Ultrasound-guided collagen injections in the treatment of supraspinatus tendinopathy: a case series pilot study.

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Aim of the present pilot study was to verify, for the first time ever, the effects of collagen injections in patients with chronic supraspinatus tendinopathy. Eighteen patients with chronic supraspinatus tendinopathy were treated with a series of 4 type I porcine collagen ultrasound-guided injections, at weekly intervals. The effects were verified at 2-week, 1-month and 3-month follow-up by means of shoulder scoring systems and sonography. A very strong evidence ($p<0.001$) of a statistically significant main effect amongst the multiple clinical observation was found. Ultrasound imaging highlighted improvement in the structural integrity of the tendon. Compared to other injection therapies, collagen injections proved to be at least equally effective, faster acting and safer.

Supraspinatus (SSP) is one of the four muscles that comprise the rotator cuff of the shoulder, the others being subscapularis, infraspinatus, and teres minor. The rotator cuff muscles work as stabilizers of the glenohumeral joint. SSP has its origin from the supraspinous fossa of the scapula and inserts into the greater tuberosity of the humerus. SSP together with the deltoid muscle adducts the arm at the shoulder by fixing the head of the humerus firmly against the glenoid fossa. SSP functions as an abductor for the initial 30° of abduction.

Rotator cuff syndrome (RCS) constitutes a spectrum of disease across a wide range of pathologies associated with injury or degenerative conditions affecting the rotator cuff. RCS is a frequent cause of pain in the shoulder and often brings to functional and labour disabilities. Within RCS, the most common muscle affected is SSP (1).

The definitive cause of SSP tendinopathy remains uncertain. Proposed mechanisms include intrinsic, extrinsic, or combined mechanisms. Extrinsic mechanisms potentially involve attrition of the tendon from contact with bone structures. Intrinsic mechanisms relate to factors that directly influence tendon health and quality, including aging, genetics, postural imbalances, vascular changes, altered loading, and surgery (2, 3). Excessive tissue load remains the most substantial causative factor in the development of SSP tendinopathy. Indeed, the prevailing pathogenesis model suggests that SSP tendinopathy occurs from a primary response of the tendon cells to overload, which results in tendon cells activation and proliferation, increase in proteoglycans, that in their turn cause collagen matrix disruption, and increased vascularisation (4).

Symptoms of RCS include pain at rest and at night, particularly if lying on the affected shoulder, and pain and weakness when lifting heavy objects or rotating the arm. Tenderness or deformity can be detected at physical examination. There is limited evidence for

Key words: shoulder impingement syndrome; rotator cuff; supraspinatus; tendinopathy; collagen; injections

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0393-974X (2020)

any of the tests commonly used in diagnosing SSP tendinopathy as being very sensitive or specific. The empty can test (Jobe's test) and the full can test (Neer test) are the most commonly employed. Patients with SSP tendinopathy may also experience a painful arc of movement between 60° and 120° of abduction, which was found to carry the highest likelihood ratio compared with other provocative tests (5).

There are three imaging options in the evaluation of SSP tendinopathy: plain radiography (X-ray), ultrasound (US), and Magnetic Resonance (MR) with or without arthrography (MRA). US, and US elastography is increasingly gaining in importance for the study of muscles and tendons (6-8). US is an excellent tool for evaluating rotator cuff: it is less expensive than MR and it allows to assess dynamic movements of the shoulder. US may be helpful to detect signs of tendinopathy and to predict improvement or worsening of the tendon health at the tissue level (9). For the shoulder there is a lack of clinically relevant, standardized and reliable US methods for assessing tendinopathy. Since US is highly influenced by clinician experience and technique, standardized US procedures for assessment of structural changes in relation to tendinopathy need to be defined. Based on the literature, consensus was made on definitions of relevant structural changes related to SSP tendinopathy, including thickening, fibrillar disruption and calcifications (10).

