographic data, ANOVA test to proof initial comparability of the groups and to check possible significant differences between groups according to age, NRS, QuickDash and EQ-5D-5L questionnaire VAS were performed using IBM SPSS version 25.

In the analysis of the collected research material, the one-way ANOVA test was used, which allowed us to check whether one independent variable (factor) affects the results of the dependent variable. The test results allowed us to determine whether the mean scores of the scales for individual control points differ statistically significantly between the groups. In order to determine between which groups there is a statistically significant difference, Tukey's post-hoc test was used. A calculation of the difference in value between the baseline IA and the T3 point for every single patient was also performed, and then the mean values of this difference was taken to compare primary outcomes in the groups.

Results

One hundred one patient were screened for eligibility. Ninety patients meeting inclusion criteria were randomized. One person from group A did not finish the therapy (for reason other than therapy intolerance) and had no T1, T2 and T3 observations. Two persons quit the study after T1 (group C/JS and group A/IT). One person left the follow-up appointment after T2 due to lack of improvement and asked for a change of therapy (group C/OF). Two patients faced total RC tear before the end of the observation – between T2 and T3 (group C/JS and A/IT) and one patient was found to have had complete RC injury at the T3 visit. Finally, eight people did not obtain the T3 control; one person did not complete the therapy, three people dropped out of further control after T1 (two patients experienced a complete tear of the RC between the visit T2 and T3) - group C/JS and group A/IT, one person from group C/OF asked to change therapy after T2 control), and one person from group A/JS refused control T3.

Recruitment and follow-up process presents Fig. 1.

The treatment has been accomplished by 89 patients (99%). All check-up visits were passed by 91.1% of patients. In 82 patients who completed therapy and obtained T3 control, three SSP total injuries were observed (3.6%). There was no participant cross-over.

Table 1 presents demographic characteristics. ANOVA test didn't reveal any significant statistical difference according to age, NRS, QuickDash and EQ-5D-5L VAS mean values in IA between groups.

Table 1

Demographic characteristics.

Total number of patients, n	**90**
Female, n (%)	42 (46.7)
Age, years, mean ± SD (range)	54.5 ± 14.7 (24–91)
Duration of complaints weeks, mean ± SD (range)	21.8 ± 28.5 (1-230)
RC tendopathy phase, n (%):	
Acute phase patients,	10 (11.1)
Subacute phase patients	27 (30.0)
Chronic phase patients	53 (58.9)
Injury type, n (%):	
Bursa Side	5 (5.6)
Joint Side	49 (54.4)
Intratendinous	22 (24.4)
Oblique and focal	14 (15.6)
Side of complaints, n (%):	
Right	49 (54.4)
Left	41 (45.6)
Dominant limb, n (%):	
Right	84 (93.3)
Left	2 (2.2)
Both	4 (4.4)

Figure 2 presents the mean NRS evolution in specific groups. A reduction in pain intensity is seen mostly in the first 6 weeks of follow-up but no significant statistical differences between groups were noticed in ANOVA. There is a slight tendency in A and C group for further improvement beyond T2.

Figure 3 presents the mean QuickDash evolution in specific group where similar pattern of mean values reduction is observed also without significant statistical differences between groups in ANOVA test for QuickDash main questionnaire.

Figure 4 presents the mean EQ-5D-5L VAS evolution in specific groups. No statistically significant differences were found. The dynamics of changes during six weeks after last injection is similarly more intense.

The ANOVA test for the EQ-5D-5L Index showed a statistically significant difference in baseline values (IA) between the groups, while no statistically significant differences were observed in the control points.

In order to check between which groups there are statistically significant differences, the post hoc test was used. The Games-Howell test was chosen due to the failure to meet the assumption of homogeneity of variance in the analyzed groups. The analysis showed differences ($p < 0.05$) between groups A (0.892) and C (0.816). It is worth noting that between groups A (0.892) and B (0.820) there is also a similar difference between the mean EQ-5D-5L indices, but the analysis showed no statistical significance ($p = 0.063$) [Fig. 5].

A calculation of the differences between the baseline IA and T3 values for every single patient was also performed. A mean value of this differences for each studied group were calculated. Figure 6 presents differences in the mean initial and final values for primary outcomes in the groups. Group B shows the highest differences in all scales, although the ANOVA test did not show statistical significance between the groups.

Lost continuity of RC between IA and T3 was found in three cases (one in each group) and the number of cases with RC regeneration confirmed in ultrasound was: A-22, B-20, C-23.

Mean increase of RC width in BS and JS type of injury for specific groups was: A – 0.7 mm, B – 0.2 mm, C – 1.3 mm. There is statistically significant difference for B and C ($p < 0.05$) in ANOVA test. [Fig. 7].

