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SUMMARY

Chronic pain is a very debilitating symptom for individuals. In approximately 70% of patients, this condition seems to manifest as an inflammatory-degenerative aetiology of the connective Tissue that predominantly affects the Musculoskeletal System. Type 1 collagen is the backbone of joint capsules, tendons (97%) and ligaments (85%). – Under physiological conditions, the quality and quantity of collagen ensure optimal joint movement. To date, the treatment of arthro-rheumatopathies is based on the combined use of pharmacological, rehabilitative and surgical treatments. Since 2010, collagen-based medical devices have been at the orthopaedist's disposal for the treatment of musculoskeletal disorders. Collagen in locally acting medical devices acts as a bio-scaffold of extra-cellular matrix through the deposition of collagen fibrils in the damaged region. Although there are still relatively few randomised clinical studies evaluating the efficacy of these medical devices, collagen infiltration therapy is a possible option in the treatment of lateral elbow pain in cases of common extensor tendinopathy and pain related to tendon pain in the supraspinatus muscle. Moreover, infiltrative collagen therapy also appears to be promising in the treatment of medial elbow pain caused by tendinopathy, in bicep and tricep tendinopathy. Further studies are required to investigate its efficacy and mode of administration deeper.

KEY WORDS

COLLAGEN, COLLAGEN MEDICAL DEVICES, INFILTRATIVE TREATMENT, CONSERVATIVE TREATMENT, TENDINOPATHY, EPICONDYLITIS, EPITROCHLEITIS, ROTATOR CUFF, ADHESIVE CAPSULITIS

TENDINOPATHIES OF THE UPPER LIMB – NEW INFILTRATIVE SOLUTIONS WITH COLLAGEN MEDICAL DEVICES

INTRODUCTION

Chronic pain is a very debilitating and widespread symptom.

In approximately 70% of patients, this condition seems to manifest as an inflammatory-degenerative aetiology of the connective Tissue that predominantly affects the Musculoskeletal System.

– The term Arthro-rheumatopathies identifies a group of inflammatory and/or degenerative diseases of the connective Tissue characterised by collagen disorders.

Collagen is a structural protein of the extracellular matrix, synthesised and ex-

creted by tenocytes (fibrocytes); it accounts for 5-6% of the human body weight.

The qualitative and quantitative organisation and composition of collagen determine the organoleptic characteristics of the different connective Tissues.

Although up to 21 different types of collagen have been identified in mammals, the most common is type 1 collagen which is the 'backbone' not only of the epidermis, but also of joint capsules, tendons (97%) and ligaments (85%).

– Under physiological conditions, the quality and quantity of collagen ensure optimal joint movement and excursion.

Degenerative processes in collagen fibres, often promoted by the presence of free radicals and inflammation typical of states of overload, ageing or injury, cause slow and imperfect neofibrillogenesis.

– This spontaneous repair leads not only to the neo-formation of misaligned, discontinuous and juxtaposed fibres, much more similar to those in a foetus than those in an adult, but also promotes neo-angiogenesis phenomena that attract clusters of inflammatory cells that feed and sustain the degenerative process.

Architectural alterations of collagen fibres frequently underlie many Arthrorheumopathies. Under these conditions, there is a loss of the characteristic anisotropy of collagen. Thus, there is a lack of two-way communication between the fibroblasts and their microenvironment; in biological terms, this results in a reduction of collagen deposition activity, the consequence of which is reduced Tissue repair.

Age, wear and tear, joint immobilisation and trauma, as well as macro/micronutrient deficiencies and the abuse of certain drugs (mainly corticosteroids and NSAIDs) can accelerate degenerative processes in type 1 collagen, and therefore lead to the development of chronic pain.

– Several studies suggest that periarticular hyperlaxity, often associated with alterations in type 1 collagen, may be one of the primary causes of joint pain. In these patients, the osteocartilaginous structures are subjected to excessive and poorly distributed loads.