There are several treatment options for SSP tendinopathy. Conservative treatment may include rest, activity modification, non-steroidal anti-inflammatory drugs (NSAIDs), and physical therapy, focused on both core and scapular muscles strengthening (11). In about 80% of patients, nonsurgical treatment relieves pain and improves function. If rest, medications, and physical therapy do not relieve pain, patients can undergo injection therapy. Several injection therapy options are available, including injection of corticosteroids, hyaluronic acid (HA), platelet-rich plasma (PRP), and natural irritants (prolotherapy). These injection treatments have shown variable effectiveness and have some criticalities. The combination of injection therapies with physical exercise can reduce recovery time (12).

Type I porcine collagen injections represent a new and refined tool in prevention and therapy of ageing of intra-articular structures, as well as of periarticular ones and of those concerning mesodermic supporting tissues (13-16). Collagen injections can stimulate synthesis, maturation and secretion of endogenous type I collagen, which is always deficient in inflammatory and/or degenerative diseases concerning the musculokeletal system and other anatomical structures of mesodermic origin (17).

Aims of this prospective pilot study were (a) to evaluate the effects of a series of 4 porcine type I collagen US-guided injections (once a week) on pain and disability in a group of patients who have been suffering from SSP tendinopathy for at least 6 months, and, (b) to verify the effects of this injection therapy on the ultrasonographic tendon structure.

MATERIALS AND METHODS

This is a prospective observational pilot study and was carried out at Federico II University Hospital in Naples, Italy. The subjects were all outpatients and we enrolled them from October 2018 to May 2019. All the patients who referred shoulder pain and disability were evaluated to verify the criteria for the enrollment and underwent ultrasound and X-ray. The inclusion criteria were: age >18 years, symptomatic SSP tendinopathy of at least 6 months of duration, pain triggered by overhead activities, positive impingement sign (Neer test), pain with supraspinatus testing (Jobe's test), ultrasound evidence of SSP tendinopathy, and lack of therapy in the last 6 months. The exclusion criteria were; previous shoulder surgery, rotator cuff tears greater than 50% of the tendon thickness, adhesive capsulitis, inflammatory arthritis, acromioclavicular joint pain, X-ray evidence of glenohumeral osteoarthritis, and previous fractures/bone tumors/osteonecrosis of the humerus. 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 met the ethical standards of the local ethics committee.

We selected 20 patients but 2 refused to take part in the trial. Finally, we enrolled 18 patients, of which 11

males and 7 females, with an average age of 52 ± 15 years. For the treatment we planned 4 US-guided injections of 2 ml porcine type I collagen, once a week. Ultrasound-guided injections for SSP tendinopathy have proved to be superior to blind interventions (18). All injections were performed by a single doctor with over 10 years of experience. Injections were performed using an anterior approach. The patients were seated on a chair with the arm in internal rotation to expose as much of the SSP tendon as possible. This position was best achieved by placing the patient's arm behind his back. A 22-gauge needle was directed towards the main hypoechoic/anechoic area of the supraspinatus tendon as guided by US until the tip of the needle was seen in the correct position and then the collagen was injected slowly. Patients were invited to keep the shoulder at rest until the day after. No other treatment was associated with collagen injections.

Patients were evaluated at the time of enrollment (T0), right before the third injection (T0), one month (T2) and three months (T3) after the last injection by means of the Constant-Murley (CM) score and the disability of the arm, shoulder and hand (DASH) questionnaire. An ultrasound evaluation of the rotator cuff was performed by a radiologist with over 20 years of experience at T0 and T3. An ordinal grading scale was assessed. The scale ranged from 0 to 5 (0 = normal tendon; 1 = thickening; 2 = disruption without calcifications; 3 = disruption with microcalcifications; 4 = disruption with macrocalcifications; 5 = partial rupture) (10).

Statistical analysis

Analysis of variance (ANOVA) for repeated measures was used to compare both CM and DASH mean scores with each other at different time points (T0, T1, T2, T3). Afterwards, Bonferroni post-hoc test was employed to perform pairwise comparisons by time points (T0/T1, T0/T2, T0/T3, T1/T2, T1/T3, T2/T3). The confidence interval was established at 95% ($p < 0.05$). With regards to US evaluation, a simple comparison between means ± standard deviation was performed at two different time points (T0 and T3).