Mean reduction of width for IT and OF type of injury for specific groups was: A – 0.7 mm, B – 0.9 mm, C – 0.3 mm. No statistically significant difference between groups in ANOVA test were found [Fig.8].Fig.8. Mean reduction of width for IT and OF type of injury for specific groups.

No significant harms, complication or unintended effects of the treatment were reported.

Discussion

Conservative treatment of PTRCI with injections of collagen and PRP as monotherapy or combined therapy showed no significant difference in efficacy.

The strength of our study is based on the first ever performed test in vivo whether really exist the potential synergy between PRP and collagen delivered into subacromial bursa in terms of tendon regeneration by randomized control trial (the authors did not find a similar study in the literature). In addition to the well-validated subjective assessment questionnaires, an ultrasound examination with six-month observation was used, which seems to be long enough to observe changes in echogenicity and possible change in tendon thickness.

The weakness of the study is certainly a small group of participants, imperfections in the methodology of RC thickness measurement in ultrasound as an operator dependent. The bias is mostly connected with difficulties to obtain the same cross-section point of reference for precise test-retest measurement.

Another bias of the study which may modify the results is the wide margin of tolerance according to rehabilitation protocol which was implemented for the participants before or in the course of the study beyond of our control, as well a sport or working activities exerted by many of them against recommendations. There were also no restrictions on taking painkillers when needed during observations period.

Degenerative rotator cuff tendinopathy appearing as PTRCI is a condition challenging to treat, mainly because of the poor regenerative potential of the tendons corelated with aging. It has been described many other factors contributing to treatment failure like: overload in the rehabilitation process, drugs (i.e. quinolones), alcohol intake, smoking, corticosteroids [9].

For over two decades there have been a growing interest in biologically active substances like growth factors, stem cells or autologous conditioned serum [10].

There are many publications about PRP's potential enhancement of healing potential after surgical repairing of RCI and decreasing ratio of re-tear. However, the data are conflicting [11, 12, 13, 14].

In vitro culture experiments clearly confirm the anabolic effect of PRP on the healing of RC lesions through cell proliferation and synthesis of collagen I [15].

However in vivo, especially without RC repair there is much confusion and the conclusions are conflicting. A protocol of PRP usage, similar to our study, brought by Freitag et al. (2014) in a case report of 60 years old patient treated with three doses of PRP for PTRCI in weekly intervals but administered not into bursa but into the partial supraspinatus tear using a lateral approach. He followed-up the outcomes throughout 52 weeks. The NRS, patient percentage perceived improvement (PPPI) and a handheld isometric dynamometer assessment of RC strength was recorded in follow-up intervals occurring at 6th, 17th, 25th and 52nd weeks revealing the best PPPI up to 90% in 17th week and slightly worse at 52nd week (70%) [16].

Scarpone et al. presented open study prospective trial without control group on 19 patients treated with a single ultrasound-guided, intralesional injection of PRP in RCT reporting satisfying results in 18 cases up to 52 weeks of follow-up [17].

The similar outcomes were achieved by Wesner et al. in their pilot study on a small group of nine participants versus control group placebo (7 with PRP and 2 with saline) in the 6 months follow-up [18].

Kesikburun et al. who also used single injection of PRP performed RCT with 1-year follow-up, where PRP injections versus placebo (saline) were injected into subacromial bursa in the group of 40 patients (20 – PRP versus 20 – saline). Injection therapy was followed by 6 weeks rehabilitation program. They found no significant differences in improving quality of life, pain, disability, and shoulder range of motion than placebo in patients with PTRCI who were treated with an exercise program [19].

However, all the above-cited studies did not have subsequent imaging control to objectify tendon regeneration.

It seems to be reasonable to raise a question of insufficient dose of single shot PRP (especially if a low volume whole blood set was used), as a possible reason of unsatisfied results. Similar questions have been raised with respect to the type of PRP that may be optimal for promoting regeneration that was confirmed in laboratory comparative studies between low and high leucocyte PRP [20, 21].

The authors have found only one prospective study performed by Nesterova et al. about the usage of collagen GUNA MD injections in PTRCI, where in 22 patients treated with intrabursal injections of total 20 vials throughout 8 weeks achieved satisfactory results by 73% of patients with 77% of recovered lesions confirmed in US [6].

Our study showed clearly that the healing potential of RC no matter how weak still exists and can be activated or augmented by external delivery of biologic active substrates although without clear difference between monotherapy or combined therapy. However many questions about the optimal PRP composition, collagen dose, administration sequence (mixture or sequential administration) and injection location depending on the type of RC injury (intraarticular or intrabursal) remain open. The most interesting seem to be unknown connection between structural integrity of RC and clinical outcomes.

Conclusions

Combined therapy of collagen and PRP in PTRCI is not more effective than separate therapies.