The joints wear out over time, leading to symptoms of Arthrosis.

– Thus, extra-articular pain is compounded by intra-articular pain, often of an inflammatory nature, which aggravates the symptoms.

To date, the treatment of Arthropathies includes various therapies, often based on the combined use of non-pharmacological treatments (shock waves, mag-

net therapy, tecar therapy, laser therapy, acupuncture), conventional pharmacological treatments (paracetamol, NSAIDs, cortisone) or non-conventional treatments (homeopathic, BrSM medicines, phytotherapy), rehabilitation treatments (assisted physiotherapy) and surgical treatments (implantation of prosthetic components or arthrodesis). Viscosupplementation with hyaluronic acid, due to its lubricating and cushioning action, administered infiltratively mainly in the hip, knee and shoulder joints, has been shown to be effective in reducing algic symptoms, although it has not yet been clarified which patients benefit most from it.

– Since 2010, Collagen Medical Devices have been an additional tool at orthopaedists' disposal (and others) for the treatment of musculoskeletal disorders. Collagen Medical Devices consist of type 1 collagen extracted from the porcine dermis, which specific and dedicated auxiliary natural excipients are associated with according to the anatomical district concerned.

These devices can be used individually or in combination with each other according to clinical needs; they are used locally through peri-articular, intra-articular, subcutaneous and/or intradermal injections (at the trigger points or at the points used in acupuncture) or, alternatively, systemically through intramuscular injections.

- The collagen in Collagen Medical Devices acts as a bio-scaffold of extra-cellular matrix through the deposition of collagen fibrils in the damaged region.
- This strengthens the anatomical and functional structure of the collagen fibres of the structures containing them.

At the same time, collagen provides mechanical support to the affected areas, restoring the anisotropy of the Tissue.

– Preclinical studies have shown how Collagen Medical Devices induce an anabolic phenotype in tenocytes by stimulating tenocyte proliferation and migration and the synthesis, maturation

and secretion of type 1 collagen through increased anisotropy conditions (1).

At the same time, clinical studies report that the efficacy of collagen is similar to that of hyaluronic acid in controlling osteoarticular pain (2), and greater than local anaesthetics in controlling lumbar and myofascial pain (3).

In clinical practice, collagen infiltrations are not only safe and easy to manage, but also appear to have the following functions:

- 1) the induction of repair and remodelling processes
- 2) an increased speed of functional recovery
- 3) the consolidation and stabilisation of results achieved with other therapeutic interventions
- 4) the secondary control of pain symptoms.

– Focusing on the upper limb, Collagen Medical Devices have been used in various inflammatory and tendon pathologies and, more specifically, in cases of Epicondylitis, Epitrochleitis, and Tendinopathy.

However, to date, there are still relatively few randomised clinical trials evaluating its effectiveness in these districts.

ELBOW

EPICONDYLITIS OR TENNIS ELBOW

Epicondylitis (Tennis Elbow), one of the main reasons for orthopaedic evaluation of elbow pain, was first described by Ferdinand Runge in 1873 as a chronic degenerative pathology of the extensor tendons at their humeral insertion.

The prevalence of Epicondylitis in the general population is 1-3%.

The diagnosis is clinical; the patient complains of lateral elbow pain exacerbated by acupressure and wrist extension against resistance.

Second-level instrumental diagnostics (arthro-CT or arthro-MRI) can be useful

in the differential diagnosis between Epicondylitis and **minor instability of the elbow condition (SMILE)**.

In the second case, the patient's symptoms imply a ligamentous hyperlaxity, especially of the radial band of the **lateral collateral ligament (R-LCL) (FIG. 1)**. This condition leads both to inflammation of the tendon structures that try to counteract it, and to the development of Chondropathy. Clinically, these patients are characterised by a positive SALT and PEPPER (supination and antero-lateral pain/posterior elbow pain by palpation-extension of the radiocapitellar joint) test (4).

– In most cases, Epicondylitis is a self-limiting condition: symptoms frequently regress 12-18 months after onset.

