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Mini Review

Hyaluronic Acid Injections in the Management of Tendinopathies. A Descriptive Review

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Received: December 18, 2018; **Published:** March 14, 2018

Abstract

Background: Tendinopathy is an umbrella term that indicates a non-rupture injury in the tendon that is exacerbated by mechanical loading. In most of the cases, these multifactorial conditions are related to overuse and characterized by activity-induced pain, local tenderness and swelling. Although tendinopathies are common, their treatment is not easy. Actually, several conservative treatments are contemplated, however there are not precise indications or guidelines and no defined conservative protocol is recommended. Recently several studies investigated the role of hyaluronic acid injections as a new way of treatment in various types of tendinopathies.

Methods: This is a review article. The aim of this manuscript is to evaluate the current evidences about the effectiveness of hyaluronic acid injections in tendinopathies.

Conclusion: Viscosupplementation with hyaluronic acid could be considered as mini-invasive and first-line approach in the treatment of tendinopathies, especially for its role in reducing pain and for its biological effects. However, the literature is still lacking about the correct type, dose and posology. Further studies about different types of hyaluronic acid in different kind of tendinopathies should be encouraged.

Keywords: *Tendinopathy; Injections; Hyaluronic Acid; Review*

Introduction

Tendons are tough bands or cords of fibrous connective tissue that usually connect muscle to bone and are capable of withstanding tension. Tendons are similar to ligament because both are made of collagen, but ligaments join one bone to another bone. They help move the bones and joints during muscle contraction. Tendons are subject to many types of injuries. Actually, different terminology is used in order to describe tendon's pathology: tendonitis, tendinosis, tendinopathy, tenosynovitis and tendon rupture [1,2]. "Tendinitis" is the inflammation of the tendon. It results from micro-tears that happen when the musculotendinous unit is overloaded with a tensile force. Tendinitis is still a very common diagnosis, but it is though that what is believe to be tendinitis is usually tendinosis. "Tendinosis" is a degeneration of the tendon's collagen in response to chronic overuse; when overuse is continued without giving the tendon time to heal and rest, such as with repetitive strain injury, tendinosis results. The term Tendinosis is used by some in preference to tendinitis to shift the focus away from inflammation. The confusion about the difference between tendinitis and tendinosis is widespread. There is a prevalent supposition that tendinosis begins with tendinitis, which then instigates a healing process that changes the collagen and weakens the tendon, becoming tendinosis. It seems to presume that micro-tears and inflammation are a precursor to collagen degeneration. However, the precise diagnosis of these conditions should be performed using a histopathological analysis that could be performed only after a biopsy. Obviously this kind of analysis is invasive and not easy to perform, so recently, Maffulli., *et al*. [3] advocated a change in