CM and DASH mean scores and standard deviations at different time points are listed in Tables I and II respectively. For repeated measures ANOVA provided very strong evidence ($p < 0.001$) of a statistically significant main effect amongst the multiple observation, both as regards to CM score and DASH questionnaire (Fig. 1). The multiple-comparison post-hoc correction (Bonferroni method) highlighted statistically significant differences between CM and DASH mean scores for each pair of time points ($p < 0.05$) except for the pair T2/T3.

US mean scores and standard deviation at T0 and T3 are listed in Table III. We observed a 27.5% reduction in the US mean score between the two time points (Fig. 2).

No adverse event has been described after collagen

Table I. *Descriptive statistics of CM score at different time points.*

	Mean	Std. Deviation
T0	53,11	12,700
T1	62,89	10,775
T2	72,17	10,450
T3	75,00	12,916

Table II. *Descriptive statistics of DASH score at different time points.*

	Mean	Std. Deviation
T0	37,72	19,078
T1	28,89	15,080
T2	19,72	10,063
T3	18,67	13,002

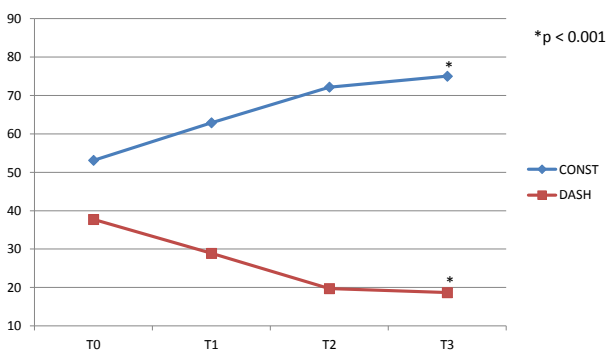

Fig. 1. *Constant score and DASH questionnaire multiple observation at different time points.*

injections, except for some cases of burning sensation at the injection site which resolved spontaneously in a few hours.

SSP tendinopathy is a frequent cause of shoulder pain but its pathophysiology is not fully understood. Treatment of SSP tendinopathy is a challenge for physicians, physical therapists and all the healthcare professionals. The current literature suggests a multidisciplinary approach: NSAIDs, exercise rehabilitation, physical therapy modalities, shock wave therapy, injection therapies, and surgery (19).

In this pilot study we wanted to evaluate the collagen injection therapy in a cohort of 18 subjects affected by SSP tendinopathy (4 US-guided injections, once a week, of type I porcine collagen). The results were evaluated by administering CM score and DASH questionnaire, before the first and the third injections, and one month and three months after the last injection. All the selected patients underwent US evaluation of SSP tendon at the time of enrollment and at 3-month follow-up. At the end of the treatment we observed a statistically significant improvement on pain and function. The positive findings were registered both in objective (CM score) and subjective (DASH questionnaire) outcome measures. Three-month post-treatment US evaluation showed reduced tendon thickness and a trend towards normalization in the tendon sonographic features.

At this stage there are not literature studies about collagen injections in the treatment of SSP tendinopathy. Several injection therapies with substances different from collagen are used in a variety of shoulder conditions and RCS. Most of the literature on injection therapies for RCS focuses on corticosteroids. Although some studies have reported efficacy in reducing pain and improving function, there is little reproducible evidence. In a 2017 meta-analysis on corticosteroid injections in rotator cuff tendinosis, Mohamadi et al. highlighted that corticosteroid injections provide minimal transient pain relief in a small number of

Table III. *Descriptive statistics of US grading score at different time points*.