Rest and anti-inflammatories are the first-line therapy. Several conservative treatments have been proposed in the literature, but none have demonstrated superior efficacy (5).

More recent meta-analyses have questioned the role of infiltration in this chronic disease, both in the short and medium term.

The results in the medium term, at 6 months, are not encouraging: it appears that corticosteroid infiltration has no advantage over saline infiltration (6).

However, in the short term, at 4 weeks (7), corticosteroids proved to be a valuable tool in controlling pain, compared to the placebo.

While corticosteroids and shock waves, which have long been used for this pathology, mainly act on pain, new regenerative therapies (PRP and collagen) or possibly R-LCL plication seem to improve the pathology.

Orthoses and shock waves are also effective for short-term (4 weeks) pain control. Regarding regenerative medicine treatments, there are still few reviews and meta-analyses with heterogeneous data.

In contrast, regenerative treatments, laser therapy (not discriminated on the basis of laser power) and botulinum toxin therapy are more effective in control-

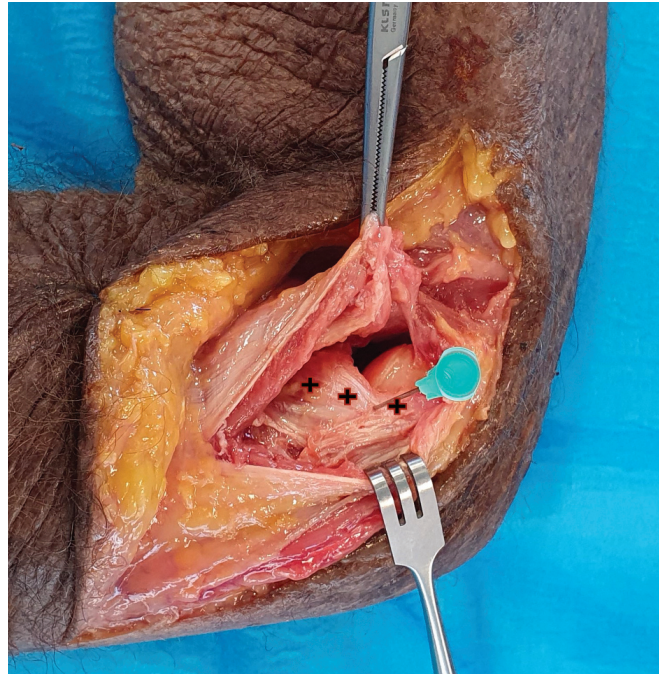


FIG. 1

Anatomical preparation of the osteo-ligament structures of the lateral compartment of the elbow, in particular the lateral collateral ligament band (R-LCL).

ling pain in the medium term (5-26 weeks).

– In the long term, shock wave treatment seems to provide better results in terms of VAS (8) than cortisone treatment; moreover, the effectiveness of shock wave treatment is separate from the type of method used (radial or focal shock waves).

Corrado *et Al.* (9) evaluated the effects of local injections of porcine type 1 collagen (5 injections at weekly intervals) on pain and disability in patients with Epicondylitis.

– The results at 1 and 3 months show a significant reduction in pain and improvement in function compared to the baseline condition of the enrolled patients.

- This pilot study demonstrates that Collagen Medical Devices achieve comparable results to hyaluronic acid and corticosteroids.

In forms resistant to conservative therapy, one must remember ligament instability pathologies and especially chronic soft Tissue ligament injuries.

This instability originates from repeated microtraumatism leading to elongation of the R-LCL and the development of SMILE.