Declarations

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Declaration of Conflicting Interests

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Figures

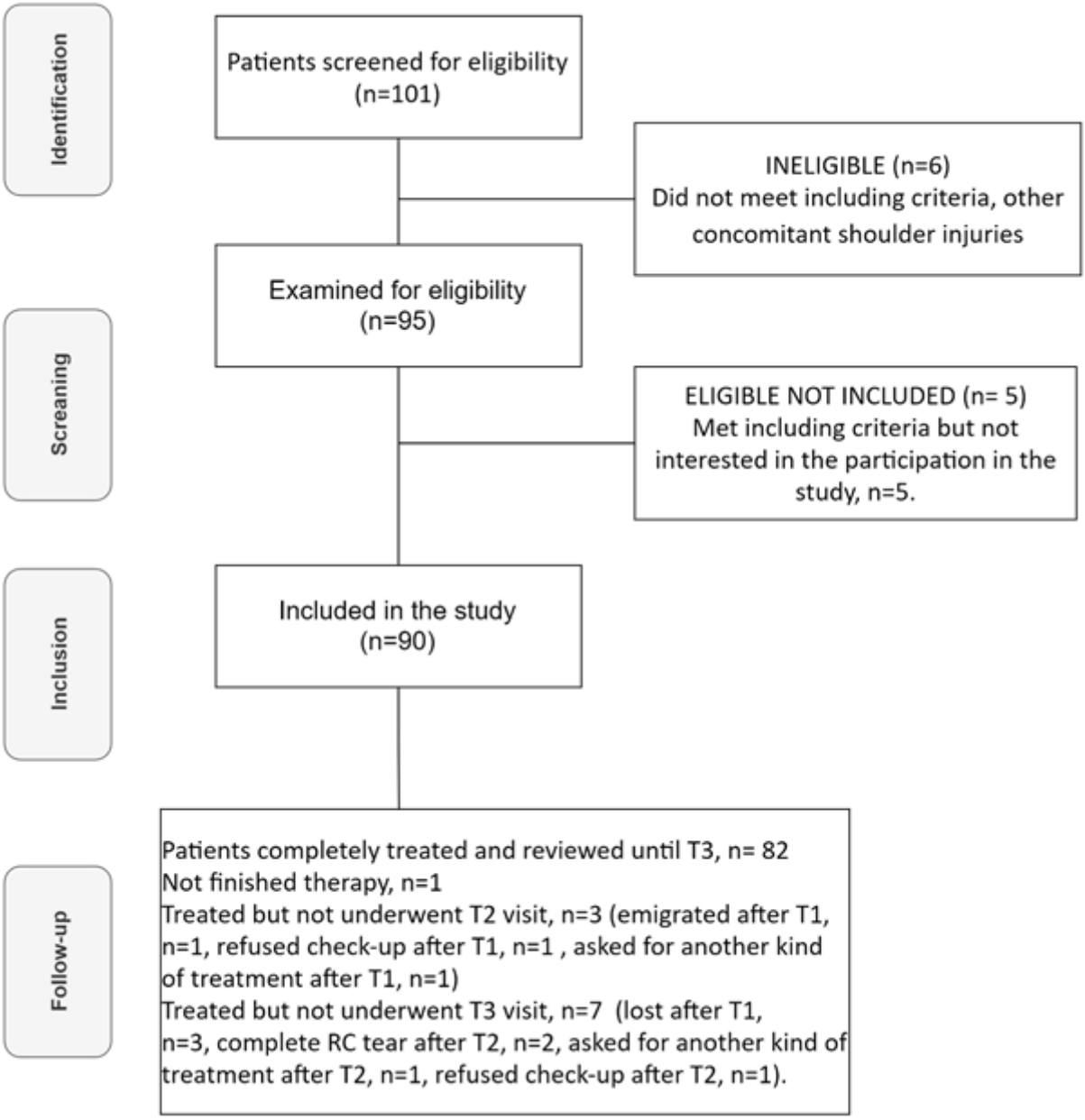

Figure 1

Enrollment and follow-up process.

