D. Schumann *et al.*
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RESEARCH ARTICLE **Open Access**

Efficacy of ultrasound-guided peritendinous injections of hyaluronic acid with peptides for the management of chronic tendinopathies: A prospective, open-label study

David Schumann
Manamohan Ghandra

Abstract
Background: Tendinopathies are common musculoskeletal disorders for which definitive management has yet to be determined. Hyaluronic acid (HA), a major component of the extracellular matrix, and lubricating peptides could constitute a combined therapeutic approach.
Aim: To assess the effectiveness and safety of US-guided peritendinous injections of a HA plus peptide formulation in the management of pain in patients with chronic Achilles, patellar, and lateral elbow tendinopathy.
Materials and Methods: Patients with chronic tendinopathy failing conventional therapy were enrolled in this prospective, open-label, single-center trial. A total of 81 tendons (40 Achilles, 25 lateral elbow, 16 patellar) belonging to 62 patients were treated with three US-guided peritendinous injections of 2 mL of HA + peptide once a week. The primary outcome was the change in pain intensity measured on a Visual Analogue Scale (VAS) from baseline (V1) to days 7 (V2), 14 (V3), and 56 (V4). Secondary outcomes were based on US measurements of tendon sagittal thickness and neovascularization (Power Doppler). Adverse events were evaluated throughout the study period.
Results: For each type of tendinopathy, significant decreases from baseline were observed in the mean VAS pain score at all follow-up visits ($p< 0.001$). This improvement was maintained at the final 56-day follow-up. Significant differences were detected by US in tendon thickness and neovascularization at V3 and V4 compared with baseline ($p< 0.05$), with the only exception being neovascularization of the patellar tendon at V3 ($p = 0.125$), which became significant by V4 ($p = 0.016$). The treatment was well tolerated, and no serious adverse events related to the study drug were reported.
Conclusions: US-guided peritendinous injections of HA with peptides provide significant and sustained pain relief, alongside improvements in tendon structure as assessed by ultrasound. This combination therapy appears to be a safe and effective option for the management of chronic, painful tendinopathies.
Keywords: Tendinopathy, hyaluronic acid, peptides, ultrasound-guided injection, pain management

*Correspondence:
Manamohan Ghandra
MD, Orthopaedic Surgeon, Injection & Orthopedic Center,
ALT hospital Johor, Malaysia

Introduction

Tendinopathies are common degenerative diseases that lead to long-term disability in millions of people around the world [1]. Contemporary pathophysiological models focus on a failed healing response with increased tenocyte apoptosis, disorganized collagen matrix with an altered type I/type III ratio and pathological neoangiogenesis [2-4]. Activity-related pain, focal tenderness, swelling and reduced range of motion (ROM) are present in patients, independently of the involved tendon [5, 6]. These alterations are reliably confirmed ultrasonographically - tendon thickening, focal hypoechogenicity and neovascularization (on Power Doppler) can be detected with elevated sensitivity and specificity - thus US has been widely recognized also as a tool for diagnostic and image-guided treatment [7-10]. There is diagnostic certainty, but no gold standard treatment: eccentric loading can induce remodeling of tendon structure in some patients but produces widely different results [4].

Pharmacological interventions, for example NSAIDs, have a debated role since they achieve only temporary symptomatic improvement and have some potential harmful long-term effects [11]. Corticosteroid injections have short-term benefit, but are usually inferior to conservative management over time and might impair the structural integrity of tendon, increasing the risk of rupture [12, 13].

In this gap of treatment, in several clinical studies peritendinous hyaluronic acid (HA) injection has been reported as an interesting option [14, 15]. HA is a key component of extracellular matrix and synovial fluid, contributing to viscoelasticity and hydration, and in vitro evidence indicates that it promotes tenocyte survival and supports type I collagen production [16, 17]. Its rheological behavior cushions at low speeds and lubricates during rapid, repetitive motion, producing a protective “gliding effect” on tendon surfaces [18, 19]. Small peptides that adhere to tendon surfaces may complement HA by acting as boundary lubricants that reduce friction and peritendinous adhesions [20].

