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EVALUATION OF THE EFFECT OF ST500® ON FUNCTIONALITY IN PATIENTS WITH TENDON INJURY OF THE LONG HEAD OF THE BICEPS: A POST-MARKET INTERVENTIONAL, SINGLE-ARM CLINICAL INVESTIGATION

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ABSTRACT – *Objective:* Shoulder pain is often associated with injuries to the long head of the biceps tendon (LHBT). First-line treatment typically involves medications and physical therapy. Hyaluronic acid (HA), as an alternative treatment, promotes viscoelasticity in tendons, and skin-penetrating peptides offer a non-invasive strategy for its transdermal delivery.

This investigation aimed to evaluate the effect of a topically applied medical device (ST500®), composed of hydrogel containing HA and peptide mixture, on shoulder functionality and symptoms in patients with LHBT injury assessed with Constant-Murley Score (CMS).

Patients and Methods: This study is a post-market interventional, single-arm clinical investigation. 35 patients were enrolled at the screening visit (V-1) and then treated with the first application at V1 (defined as baseline visit). Patients continued the application of ST500® twice a week for six weeks and were followed up for three visits (V2-V4) at weeks 2, 6, and 10, respectively. Satisfaction rate and tolerance were evaluated using the Likert scale. High-resolution ultrasound (HRUS) was used to determine tendon lesions and effusion. A digital goniometer was used to assess the range of motion (ROM) of the arm and to register the elevation and abduction degrees.

Results: 33 patients were included in the analysis. The treatment with ST500® was safe and well-tolerated, with only one patient reporting mild local swelling. The Likert Scale showed that patients were satisfied with the product. The efficacy was assessed by observing the increase of CMS from V1 to V3-V4. After the treatment, comparing V1 and V4 (end of the study), CMS significantly improved (p<0.0001); in addition, ROM values showed significant improvement in elevation (p=0.032) and abduction (p<0.0001). Furthermore, HRUS imaging showed a significant reduction in effusion (p<0.0001) and a decrease in the total number of lesions, although not significant (p=0.157).

Conclusions: a 6-week topical application of ST500® significantly improved pain and function in patients with LHBT injury. Further studies are needed, comparative and in a larger population, to investigate the device's effectiveness in patients affected by different types of tendinopathies.

KEYWORDS: Clinical investigation, Hyaluronic acid, Peptides, ST500®, Tendon injury.

INTRODUCTION

Shoulder pain is a very common musculoskeletal disorder, with a 1-year prevalence in the general population estimated between 20% and 50%[1,2]. Due to its anatomical features, the long head of the biceps tendon (LHBT) is often affected by conditions mainly caused by biceps instability, inflammatory, degenerative, and traumatic events[3]. It has been estimated that LHBT injuries represent 96% of all rotator cuff (RC) tears[4], and since they occur in up to 50% of the population, damage to the LHBT is a prevalent clinical problem[5]. LHBT lesions rarely appear in isolation and are often linked to other shoulder pathologies[6]. Age and overuse, typically associated with repetitive overhead activities, contribute to tendon degeneration and tendinopathy[7]. Because the common symptoms of LHBT injury are similar to those of RC tears, diagnosing isolated LHBT injury is usually difficult[8-10]. LHBT injury can be debilitating and often impacts an individual's quality of life due to persistent pain, long periods of rest, and modification to daily work and sports activities. First-line treatment of LHBT disorders is non-operative and generally includes rest, use of non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroid injections (CSIs) into the bicipital sheath, and physical therapy[11]. Failed non-operative management indicates the need for surgical treatment[12]. However, prolonged use of anti-inflammatory drugs can have side effects, and surgical procedures can lead to complications.