clinical terminology from tendinitis to tendinopathy. Both terms are used as generic descriptors for pain and lump of injured tendon, with a no real distinction of a presence or an absence of inflammation. The term "Tendinopathy" could be considered as an umbrella term that indicates a non-rupture injury in the tendon that is exacerbated by mechanical loading. Tendinopathies represent one of the most frequent sport injuries, but they are also frequent in non-sportive population. The causes that could lead to a tendinopathy are various, the aetiology could be considered as multifactorial, and is often related to overuse. Commonly affected areas include the shoulders, elbows, wrists, knees, fingers and backs of the heels. Symptoms can include: pain, worse when the affected area moves, stiffness, may be worse in the morning, weakness in the affected area or being unable to move a joint, a sensation that the tendon is grating or crackling as it moves and swelling, with heat or redness. Speaking about disorders affecting the tendons, tendinopathies linked to rheumatologic pathologies such as rheumatoid arthritis and negative serum arthritis, such as psoriatic arthritis, should certainly be mentioned. Besides the joint structures, which are classically affected, with stiffness (especially in the morning), pain and swelling in one or more joints, usually with asymmetric character and reduction of the amplitude of the movements, tendons can also be affected, with tenosynovitis, which may also represent the first symptom of the disease, with the possibility, albeit rare, of tendon rupture and bursitis of the main joints [4]. Some characteristic manifestations allow to distinguish psoriatic arthritis from other arthropathies. This form of arthritis appears in carriers of cutaneous psoriasis with a frequency ranging from 8 to 19%. These distinctive signs include dactylitis (the so-called "sausage" finger) and enthesitis, an inflammation that covers the bone insertion point of tendons and ligaments, the enthesis, in fact, is often referred to as entesoartritis. The latter condition manifests itself more frequently in the Achilles tendon or in the plantar fascia [5]. Nowadays ultrasounds and magnetic resonance imaging are commonly used to diagnose and for an etiological distinction between the inflammatory and non-inflammatory conditions. Although tendinopathies are common, their treatment is not easy and has different treatment goals and timelines. The first treatment goal for tendinopathies is to reduce inflammation. Conservative care consists, in the acute phase, of rest, ice, compression, and elevation. This is usually followed by physical or medical therapy as local injections (cortisone, platelet rich plasma, and hyaluronic acid), extracorporeal shock waves, laser-therapy, ultrasound-therapy, stretching, eccentric exercise, life style modification, topical applications, as well as oral nonsteroidal anti-inflammatory drugs [6]. When conservative care fails, surgical intervention is sometimes contemplated [7]. Recently, the anti-inflammatory and lubrication properties of Hyaluronic acid have been drew the scientific community's interest to treat tendinopathies [8,9]. Hyaluronic acid is a polysaccharide present in the extra cellular matrix of many mature tissue [10]. Many chronic injuries could modify the concentration of hyaluronic acid in synovial fluid. Balasz and Denlinger [11] first, introduced the concept of visco-supplementation to supplement or replace the synovial fluid in a pathological joint to alleviate pain and promote the healing of intra- articular injuries. Although hyaluronic acid is rapidly cleared from the injected site, the rationale for its use lies in its multiple interactions. Hyaluronic acid, also administered exogenously, has not only mechanical effects, but also multiple effects in terms of signal transduction in different cell types and contributes to the maintenance of homeostasis. Several studies have shown that hyaluronic acid interacts with the "CD44" receptors, present on the surface of chondrocytes, stimulating the production of new endogenous hyaluronic acid (viscoinduction) and exerting an anti-inflammatory action counteracting potentially harmful mechanisms (chemotaxis of some inflammatory cells, PGE2 synthesis and free radicals) [12]. Experiments conducted on human macrophages have shown its ability to interfere with the expression of PGE2 and of the cyclo-oxygenase 2. Further mechanisms contributing to the anti-nociceptive effect are the inhibition of arachidonic acid release from fibroblasts and the activation of opioid receptors [13]. Hyaluronic acid injections represent a widely used way of treatment; their effectiveness is confirmed by several studies especially as regard osteoarthritis [14]. In the past, it was observed that hyaluronic acid intra-articular injection in hip joints could change the walking pattern, as measured by instrumental gait analysis, in a population affected by knee osteoarthritis [15-17].

Actually, in literature there are several studies about hyaluronic acid injections and the treatment of tendons disorders [18,19]. However, there are not strong evidences about its use in tendinopathies.

The aim of this literature review is to analyses studies relating to the use of hyaluronic acid in the treatment of tendinopathies and assess the effectiveness of it.

Material and Methods

We performed a systematic search in PubMed, Medline, PEDro and Google Scholar electronic databases of articles assessing the treatment of tendinopathy with viscosupplemention of hyaluronic acid published in English only, published in the last five years. We used various combinations of the following key words and MesH terms "hyaluronic acid", "hyaluronate", "tendinopathy", "tendinosis", "tendinitis", "infiltration", "hyaluronic injections", "viscosupplementation". Pilot studies, case reports, letter to authors, editorials, technical notes and narrative review articles were excluded.

Results

The initial search yielded 64 articles, of which 11 were identified as relevant after screening of titles/abstract. Full texts were retrieved. The 11 studies included 4 articles on shoulder, 2 on elbow, 2 on hand, 1 on knee and 2 on ankle and foot tendinopathies. We didn't include studies about hip tendinopathies treated with peritendinous hyaluronic acid injections because there are not evidences in literature in the last 5 years.

Shoulder tendinopathies treated with intra-articular injection

Özgen., *et al*. [20] evaluated the short- and long-term effect of intra-articular sodium hyaluronate (SH) in patients with a supraspinatus tendinitis that have shoulder pain on the clinical symptoms of the patients through comparison with conventional physiotherapy methods. 24 patients were randomized into two groups, that received SH injection and physical therapy respectively. They discovered similar effects in short- and long term between physical therapy modalities and sodium hyaluronate application for supraspinatus tendinitis.