The objective of this prospective, open-label study was to evaluate the efficacy and safety of three ultrasound-guided peritendinous injections of a combined HA-peptide formulation (patented Reganemed Gmbh) for pain relief in chronic Achilles, patellar, and lateral elbow tendinopathies.

Materials and methods

Study Design

This is an investigator-driven, prospective, open-label, monocentric trial aimed at evaluating the efficacy of ultrasound-guided peritendinous injections of HA+peptide (20 mg/ml HA+10 mg/ml) in pain relief in patients with chronic tendinopathies. Local Institutional Ethics Committee approval was obtained for the study protocol, and the study was conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonisation Guideline for Good Clinical Practice. All patients gave written informed consent before inclusion.

Participants

Patients were enrolled between 2020 and 2023, during a three-year period. Adults (≥18 years old) of either sex with a diagnosis of chronic Achilles, patellar, or lateral elbow tendinopathy were eligible. The diagnosis was considered to be confirmed by tendon swelling, pain on palpation, painful restricted motion, and a VAS pain score ≥50 mm. Symptom duration had to be at least six weeks, and patients must not have responded to traditional conservative treatment (such as physical therapy, NSAIDs) for at least one month before screening.

The exclusion criteria were recent tendon surgery, lactation or pregnancy, and uncontrolled diabetes mellitus (glycosylated hemoglobin >6.7%). Systemic or topical corticosteroids in the month prior, or NSAID therapy in the 10 days prior to the first injection, were also exclusion criteria. Concomitant use of analgesics or physiotherapeutic measures was not allowed during the study. Age, sex, weight, height, and metabolic risk factors (hypothyroidism, diabetes, hypercholesterolemia) were obtained for all subjects.

Intervention: Ultrasound-Guided Injection Procedure

All of the injections were given under ultrasound guidance by a senior orthopaedic surgeon. Each patient received three peritendinous injections at weekly intervals. A total of 2 mL of a sterile combination of hyaluronic acid and peptides (RecoverTendo™) in a pre-filled syringe was used for each injection.

For patellar tendinopathy: While in the supine position and with the knee slightly flexed, a 22G needle was placed under US guidance toward the distal lower pole of the patella. The needle was positioned in a cranio-caudal direction at an angle of 45° toward Hoffa's fat pad, and the solution was slowly infiltrated into the peritendinous space.

Outcome Measures

The primary efficacy endpoint was the change in pain intensity from baseline (V1) as measured by a 10-cm VAS (0 = no pain, 10 = extreme pain). Assessments were performed at baseline and at each follow-up visit: day 7 (V2), day 14 (V3), and day 56 (V4).

Secondary endpoints included changes in tendon morphology and vascularity as assessed by US at V3 and V4. Tendon structure was evaluated by measuring maximum sagittal thickness (in mm). Neovascularization was assessed using Power Doppler and graded on a semi-quantitative scale from 0 to 3, where 0 = no vascularization, 1 = mild, 2 = moderate, and 3 = severe, according to the method described by Hoksrud et al. (reference 24 from the provided list, though the author name is corrected here for accuracy). A clinical evaluation for signs of inflammation (redness, warmth, swelling, tenderness, crepitus) was also performed at each visit. Safety was assessed by monitoring and recording all adverse events (AEs), whether related to the study treatment or not, throughout the study period.

Statistical Analysis

Statistical analyses were performed using SAS® software (SAS Institute, Inc., Cary, NC, USA). As this was an exploratory, open-label study, a formal a priori sample size calculation was not performed; however, the enrolled population was deemed sufficient to detect significant changes at a 5% significance level. All tests of hypotheses were two-sided. VAS pain scores and tendon properties (thickness, vascularity grade) from baseline to each follow-up visit were

compared between groups by the two-sample T-test or Wilcoxon rank-sum test for non-normal outcomes. Statistical significance was considered at $p \leq 0.05$. An analysis of covariance (ANCOVA) model was used to assess the mean difference in the pain reduction from baseline to day 56, controlling for the following potential confounders existing at baseline: sex, age, type of tendon treated, number of injections, and number of metabolic risk factors. The safety population included all patients who received at least one injection; the efficacy population had all those who received at least one injection and had at least one post-baseline assessment.

