

The role of viscosupplementation in patellar chondropathy

Sergio Ricardo da Costa , Roberto Freire da Mota e Albuquerque, Camilo Partezani Helito and Gilberto Luis Camanho

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Abstract: Patellar chondropathy has a high incidence in the general population, being more common in patients younger than 50 years, female and recreational athletes, and overweight and obese patients. The most common complaints are pain, limited mobility, crepitus, difficulty climbing and descending stairs, and joint instability, usually showing unsatisfactory results with anti-inflammatory, physiotherapy, rehabilitation, and many other conservative treatment methods. The presumed hyaluronic acid (HA) disease-modifying activity may include effects on cartilage degradation, endogenous HA synthesis, synoviocyte and chondrocyte function, and other cellular inflammatory processes. Currently, HA is widely used as a safe and effective conservative treatment for osteoarthritis in the knee and other joints. HA improves the physiological environment in an osteoarthritic joint and the shock absorption and lubrication properties of the osteoarthritic synovial fluid, thus restoring the protective viscoelasticity of the synovial HA, reducing the pain, and improving the mobility. The complete mechanism of HA in the joint is not fully understood, but a wide range of actions in the joint is recognized. Its anti-inflammatory, analgesic, and chondroprotective action is related to the modulation of the intra- and extracellular inflammation cascade. HA has been shown to be safe and effective in the treatment of pain related to patellar chondropathy.

Keywords: knee/aetiology, knee joint/physiopathology, osteoarthritis, patellofemoral pain syndrome/physiopathology, viscosupplementation

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Introduction

This narrative review will provide an overview for clinicians of recent advances in knowledge on the use of hyaluronic acid (HA) and patellar chondropathy, taking into account the causes of femoral patellar pain and the mechanism of action of HA in the joint.

Patellar chondropathy has a high incidence in the general population (1.5–7.3%) in the United States, being more common in patients younger than 50 years, in female athletes (13–17%),^{1–3} recreational athletes, and overweight and obese patients. The most common complaints are pain, limited mobility, crepitus, difficulty climbing and descending stairs, and joint instability, usually showing unsatisfactory results with anti-inflammatory, physiotherapy, rehabilitation, and many other conservative treatment methods.

Historically, the terms “internal derangement” of the knee and “chondromalacia patellae” have been used almost synonymously as a cause of anterior knee pain. Konrad Būdinger was the first to associate chondral fissures with traumatic knee injuries in 1906.⁴

The term “patellar chondropathy” refers to degenerative changes in the articular cartilage of the patella that often cause symptoms such as pain, crepitus, and joint effusion. Patellofemoral arthritis refers to degenerative changes and a significant cartilage loss in the articular surface of patella and in the femoral trochlea. According to the scientific literature, chondropathy may progress to patellofemoral or tibiofemoral osteoarthritis, requiring a precise diagnosis, an appropriate treatment, and an accurate follow-up as preventive measures.⁵

Correspondence to:
Sergio Ricardo da Costa
PhD Program for
Musculoskeletal
System Sciences,
Instituto de Ortopedia e
Traumatologia, Hospital
das clínicas HCFMUSP,
Faculdade de Medicina,
Universidade de Sao
Paulo, 333 Ovídio Pires
de Campos St., Cerqueira
César, São Paulo, SP
05403-010, Brazil
drsergioricosta@gmail.com

Roberto Freire da Mota e Albuquerque
Camilo Partezani Helito
Gilberto Luis Camanho
Knee Surgery Division,
Instituto de Ortopedia e
Traumatologia, Hospital
das clínicas HCFMUSP,
Faculdade de Medicina,
Universidade de São
Paulo, São Paulo, SP,
Brazil

The aetiology of patellofemoral pain is quite diverse: the patellar cartilage, subchondral bone, synovial plicae, anterior joint capsule, infrapatellar fat pad, and tendons certainly have their role in this process. The participation of the extensor mechanism is important since we have seen patients with pain and intact cartilage, as well as anatomic and mechanical changes: Q angle, patellar instability, shape, positioning, and patellar contact area.⁶

The hyaline cartilage is completely aneural, so surface defects are not believed to produce pain. Dye *et al.*⁷ published an article explaining the conscious perception of intraarticular (IA) pain through the palpation of its structures when researching the origin of patellofemoral pain. The synovium, infrapatellar fat pad, and anterior joint capsule were highly susceptible to pain, but the patellar cartilage palpation did not cause any painful sensation. This study reinforces the idea that pressure under the subchondral bone plays a role in the genesis of anterior knee pain.