Therefore, alternative treatments are needed to improve symptoms and shoulder functionality while reducing the risk of complications associated with pain medications. Hyaluronic acid (HA) is a naturally occurring polymer that belongs to a group of heteropolysaccharides called glycosaminoglycans. In addition to being present in several other tissues, HA is largely found in the extracellular space of tendons, where it promotes viscoelasticity and tendon gliding by reducing adhesions[13]. Thanks to its high ability to bind with water molecules, one of its main functions is to lubricate joints and muscles. The unique viscoelastic nature of HA, along with its biocompatibility and non-immunogenicity, has led to its use in various clinical applications, including the supplementation of joint fluid in arthritis and tendinopathies[14]. Indeed, exogenous HA is unlikely to induce adverse reactions, even after repeated administrations. Although intra-articular injection of HA has shown[4,15] high efficacy in the treatment of shoulder tendinopathy without severe adverse effects, it is nevertheless an invasive procedure that must be carefully performed by an orthopedic physician. In contrast, the topical application of HA-based formulations could be an alternative, non-invasive, and more comfortable approach for patients suffering from LHBT injury, helping to avoid potential complications associated with invasive HA injections.

Several studies in the literature have shown that HA alone hardly penetrates intact skin due to its hydrophilicity and high molecular weight. Therefore, carriers are often needed to deliver the macromolecule into the deepest layers of the skin[16]. Among the types of carriers used, skin-penetrating peptides are attracting increasing attention as a non-invasive strategy for transdermal delivery of macromolecules such as HA[17,18]. Oligopeptides, or more simply "peptides", are short chains of amino acids joined together by peptide bonds. Peptides contribute to skin conditioning, allowing better passage of topically applied macromolecules such as HA. ST500® (**Supplementary Figure 1**) is a medical device composed of a hydrogel containing HA and a peptide mixture, designed to be applied to intact skin to limit the physiological degeneration of tissues and improve joint and tendon function. The mechanism of action outlined for ST500® (Contrad Swiss SA, Lugano, Switzerland) consists of mechanically improving tendon function through the action of the HA included in the formulation. Based on the characteristics and toxicological features of the ingredients/components, the medical device ST500® has been shown to be safe for topical application from a biological risk perspective.

Therefore, the aim of this single-arm, post-market, confirmatory, interventional clinical investigation was to evaluate the effect of HA-based gel containing a peptide mixture, topically applied, on shoulder functionality and symptoms in patients affected by LHBT lesions.

PATIENTS AND METHODS

Patient Enrollment and Follow-Up

This is a post-market interventional, single-arm clinical investigation. The study was conducted according to ISO 14155:2020, Good Clinical Practice guidelines, local laws and obligations, and the World Medical Association Declaration of Helsinki. The study was approved by the independent Ethics Committee of Insubria (number CTD-SW ST500, date of approval 12/10/2021). A signed copy of the informed consent was collected from each enrolled patient.

Inclusion criteria were: age ≥18 years, presence of symptomatic, unilateral or bilateral LHBT injury of mild or moderate severity, assessed according to Constant-Murley Score (CMS≤70)[19]. Exclusion criteria were: other clinical conditions of the shoulder requiring surgical intervention, partial and full rotator cuff tears, LHBT lesions classified as type IV, V, or VI, previous shoulder surgery, immune system illnesses, uncontrolled systemic diseases, infectious or inflammatory processes or damaged skin near the area of treatment, ongoing cutaneous allergies, serious and chronic pathological skin conditions, allergy to device components, any other systemic or local therapy for the treatment of LHBT injury (only physiotherapy allowed) or other inflammatory diseases or painful states, drug and/or alcohol abuse, mental issues, pregnancy or breastfeeding.

Patients who were seen at the Orthopedic and Traumatology Unit of the Luini Confalonieri Hospital, Luino (Italy), between November 2021 and October 2022 were screened for the study. A total of 35 patients satisfied the study criteria and were enrolled.

Each patient underwent a screening visit (V-1), a baseline visit (V1), and three scheduled visits (V2-V4). Two weeks (V2) after V-1, the patient was contacted by telephone to monitor product safety and compliance with the protocol. V3 was conducted at the end of treatment after six weeks, and V4 was a follow-up visit after ten weeks. At V1, V3 and V4, the CMS was collected.