Shoulder tendinopathies treated with intralesional injections

Merolla., *et al*. [21] studied 48 patients with rotator cuff tendinopathy (> 4 months) randomized into 2 groups with 2 under ultrasonoguided sub acromial injection of hyaluronic acid (25 patients) 14 days apart and with only a rehabilitation program (23 patients) respectively. At the follow-up, six months later, they observed that sub acromial hyaluronic acid injections was more effective on pain and algofunctional scores than rehabilitation alone. Penning., *et al*. [22] in a three-arm randomised controlled trial, enrolled 159 patients with sub acromial impingement and randomised to treatment with sub acromial injections using lidocaine with one of hyaluronic acid (51 patients), corticosteroid (53 patients) or placebo (55 patients). The patients were evaluated by a follow up at 26 weeks by a VAS scale that represent the primary outcome. Secondary outcomes included the Constant Murley score, shoulder pain score, functional mobility score, shoulder disability questionnaire and pain-specific disability score. At the end of the study, the authors were not to show a convincing benefit from hyaluronic acid injections compared with corticosteroid or placebo injections, because corticosteroid injections produced a significant reduction in pain from 3 to 12 weeks, but in the long term the placebo injection produced the best results. Moghtaderi., *et al*. [23], in a double blind placebo controlled clinical trial, evaluated effectiveness of ultrasonography guided sub acromial sodium hyaluronate injection in 40 patients with impingement syndrome without rotator cuff complete tear. Patients were randomized in 2 groups: a case group ultrasonography guided injected by 20mg of sodium hyaluronate and control group by 0.9% normal saline. Both groups received 3 weekly injections. The pain-VAS score was evaluated before first injection and one week after each injection. At the end of the treatment, it was a significant decrease of VAS score meaning that sub acromial injections of sodium hyaluronate are effective in treating rotator cuff disease without complete tears.

Elbow tendinopathies treated with intralesional injections

Bernetti., *et al*. [24] compared the long-term effectiveness of the infiltration of local corticosteroids versus a protocol of one infiltration of local corticosteroid followed by three infiltrations of low molecular weight hyaluronic acid in eleven patients practicing tennis as a hobby, who were diagnosed a humeral epicondylitis. They find that the better way of treatment was the combination of methylprednisolone acetate 40 mg/ml with 0.8 ml lidocaine plus injection of 1 ml of low hyaluronic acid 10 days later and once a week for two more times.

Tosun., *et al*. [25] compared the effects of a combination of sodium hyaluronate with chondroitin sulphate injection versus a triamcinolone injection for the treatment of lateral epicondylitis. They randomized 57 patients in 2 groups: 25 patients received a single injection of a solution containing the combination of sodium hyaluronate with chondroitin sulphate and procaine H-Cl, and the rest (32 patients) received a single injection of a solution of triamcinolone and procaine H-Cl. The pain and the function outcome measures were evaluated using the "Patient-Rated Tennis Elbow Evaluation" at the beginning of the study and during the follow-up at 3 and 6 months after the injections. They concluded that a single injection of a combination of sodium hyaluronate with chondroitin sulphate to treat patients with lateral epicondylitis, may offer better pain benefits for 6 months after injection of triamcinolone.

Hand tendinopathies treated with intra-articular injection

Orlandi., *et al*. [26], to compare the six-month outcome of three different ultrasound-guided treatments for De Quervain's disease (DQD), treated 75 patients (51 F, 24 M, mean age ± standard deviation = 45.3 ± 9.8 years) with DQD. VAS scale, reduced disability score (quick-DASH), and retinaculum thickness were evaluated at baseline and after one (excluding retinaculum thickness), three, and six months. Patients were randomized into three groups of 25 patients each treated under ultrasound guidance: Group A with 1 ml methylprednisolone acetate, Group B with 1 ml methyl-prednisolone acetate + 15 day delayed 2 ml saline 0.9, Group C with 1 ml methyl-prednisolone acetate + 15 day delayed 2 ml low molecular weight hyaluronic acid. After six months, they concluded that addition of hyaluronic acid to ultrasound-guided injections of steroids to treat DQD seems to improve the outcome and to reduce the recurrence rate.