3h	T0	T3	ΔT0-T3	%ΔT0-T3
Totale score	51	37	-14	-27,5
Mean	2,8	2	-0,8	
Standard deviation	1,5	1,9		

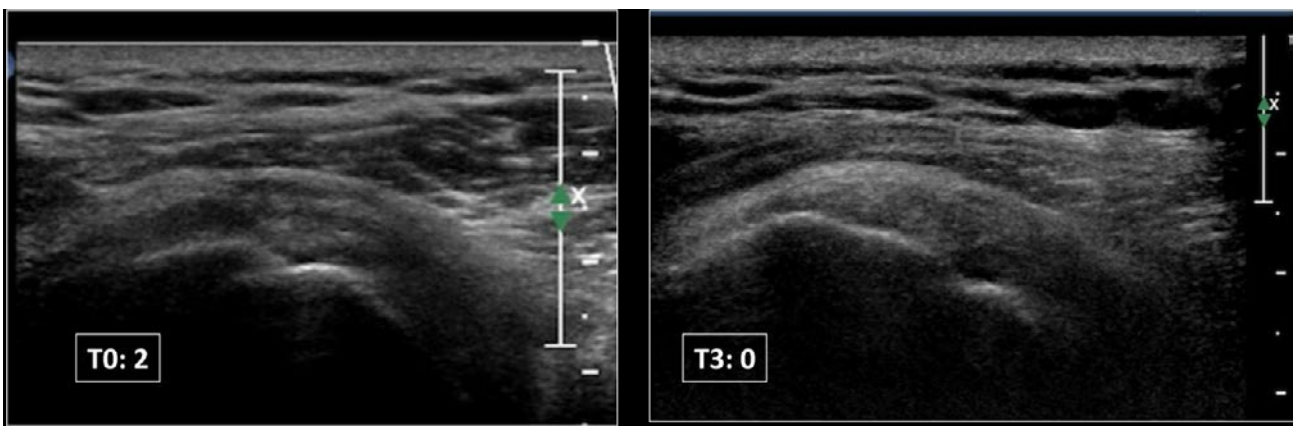

Fig. 2. *Sonographic assessment of a patient with supraspinatus tendinopathy who switched from a pre-treatment score of 2 to a post-treatment score of 0.*

patients, that they cannot modify the natural history of the disease, and that, given the potential to accelerate tendon degeneration associated with corticosteroids, they have limited appeal (20). Another injection therapy that has been described for the treatment of chronic painful rotator cuff tendinopathy is prolotherapy or hypertonic dextrose injection. The literature on prolotherapy in the shoulder is limited to small retrospective series. A recent prospective, randomized, double blinded clinical trial by Cole et al. aimed to compare glucose prolotherapy injection into the SSP tendon with corticosteroid injection into the subacromial bursa for treatment of SSP tendinopathy. Authors concluded that glucose prolotherapy offers no additional benefit over subacromial corticosteroid injection (21). The use of PRP for the treatment of RCS has been extensively studied through multiple RCTs and meta-analyses.

The variability on the composition of PRP produced make it difficult to draw any definitive conclusions on the efficacy of PRP treatment of RCS. In 2019 Hurley et al. performed a systematic review of the literature on the use of PRP for non-operative treatment of RCS. The authors stated that the currently limited available evidence suggests that in the short term PRP injections may not be beneficial and that interpretation of the literature is confounded by the lack of reporting of the cytology and characteristics of PRP (22). The peritendinous administration of hyaluronic acid (HA) has shown promising results in clinical trials including patients with various disorders involving tendons in the rotator cuff. However, the superiority of HA over other interventions in scales assessing pain is controversial, and few studies have evaluated the efficacy of HA in the treatment of lesions affecting a tendon. In their 2017 multicenter, randomized, controlled trial, Flores et al. found that combined treatment with peritendinous 2% HA injections and physical therapy promotes faster recovery in patients with SSP tendinopathy (23). Recently mesenchymal stem cells (MSCs) derived from bone marrow and adipose have garnered the most attention for use in RCS. Nevertheless, only a few studies have examined the effect of augmentative MSC therapy on RC repair in humans, with early results suggesting a possible improvement in repair site healing (24).