– From an arthroscopic diagnostic point of view, the symptoms are characterised by Annular Drive Through (ADT), defined as the possibility of passing through a shaver measuring 4.2 mm between the head of the radial capitellum and the annular ligament; R-LCL pull-up sign (RPS), defined as the possibility of mobilising the radial band of the lateral collateral to more than 1 cm in the direction of the *capitulum humerii*; Loose Collar Sign (LCS), defined as the exposure of the neck of the radial capitellum beyond the cartilaginous portion when the elbow is flexed at 90°; anterior and/or anteromedial synovitis; Chondropathy of the Lateral Aspect of the Capitellum (CLAC); lateral lesion of the capsule at the radiohumeral joint and antero-peripheral chondropathy of the radial capitellum (10).

If conservative treatment should fail, surgery for the synovectomy and fasciotomy of the short radial extensor carpal tendon, possibly associated with its repair/reinsertion, can be carried out using an open, percutaneous or arthroscopic approach in cases where pure Epicondylitis is suspected.

In the case of SMILE, the treatment of choice is the arthroscopic plication of the radial band of the lateral collateral

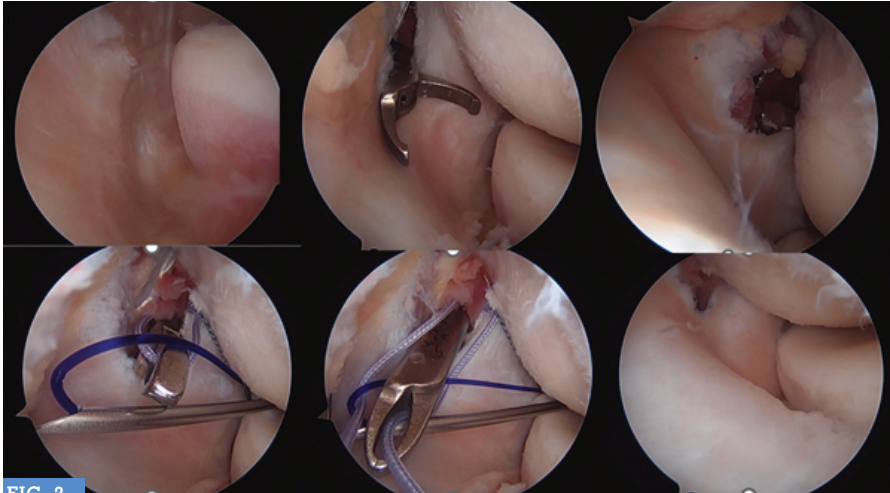


FIG. 2

Image sequence illustrating the arthroscopic R-LCL radial band plication procedure.

ligament and re-tensioning it at humeral level using a single- or multi-suture anchor (11) (FIG. 2).

The technique provides good patient satisfaction and good clinical results. Although this technique has proven effective, it can lead to a post-operative loss of extension.

Therefore, it must be emphasised that this intervention is particularly indicated in cases of pain resistant to conservative therapies.

– Collagen appears to be an excellent solution, especially in terms of cost/benefit analysis for the patient compared to other treatments.

EPITROCHLEITIS OR GOLFER'S ELBOW

As with Epicondylitis, Epitrochleitis (Golfer's Elbow), has been described as a tendinosis of the flexor-pronator mass at its humeral origin in the area where the flexor radius of the carpus and the pronator rotator join.

It has a lower prevalence than Epicondylitis (<1%), and appears to be caused by repeated microtrauma resulting in an angiofibrotic hyperplasia. Those most at risk are carpenters, plumbers and overhead athletes.

– The scientific literature shows that infiltrative therapy for medial pain control

only has a place in the treatment of pain that is not controlled by physical therapies (12); moreover, infiltrative therapies do not appear to accelerate the improvement of pain symptoms. Treatment with corticosteroids proves to be effective compared to the use of local anaesthetics (13), but as in the case of Epicondylitis, an advantage is only clear in pain management in the short term (6 weeks), whereas this advantage is not seen at 3 months and 1 year after treatment. Stahl (13) also points out the disadvantages of local corticosteroid therapy such as adipose atrophy and the skin dyschromia.