Both satisfaction rate and tolerance to the treatment were evaluated using a five-point Likert scale[20]: (1) Strongly disagree; (2) Disagree; (3) Neither agree nor disagree; (4) Agree; (5) Strongly agree.

Treatment with ST500®

ST500® is a medical device, a water and glycerin-based monodose gel containing sodium hyaluronate and a peptide mixture in a 1.5 mL monodose vial. ST500® is a hydrogel formulated as follows: demineralized water, glycerin, propylene glycol, Polyethylene Glycol (PEG)-40 hydrogenated castor oil, phenoxyethanol, carbomer, xanthan gum, disodium EDTA, panthenol, sodium hydroxide, sodium hyaluronate, benzoic acid, dehydroacetic acid, ethylhexylglycerin, SH-Polypeptide-29 and SH-Tripeptide-1.

The treatment was performed twice weekly for six weeks for each target area. After the first application at the baseline visit (V1), the treatment was repeated for two days per week for six weeks at home. Patients were required to apply the treatment twice a week every three days. The patients applied the content of the single-dose vial to the painful area using a dedicated patch, which was kept in place for 4 to 8 hours.

Assessment of Tendon Effusion, Lesion and Shoulder Range of Movement

High-resolution ultrasound (HRUS) was used to determine tendon effusion. The instrument used was the LogiQ, General Electric (GE) Healthcare (Chicago, IL, USA). The presence of effusion and lesion was classified as missing, absent, mild, and moderate.

A digital goniometer was used to assess the range of motion (ROM) and to register the elevation and abduction degrees. The assessment of tendon effusion, lesion, and shoulder ROM was always performed by the same orthopedic doctor.

Statistical Analysis

Sample size calculation was performed assuming a minimum difference of 20% between CMS (equal to 10 points) evaluated between V-1 and V4, with a standard deviation (SD) of 16, a medium Pearson's correlation of 30% between two time points, and a type I error of 5% Thirty-one patients were considered sufficient to reach a statistical power greater than 80%.

Additionally, planning to enroll a total of 35 subjects would allow for a 10% drop-out rate.

The distribution of continuous variables was tested for normality using the Kolmogorov-Smirnov test. Based on the result of this test, a *t*-test for paired data was applied to evaluate the change of CMS between study visits.

A Wilcoxon signed-rank test was applied to data on effusion levels assessed by HRUS, while the differences between proportions in the presence of lesions were analyzed using McNemar's test.

Statistical power calculation and analysis were performed using SAS® software, v. 9.4 (Cary, NC, USA), and GraphPad Prism software, v. 10.1 (La Jolla, CA, USA). Differences were considered statistically significant for p-values <0.05.

RESULTS

Enrolled Patients

As determined by the sample size calculation, 35 patients were enrolled in this study. Thirty-three patients completed the study correctly. All the patients were included in the Safety Analysis Set (SAS) because they all started the treatment. Two patients (5.7%) were not included in the analysis: one due to non-compliance, and the other underwent surgery.

Demographic and Other Characteristics of the Enrolled Patients

Table 1 shows the baseline characteristics of the enrolled patients.

Table 1. Baseline characteristics of the enrolled patients.

		Overall (N=35)
Age (year)		
	Mean±SD	55±14
	Median (Min-Max)	57 (22-76)
Sex		
Male	**N (%)**	12 (34.3)
Female	**N (%)**	23 (65.7)
Ethnic group		
Caucasian	**N (%)**	35 (100.0)
Smoking status		
Non-smoker	**N (%)**	31 (88.6)
Smoker	**N (%)**	4 (11.4)
Abuse of alcohol		
No	**N (%)**	35 (100.0)

SD: standard deviation.

