

Hyaluronic acid and tendon lesions

Jean-François Kaux^{1,2,3}
 Antoine Samson^{1, 2}
 Jean-Michel Crielaard^{1,2,3}

¹ Department of Physical Medicine and Sports Traumatology, CHU Liège, Belgium

² Multidisciplinary Department for Medicine and Sports Traumatology (SPORTS), CHU Liège, Belgium

³ Department of Sports and Rehabilitation Sciences, University of Liège, Belgium

Corresponding author:

Jean-François Kaux
 Department of Physical Medicine and Sports Traumatology, CHU and University of Liège
 Avenue de l'Hôpital, B35
 4000 Liège, Belgium
 E-mail: jfkau@chu.ulg.ac.be

Summary

Introduction: recently, the viscoelastic properties of hyaluronic acid (HA) on liquid connective tissue have been proposed for the treatment of tendinopathies. Some fundamental studies show encouraging results on hyaluronic acid's ability to promote tendon gliding and reduce adhesion as well as to improve tendon architectural organisation. Some observations also support its use in a clinical setting to improve pain and function. This literature review analyses studies relating to the use of hyaluronic acid in the treatment of tendinopathies.

Methods: this review was constructed using the Medline database via Pubmed, Scopus and Google Scholar. The key words hyaluronic acid, tendon and tendinopathy were used for the research.

Results: in total, 28 articles (in English and French) on the application 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.

Conclusions: preclinical studies demonstrate encouraging results: HA permits tendon gliding, reduces adhesions, creates better tendon architectural organisation and limits inflammation. These laboratory observations appear to be supported

by limited but encouraging short-term clinical results on pain and function. However, controlled randomised studies are still needed.

KEY WORDS: hyaluronic acid, tendinopathy, tendon, healing, cicatrization.

Introduction

Tendon lesions are very common in sportsmen and physical workers¹. Their physiopathology is multifactorial, including intrinsic and extrinsic factors, which can be modified or not². Even if detrained tendons present the same histological structure as chronic tendinopathies, however, this condition remains an overuse pathology which is often difficult to treat². For this reason, various new treatment have been developed¹ such as platelet-rich plasma (PRP)³ or growth factors⁴ infiltrations. Recently, the anti-inflammatory and lubrication properties of HA have also been suggested for the treatment of these pathologies⁵.

Hyaluronic acid (HA) is a polysaccharide with a high molecular weight (between 100 kDa and 10 MDa), mainly found in the extracellular matrix where it plays different roles at various places in the organism⁵. Its half-life is only three to five minutes in the circulation, less than a day in tissue, and between one and three weeks in cartilage. This speed of renewal means that this polymer is constantly synthesised and degraded⁵. HA can be categorised into three groups based on molecular weight:

- low molecular weight: MW < 1MDa;
- medium molecular weight: 1MDa < MW < 2MDa;
- high molecular weight: MW > 2MDa.

HA ensures the viscoelasticity of liquid connective tissues such as the synovial joint and the corpus vitreum of the eye⁵. As a result of this ability, its role in the body is, among other things, to bind to water and to lubricate mobile parts of the body such as the joints and muscles⁵. Intra-articular injections of synthetic HA are widely used in the medical treatment of osteoarthritis⁶⁻⁸.

Industrially, HA is obtained through two different procedures:

- extraction from rooster combs, after grinding and chemical treatment⁵;
- purification and bacterial fermentation⁵.

The viscosity of the gel which is obtained is proportional to the length (molecular weight, expressed in Daltons) of the polymer fibres. This viscosity will de-

termine how quickly the product degrades after implantation.

One major absolute contraindication is hypersensitivity to one of the ingredients. Potential undesirable side-effects are pain, a feeling of heat, haematoma, redness and swelling.

Material and methods

This literature review was constructed using the Medline database via Pubmed, Scopus and Google Scholar, according to the recommendations of the Journal⁹. Articles published in English and French, up to the 30th of September 2015, were found using the following key words alone or in combination: *hyaluronic acid, hyaluronan, tendon, tendinopathy, treatment* (in English) and *acide hyaluronique, tendon, tendinopathie, traitement* (in French). In total, only 28 articles on HA as applied to tendons were selected for their relevance and scientific quality: 13 for the *in vitro* part, 7 for the animal *in vivo* part and 8 for the human section.