Results

A total of 62 patients were treated and analyzed, with 81 painful tendons included. The distribution of involved tendons was: 40 Achilles (49.3%), 25 lateral elbow (30.9%), and 16 patellar (19.8%) (Figure 1).

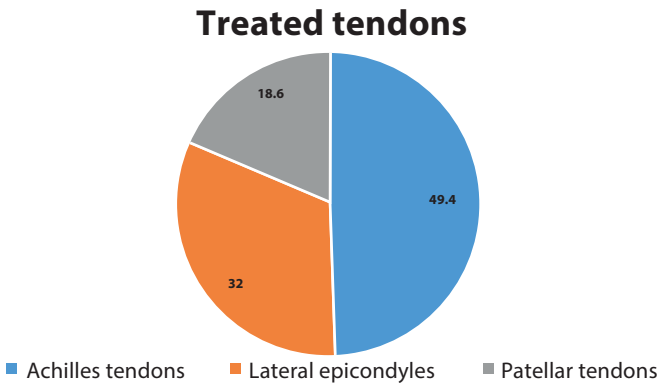

Fig 1: Subject disposition

The study group was composed of 47 (75.8%) males and 15 (24.2%) females, with a mean age of 46.1 years (SD ±12.5). The patient demographics are shown in Table 1. Hypercholesterolemia (16.1%) and hypothyroidism (9.7%) were the most common metabolic riskfactors, whereas the vast majority of patients (98.4%) did not have diabetes.

Table 1: Baseline Demographic and Clinical Characteristics of the Study Population (N=62)

Characteristic	Value
Age (years)	
Mean ± SD	46.1 ± 12.5
Range	18–75
Gender, n (%)	
Male	47 (75.8)
Female	15 (24.2)
Weight (kg)	
Mean ± SD	74.0 ± 9.8
Range	55–91
Height (cm)	
Mean ± SD	158.3 ± 8.7
Range	145–182
Metabolic Risk Factors, n (%)	
Hypercholesterolemia	10 (16.1)
Hypothyroidism	6 (9.7)
Diabetes mellitus	1 (1.6)
Tendons Treated (n=81), n (%)	
Achilles tendon	40 (49.4)
Lateral elbow tendon	25 (30.9)
Patellar tendon	16 (19.8)

SD: Standard deviation

A statistically significant reduction in mean VAS pain scores from baseline was observed at all post-treatment time points (V2, V3, and V4) for each type of tendinopathy ($p < 0.001$) (Figure 2).

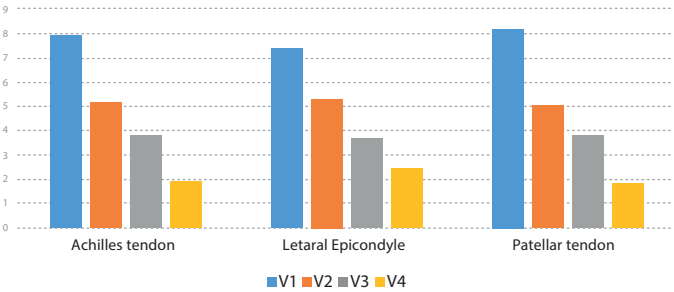

Fig 2: Mean pain intensity on VAS at each evaluation, by site of treated tendon. Legend: V1 Baseline; V2 Day 7; V3 Day 14; V4 Day 56

In the Achilles tendinopathy group (n=40), mean VAS decreased progressively from 7.72 cm (SD ±1.24) at baseline to 7.36 cm (SD ±0.88) at V2, 3.72 cm (SD ±1.98) at V3, and 2.07 cm (SD ±2.10) at V4.