Concerning the medical history, five patients (16.7%) had a neoplasm, and eight patients (22.9%) had cardiovascular disorders. There were also two patients (5.7%) with a history of endocrine disorders, three patients (8.6%) with metabolism and nutrition disorders, three patients (8.6%) with respiratory, thoracic, and mediastinal disorders, two patients (5.7%) with gastrointestinal disorders, four patients (11.4%) with musculoskeletal and connective tissue disorders, and five patients (16.7%) with a history of surgical procedures.

Safety and Satisfaction Rate Assessment

During the study, six patients experienced at least one adverse event, with one classified as possibly related (“light local swelling”). No signs of allergy, lesions, or infections were recorded throughout the study’s duration.

Patient satisfaction assessed through a Likert Scale at the end of the study showed a mean value of 3.8±1.0 (median value 4.0), indicating that patients were satisfied with the study product.

Efficacy of the ST500®

The primary endpoint was to evaluate the clinical performance of ST500® in increasing shoulder functionality in patients affected by LHBT injury in terms of the difference (%) in the CMS between V1 (baseline visit) and V4. Compared to baseline values, there was a mean increase of 8.3 points in the CMS

at the end of the study (4 weeks after the end of a 6-week treatment period) (Table 2). Nevertheless, the improvement defined by the primary endpoint (20% difference, equal to 10 points) was not achieved. However, all differences between V1 and final values at V3 and V4 were statistically significant (p<0.0001). A significant difference in the CMS values was also observed between V3 and V4 (p<0.0001). Figure 1A shows the CMS values from V1 to V4.

Table 2. Constant-Murley Score.

CMS Total Score	N	Mean (SD)	*p*-value (paired *t*-test)
V1	**33**	52.9 (7.5)	
Difference V1-V3	**33**	5.3 (4.3)	<0.0001
V3	**33**	58.2 (6.2)	
Difference V1-V4	**33**	8.3 (5.5)	<0.0001
V4	**33**	61.2 (7.5)	
Difference V3-V4	**33**	3.0 (3.6)	<0.0001