Recently, Sanchis-Alfonso *et al.*⁸ observed the presence of neural growth factor (NGF) and substance P in the lateral retinaculum of patients with isolated symptomatic patellofemoral malalignment. NGF is a neurotrophin that is released during axonogenesis and inflammation and stimulates neural sprouting. It is involved in pain mechanisms by stimulating the release of neuroceptive mediators and attracting lymph cells and mastocytes, potentially releasing more cytokines, including NGF, perpetuating the cycle.

The envelope theory proposed by Dye suggests a relationship between the load (force) supported by the patellofemoral joint and the frequency of such load. Setting up zones of physiological functioning: the zone of homeostasis is within the physiological load and frequency parameters sustained by the joint for long periods without causing structural damage; when the force or frequency is excessive, the zone of structural failure of the cartilage is reached.⁹ Currently, studies with 3-T MRI demonstrate bone oedema and cartilage injuries within the context of repetitive trauma sports, such as long-distance running, football, and basketball, partially corroborating this theory.^{10,11}

Viscosupplementation

HA came into clinical use in Japan and Italy 1987, in Canada in 1992, in Europe in 1995, and in the

United States in 1997. Dr Endre Balaz proposed the concept of viscosupplementation in 1974 as an attempt to recover the characteristics of the synovial fluid altered in osteoarthritis (OA).¹²

Currently, HA is widely used as a safe and effective conservative treatment for OA¹³ in the knee and other joints. HA improves the physiological environment in an osteoarthritic joint and the shock absorption and lubrication properties of the osteoarthritic synovial fluid, thus restoring the protective viscoelasticity of the synovial HA, reducing the pain and improving mobility.¹⁴ According to the Osteoarthritis Research Society International classification,¹⁵ HA currently is a recommended conservative treatment for all OA degrees and has been used safely and widely around the world and in other joints (hip, shoulder, and ankle).

HA is a polysaccharide that consists of a long chain of disaccharides (β -D-glucuronyl- β -D-N-acetylglucosamine). It is a natural component of the cartilage and other tissues and plays an essential role in the viscoelastic properties of the synovial fluid. Its biological functions include maintaining the elastoviscosity of connective tissues, such as the joint synovial fluid and ocular vitreous, and controlling the tissue hydration and water transport. HA is highly hygroscopic, which is important to modulate the tissue hydration and the osmotic balance. In addition to its function as a passive structural molecule, HA also acts as a signalling molecule, interacting with cell surface receptors and regulating cell proliferation, migration, and differentiation, as well as numerous receptor-mediated roles in cell detachment, mitosis, migration, and development, and in the metastasis of tumours and inflammation.¹⁶⁻¹⁹

The mechanism of action of HA in the joint

The complete mechanism of HA in the joint is not fully understood, but a wide range of actions in the joint is recognized. It is known that the HA injected into the joint lasts a few hours or even a few days, being eliminated by the liver. In contrast, its effects can last for months. Its anti-inflammatory, analgesic, and chondroprotective action is related to the modulation of the intra- and extracellular inflammation cascade.^{20,21}

The osteoarthritic environment contains a series of cytokines (IL-6, IL-8, IL-B1), metalloproteinases, nitric oxide, arachidonic acid, and other

proteins that act in the inflammatory cascade of OA. Exogenous HA has an inhibitory effect on this cascade, modulating the harmful effect of these substances on the cartilage.^{22,23}

HA can bind to specific proteins called hyaladherin.²⁴ Some of these are membrane proteins, such as CD44 (Cluster of Differentiation 44), acting as a modulator of the immune system by inhibiting the interleukins IL-1 β and IL-6 and the expression of matrix metalloproteinase, reducing the PGE2 synthesis, contributing to the chondroprotection and proteoglycan/glycosaminoglycan synthesis, and having anti-inflammatory and subchondral effects. The release of cytokines also interferes with the regular cycle of the OA and, for all these reasons, HA is considered a disease-modifying drug.^{25,26}

HA also reduces the activity of macrophages and the production and migration of polymorphonuclear leukocytes that are important for tissue repair and chronic inflammation, playing an immunomodulatory role in the genesis of cartilage catabolism.²⁷

The IA HA therapy acts through a series of pathways, including the suppression (down-regulation) of pro-inflammatory cytokines *via* inhibition of cell surface receptors, such as the CD44 determinant, toll-like receptors 2 and 4, and layilin. This effect appears to be dependent on the HA molecular weight.²⁸