Hand tendinopathies treated with intralesional injections

Liu., *et al*. [27], to investigate the effects of hyaluronic acid versus steroid injections for trigger fingers in adults using ultrasound-guided injection, treated, 36 subjects with the diagnosis of trigger finger, randomized into hyaluronic acid and steroid injection groups; both study medications were injected separately via ultrasound guidance with one injection. The classification of trigger grading, pain, functional disability, and patient satisfaction were evaluated before the injection and 3 weeks and 3 months after the injection using VAS scale, Quinnell scale and Michigan Hand Outcome Questionnaire. At the end of the study, ultrasound-guided injection of HA demonstrated promising results for the treatment of trigger fingers.

Hip tendinopathies treated with intra-articular injection

There is a lack of recent evidences about the use of hyaluronic acid to treat hip tendinopathies. Studies about this articulation are focused on intra-articular use of hyaluronic acid as a possible treatment in order to treat tendinopathies secondary to osteoarthritis processes. Frizziero., *et al*. [28], in a review article, evaluated the current evidences about the effectiveness of conservative management in hip tendinopathies (including hyaluronic acid injections) concluding that conservative treatment is effective in the treatment of hip tendinopathies and may be considered as first-line approach.

Knee tendinopathies treated with intralesional injections

Muneta., *et al*. [29] described the appropriate indication for injections of hyaluronic acid in the Patellar tendinopathy in athletic patients based on the authors' pilot cases. Fifty patients, graded stage 2 or 3 by Blazina's classification, were treated. The total number of injections was 135, and there were an average of 2.0 injections per case (1 - 11). They concluded that hyaluronan injection therapy is an optional but effective treatment for athletic patients with patellar tendinopathy.

Ankle and foot treated with intralesional injections

Lynen., *et al*. [30], in a randomized study, compared the safety and efficacy of hyaluronan injections with standard extracorporeal-shock-wave therapy in the treatment of painful mid-portion Achilles tendinopathy. They enrolled 62 participants were randomized in two group: the first treated with two peri-tendinous hyaluronic acid injections versus a second with three extracorporeal shock wave therapy applications at weekly intervals. The primary efficacy criterion was the VAS score at 3 months post-treatment, compared to baseline val-

ues. At the end, two peri-tendinous hyaluronic acid injections showed greater treatment success in Achilles mid-portion tendinopathy compared to standard extracorporeal shock wave therapy. Gorelick., *et al*. [31] reviewed 56 patients with insertional achilles tendinopathy treated between 2007 and 2012, divided into three groups: the first group treated by the corticosteroid injection, the second group treated by single hyaluronate injection and the third group treated by rest, splint, NSAIDs, and physiotherapy. After one year, patients that treated by a single hyaluronate injection showed excellent results for a long time in comparison with corticosteroids injections and the conservatively treated patients, according to FADI and VAS scores. It seems that hyaluronate injection therapy is superior to steroid therapy and non-invasive conservative treatment for insertional achilles tendinopathy.