In the patellar tendinopathy group (n=16), mean VAS decreased from 7.79 cm (SD ±0.93) at baseline to 5.13 cm (SD ±1.48) at V2, 3.78 cm (SD ±1.64) at V3, and 2.40 cm (SD ±2.09) at V4.

In the lateral elbow tendinopathy group (n=25), mean VAS decreased from 8.19 cm (SD ±0.79) at baseline to 5.25 cm (SD ±1.80) at V2, 3.39 cm (SD ±1.91) at V3, and 1.74 cm (SD ±2.17) at V4.

The ANCOVA model, adjusting for sex, age, tendon type, number of injections, and risk factors, confirmed that the magnitude of pain reduction was similar across all three tendon groups, with no statistically significant differences detected between them ($p > 0.05$).

A significant reduction in mean sagittal tendon thickness from baseline was observed at both V3 and V4 for all tendinopathy types ($p < 0.05$) (Figure 3).

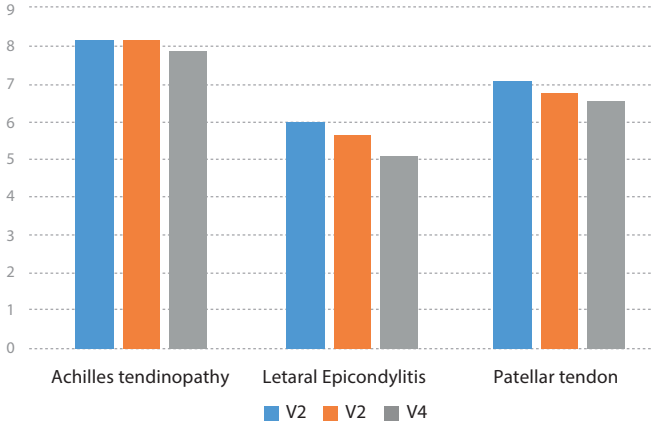

Fig 3: Mean sagittal thickness on US at each evaluation by site of treated tendon. Legend: V1 Baseline; V3 Day 14; V4 Day 56

For the Achilles tendon, thickness decreased from 9.33 mm (SD ±2.24) at baseline to 8.37 mm (SD ±2.37) at V3 and 8.40 mm (SD ±2.23) at V4. Patellar tendon thickness reduced from 7.15 mm (SD ±1.59) to 6.48 mm (SD ±1.33) at V3 and 6.26 mm (SD ±1.46) at V4. Lateral elbow tendon thickness decreased from 6.18 mm (SD ±0.73) to 5.70 mm (SD ±0.90) at V3 and 5.28 mm (SD ±0.87) at V4.

Power Doppler assessment revealed a significant decrease in neovascularization grade for each tendon at V3 and V4 when compared to baseline (Figure 4).

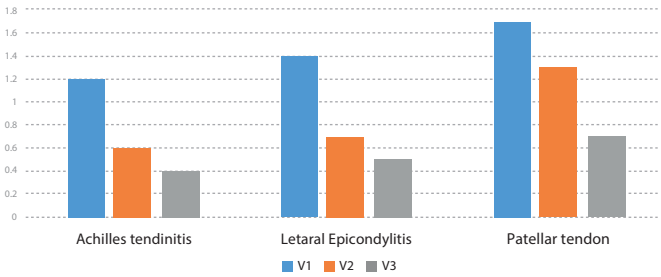

Fig 4: Mean vascularization on US at each evaluation by site of treated tendon. Legend: V1 Baseline; V3 Day 14; V4 Day 56

The sole exception was for the patellar tendon at the V3 time point, where the reduction did not reach statistical significance ($p = 0.125$). However, by the final follow-up at V4, the reduction in neovascularization for the patellar tendon was significant compared to baseline ($p = 0.016$).

The treatment was very well tolerated. No serious adverse events were reported during the study. One patients experienced non-serious adverse events: episode of mild lumbosciatic syndrome. Neither event was considered by the investigators to be related to the study medication (HA + peptide).

