Hyaluronic Acid on Tendon Physiology

Subjects: Allergy

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Hyaluronic acid (HA) is a non-sulphated glycosaminoglycan formed by repetitive units of glucuronic acid and N-acetyl glucosamine. HA is widely present in the extracellular matrix in vertebrates and invertebrates to confer mechanical support, viscoelastic and hygroscopic properties, and anti-inflammatory effects to cells and tissue. HA is one of the fundamental components of cartilage and tendon tissue, contributing to their viscoelastic properties.

Keywords: hyaluronic acid ; receptor ; tendon ; tendinopathy ; inflammation ; viscoelastic ; hygroscopic ; effect

1. Introduction

Hyaluronic acid (HA) is a non-sulphated glycosaminoglycan formed by repetitive units of glucuronic acid and N-acetyl glucosamine. HA is widely present in the extracellular matrix in vertebrates and invertebrates to confer mechanical support, viscoelastic and hygroscopic properties, and anti-inflammatory effects to cells and tissue. HA is one of the fundamental components of cartilage and tendon tissue, contributing to their viscoelastic properties [1][2][3][4][5]. HA enhances the cellular activities of fibroblasts, including their adhesivity, extracellular matrix (ECM) synthesis, and proliferation, but, despite its influence on cells and tendon structure, its role on the biomechanical function is still not clarified [6][7]. The ECM of tendons is predominantly composed of type I collagen (**Figure 1**) and proteoglycans, with a small amount of the other types of collagen (type II, III, V, VI, IX, XI) (**Table 1**). The predominant cells type within the tendon are tenoblasts or tenocytes, accounting for 90–95% of cells present in tendon tissue between collagen fibres [8]. Tenoblasts and tenocytes show different metabolic features: while tenoblasts have high activity, tenocytes are metabolically less active. Both types of cells produce collagen, elastin, ECM, and proteins [9]. Other types of cells present in lesser quantities include chondrocytes at the bone attachment and insertion sites, synovial cells in the tendon sheath, and vascular cells, capillary endothelial cells, and arterioles' smooth muscle cells. All cells that produce the ECM are involved in endogenous HA production as well. HA injections are widely used to treat osteoarthritis (OA), but their efficacy in the management of tendinopathies is still debated [10]. Tendinopathies are characterised by tendon structure disruption, ineffective neovascularisation, decreased collagen I, and enhanced collagen II production [10]. Recently, the anti-inflammatory and viscoelastic effects of HA on connective tissue have been suggested to warrant the use of HA for the treatment of tendinopathies [11]. Some studies proved and support its use to improve function and reduce pain in tendinopathies [12][13], avoiding the complications of corticosteroids [14].

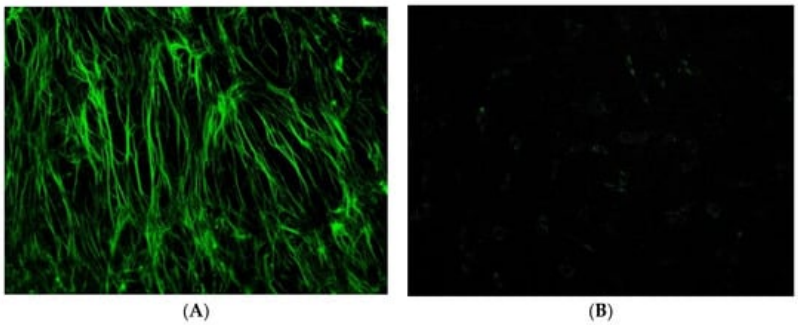

Figure 1. (**A**) Type I collagen in tenocytes, harvested from degenerated human supraspinatus tendon, stimulated for 14 days with 1000 µg/mL (>500 KDa) of HA; (**B**) untreated cells.

Table 1. ECM components of tendons.