Some *in vitro* studies demonstrate that HA of high molecular weight can down-regulate the gene expression of aggrecanase-2, TNF- α , IL-8, and nitric oxide synthase in the synoviocyte culture of patients with early-stage OA.²⁹ The down-regulation of these inflammatory mediators suggests that HA of high molecular weight may have an anti-inflammatory and analgesic effect by inhibiting the leukocyte migration, free radical inactivation, and chemotaxis.³⁰⁻³²

The presumed HA disease-modifying activity may include effects on cartilage degradation. Indeed, exogenous HA can enhance chondrocyte synthesis of endogenous HA and proteoglycans, prevent cartilage degradation and promote its regeneration, and inhibit cellular inflammatory processes.³³

Thus, HA therapy would also be effective in the treatment of post-traumatic, degenerative joint

diseases, post-arthroscopy, post-surgical recovery, wound healing, and after prolonged immobilization.^{14,34-37}

The term 'viscoinduction' was created to describe the phenomenon of the clinical benefits of HA.³⁸ Viscoinduction ensures that clinical efficacy is maintained for several months, despite the half-life of IA HA being only a few days, which suggests that exogenous HA induces endogenous HA synthesis, possibly stimulating the regenerative process in the joint. Some *in vitro* studies indicate that synoviocytes from osteoarthritic joints resume the HA production after exposure to exogenous HA, restoring the viscoelastic properties of the synovial fluid – damping, lubrication, elasticity –, which change with the OA evolution.³⁹

HA agents are generally administered as a weekly injection over 1–5 weeks and, although they have a slower onset of action compared with the steroid treatment, the pain relief obtained usually lasts longer – for up to several months, and without the harmful risks of steroids. In the literature, we find a long discussion about the tolerability and safety of using HA in the treatment of osteoarthritis.⁴⁰

There are several presentations of HA marketed worldwide (80 or more), with different characteristics: origin (animal or biofermentation); molecular weight (from 500 to 9000 kDa); molecular structure (linear, cross-linked, and a mixture of both); concentration (from 0.8 to 30 mg/ml); volume per ampoule (from 0.5 to 6.0 ml); and application regime (from one to five applications). Some presentations include additives, such as mannitol or sorbitol. This great variability of products makes it difficult to establish a relevant clinical difference between them, especially concerning the molecular weight and application regime. In this regard, in a comparative study with more than 400 patients, Berenbaum *et al.*⁴¹ demonstrate better results on the Western Ontario and McMaster Universities (WOMAC) and visual analogue scales after a six-month follow-up with an intermediate molecular weight HA than with a low molecular weight HA.

In a review of 64 articles, Altman *et al.*⁴² demonstrate that HA differs greatly in the property and intrinsic characteristic of each product. However, this review shows significantly better results in terms of safety and efficacy when products with a molecular weight above 3000 kDa are used. This fact can help the clinician in choosing the HA among the available products.

Table 1. Chondropathy and hyaluronic acid in the medical literature.

Study	N	Type	Follow-up	Findings
Hempfling ⁴⁴	80	Prospective	24 months	HA + debridement = debridement, except 100 m walk
Magarelli <i>et al.</i> ⁴⁵	–	Prospective	12 months	MRI is a useful tool to evaluate chondral alterations after HA injections. MRI represents a useful tool to evaluate the grade of chondromalacia patellae and also to follow the cartilage modification induced by HA therapy
Jazrawi and Rosen ⁴⁶	–	Meta-analysis	Discusses the clinical improvement of patients with meniscal, chondral, and ACL injuries	
Filardo <i>et al.</i> ⁴⁷	192	Blind, prospective	12 months	HA = PRP in KOOS, IKDC, and VAS scores
Shah <i>et al.</i> ⁴⁸	–	Prospective	12 months	T1 rho MRI evaluated proteoglycans × WOMAC, VAS
Tamburrino and Castellacci ⁴⁹	40	Prospective	6 months	Improvement in KOOS AND VAS
Hart <i>et al.</i> ⁵⁰	86	Prospective	6 months	Improvement in KOOS
Di Martino <i>et al.</i> ⁵¹	189	Blind, prospective	64 months	HA = PRP in KOOS, IKDC, and VAS scores
Astur <i>et al.</i> ⁵²	63	Prospective	6 months	HA + better physiotherapy
Zhang <i>et al.</i> ⁵³	88	prospective	12 months	Better WOMAC and Lequesne

ACL, anterior cruciate ligament; HA, hyaluronic acid; IKDC, International Knee Documentation Committee; PRP, Platelet-rich plasma; KOOS, Knee injury and Osteoarthritis Outcome Score; MRI, magnetic resonance imaging; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities.

In their review article, Johal *et al.*⁴³ suggest that HA with high molecular weight or cross-linking HA are safe options for pain reduction in younger patients with knee osteoarthritis.