Discussion

Tendinopathies represent a substantial burden in primary and specialist care, accounting for a considerable proportion of musculoskeletal consultations, yet the search for a universally accepted gold-standard treatment continues [18]. Although the efficacy and safety of hyaluronic acid in the treatment of osteoarthritis are well established [21, 22], the evidence for its application in the treatment of tendon diseases is relatively limited. This study aimed to investigate the effectiveness and safety of a novel peritendinous HA and peptide solution in patients with chronic painful Achilles, patellar, and lateral elbow tendinopathy.

The main result in our study was a marked, long-lasting reduction of pain after three once-a-week injections of HA + peptide. This is consistent with the findings of Kumai et al. [23], who found that a single injection of high-molecular-weight HA induced rapid but short-term pain relief in patientszz with insertional tendinopathies. In this study, we observed an immediate analgesic effect and a gradual and persistent reduction in pain at the 56-day follow-up visit. This sustained effect allows us to hypothesize that a series of three injections can produce a prolonged outcome that goes beyond the immediate post-injection phase, probably influencing the underlying pathological process in patients who do not respond to conventional therapies. Our findings are further corroborated by Frizziero et al. [4], who reported that three injections of HA provided superior and more rapid clinical improvement compared to extracorporeal shock-wave therapy (ESWT) in patients with rotator cuff tendinopathy, with effects lasting up to three months.

The improvement in pain was paralleled by favorable structural changes observed on ultrasound. We noted a significant reduction in tendon thickness and a marked decrease in neovascularization, a finding consistent with the work of Lynen et al. [24]. In their randomized trial on mid-portion Achilles tendinopathy, they found that peritendinous HA injections were superior to ESWT in reducing neovascularization, with over half of the HA-treated patients showing an absence of Power Doppler signal at follow-up. In our study, the reduction in neovascularization was significant for all tendons at the final follow-up, reinforcing the potential of HA to positively influence the aberrant healing response characteristic of chronic tendinopathy. The transient lack of significant neovascularization reduction at V3 in the patellar tendon subgroup may be attributed to the smaller sample size (n=16) and warrants further investigation in a larger cohort.

The observed clinical and structural improvements may be attributable to the synergistic mechanisms of the two active components. Hyaluronic acid is known to restore the viscoelastic properties of the extracellular matrix, promote a favorable collagen I/III ratio by tenocytes, and reduce friction through its "gliding effect" [17, 18]. The retention of peptides binding to the tendon surface might further contribute to this effect, by means of a boundary lubrication mechanism that reduces surface-to-surface contact and consequently shear stress [20]. The marked decrease in tendon thickness and vascularity we demonstrated could be a deferred effect of this mechanical shielding, since friction reduction might diminish microtrauma with subsequent downregulation of local inflammatory and angiogenic responses.

There are number of limitations to this study which should be considered when interpreting the results. First, the open-label, single-center design without a control group introduces the potential for bias, particularly the placebo effect. Second, the follow-up period of 56 days, while adequate to assess short-term efficacy, is insufficient to determine the long-term durability of the treatment effect. Third, the study lacked functional outcome scores specific to each tendon (e.g., VISA-A for Achilles, VISA-P for patellar tendinopathy), which would have provided a more comprehensive assessment of patient-reported functional recovery. Finally, the sample size, while adequate for detecting a significant signal, was not based on a formal power calculation, and the results, particularly for the smaller patellar tendon subgroup, should be considered preliminary.

Despite these limitations, this study provides clinically valuable evidence that a course of three US-guided peritendinous injections of a HA + peptide combination is a safe, well-tolerated, and effective intervention for reducing pain and improving tendon structure in the short-term management of chronic lower and upper limb tendinopathies.

Conclusion

The findings of this prospective, open-label study demonstrate that ultrasound-guided peritendinous injections of hyaluronic acid combined with peptides lead to significant and clinically meaningful reductions in pain, accompanied by objective improvements in tendon thickness and neovascularization as assessed by ultrasound. This therapeutic effect was consistent across Achilles, patellar, and lateral elbow tendinopathies. The excellent safety profile and high tolerability observed suggest that this combination therapy represents a viable and effective option in the management of patients suffering from chronic, painful tendinopathies who have not responded to conventional

treatments.