Eventually, several newer injection therapies have gained popularity in the treatment of SSP tendinopathy. However, the existing evidence for each type of therapy is currently limited and some of them have shown a lack of safety due to their potential side effects (25). Another limitation of several injection therapies for tendinophaties is the high cost, which make them accessible only to a limited number of patients.

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 stated that this is a pilot study and that it is currently the only study in the literature on the effectiveness of collagen injection therapy in SSP tendinopathy.

In conclusion, this pilot study has shown that a series of 4 type I porcine collagen US-guided injections, at weekly intervals, is able to reduce significantly pain symptoms and improve the function in a group of 18 patients with chronic SSP tendinopathy. Moreover, the positive clinical findings have been confirmed by ultrasonographic features. Finally, we can state that there are grounds for carrying out an RCT to confirm our preliminary data.

REFERENCES

1. Sambandam SN, Khanna V, Gul A, Mounasamy V. Rotator cuff tears: An evidence based approach. World J Orthop. 2015; 6(11):902-18
2. Corrado B, Ciardi G. Facioscapulohumeral distrophy and physiotherapy: a literary review. J Phys Ther Sci 2015; 27(7):2381-5. doi: 10.1589/jpts.27.2381.
3. Corrado B, Ciardi G, Servodio Iammarrone C, Arpino G. Home Exercise Program is an effective tool in improving upper limb function and quality of life in breast cancer survivors: A retrospective observational study. Journal of Human Sport and Exercise. 2018; 13(4)926-39. doi: https://doi.org/10.14198/jhse.2018.134.19
4. Cook J, Purdam C. Is compressive load a factor in the development of tendinopathy? Br J Sports Med 2012; 46(3):163e8
5. Hermans J, Luime JJ, Meuffels DE, et al. Does this patient with shoulder pain have rotator cuff disease?: the rational clinical examination systematic review. JAMA 2013; 310:837-47.
6. Domenichini R, Pialat JB, Podda A, Aubry S. Ultrasound elastography in tendon pathology: s tate of the art. Skeletal Radiol. 2017; 46(12):1643-1655. doi: 10.1007/s00256-017-2726-2.