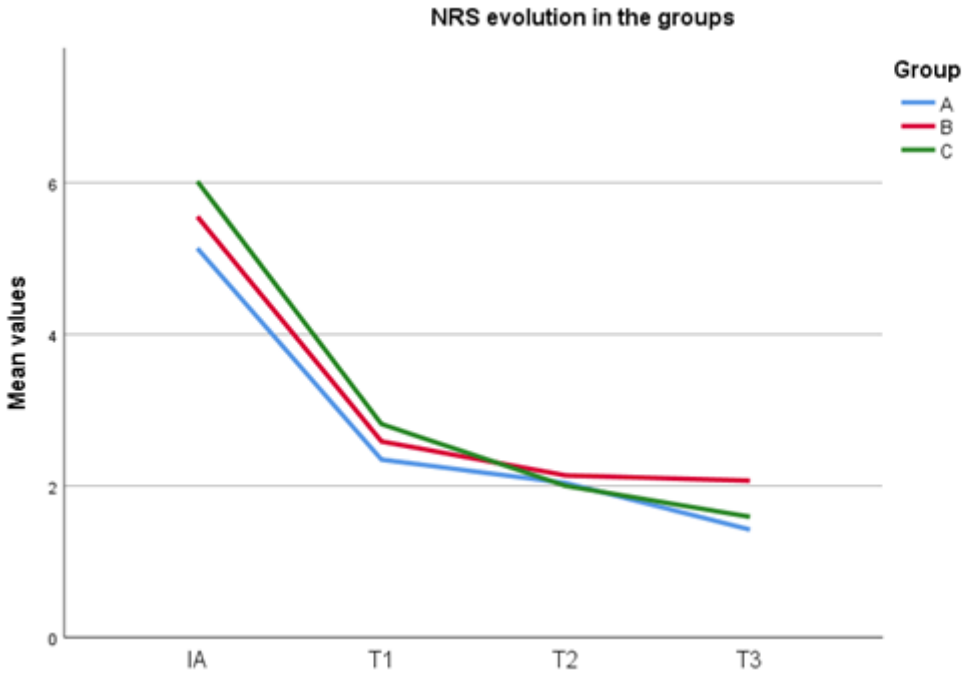

Figure 2

Mean NRS evolution in specific groups.

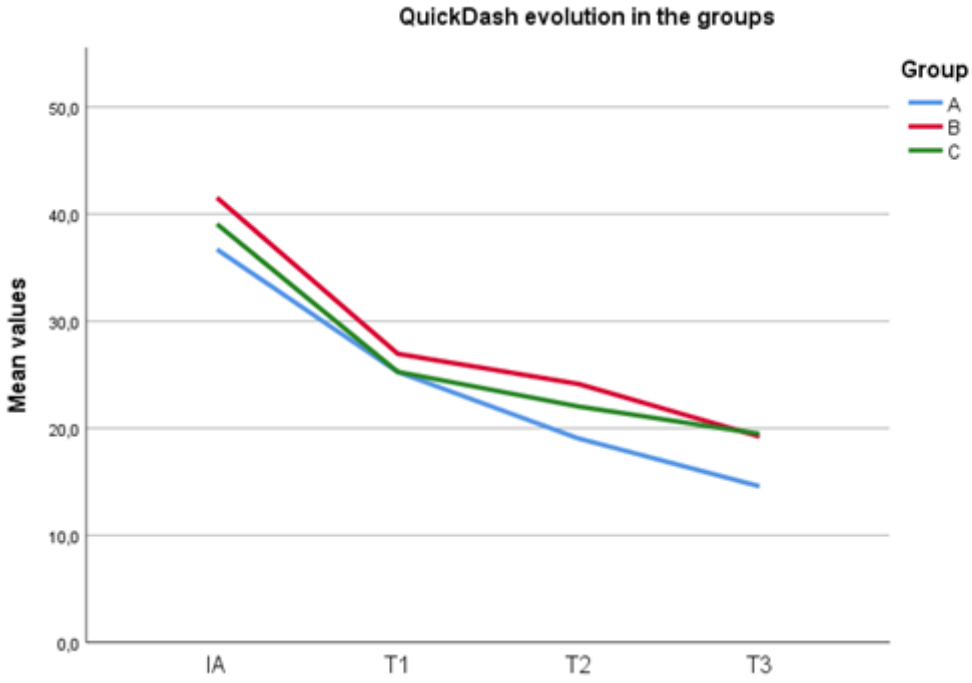

Figure 3

Mean QuickDash evolution in specific groups.