CMS: Constant-Murley Score

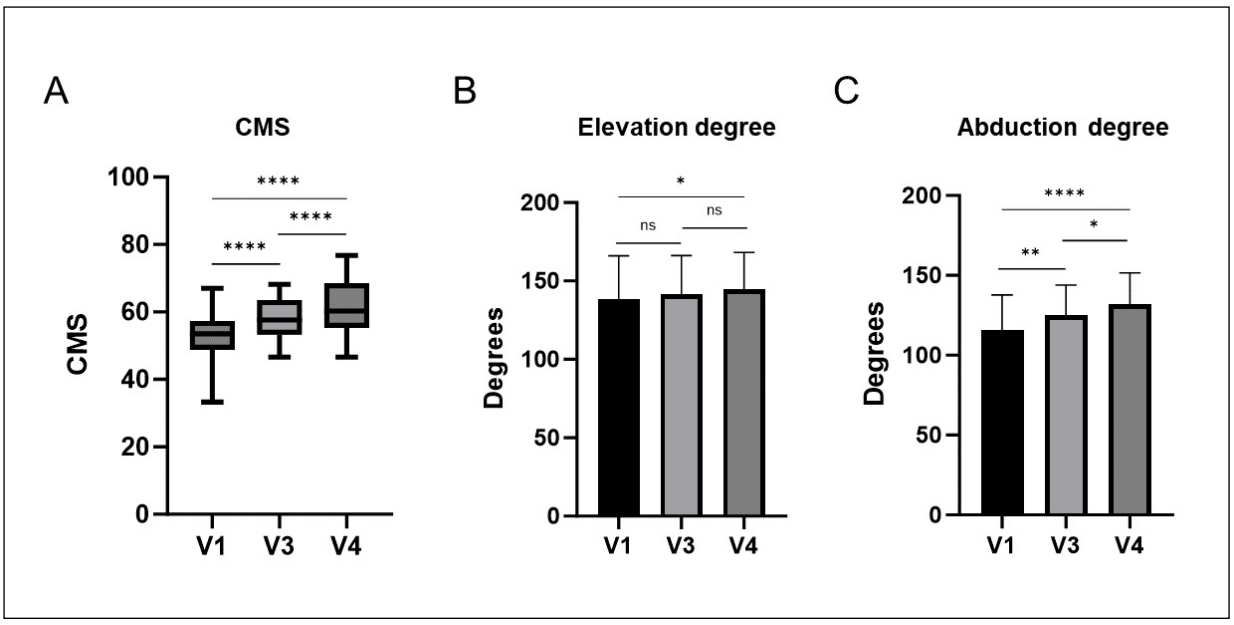

Figure 1. A, difference (%) in the Constant-Murley Score (CMS) between V1 (baseline visit) and V4 (follow-up visit after ten weeks). Range of motion values, expressed as elevation (**B**) and abduction (**C**) degree at the baseline visit (V1), at six weeks (V3), and at ten weeks after treatment (V4). *p≤0.05; **p≤0.01; ***p≤0.0001; not significant (ns).

The performance of ST500® was also assessed through HRUS and range of motion. HRUS showed a significant improvement in terms of tendon effusion at the end of the treatment (V3, p=0.0016) and at the end of the study (V4, p<0.0001) compared to baseline (Table 3).

Range of motion values, expressed as elevation and abduction degree, showed a significant difference in shoulder movement before (V1) and after treatment (V4) (p=0.0320 and p<0.0001, respectively) (Tables 4 and 5). Abduction degree values showed an increase from V1 to V3 (p=0.0042) and from V3 to V4 (p=0.0460) (Table 5), while elevation degree did not improve significantly when comparing V1-V3 and V3-V4 (p=0.1856 and p=0.1245). Figures 1B and 1C show the range of motion values of elevation and abduction degree.

Table 3. High-resolution ultrasound assessment of tendon effusion.

Effusion		V1	V3	V4	p^1	p^2
					0.0016	<0.0001
Missing	N (%)		1 (2.9)			
Absent	N (%)	1 (3.0)	7 (20.6)	13 (39.4)		
Mild	N (%)	18 (54.5)	20 (58.8)	20 (60.6)		
Moderate	N (%)	14 (42.4)	6 (17.6)			

Wilcoxon signed-rank test was applied for this data to calculate *p*-values. [1]: *p*-value for the comparison between median value or proportion at V1 and median value or proportion at V3. [2]: *p*-value for the comparison between median value or proportion at V1 and median value or proportion at V4.

Table 4. Elevation range of motion (ROM).

Elevation ROM	N	Mean (SD)	*p*-value (paired *t*-test)
V1	33	138.3 (27.8)	
Difference V1-V3	33	3.2 (13.5)	0.1856
V3	33	141.5 (24.8)	
Difference V1-V4	33	8.3 (5.5)	0.0320
V4	33	144.5 (23.7)	
Difference V3-V4	33	3.03 (11.04)	0.1245

Table 5. Abduction range of motion (ROM).

Abduction ROM	N	Mean (SD)	*p*-value (paired *t*-test)
V1	33	115.9 (21.8)	
Difference V1-V3	33	8.9 (16.7)	0.0042
V3	33	124.8 (19.1)	
Difference V1-V4	33	15.8 (19.0)	<0.0001
V4	33	131.7 (20.0)	
Difference V3-V4	33	6.8 (18.9)	0.0460

Assessment of Regenerative Processes

The assessment of the presence of lesions by HRUS revealed that at V1, 12 (36.4%) had a lesion, while 8 patients (23.5%) had a lesion at V3. However, the difference between proportions, analyzed with McNemar's test, was not statistically significant (p=0.1025) (Table 6). The same pattern was observed in terms of difference between V1 and V4, with presence of lesion occurring in 8 patients (24.2%) at V4 (p=0.1573) (Table 6).

Table 6. Presence of lesions assessed by high-resolution ultrasound assessment.