Conflict of Interest Statement: The authors declare no conflicts of interest.

Funding Statement: This research received no external funding.

Ethical Approval: This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Local Institutional Ethics Committee. Written informed consent was obtained from all participants prior to their inclusion in the study.

Informed Consent: Written informed consent was obtained from all participants.

Data Availability Statement: The data supporting this study are available from the corresponding author upon reasonable request.

Author Contributions: M.G. and D.S. contributed equally to this work, including study design, data collection, analysis, manuscript writing, and final approval.

References

1. Maffulli N, Longo UG, Loppini M. Current treatment options for tendinopathy. Expert Opinion on Pharmacotherapy. 2010;11(13):2177-2186.
2. Del Buono A, Battery L, Denaro V, Maccauro G, Maffulli N. Tendinopathy and inflammation: Some truths. International Journal of Immunopathology and Pharmacology. 2011;24(1 Suppl 2):45-50.
3. Cook JL, Purdam CR. Is tendon pathology a continuum? A pathology model to explain the clinical presentation of load-induced tendinopathy. British Journal of Sports Medicine. 2009;43(6):409-416.
4. Frizziero A, Vittadini F, Barazzuol M, Gasparre G, Finotti P, Meneghini A, et al. Extracorporeal shockwaves therapy versus hyaluronic acid injection for the treatment of painful non-calcific rotator cuff tendinopathies: Preliminary results. Journal of Sports Medicine and Physical Fitness. 2016;57(9):1162-1168.
5. Abate M, Silbernagel KG, Siljeholm C, Di Iorio A, De Amicis D, Salini V, et al. Pathogenesis of tendinopathies: Inflammation or degeneration? Arthritis Research and Therapy. 2009;11(3):235.
6. Ackermann PW, Renström P. Tendinopathy in sport. Sports Health. 2012;4(3):193-201.
7. Paavola M, Kannus P, Järvinen TA, Khan K, Józsa L, Järvinen M. Achilles tendinopathy. Journal of Bone and Joint Surgery American Volume. 2002;84(11):2062-2076.
8. Gisslen K, Alfredson H. Neovascularisation and pain in jumper's knee: A prospective clinical and sonographic study in elite junior volleyball players. British Journal of Sports Medicine. 2005;39(7):423-428.
9. Ohberg L, Lorentzon R, Alfredson H. Neovascularisation in Achilles tendons with painful tendinosis but not in normal tendons: An ultrasonographic investigation. Knee Surgery, Sports Traumatology, Arthroscopy. 2001;9(4):233-238.
10. Knobloch K, Kraemer R, Lichtenberg A, Jagodzinski M, Gossling T, Richter M, et al. Achilles tendon and paratendon microcirculation in midportion and insertional tendinopathy in athletes. American Journal of Sports Medicine. 2006;34(1):92-97.
11. Kaux JF, Forthomme B, Le Goff C, Crielaard JM, Croisier JL. Current opinions on tendinopathy. Journal of Sports Science and Medicine. 2011;10(2):238-253.
12. Coombes BK, Bisset L, Vicenzino B. Efficacy and safety of corticosteroid injections and other injections for management of tendinopathy: A systematic review of randomised controlled trials. Lancet. 2010;376(9754):1751-1767.
13. Smidt N, van der Windt DA, Assendelft WJ, Deville WL, Korthals-de Bos IB, Bouter LM. Corticosteroid injections, physiotherapy, or a wait-and-see policy for lateral epicondylitis: A randomised controlled trial. Lancet. 2002;359(9307):657-662.
14. Meloni F, Milia F, Cavazzuti M, Doria C, Lisai P, Profili S, et al. Clinical evaluation of sodium hyaluronate in the treatment of patients with supraspinatus tendinosis under echographic guide: Experimental study of periarticular injections. European Journal of Radiology. 2008;68(1):170-173.
15. Petrella RJ, Cogliano A, Decaria J, Mohamed N, Lee R. Management of tennis elbow with sodium hyaluronate periarticular injections. Sports Medicine, Arthroscopy, Rehabilitation, Therapy and Technology. 2010;2(1):4.
16. Abate M, Schiavone C, Salini V. The use of hyaluronic acid after tendon surgery and in tendinopathies. BioMed Research International. 2014;2014:783632.
17. Wiig M, Abrahamsson SO, Lundborg G. Effects of hyaluronan on cell proliferation and collagen synthesis: A study of rabbit flexor tendons in vitro. Journal of Hand Surgery American Volume. 1996;21(4):599-604.
18. Akasaka T, Nishida J, Araki S, Shimamura T, Amadio PC, An KN. Hyaluronic acid diminishes the resistance to excursion after flexor tendon repair: An in vitro biomechanical study. Journal of Biomechanics. 2005;38(3):503-507.
19. Kolodzinskyi MN, Zhao C, Sun YL, An KN, Thoreson AR, Amadio PC, et al. The effects of hylan G-F 20 surface modification on gliding of extrasynovial canine tendon grafts in vitro. Journal of Hand Surgery American Volume. 2013;38(2):231-236.
20. Kisiday J, Jin M, Kurz B, Hung H, Semino C, Zhang S,et al. Self-assembling peptide hydrogel fosters chondrocyte extracellular matrix production and cell division: Implications for cartilage tissue repair. Proceedings of the National Academy of Sciences of the United States of America. 2002;99(15):9996-10001.
21. Monticone M, Frizziero A, Rovere G, Vittadini F, Uliano D, La Bruna S, et al. Hyaluronic acid intra-articular injection and exercise therapy: Effects on pain and disability in subjects affected by lower limb joints osteoarthritis. European Journal of Physical and Rehabilitation Medicine. 2016;52(3):389-399.
22. Bruyère O, Cooper C, Pelletier JP, Maheu E, Rannou F,