ECM Components	%
Collagen	86% (type I: 98%)
Proteoglycan	1–5%

ECM Components	%
Elastin	2%
Decorin	<1%
Aggrecan	<1%
Other proteins	<1%

2. Patellar Tendinopathy and HA

Patellar tendinopathy is common in sports in which athletes jump, as in volleyball, basketball, or triple jump [15]. Kumai et al. evaluated the effects of a single high molecular weight HA injection in patients with patellar tendinopathy, finding improvement in pain and visual analogue scale (VAS) values at short-term follow-up (one week) [13]. Muneta et al. treated 50 young athletes with two high molecular weight HA injections without ultrasound (US) guidance. This was effective, safe, and repeatable [16]. Fogli et al. showed that a cycle of one HA injection a week for three weeks was effective and safe in patellar tendinopathy, with a significant decrease in pain, mean VAS values, and improvement of US appearance [17]. Kaux et al. compared US-guided injections of platelet-rich plasma (PRP) versus two HA injections, reporting that both treatments could be effective. The PRP group showed significant improvement in quadriceps strength, while HA had a greater impact on the improvement of symptoms [18]. Recently, Frizziero et al. showed good results after three medium molecular weight US-guided HA injections. This entry reported pain relief and improvement of the Victorian Institute of Sport Assessment for the patellar tendon (VISA-P) values at 90 days follow-up, with a decrease in vascularisation and tendon thickness at US and Power Doppler analysis [10].

3. Achilles Tendinopathy and HA

Achilles tendinopathy affects mainly athletes, especially runners, but also non-athletes [19]. The therapeutic use of HA in Achilles tendinopathy has been recently described (**Figure 2** A,B). Lynen et al. compared the effects of two HA peritendinous injections with shockwave therapy in patients with mid-portion Achilles tendinopathy. At 6 months, patients treated with HA injections reported better outcomes, with greater symptom improvement and restored function [14]. Similarly, Fogli et al. and Frizziero et al. showed that three US-guided medium molecular weight HA injections induce a clinically relevant increase in VISA-A values, pain relief, and US parameters improvement [10][17]. Recently, Gervasi et al. investigated the clinical, viscoelastometric, and biochemical effects of three US-guided medium molecular weight HA injections in runners with unilateral Achilles tendinopathy. Indeed, patients reported improvement in clinical assessment, decreased pain and stiffness of the tendon, and reduction in the viscoelastometric and functional asymmetry between the affected tendon and the healthy limb [20][21].

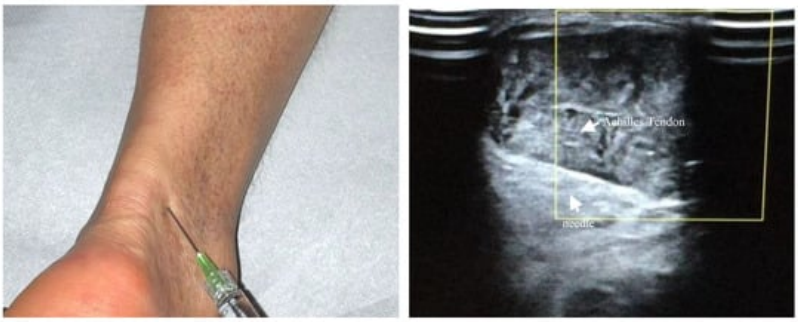

Figure 2. (**A**) Injection of HA in a dorsolateral approach of Achilles tendon; (**B**) US visualisation (5–12 MHz linear probe and PRF set at 0.5 kHz) of the needle (22-gauge) introduced at a 30-degree angle in the mesotendon, with the probe in a transverse plane.

4. Epicondylitis and HA

Lateral epicondylitis is a common cause of chronic elbow pain and affects 1% to 3% of the general population per year [22]. The tendon structures most affected are the insertions of the extensor of the forearm, located on the lateral side of the elbow [22]. Petrella et al. compared outcomes in patients who received HA injections versus a control group, who received an injection of 1.2 mL of a saline placebo, finding significantly greater improvement in VAS pain at rest and after grip testing up to 1-year follow-up [23]. Khan et al. reported the efficacy of a single HA injection in the management of moderate

epicondylitis (VAS pain score < 7), while it was not effective in severe lateral epicondylitis [24]. In a prospective randomised trial, Tosun et al. compared a combined HA-chondroitin sulphate injection versus a corticosteroid injection, showing an equal reduction in pain and improvement of function in the short term, while HA resulted in better outcomes at long-term follow-up [25].

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