Lesion		V1	V3	V4	p^1	p^2
					0.1025	0.1573
Missing	**N (%)**		1 (2.9)			
Absent	**N (%)**	21 (63.6)	25 (73.5)	25 (75.8)		
Present	**N (%)**	12 (36.4)	8 (23.5)	8 (24.2)		

McNemar's test was applied for this data to calculate *p*-values. [1]: *p*-value for the comparison between median value or proportion at V1 and median value or proportion at V3. [2]: *p*-value for the comparison between median value or proportion at V1 and median value or proportion at V4.

DISCUSSION

The present study demonstrated that the topical application of ST500® is safe and effective in alleviating symptoms in patients with LHBT lesions. The product was well tolerated by patients, with no local reactions observed except for one case of light local swelling, which was classified as possibly device-related. Although the study was statistically adequate, further studies enrolling a larger cohort of patients and including a control group are highly recommended.

At the end of the study, patients were generally satisfied with the product. This is likely due to the non-invasive, topical, and convenient method of administration and the improvement in shoulder functionality. Although the performance data showed that a 6-week treatment with ST500® did not result in the hypothesized 10-point improvement in shoulder functionality on the CMS, there was a significant increase of 8 points on the CMS at the end of the study compared to the baseline visit. By stratifying patients based on the presence of more or less pain before treatment, the CMS improved slightly, but still not enough to reach the primary endpoint.

By the end of the study, effusion within the biceps long head tendon sheath had significantly improved, and there was a significant increase in shoulder range of movement.

The product is particularly innovative for the treatment of tendinopathies, especially due to its versatility for topical use. Similar devices such as AI500® and CR500®, which contain HA with added peptides, have been used to treat joint diseases and have shown[21-23] efficacy in reducing inflammation and pain commonly found in joint diseases.

The improvement in functional parameters observed in this study is likely mediated by the activity of the HA and peptides mixture of the ST500®, which act synergistically to promote tendon homeostasis. HA modulates the expression of inflammatory mediators[24], while the skin-conditioning peptides[17] in the formulation aid its skin permeation and support the anti-degenerative effects on tendons. One of the peptides, SH-Polypeptide-29, is derived from interleukin-3 (IL-3), a potent growth-promoting cytokine involved in various cell activities such as growth, differentiation and apoptosis[25]. The second peptide, SH-Tripeptide-1, is synthetically produced to mimic a portion of fibroblast growth factor 1 (FGF-1), which stimulates tendon healing by boosting cell proliferation and angiogenesis[26-28]. In addition, FGF-1 is also known to stimulate fibroblast proliferation and collagen formation[29,30], promoting tendon matrix deposition.

In this context, SH-Polypeptide-29 peptide and SH-Tripeptide-1 may stimulate tendon cell proliferative processes and promote tendon matrix synthesis. Notably, key growth factors like FGF-1 tend to lose their biological functional activity rapidly when injected as free solutions, limiting their application in tendon healing[26]. Tendon healing is a long-lasting process requiring factors to be adsorbed or encapsulated in materials that protect them from degradation and preserve their biological activity. Therefore, appropriate materials and substrates must be developed to deliver and release them in damaged tendons. The use of a patch, as in the present study, allows for modulated dosage of active biomolecules and convenient, repeated application for the patient.

Regarding the study limitations, the absence of randomization cannot completely exclude the possibility of a natural and physiological improvement of LHBT injury. The efficacy of the product should be confirmed in a larger cohort of patients. However, data extrapolated from the analyses, which possess sufficient statistical power, suggest that the improvement is likely due to the treatment itself.

CONCLUSIONS

In conclusion, while a longer treatment period may be necessary to confirm the clinical performance of the medical device in terms of CMS, a 6-week topical application of ST500® significantly improved tendon effusion and shoulder movement in patients with LHBT lesions. Further studies are warranted to investigate the effectiveness of the product in a larger cohort of patients with a spectrum of tendon diseases, possibly in comparison with gold-standard treatments.

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Authors' Contributions:

E.P.: investigation, writing-review, and editing; L.F.: analysis, investigation, data curation, writing, original draft preparation; L.B.: investigation, writing-review and editing, supervision, funding acquisition.