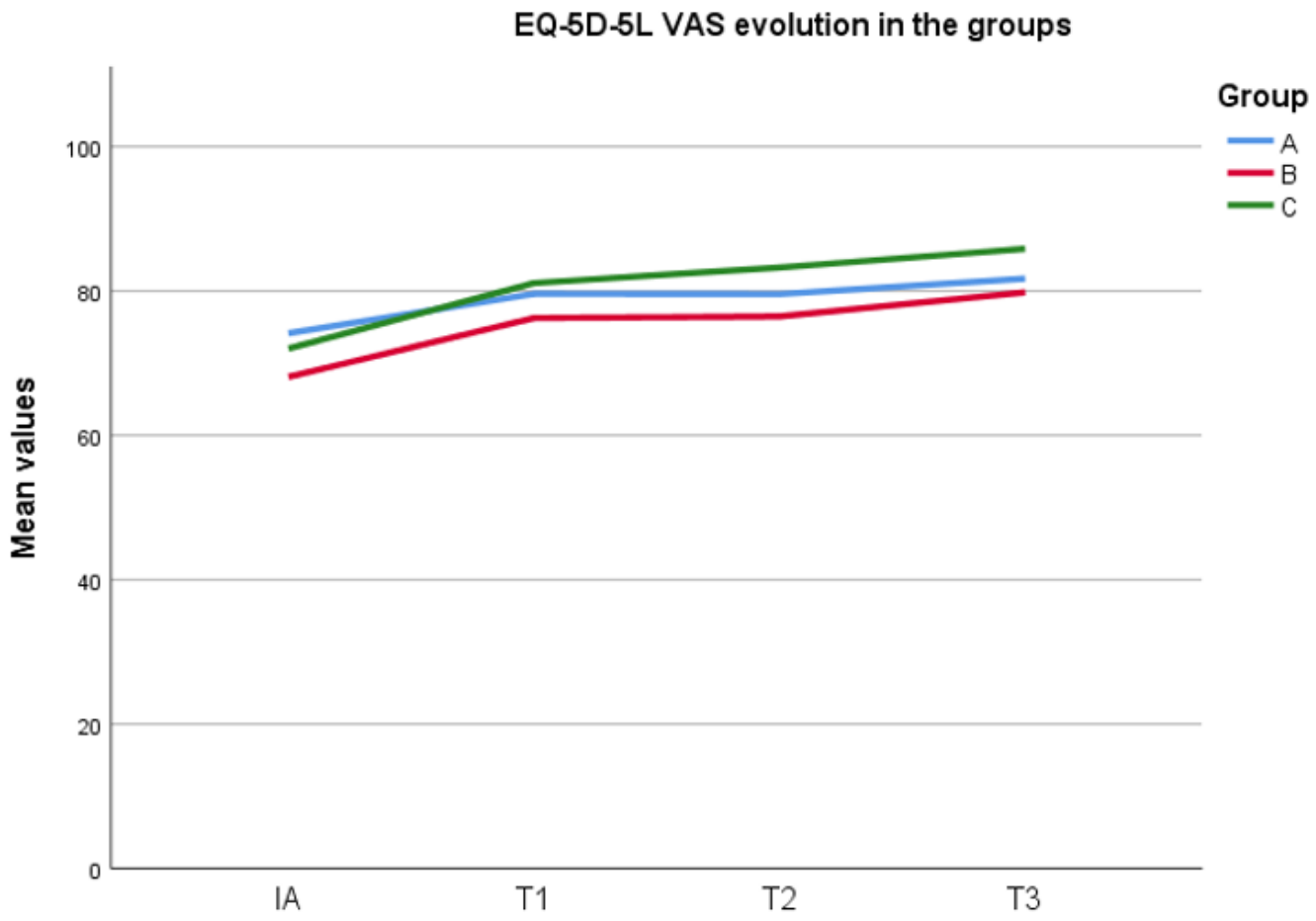

Figure 4

Mean EQ-5D-5L VAS evolution in specific groups.