Results

In vitro experiments

Even if the first published paper studying the effect of HA on tendons of rabbits has not shown any effect on the functional strength of tendons after healing *in vitro*¹⁰, several Authors have sought to identify the ability of HA to improve tendon gliding.

Sun et al. used 30 canine peroneus longus, randomised into five groups, and immersed for 30 seconds in one of the following five solutions: saline solution, gelatin, carbodiimide and HA (cd-HA) and gelatin (cd-gelatin) and cd-gelatin-HA¹¹. The tendons were first placed in an incubator at 100% humidity at 37°C, before being wrapped in damp cloths for one hour. Gliding resistance for each tendon was measured before the surfaces of the tendons were coated in the various solutions. After 500 cycles, gliding resistance for the tendons coated in saline solution increased significantly, by a factor of 10, while the cd-gelatin and cd-gelatin-HA did not significantly change. In addition, under microscopy, the surface of the tendons in the saline, gelatin and cd-HA solutions were rough, presenting a network of disorganised fibres. In contrast, the surface of the tendons immersed in the gelatin-cd-HA solution appeared smoother than in the other groups. These observations were confirmed by the study of Nishida et al., which suggest that HA may improve the gliding function of canine flexor tendons¹².

Taguchi et al. wanted to identify whether these results could be transposed to human tendons¹³. They used 16 human extrasynovial palmaris longus tendons which were divided into two and then immersed randomly in one of the following four solutions: saline solution, carbodiimide-gelatin-HA (cg-gelatin-HA),

carbodiimide-gelatin-lubricin and cd-gelatin-HA-lubricin. The results, after 1,000 flexion/extension cycles, show that the tendons treated with saline solution presented significantly higher gliding resistance than other groups. These findings, suggesting that HA may limit tendon adhesions, has already been observed in a previous study of Akasaka et al¹⁴.

In addition to its effects on tendon biomechanics, the researchers looked at the influence of HA on tendon regeneration.

Yamada et al. sought to determine the influence of HA on cell proliferation and mRNA expression of type I and type III procollagens¹⁵. They used tendons from 10 subjects suffering from rotator cuff disease who had undergone surgical repair to the cuff. For each fragment, the tendon tissue was separated from the synovial tissue, cut into small pieces and cultured in solutions containing various concentrations of HA (1.0 to 5.0 mg/mL). The results showed HA binding to its receptors and a reduction in cell proliferation in a dose-dependent manner in comparison with untreated cells. In addition, the expression level of procollagen $\alpha 1$ (I) mRNA did not significantly reduce in contrast to the expression of procollagen $\alpha 1$ (III) mRNA in a dose-dependent manner.

Another study by Shimpuku et al. analysed the suture site of the supracoracoid tendon in chickens after injection of HA¹⁶. As well as confirming that HA treatment does not increase the production of $\alpha 1$ (I) procollagen, the team was able to show early restoration of tendon continuity at the laceration site in comparison with the control group treated with saline solution. Wiig et al. had compared the effect of HA on cell proliferation and synthesis of matrix component in intrasynovial deep extensor tendons and extrasynovial peroneus tendons of rabbits¹⁷. They observed that HA modulates cell proliferation unequally in intra- and extrasynovial tendons, but without affecting the matrix component synthesis. This can be partly explained by a difference in biochemical composition and cellular capacities of tendons and by a possible difference in HA sensitivity and in its mechanism of action.

Osti et al. had compared 4 different HA preparation by their molecular weight on human tendon derived cells from rotator cuff tears¹⁸. They observed that all the HA increased the cell viability and the proliferation at 24 hours compared to control cells (without HA). Furthermore, the synthesis of collagen type I was stimulated over 14 days, without increase in collagen type III. However, these observations were significantly higher in the high molecular weight HA groups.