Although there is an advantage, albeit limited in time, in the treatment of Epitrochleitis with corticosteroids, the same therapy shows no advantage in the management of pain caused by other pathologies, which can manifest as medial elbow pain, such as **medial collateral ligament (MCL) injury**, ulnar nerve neuritis and Snapping Triceps Syndrome.

Differential diagnosis is therefore crucial.

In the case of MCL injury in professional athletes, PRP infiltrative therapy has been suggested, which seems to show excellent results even in the short term, with an early return to playing sport in 12 weeks.

– Collagen Medical Devices used by means of ultrasound-guided infiltrations also have their place in this treatment space.

At clinical evaluation, patients who are candidates for arthroscopic retensioning do not present a joint deficit, but complain of medial pain that can arise during dynamic manoeuvres without evidence of any major instability.

The lesion may be visible on a basal MRI in important cases or may require second-level examinations such as arthro-CT or arthro-MRI, which enable ligamentous lesions and cartilage defects to be identified with precision.

The medial collateral MCL consists of 3 band (FIG. 3): the front band, the back band and the transverse band.

– The anterior band is the main stabiliser of the elbow in valgus stresses and contributes approximately 30% at 0° of flexion and more than 50% at 90°.

Elongations of the MCL due to repeated microtrauma/stress, as in the case of the above-mentioned LCL, can lead to the development of a painful medial microinstability condition.

Most of these lesions, with reference to the classification by Marinelli *et Al.* (14), fall under instability due to chronic recurrent soft Tissue injuries.

A cadaver study showed that when throwing, tensile forces reach higher values (290N) than those tolerated by the anterior band (260N).

Therefore, repeated actions can lead to the accumulation of microtrauma and result in the development of a chronic elongation of the ligament due to overuse.

The arthroscopic surgical technique involves retensioning using a single- or multiple-suture anchor to retension the anterior band of the MCL.

– This procedure finds its indication in the treatment of patients with recurrent medial pain in the absence of signs of major instability in subjects with low to medium functional demands and with pain resistant to conservative treatment.

TENDINOPATHIES OF THE TRICEPS AND BICEPS BRACHII MUSCLES

To date, little evidence exists in the scientific literature on the use of infiltrative therapies in cases of Tendinopathies involving the triceps or biceps brachii muscles.

– PRP or collagen treatment can be considered for the treatment of Tendinopathies that are resistant to conservative treatment for the m. triceps.

The indication for the treatment of these diseases with PRP infiltrative therapy is still weak and requires further study.

The use of ultrasound-guided PRP infiltrations seems to give good results in the case of distal tendinitis of the biceps brachii muscles (15).

SHOULDER

ROTATOR CUFF TENDINOPATHY

Pathologies affecting the **rotator cuff (RC)** tendons are very common and range from Tendinopathies to partial and complete injuries.

In individuals > 70 years old, the prevalence of these injuries sits at 50%.

Although all tendons of the RC can be affected, the tendon most frequently involved is that of the supraspinatus muscle.

The aetiology can be traumatic; often several intrinsic factors, such as altered vascularisation and connective Tissue pathologies, can lead to pain in these tendons.

Tendon damage is frequently the consequence of intrinsic and extrinsic factors.

– Clinically, patients report pain, especially at night, and functional powerlessness that impairs daily activities, especially in limb elevation between 60° and 120°, more commonly defined as a 'painful arc of motion'.