Branco J, et al. A consensus statement on the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis algorithm for the management of knee osteoarthritis: From evidence-based medicine to the real-life setting. Seminars in Arthritis and Rheumatism. 2016;45(4 Suppl):S3-S11.
23. Kumai T, Muneta T, Tsuchiya A, Shiraishi M, Ishizaki Y, Sugimoto K, et al. The short-term effect after a single injection of high-molecular-weight hyaluronic acid in patients with enthesopathies: A preliminary study. Journal of Orthopaedic Science. 2014;19(4):603-611.
24. Lynen N, De Vroey T, Spiegel I, Van Ongeval F, Hendrickx NJ, Stassijns G. Comparison of peritendinous hyaluronan injections versus extracorporeal shock wave therapy in the treatment of painful Achilles tendinopathy: A randomized clinical efficacy and safety study. Archives of Physical Medicine and Rehabilitation. 2017;98(1):64-71.
25. Hoksrud A, Ohberg L, Alfredson H, Bahr R. Color Doppler ultrasound findings in patellar tendinopathy (jumper's knee). American Journal of Sports Medicine. 2008;36(9):1813-1820.
26. Frizziero A, Salamanna F, Della Bella E, Vittadini F, Gasparre G, Nicoli Aldini N, et al. The role of detraining in tendon mechanobiology. Frontiers in Aging Neuroscience. 2016;8:43.
27. Frizziero A, Vittadini F, Fusco A, Giombini A, Masiero S. Efficacy of eccentric exercise in lower limb tendinopathies in athletes. Journal of Sports Medicine and Physical Fitness. 2016;56(11):1352-1358.
28. Frizziero A, Vittadini F, Gasparre G, Masiero S. Impact of oestrogen deficiency and aging on tendon: Concise review. Muscles, Ligaments and Tendons Journal. 2014;4(3):324-328.
29. Oliva F, Piccirilli E, Berardi AC, Frizziero A, Tarantino U, Maffulli N. Hormones and tendinopathies: The current evidence. Advances in Experimental Medicine and Biology. 2016;920:133-138.