Discussion

In the scientific literature, there is no unanimous consensus for the treatment of tendinopathy with hyaluronic acid. Probably a reason of this disagreement is the lack of standardisation in the therapeutic process. In the last five years, many authors try to find a common path to be followed. The purpose of using hyaluronic acid for the treatment of tendinopathy suggest from vitro and animals experiment. Osti., *et al*. [32] had compared 4 different hyaluronic acid preparation by their molecular weight on human tendon derived cells from rotator cuff tears. They observed that all the hyaluronic acid increased the cell viability and the proliferation at 24 hours compared to control cells (without hyaluronic acid). Also, Frizziero., *et al*. [33] compared the mechanobiology of patellar tendons of rats randomized into 3 groups (untrained, trained and detrained) who demonstrated that hyaluronic acid is effective in the maintenance of the structural properties of patellar tendon and enthesis in detrained rats. One of the first relevant studies about the use of hyaluronic acid in tendinopathies it is made by Petrella., *et al*. [34] in the 2010. They try to determine the efficacy and safety of peri-articular hyaluronic acid injections in chronic lateral epicondylosis (tennis elbow), compared a group of 165 competitive racquet sports athletes presenting with chronic lateral epicondylosis for more than three months, that received two injections of 1.2 ml of hyaluronic acid, with a control group (166 athletes) received a saline solution of 1.2 ml. Follow-up examinations were conducted after 7, 14, 30, 90 and 356 days and consisted of a VAS at rest and during measurement of grip strength using a Jamar dynamometer, an elbow disability scale, a functional scale, a satisfaction scale and a measure of time to return to pain-free sport. After one year, there was a significant improvement in pain at rest and grip. Few years later, Kumai., et al. [35] studied the effects of a 2,5 mL hyaluronic acid injections in a total of 61 patients with enthesopathies (16 lateral epicondylitis,14 patellar tendinopathy, 15 insertional Achilles tendinopathy, 16 plantar fasciitis) after 1 week from the hyaluronic acid treatment. They found a significant decrease of vas scale suggesting the efficacy of injections of hyaluronic acid for enthesopathies in the short-term. Recently, Kaux., *et al.* [36] in a literature review analyses studies, investigated the use of hyaluronic acid in the treatment of tendinopathies. 28 articles about the use of hyaluronic acid to tendons were selected for their relevance and scientific quality, including 13 for the *in vitro* part, 7 for the *in vivo* animal part and 8 for the human section. This studies demonstrated that hyaluronic acid permits tendon gliding, reduces adhesions, creates better tendon architectural organisation and limits inflammation. Osti., *et al*. [37], in another review including 11 articles, documented the potential benefit and adverse effects of hyaluronic acid injection into the shoulder with rotator cuff tears. 1102 patients were evaluated clinically after different hyaluronic acid injection compare with corticosteroid injection, physically therapies, saline solution injection and control groups. They affirmed that intra-articular injection with hyaluronic acid is effective in reducing pain and improving function in shoulder with rotator cuff tears and without severe adverse reaction. Sayegh., *et al*. [38], in a recent meta-analysis, studied the difference between nonsurgical treatment, including hyaluronic acid, of lateral epicondylitis and observation only or placebo provides. They concluded that pooled data from RCTs indicated a lack of intermediate- to long-term clinical benefit after nonsurgical treatment of lateral epicondylitis compared with observation only or placebo. Piccirilli., *et al*. [39], in a systematic review and meta-analysis study, investigated the viscosupplementation with exogenous hyaluronic acid to improve synovial fluid properties and to decrease pain. They selected 26 articles and concluded that hyaluronic acid shows to improve synovial inflammation.

The effects of hyaluronic acid have also been investigated in the post-operative period. Abate., *et al*. [40], in a review study, summarized the current knowledge on the use of hyaluronic acid after tendon surgery and in tendinopathies. Different hyaluronic acid compounds demonstrated to be able for reduced formation of scars and granulation tissue after tendon repair, less adhesions and gliding resistance, and improved tissue healing. The success of this therapy is attributable to the anti-inflammatory activity and to the lubricating action on

the sliding surface of the tendon. Gentile., *et al*. [41] treated ten patients affected by achilles tendon injuries resulting from post-surgical complications subsequent to tenorrhaphy with autologous platelet-rich plasma in combination with hyaluronic acid to evaluate the improvement of lesions with wound closure. This treatment demonstrated to be effective in healing and regeneration of soft and hard tissues. The treated area preserved a satisfying strength in plantar flexion and extension of the ankle. The functional rehabilitation in terms of deambulation and joint mobility was complete. Özgenel and Etöz [42] enrolled 22 patients with isolated zone-II flexor tendon injury of the index fingers to investigate the efficacy of three injections of hyaluronic acid versus placebo (saline) over a two-week period on functional outcomes after tendon repairs. This study suggests that repetitive injections of hyaluronic acid can improve clinical outcomes evaluated using the Strickland classification presumably due to the effect on decreasing adhesions in primary tendon repairs.

Conclusions

The study of scientific literature has shown that there is a lack of scientific evidence regarding the use of hyaluronic acid in the treatment of the most common tendinopathies. Another critical emerged is that there is an absence of a consensus both on the actual effects of the use of hyaluronic acid in tendinopathies therapy and there is no conformity on both the type of hyaluronic acid used, as well as on the dose and the way of administration of it. More studies are needed, with a sufficient number of patients and a careful methodology in order to clarify the effects of the use of hyaluronic acid in tendinopathies.

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Volume 9 Issue 4 April 2018