Neumann et al. looked at the effects of HA on proinflammatory action caused by advanced glycation endproducts (AGEs)¹⁹. The team compared the efficacy of a preparation of HA with a 'high' molecular weight (HMW-HA - >1.2MDa) to a preparation of HA with a low molecular weight (LLW-HA - 0.2-0.5MDa) on the production of AGEs and activation of proinflammatory cytokines on murine macrophages. Their results show that HMW-HA, with a molecular weight greater than 1.2 MDa, inhibits the inflammation signalling pathway (NF-kB) caused by AGEs and that

this effect reduces with the molecular weight of HA. Moreover, the results show that low molecular weight HA (<0.5MDa) is proinflammatory.

Tanimoto et al. studied the effect of proinflammatory cytokines on HA-synthetase (HAS) mRNA expression using rabbit synovial membrane cells, cultured in inflammatory conditions IL1- β and TNF- α were used²⁰. Their results showed that proinflammatory cytokines increase HAS mRNA expression and, consequently, may contribute to the accumulation and fragmentation of HA. Low molecular weight HA molecules no longer played their lubricating role in an optimal way. A study by Smith et al. highlighted the effect of adding exogenous HA to endogenous HA synthesis in synovial fibroblasts²¹. Human synovial fibroblasts obtained during biopsies or arthroplasties were cultured. Different molecular weights of HA were then added. The results clearly showed that *in vitro* HA synthesis by these cells increased when the concentration and molecular weight of the added HA was increased.

The recent study of Nakamura et al., comparing the effects of corticosteroids or HA used in subacromial injection on cell proliferation, in human tendon fibroblasts from rotator cuff tears and in rats after surgical lesion, demonstrated that HA possesses anti-inflammatory and anti-adhesive activities in tendon and synovial fibroblasts. In contrast to CS, HA caused no adverse effects and appears to be relatively safe²².

Animal experiments

Zhao et al. wanted to identify the effect of HA on the reduction of adhesions and on functional improvement after failed tendon reconstruction²³. To simulate this situation, 28 flexor tendons from the 2nd and 5th digits of dogs were lacerated and repaired. One graft tendon in each dog was treated with an injection of saline solution, and the other with an injection of HA (1%) combined with lubricin (cd-HA-lubricin). Six weeks after the surgical operation, the allografts treated with cd-HA-lubricin showed decreased adhesions at the proximal extremity, improved digit function and increased graft gliding ability. However, rupture resistance at the proximal and distal repair sites was lower in the treated group than in the control group. Moreover, histological analysis showed delayed healing in the treated group. A study by Oryan et al. aimed to assess the effects of high molecular weight (1.6MDa) HA (0.9%) on the healing of flexor tendons in the digits of rabbits after lesion and repair through surgical suture²⁴. Injections were administered to 40 rabbits, randomly divided into two equal groups of injured treated with HA and injured untreated. The results showed a significant reduction in the diameter of the treated tendons and an increase in echogenicity. In addition, the dry weight of the injured tendons had significantly increased in comparison with the non-treated tendons. The treatment also significantly improved tenoblast numbers and the diameter and density of collagen fibrils. Yoshida et al. also demonstrated that high molecular weight HA (2700 kDa) was effective for pain relief and for partial restoration of the

patellar tendinopathy in a rat model, compared to saline or nothing (control group)²⁵.

The Liang et al. team wanted to show the effect of the presence of tenocytes when injecting HA into the Achilles tendons of rats at an early healing stage²⁶. After transection and suture of the Achilles tendon, 96 rats were randomised into three groups: one group (THA) received an injection of 1.0 kDa HA (1.5%) with tenocytes (5×10^5), one HA group received the same injection without tenocytes, and a control group received a saline solution injection. A significant difference in recovery, tendon stiffness and locomotive ability was observed in the THA group. The THA group also had a shorter healing time, ending the inflammatory phase and starting the proliferation phase from day 7, while the non-treated and HA groups were still in the inflammatory phase of the healing process on day 7. Acceleration of the inflammatory process through injection of THA may be the main reason for this functional improvement. In addition, the few differences measured between the tendons treated with HA and the tendons injected with saline solution may be explained by the low molecular weight (1.0 kDa) of HA used. This study shows that adding tenocytes to HA injections may positively influence tendon repair by reducing inflammatory response time. However, the use of low molecular weight HA in this study makes comparisons with THA difficult. Moreover, the use of THA appears to be more appropriate for surgical interventions on tendons than in tendinopathies, given the constraints of removing tenocytes.