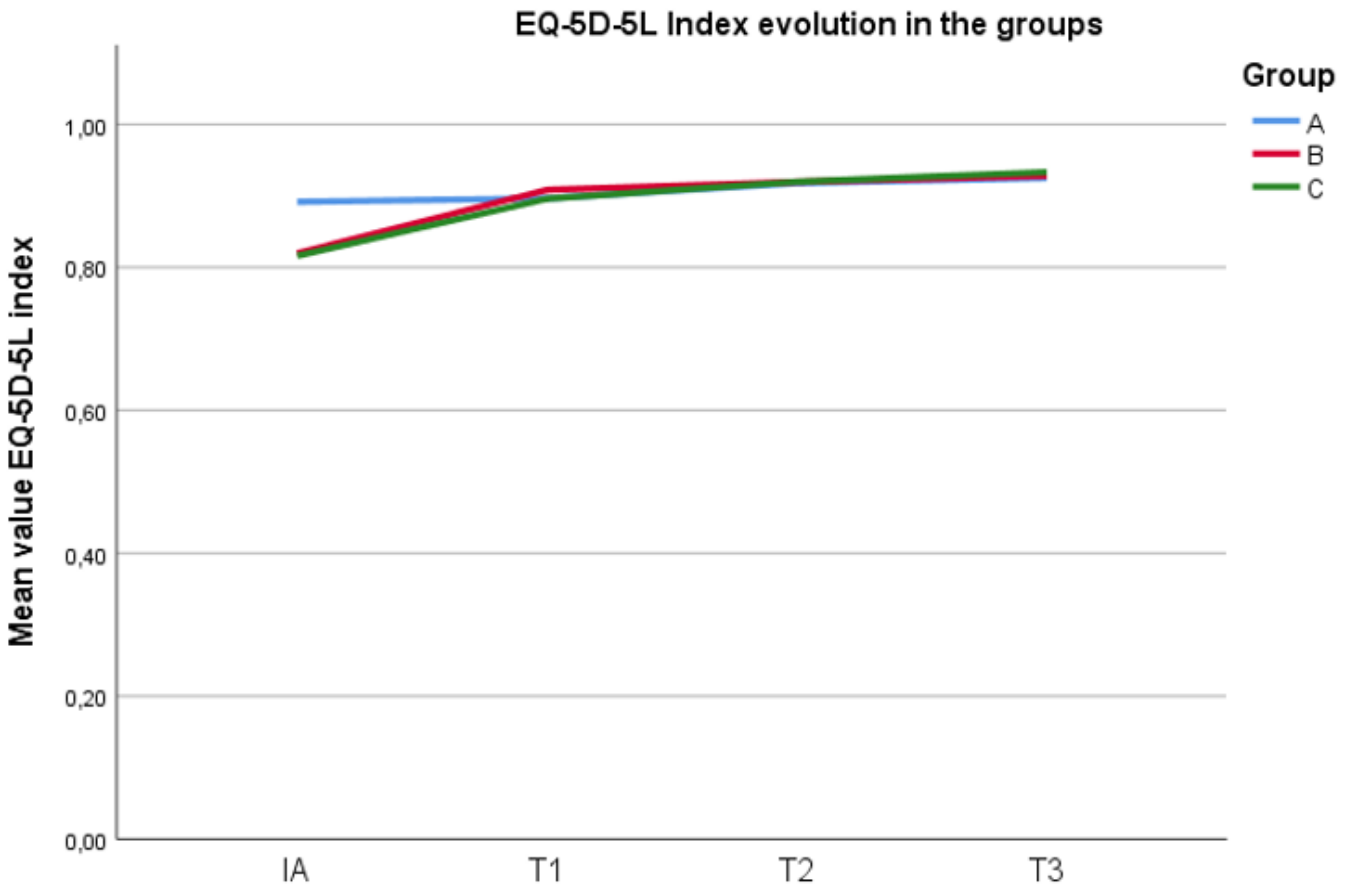

Figure 5

EQ-5D-5L Index evolution in the groups.