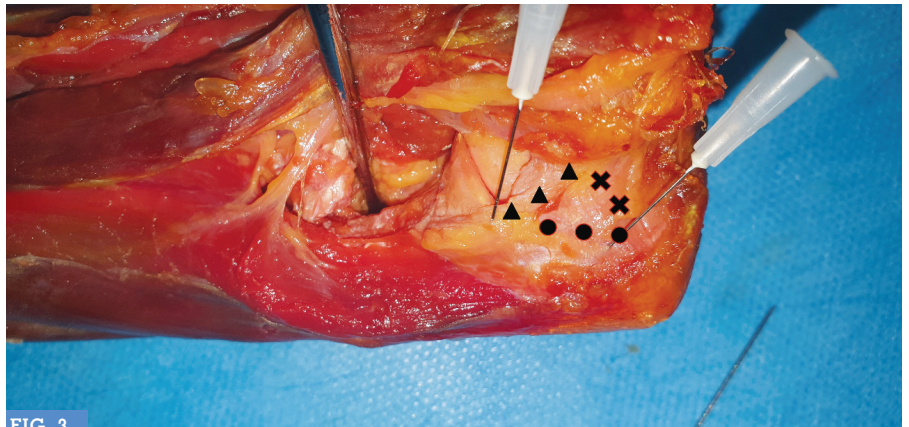


FIG. 3

Anatomical preparation showing the ligamentous complex of the MCL: anterior band (triangles), posterior band (crosses) and transverse band (dots).

– The aim of the treatment is to improve algic symptoms and the functional recovery of the shoulder joint.

In chronic injuries, often with a degenerative basis, conservative treatment is based on the use of anti-inflammatories, rest, physiotherapy, and possible infiltrations. Intra-articular cortisone infiltration is able to resolve painful symptoms in the short term, but may further aggravate the Tendinopathy if infiltrated intra-tendonously.

Its use should not be repeated over time. Should conservative treatment fail, individuals may opt for arthroscopic RC repair surgery.

In the event of the arthrotic degeneration of the entire glenohumeral joint, the implantation of a reverse shoulder prosthesis is the gold standard of treatment.

When it comes to acute post-traumatic injuries, the preferred approach is to attack the pathology with an arthroscopic surgical intervention right from the start, in order to allow a better functional recovery.

– Infiltrative treatment with Collagen Medical Devices finds its indication and place in rotator cuff Tendinopathies, as well as in partial lesions.

Tendinopathy often arises as a result of a functional overload involving cellular

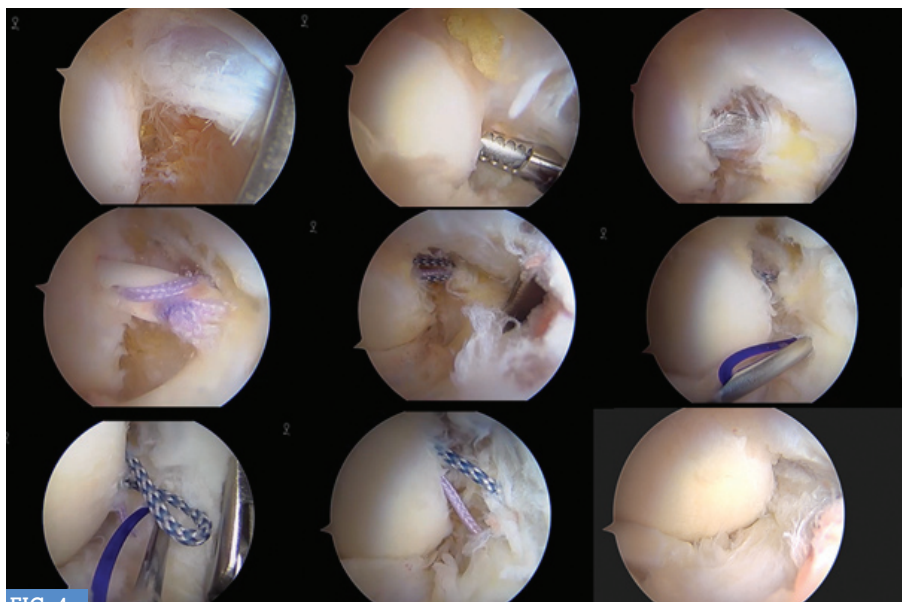


FIG. 4

Image sequence illustrating the arthroscopic MCL plication procedure.

activation and an increase in proteoglycans, and thus an alteration of the collagen matrix.