7. Vola EA, Albano M, Di Luise C, Servodidio V, Sansone M, Russo S, Corrado B, Servodio Iammarrone C, Caprio MG, Vallone G. Use of ultrasound shear wave to measure muscle stiffness in children with cerebral palsy. J Ultrasound. 2018; 21(3):241-247. doi: 10.1007/s40477-018-0313-6.
8. Corrado B, Albano M, Caprio MG, Di Luise C, Sansone M, Servodidio V, Russo S, Vallone G, Vola EA, Servodio Iammarrone C. Usefulness of point shear wave elastography to assess the effects of extracorporeal shockwaves on spastic muscles in children with cerebral palsy: an uncontrolled experimental study. MLTJ 2019; 9(1):124-130. doi: 10.32098/mltj.01.2019.04
9. Vasishta A, Kelkar A, Joshi P, Hapse R. The value of sonoelastography in the diagnosis of supraspinatus tendinopathy-a comparison study. Br J Radiol. 2019; 92(1095):20180951. doi: 10.1259/bjr.20180951.
10. Ingwersen KG, Hjarbaek J, Eshoej H, Larsen CM, Vobbe J, Juul-Kristensen B. Ultrasound assessment for grading structural tendon changes in supraspinatus tendinopathy: an inter-rater reliability study. BMJ Open. 2016; 6(5):e011746. doi: 10.1136/bmjopen-2016-011746
11. Lewis J. Rotator cuff related shoulder pain: Assessment, management and uncertainties. Man Ther 2016; 23:57-68. doi: 10.1016/j.math.2016.03.009.
12. Lin MT, Chiang CF, Wu CH, Huang YT, Tu YK, Wang TG. Comparative effectiveness of injection therapies in rotator cuff tendinopathy: a systematic review, pairwise and network meta-analysis of randomized controlled trials. Archives of Physical Medicine and Rehabilitation. Arch Phys Med Rehabil. 2019; 100(2):336-349.e15. doi: 10.1016/j.apmr.2018.06.028.
13. Furuzawa-Carballeda J, Lima G, Llorente L, et al. Polymerized-type I collagen downregulates inflammation and improves clinical outcomes in patients with symptomatic knee osteoarthritis following arthroscopic lavage: a randomized, double-blind, and placebo-controlled clinical trial. ScientificWorldJournal. 2012; 2012:342854. doi: 10.1100/2012/342854
14. Martin LS, Massafra U, Bizzi E, Migliore A. 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"). BMC Musculoskelet Disord. 2016; 17:94. doi: 10.1186/s12891-016-0948-4
15. Nitecka-Buchta A, Walczynska-Dragon K, Batko-Kapustecka J, Wieckiewicz M. Comparison between collagen and lidocaine intramuscular injections in terms of their efficiency in decreasing myofascial pain within masseter muscles: a randomized, single-blind controlled trial. Pain Res Manag. 2018; 2018:8261090. doi: 10.1155/2018/8261090
16. Corrado B, Mazzuoccolo G, Liguori L, Chirico VA, Costanzo M, Bonini I, Bove G, Curci L. Treatment of lateral epicondylitis with collagen injections: a pilot study. MLTJ 2019; 9(4):584-589. DOI: 10.32098/mltj.04.2019.14
17. Randelli F, Menon A, Giai Via A, et al. Effect of a collagen-based compound on morpho-functional properties of cultured human tenocytes. Cells. 2018; 7(12). pii: E246. doi: 10.3390/cells7120246
18. Abat F, Campos J, Torras J, Madruga M, Planells G, Rodriguez-Baeza A. Comparison of ultrasound-guided versus blind interventions for supraspinatus tendinopathy: a cadaveric study. MLTJ 2019; 9(3):328-337. doi: 10.32098/mltj.03.2019.06
19. Andres BM, Murrell GAC. Treatment of tendinopathy: what works, what does not, and what is on the horizon. Clin Orthop Relat Res 2008; 466(7):1539–1554.
20. Mohamadi A, Chan JJ, Claessen FM, Ring D, Chen NC. Corticosteroid injections give small and transient pain relief in rotator cuff tendinosis: a meta-analysis. Clin Orthop Relat Res. 2017; 475(1):232-243. doi: 10.1007/s11999-016-5002-1.
21. Cole B, Lam P, Hackett L, Murrell GAC. Ultrasound-guided injections for supraspinatus tendinopathy: corticosteroid versus glucose prolotherapy - a randomized controlled clinical trial. Shoulder Elbow. 2018; 10(3):170-178. doi: 10.1177/1758573217708199
22. Hurley ET, Hannon CP, Pauzenberger L, Fat DL, Moran CJ, Mullett H. Nonoperative treatment of rotator cuff disease with platelet-rich plasma: a systematic review of randomized controlled trials. Arthroscopy. 2019; 35(5):1584-1591. doi: 10.1016/j.arthro.2018.10.115.
23. Flores C, Balius R, Álvarez G, Buil MA, Varela

L, Cano C, Casariego J. Efficacy and Tolerability of Peritendinous Hyaluronic Acid in Patients with Supraspinatus Tendinopathy: a Multicenter, Randomized, Controlled Trial. Sports Med Open. 2017; 3(1):22. doi: 10.1186/s40798-017-0089-9.

24. Kim YS, Sung CH, Chung SH, Kwak SJ, Koh YG. Does an Injection of Adipose-Derived Mesenchymal Stem Cells Loaded in Fibrin Glue Influence Rotator Cuff Repair Outcomes? A Clinical and Magnetic Resonance Imaging Study. Am J Sports Med. 2017; 45(9):2010-2018. doi: 10.1177/0363546517702863.
25. Lin KM, Wang D, Dines JS. Injection Therapies for Rotator Cuff Disease. Orthop Clin North Am. 2018; 49(2):231-239. doi: 10.1016/j.ocl.2017.11.010.