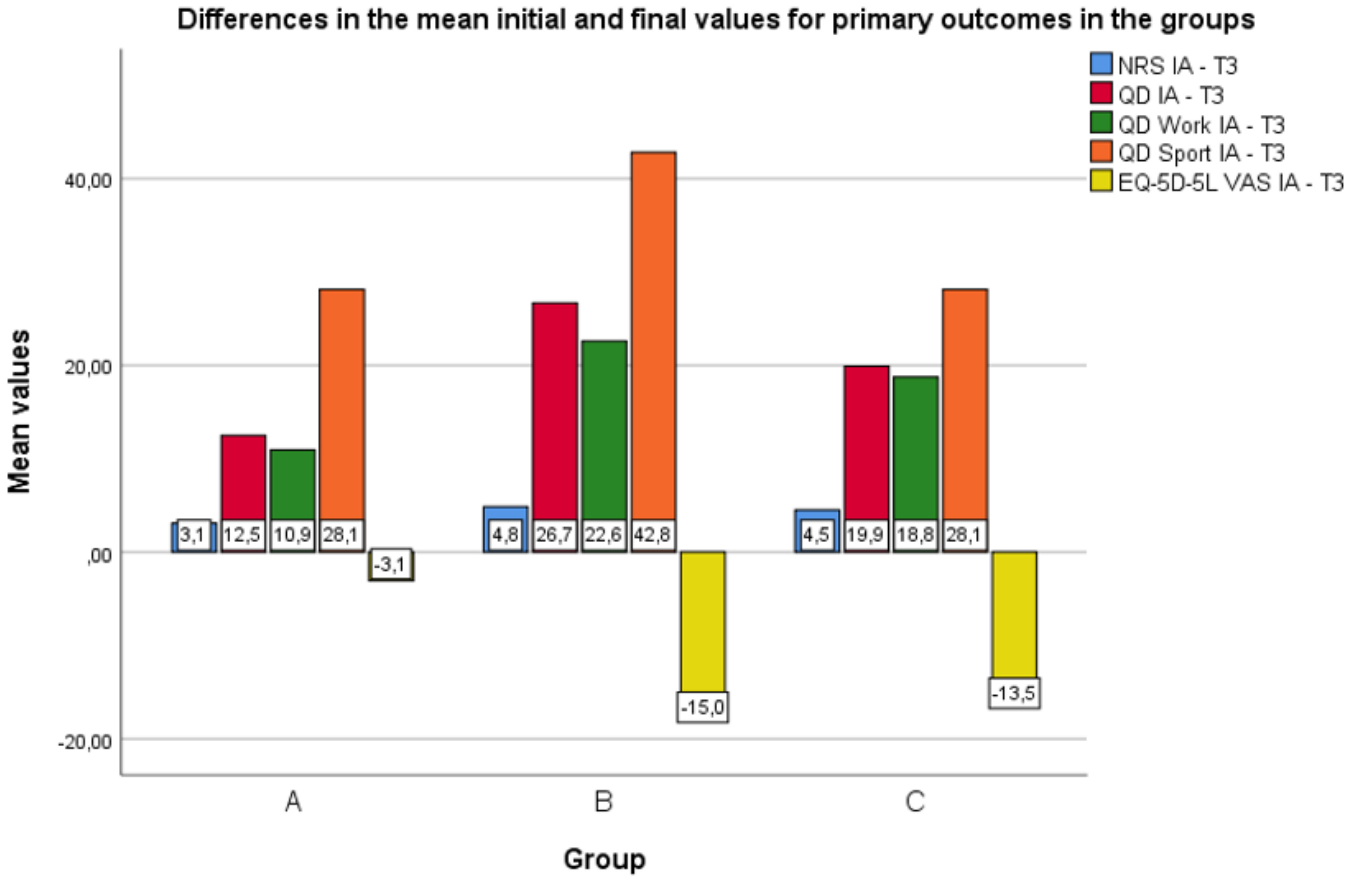

Figure 6

Differences in the mean initial and final values for primary outcomes in the groups.