The recent series of Salamanna et al. comparing the mechanobiology of patellar tendons of rats randomized into 3 groups (untrained, trained and detrained), demonstrate that discontinuing training activity in the short term alters tenocyte synthetic and metabolic activity and that repeated peri-patellar infiltrations of HA during detraining allow the maintenance of tenocyte anabolic activity²⁷: higher proliferation rate and viability, and increased synthesis of C-terminal-propeptide of type I collagen, fibronectin, aggrecan, tenascin-c and matrix-metalloproteinase-3. These results are reinforced by those of Frizziero et al., comparing the same groups, who demonstrated that HA is effective in the maintenance of the structural properties of patellar tendon and enthesis in detrained rats²⁸.

Contrary of the *in vitro* observation, Yamaguchi et al. suggested that both hyaluronic acid and steroid injections suppressed of inflammation (evaluated by the expression of calcitonin related peptide - CGRP) in a rotator cuff of rats, which thought to be provided pain relief (analyzed by the gait analysis)²⁹. While there were no significant differences, the suppression of CGRP expression and the improved gait after hyaluronic acid and steroid injections suggested that both methods were effective for rat rotator cuff tear model.

Human experiments

Meloni et al. examined the effect of periarticular injection of HA in patients suffering from a supraspinatus

tendinopathy³⁰. A total of 56 patients participated in the study and were randomised into two equal groups: one group treated with an injection containing 20 mg of HA (concentration: 20mg/2ml, molecular weight: 0.5-0.7 mDa) in 2 ml of lidocaine (1%) and 2 ml of physiological liquid (0.9%) and a control group receiving an injection of 4 ml of physiological solution (0.9%). Lidocaine is used to reduce pain due to the injection. After the first injection, the injection was repeated once a week for four weeks. During this period, analgesics were prescribed for three days after each injection. After one year, 19 of the 28 patients who had received HA were satisfied with their treatment, while all patients in the control group said they were dissatisfied after their injections. Joint extension remained identical throughout the follow-up. At months 1 and 3 following the injection, a significant improvement in pain in the treated group in comparison with the control group was noted. However, after one year, this pain had increased in the treated group. Moreover, no significant difference in tendon structure was observed during the ultrasound scan between the two groups either at the start or at the end of the follow-up.

Petrella et al. treated 330 competitive racquet sports athletes presenting with chronic lateral epicondylitis for more than three months³¹. Two injections were administered one week apart, into the subcutaneous tissue and muscle one centimeter from the lateral epicondyle toward the primary point of pain using a two-dimensional fanning technique: the treated group received an injection of 1.2 ml of HA (high but unspecified molecular weight) at 1% and the control group 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. Moreover, the scores on all scales had significantly improved in the treated group in comparison with the control group. The time to return to pain-free sport was assessed at 18 days (+/-11 days) in the treated group.

The efficiency of an HA injection for treating patellar tendinopathies was determined in fifty patients³² with stage 2 or 3 using Blazina's classification³³. The injected solution contained 2.5 mg of HA with a molecular weight of 900 kDa in 2.5 ml of physiological liquid and 1 ml of lidocaine. The effectiveness was assessed on the basis of pain during sport, using the modified Roles and Maudsley scores³⁴. After treatment, 54% of cases were 'excellent', and 40% of cases were 'good'. The results of this study are based on the subjective views of the athletes and their trainers. With a view to reducing post-surgical adhesions of digital flexor tendons, Riccio et al. studied 45 patients randomly assigned to two groups: a control receiving a placebo (n=10), and a treated group receiving an injection of HA (high but unspecified molecular weight) (n=26)³⁵. All patients were assessed at 30,

60, 90 and 180 days after surgery by testing active motion, with functional capacity being assessed using the quick-DASH questionnaire and the number of working days lost after surgery. Patients in the treated group showed better recovery of digital motion at all time intervals (improvement of 27% in the HA group compared to 10% in the control group, and 43 to 28% respectively at day 180), and returned to work earlier. However, no significant difference could be shown in terms of functional score between the two groups.