Conflict of Interest:

Dr. Luca Forte is an employee of Contrad Swiss SA. The other authors do not have competing interests.

Informed Consent:

Informed consent was obtained from all subjects involved in the study.

Ethics Approval:

The study was approved by the Ethics Committee of Insubria (CTD-SW ST500, No. 87, 12/10/2021).

Data Availability:

The data that support the findings of this study are openly available at: https://osf.io/5fkac/?view_only=869c5794877b-4c83859a778b2b5f4586.

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REFERENCES

1. Walker-Bone K, Palmer KT, Reading I, Coggon D, Cooper C. Prevalence and impact of musculoskeletal disorders of the upper limb in the general population. Arthritis Rheum 2004; 51: 642-651.
2. Djade CD, Porgo TV, Zomahoun HTV, Perrault-Sullivan G, Dionne CE. Incidence of shoulder pain in 40 years old and over and associated factors: A systematic review. Eur J Pain 2020; 24: 39-50.
3. Churgay CA. Diagnosis and Treatment of Biceps Tendinitis and Tendinosis. Am Fam Physician 2009; 80: 470-476.
4. Harwood MI, Smith CT. Superior labrum, anterior–posterior lesions and biceps injuries: diagnostic and treatment considerations. Prim Care Clin Off Pract 2004; 31: 831-855.
5. Gomoll AH, Katz JN, Warner JJP, Millett PJ. Rotator cuff disorders: Recognition and management among patients with shoulder pain. Arthritis Rheum 2004; 50: 3751-3761.
6. Nho SJ, Strauss EJ, Lenard BA, Provencher MT, Mazzocca AD, Verma NN, Romeo AA. Long Head of the Biceps Tendinopathy: Diagnosis and Management. J Am Acad Orthop Surg 2010; 18: 645-656.
7. Hsu D, Anand P, Mabrouk A, Chang KV. Biceps Tendon Rupture. StatPearls; 2024.
8. Chen CH, Hsu KY, Chen WJ, Shih CH. Incidence and severity of biceps long head tendon lesion in patients with complete rotator cuff tears. J Trauma 2005; 58: 1189-1193.
9. Kajiwara D, Ochiai N, Hashimoto E, Hirosawa N, Akimoto N, Nojima D, Shimada Y, Ise S, Ohtori S. Imaging and histological evaluation of the long head of the biceps tendon in the presence of different types of rotator cuff tears. BMC Musculoskelet Disord 2023; 24: 230.
10. Diplock B, Hing W, Marks D. The long head of biceps at the shoulder: a scoping review. BMC Musculoskelet Disord 2023; 24: 232.
11. Longo UG, Loppini M, Marineo G, Khan WS, Maffulli N, Denaro V. Tendinopathy of the tendon of the long head of the biceps. Sports Med Arthrosc Rev 2011; 19: 321-332.