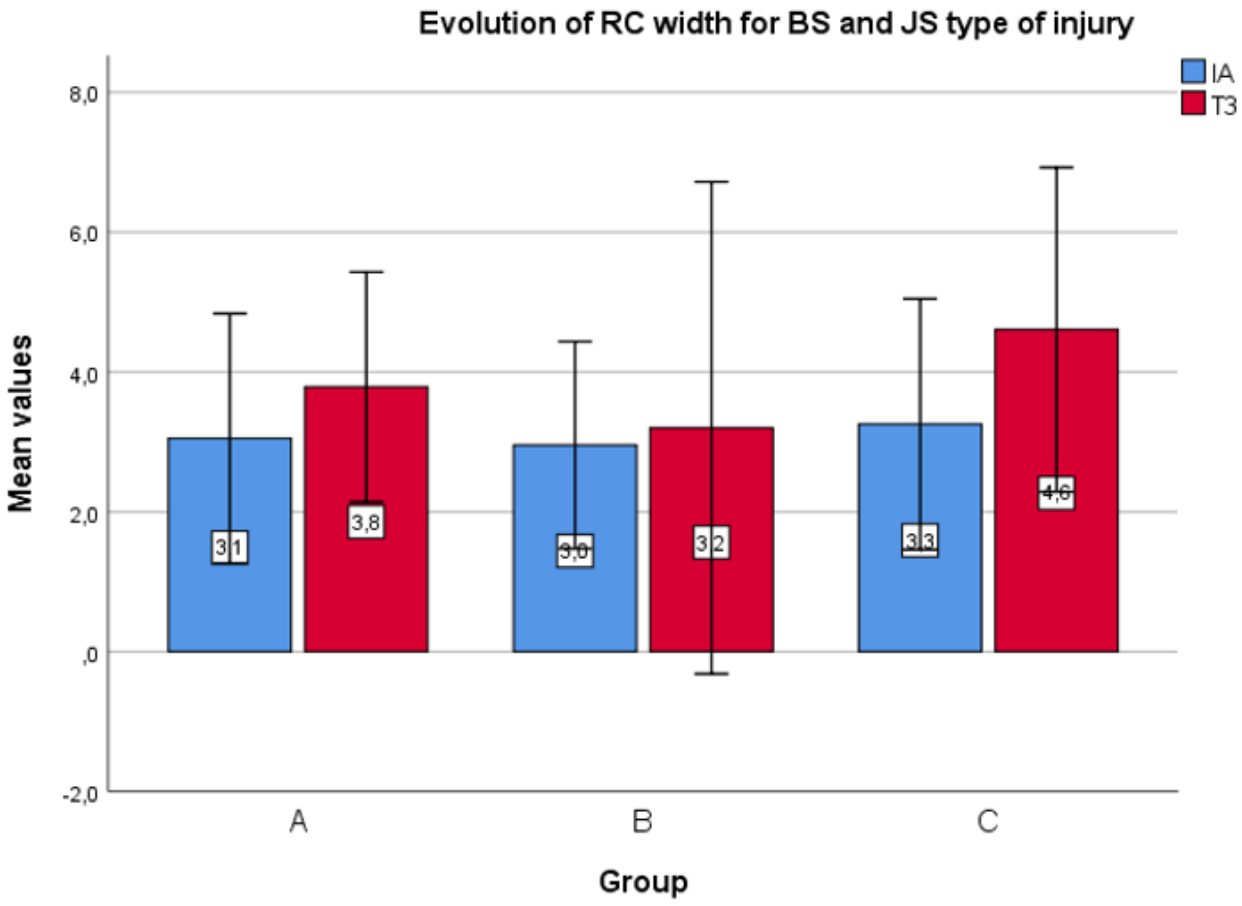

Figure 7

Mean increase of width for BS and JS type of injury for specific groups.

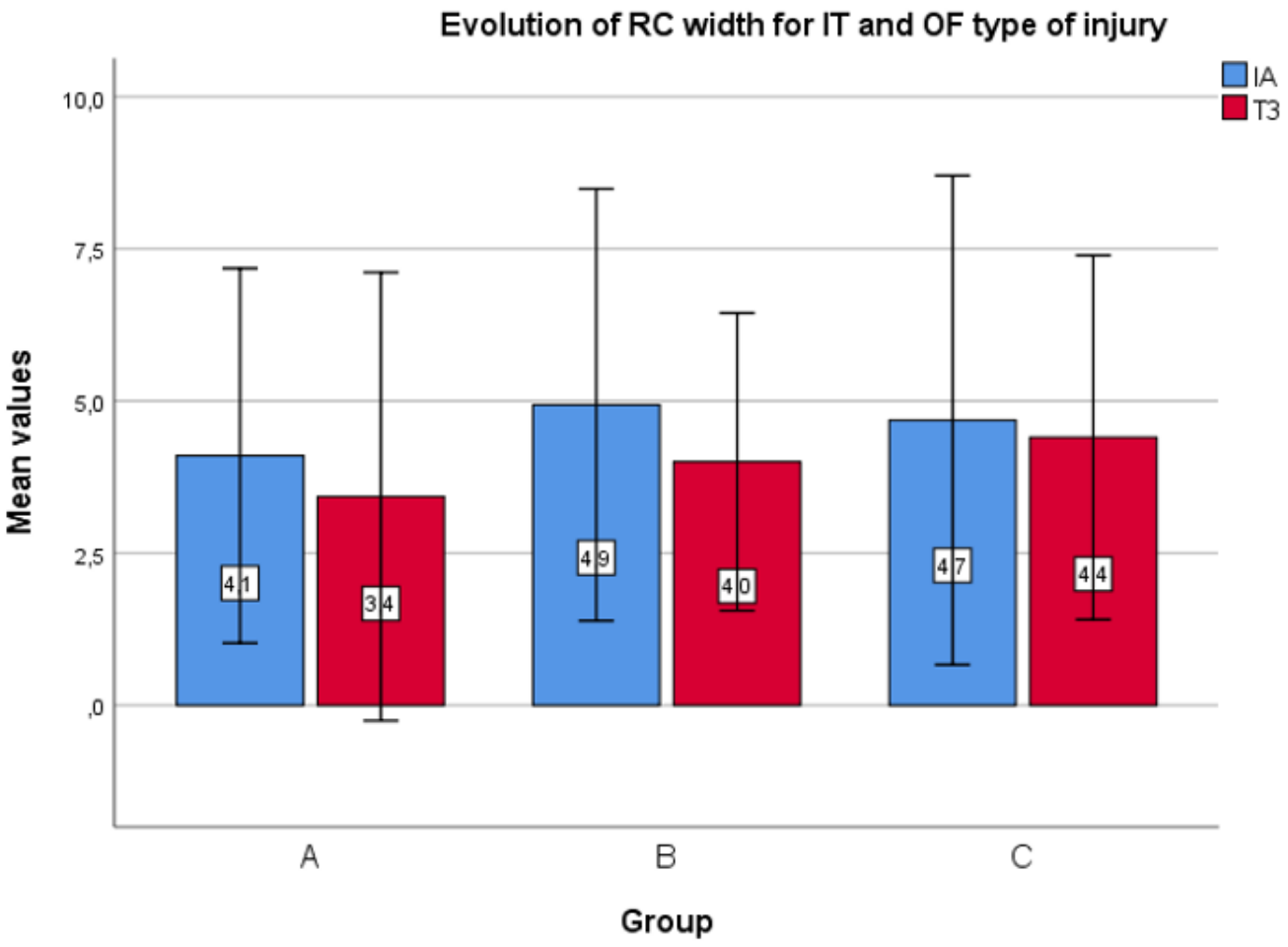

Figure 8

Mean reduction of width for IT and OF type of injury for specific groups.