More recently, HA injections has been used to treat the flexor muscle in the index finger after surgical suture³⁶. 11 were treated with three HA injections (0.4 ml of high molecular weight: 1.0-2.9 MDa and high concentration: 15 mg/ml) and 11 received a placebo saline solution of identical volume. Three injections were administered: one at the time of the surgical intervention and two others one week apart. The two groups followed the same rehabilitation protocol after the operation. The results showed no differences between the two groups in terms of extension after three weeks. However, at three months and over the long term, significant functional improvement of total active range of joint motions (p=0.002 and p=0.001 respectively) was noted in the treated group in comparison with the placebo.

The short- and long-term effect of intra-articular injection of HA in patients suffering from supraspinatus tendinopathy³⁷ was assessed in 24 patients randomised into two groups, each received three injections of 2 ml of HA (16 mg/2 ml with a molecular weight of 6.0 MDa), following traditional physical therapy treatment. TENS current, ultrasound therapy, thermotherapy (hotpack) and exercises at home (movements, stretches and eccentric exercises). Follow-up consisted of algo-functional score, measurement of active and passive joint extension conducted at three weeks, three months and four years post-injection. A significant improvement in most of the parameters measured was seen within both groups, but no significant difference was observed for the pre-injection VAS in comparison with the VAS conducted at three weeks and three months post-injection.

The series of Merolla et al. enrolled 48 patients with rotator cuff tendinopathy for more than 4 months randomized into 2 groups: one group with 2 ultrasound-guided subacromial injection of HA (N=25) 14 days apart and one group with only a rehabilitation program (N=23)³⁸. The follow-up went up to 6 months. They observed that subacromial HA injections was more effective on pain and algo-functional scores than rehabilitation alone, and this injection was a safe treatment for patients suffering from rotator cuff tendinopathy.

A recent study of Kumai et al. evaluated the effects of a 2,5 mL HA (high-molecular-weight: 2700 kDa) injections, over a period of 1 week, in a total of 61 patients with enthesopathies: 16 with lateral epicondylitis, 14 with patellar tendinopathy, 15 with insertional Achilles tendinopathy, and 16 with plantar fasciitis³⁹. They observed a significant decrease of pain (VAS) for the 4

sites (-2.20 ± 2.26 for the 4 sites overall), suggesting the efficacy of injections of HA for enthesopathies in the short-term.

Discussion

Tendinopathies are very common condition in sports and working population¹. Tendinopathy and tenosynovitis disturbs tendon gliding. The application of HA can reduce tendon glide resistance¹⁰⁻¹⁴. Several earlier studies have shown the link between the inhibition of fibroblast proliferation and a reduction in type III collagen concentration in the tendon, with a reduction in the formation of adhesions at the tendon healing site⁴⁰⁻⁴². By limiting the proliferation of fibroblasts and by stabilizing the concentration of type III collagen, HA may reduce the risk of adhesions¹⁰⁻¹². It is still discuss if HA can stimulate or not the synthesis of type I collagen to improve the tendon structure and resistance^{5,18}, but it is demonstrated that HA improve cell viability and proliferation^{17,18}. HA appears to inhibit the expression of key intermediaries for the inflammatory signaling pathways (NF- κ B), in a dose-dependent manner^{19,43}. By reducing the expression of proinflammatory factors, adding exogenous HA reduces the fragmentation of endogenous HA and stimulates synovial synthesis of endogenous HA^{16,26,36}. Concerning the therapeutic protocol for HA injections for tendinopathies, comparatively to other recent treatments for these conditions, where post-injection rehabilitation could be crucial⁴⁴, such as PRP for example⁴⁵, only 1 or 2 injections alone are described for HA treatments^{30-32,35-39}. However, comparatively to PRP treatments, where it exist a wide variability in the administered product^{46,47}, the molecular weight and the concentration of HA are known¹⁸; high molecular weight HA seems to have a better effect on tendons¹⁸ in the short-term.

Conclusion

Some *in vitro* and animal *in vivo* studies demonstrate encouraging results in terms of the ability of HA to encourage tendon gliding and to reduce adhesions as well as creating better tendon architectural organisation. Moreover, the injection of HA may limit the proinflammatory effect by restoring viscoelasticity and by stimulating the endogenous synthesis of HA. These laboratory observations appear to be supported by limited but encouraging short-term clinical results on pain and function as well as on the return to sport. However, controlled randomised studies are still needed.

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