Corrado *et Al.* (16) showed that, following treatment with a course of 4 infiltrations of porcine type 1 collagen under ultrasound guidance, at the site of least hypoechogenicity of the tendon there was a 30% improvement in tendon quality on ultrasound assessment and an improvement in clinical scores.

– The use of collagen also appears to be effective in the treatment of partial lesions (16).

In these cases, the studies reported in the literature have lower levels of evidence, and are often case reports.

These show that, as early as three months after treatment, regression of the partial RC lesion is evident on both ultrasound and MRI scans.

- At 18 months, however, there is a real repair of the lesion.

– The authors claim that the benefit of infiltrative treatment relates to the stimulation of endogenous collagen synthesis and the reorganisation of damaged pathological fibres.

This hypothesis is confirmed in the work of Kaizawa *et Al.* (17), designed in an animal model, in which 58 shoulders were treated to repair an iatrogenic RC lesion in combination with a human-derived collagen-rich hydrogel.

– In this study, biomechanical analyses showed both higher tensile strength and greater robustness.

During the remodelling phase, the scar Tissue, composed mainly of type 3 collagen, undergoes remodelling from type 3 collagen to type 1 collagen.

A higher ratio of type 1 collagen to type 3 collagen makes the tissue more resistant to breakdown. However, injecting collagen at the repair site did not accelerate healing after RC repair, and semi-quantitative histological analysis did not demonstrate improved collagen organisation at the 8-week follow-up.

ADHESIVE CAPSULITIS

Adhesive capsulitis (frozen shoulder) is a very painful shoulder pathology characterised by a progressive loss of active and passive movement in all planes of the glenohumeral joint, in the absence of mechanical causes.

– This condition affects 2-5% of the population and most frequently the post-menopausal female population, between 40 and 60 years of age.

It is frequently associated with endocrine disorders, mainly Diabetes mellitus, thyroid disorders or in patients with corticotropin deficiency.

Several stages of the pathology have been identified: the initial or inflammatory phase involves significant symptoms of pain but movement is still preserved; it is characterised by a progressive fibroblastic proliferation with an increased production of collagen and the recruitment of inflammatory cells; in the second phase, the freezing stage, the patient complains of progressive stiffness and pain which may last from 2 to 9 months; the third phase, the frozen shoulder stage, is characterised by progressive stiffening with no pain which may last for 4-12 months; the fourth phase, the thawing stage, is where the condition resolves and there is a progressive recovery of ROM (Editor's note: ROM = range of motion) over a time span of 12 to 42 months.

This condition is self-limiting, often bilateral and significantly affects the patient's quality of life. The diagnosis is clinical, with a total impairment of joint movement which is particularly evident during rotations.

– The gold standard of treatment in these cases involves the use of anti-inflammatory drugs, and in particular cortisone infiltration (sub-acromial) or orally during the inflammatory phase, and physiotherapy for a few months during the stiffness phase.

In cases where there is no response to treatment, arthroscopic capsular lysis is

the treatment of choice: tenotomy of the LHB, lysis of the rotator interval, the anterior capsule and, when necessary, the posterior capsule is performed.

The use of collagenases for the treatment of this disease has been studied in animal models.

Karahan *et Al.* (18) show that subacromial infiltration of collagenase is more effective than corticosteroids not only in improving the abduction angle but also on a histochemical and histological level. Furthermore, subacromial infiltration of collagenase does not result in damage to the articular cartilage, demonstrating that the product has not entered the glenohumeral joint.

Further clinical studies are required, however, to evaluate the efficacy, safety and method of administration of this treatment.

CONCLUSIONS

Infiltrative therapy with Collagen Medical Devices is a possible option when it comes to treating lateral elbow pain in cases of a Tendinopathy of the common extensor tendon and pain related to tendon distress of the supraspinatus muscle.

– In addition, infiltrative therapy with Collagen Medical Devices appears to be promising in the treatment of medial pain caused by Tendinopathy of the triceps and biceps brachii muscles.

Further studies are required to investigate its efficacy and mode of administration deeper. ■

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