12. Frank RM, Cotter EJ, Strauss EJ, Jazrawi LM, Romeo AA. Management of Biceps Tendon Pathology: From the Glenoid to the Radial Tuberosity. J Am Acad Orthop Surg 2018; 26: e77-e89.
13. Kaux JF. Hyaluronic acid and tendon lesions. Muscles Ligaments Tendons J 2016; 5: 264-269.
14. Abate M, Schiavone C, Salini V. The Use of Hyaluronic Acid after Tendon Surgery and in Tendinopathies. BioMed Res Int 2014; 2014: 783632.
15. Cai Y, Sun Z, Liao B, Song Z, Xiao T, Zhu P. Sodium Hyaluronate and Platelet-Rich Plasma for Partial-Thickness Rotator Cuff Tears. Med Sci Sports Exerc 2019; 51: 227-233.
16. El-Refaie WM, Elnaggar YSR, El-Massik MA, Abdallah OY. Novel Self-assembled, Gel-core Hyaluosomes for Non-invasive Management of Osteoarthritis: In-vitro Optimization, Ex-vivo and In-vivo Permeation. Pharm Res 2015; 32: 2901-2911.
17. Chen M, Gupta V, Anselmo AC, Muraski JA, Mitragotri S. Topical delivery of hyaluronic acid into skin using SPACE-peptide carriers. J Control Release 2014; 173: 67-74.
18. Menegatti, S, Zakrewsky M, Kumar S, Sanchez De Oliveira J, Muraski JA, Mitragotri S. De Novo Design of Skin-Penetrating Peptides for Enhanced Transdermal Delivery of Peptide Drugs. Adv Healthc Mater 2016; 5: 602-609.
19. Constant CR, Gerber C, Emery RJH, Søjbjerg JO, Gohlke F, Boileau P. A review of the Constant score: Modifications and guidelines for its use. J Shoulder Elbow Surg 2008; 17: 355-361.
20. 5-Point Likert Scale. in Handbook of Disease Burdens and Quality of Life Measures. In: Preedy, V.R., Watson, R.R. (eds) Handbook of Disease Burdens and Quality of Life Measures. Springer, New York, NY; 2010.
21. Colombini, A, Doro G, Ragni E, Forte L, de Girolamo L, Zerbinati F. Treatment with CR500® improves algofunctional scores in patients with knee osteoarthritis: a post-market confirmatory interventional, single arm clinical investigation. BMC Musculoskelet Disord 2023; 24: 647.
22. Masotti G, Fisher N, Sorrentino J. Un nuovo prodotto topico a base di peptidi e acido ialuronico per la mialgia e il dolore articolare. Giornale Italiano di Ortopedia e Traumatologia 2023; 49: 50-58.
23. Bonanzinga, T, De Sensi AG, Balzarini B, Doro G, Bertolino L, Forte L, Kon E. An Innovative Topical Medical Device with Hyaluronic Acid and Polypeptides in Patients with Reduced Knee Function. J Funct Morphol Kinesiol 2024; 9: 31.
24. Altman R, Bedi A, Manjoo A, Niazi F, Shaw P, Mease P. Anti-Inflammatory Effects of Intra-Articular Hyaluronic Acid: A Systematic Review. Cartilage 2019; 10: 43-52.
25. Pant H, Hercus TR, Tumes DJ, Yip KH, Parker MW, Owczarek CM, Lopez AF, Huston DP. Translating the biology of β common receptor-engaging cytokines into clinical medicine. J Allergy Clin Immunol 2023; 151: 324-344.
26. Yun YR, Won JE, Jeon E, Lee S, Kang W, Jo H, Jang JH, Shin US, Kim HW. Fibroblast Growth Factors: Biology, Function, and Application for Tissue Regeneration. J Tissue Eng 2010: 1: 218142.
27. Moya ML, Garfinkel MR, Liu X, Lucas S, Opara EC, Greisler HP, Brey EM. Fibroblast Growth Factor-1 (FGF-1) Loaded Microbeads Enhance Local Capillary Neovascularization. J Surg Res 2010; 160: 208-212.
28. Uriel S, Brey EM, Greisler HP. Sustained low levels of fibroblast growth factor-1 promote persistent microvascular network formation. Am J Surg 2006; 192: 604-609.
29. Da Fonseca TS, Silva GF, Guerreiro-Tanomaru JM, Sasso-Cerri E, Tanomaru-Filho M, Cerri PS. Mast cells and immunoexpression of FGF-1 and Ki-67 in rat subcutaneous tissue following the implantation of Biodentine and MTA Angelus. Int Endod J 2019; 52: 54-67.
30. Silva GF, Guerreiro-Tanomaru JM, da Fonseca TS, Bernardi MIB, Sasso-Cerri E, Tanomaru-Filho M, Cerri PS. Zirconium oxide and niobium oxide used as radiopacifiers in a calcium silicate-based material stimulate fibroblast proliferation and collagen formation. Int Endod J 2017; 50 Suppl 2: e95-e108.