HA and patellar chondropathy

Although the topic is important, there are still few articles published. Some authors have sought to demonstrate scientific evidence on the use of HA in patellar chondropathy to demonstrate the clinical improvement achieved and understand the mechanism of the HA action. See Table 1.

To understand the mechanism of HA action, Shah *et al.*⁴⁸ demonstrated in a study with 10 patients a reduction in mean values of T1 rho magnetic resonance imaging (MRI) in six of nine patellar segments in six weeks, suggesting an increase in the content of proteoglycans. Simultaneously, there was an improvement on the

Western Ontario and McMaster Universities (WOMAC) visual analogue scale (VAS), and International Knee Documentation Committee (IKDC) scores, suggesting that HA could alter the natural course of the disease. T1 rho is an MRI modality that provides detailed images of the cartilage quality, allowing the quantification of early physiological changes in the cartilage considering the proteoglycan content.

Hempfling⁴⁴ demonstrated benefits with the use of HA after arthroscopic debridement when compared with debridement alone in a knee with chondral injuries. Magarelli *et al.*⁴⁵ observed patellar cartilage changes on MRI in patients with chondropathy after treatment with HA. According to Jazrawi and Rosen,⁴⁶ some clinical trials demonstrate the benefit of IA HA injections in younger patients with acute knee injuries, including symptomatic meniscal injuries and isolated anterior cruciate ligament injury with chondral injury.

The use of HA showed promising results in patients undergoing knee arthroscopy, and IA HA also showed direct antinociceptive effects that may contribute to its benefit in patients with patellofemoral pain. In a prospective, randomized, double-blind clinical study, Hart *et al.*⁵⁰ found no difference between two groups of patients submitted to a single injection of HA (Synvisc One) compared with the placebo group after 6 months. The parameters analysed were the Kujala scale and VAS, Tegner activity rating, Knee injury and Osteoarthritis Outcome Score (KOOS), normalized maximal voluntary knee extension torque, and central activation ratio, as measured at baseline and at 1, 3, and 6 months post-randomization. Tamburrino and Castellacci⁴⁹ published an article with good results with two applications of a hydrogel based on a HA derivative (HYADD4-g) in 40 professional football players from the Italian League evaluated according to KOOS and VAS at 1, 3, and 6 months of follow-up. Lohse *et al.*⁵⁴ published a case series involving children and adolescents from 10 to 16 years old with patellofemoral chondropathy. Thirteen of the 16 patients had excellent or good results and returned to their sports activities when submitted to one or three injections of IA HA. Although it is a case series, this study indicates the possibility of using HA safely in this group age. In a comparative, prospective study involving 189 patients with a mean age of 54 years and with a painful and degenerative condition in the knee, including chondropathy, Filardo *et al.*⁴⁷ found no difference between the groups treated with HA and with platelet-rich plasma over 12 months in the IKDC, Tegner, KOOS, and VAS scores. Patients were subsequently followed up at 64 months and the results remained unchanged.^{51,55} Astur *et al.*⁵² showed that 70 patients undergoing treatment for chondral patellar injuries of grades II or III with the use of exogenous IA HA associated with physiotherapy rehabilitation had better results for pain and knee function when compared with patients undergoing only physiotherapy treatment 3 and 6 months after diagnosis.

In a prospective study with 88 patients and a 52-week follow-up, Zhang *et al.*⁵³ showed that patients from a patellofemoral arthritis group and an early chondropathy group had significantly decreased WOMAC scores and Lequesne scores at four, 12, 26, and 52 weeks after HA injections when compared with the baseline scores. However, no significant difference was found between the two groups in WOMAC scores and

Lequesne scores at four or 12 weeks after the injections. These scores at 26 and 52 weeks after the injections were significantly higher in the patellofemoral arthritis group than in the early chondropathy group.

The control of joint pain in patellar chondropathy involves understanding the complex mechanism of inflammation and tissue damage and repairs modulated by various inflammatory mediators, such as cytokines, tumour necrosis factor, prostaglandin-E, bradykinin, and substance P, as well as the roles played by the immune system, collagen production, and cell apoptosis.⁵⁶ It is hard to believe that a single molecule or drug can make it alone, therefore, so far, the multimodal treatment of pain seems to be the answer.

Conclusion

The search for disease-modifying drugs for the treatment of OA has become a priority in the field of orthopaedics. HA has been shown to be safe and effective in the treatment of pain related to OA in the knee and other joints, confirming that HA may have some disease-modifying property.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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ORCID iD

Sergio Ricardo da Costa  <https://orcid.org/0000-0001-7224-0319>

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