Abstract

Knee osteoarthritis (KOA) is a disease of wear and tear, leading to disability and ultimate surgical treatment. KOA has multiple etiologies and is considered a disorder of physiological processes that is manifested by progressive lesions of articular cartilage caused by chondrolysis, synovial membrane inflammation and subchondral osteophytes production. Modalities that limit the progression of the KOA and rehabilitation are a constant interest for clinicians and medical researchers. Various physical therapies and pharmacological strategies are currently used for pain management, with no clear benefit in terms of inhibiting disease progression. In this context, the use of exogenous hyaluronic acid (HA) (that is a vital component of the synovial fluid and involved in lubricating all synovial joints) has been explored as viable alternative to alleviate knee pain and temporarily restore knee function. In the following, we will review the use of HA injections associated with the physiotherapeutic recovery plan in the treatment of KOA. The therapeutic effects of the HA is still a matter of debate in the field, with no consensus being reached so far and thus, difficult to evaluate. However, much research has to be done to understand the therapeutic efficacy of HA alone or in combination with physical therapies and the role that other factors may play in unraveling its beneficial effects on the KOA.

Key words: knee, osteoarthritis, hyaluronic acid, physiotherapy, rehabilitation,

Introduction

Osteoarthritis (OA) is a chronic condition of the locomotor system that affects the joints and spine in the middle-aged population, leading to disability. Symptomatic knee injury affects 250 million people worldwide, both men and women (1). Progression of the disease is associated with age and ultimately leads to total loss of articular cartilage. Unfortunately, non-surgical and physical therapies have been shown to have limited long-term efficiency and high toxicity generated by extended use of medication.

Osteoarthritis clinical and paraclinical evaluation

The main manifestations of the knee OA (KOA) are defined by the slow but progressive destruction of articular cartilage, along with changes in the subchondral bone surface and synovia. KOA is a disease with multiple etiologies in which articular "wear and tear" is not the main cause as thought, but rather a disorder of physiological processes that is manifested by progressive lesions of articular cartilage and other structures (2). In terms of KOA classification, it may be primitive where trigger factors are not fully known; and secondary KOA in which local and / or systemic trigger factors are known. The basis of KOA processes is the aging of biomechanical systems, degradation being caused by chondrolysis, inflammation of the synovial membrane, and subchondral osteophytes production. Early physiopathological KOA is characterized by increased hydration of the cartilage matrix, leading to loosening the collagen network and altering the distribution of proteoglycans. The cartilage becomes irregular and the first cracks and tears appear. Progression of the disease is correlated with increased stress in chondrocytes, loss of elasticity and exposure to degrading enzymes (2). Later changes of KOA are characterized by osteophytes formation, subchondral bone cysts, and cartilage ulcerations from focal to diffuse areas. Late changes also have other features such as: soft tissue damage around the joints, proximal muscle weakness, abnormal ligament laxity and inflammatory infiltrations in the synovium. The inflammatory and destructive factors in KOA are: the presence of adipokines (3), IL-1 and TNF-α cytokines, which regulate matrix metalloproteinase (MMP) gene
expression, which participates in cartilage destruction and inhibits repair processes; pro-inflammatory cytokines IL-6, IL-8, IL-11, IL-17 and IL-4, IL-10, IL-13 anti-inflammatory cytokines and the presence of MMP degradation enzymes (2, 3). The diagnosis of KOA is classified according to the Kellgren and Lawrence (KL) evaluation system, which is a widespread radiological diagnosis tool (4). Antero-posterior radiographic images are performed to realize the stage of KOA on a zero to four scale; zero for the healthy knee and four for maximum narrowing of the joint space. Clinical diagnosis of KOA contains three important symptoms: short term knee pain, morning stiffness and functional limitation. Clinical signs are: crepitation, limited range of motion and bone deformation (5). Functional examination is largely based on measuring the Range Of Motion (ROM) for the flexion and extension of the knee, which can be performed both, actively and passively (6). The muscular force of the extensor of the knee is another key element in KOA evaluation. The phenomenon is known as "arthrogenic inhibition" of quadriceps muscle, inhibition resulting in increased muscle weakness being closely related to disease progression (7). Chronic pain in KOA is a complex that includes important nociceptive components, and neuropathic elements (8). Another consideration is functional gait evaluation of KOA by observing abnormal movements, distorted or compensated indirectly, that may indicate instability ligament and muscle failure.

**Osteoarthritis treatment and recovery**

KOA treatment and rehabilitation is still a subject of debate discussed by multiple disciplines, each developing treatment guidelines specific to the methods used. Unfortunately, no cure for KOA has yet been found, however many ways of preventing and limiting the progression of disease have been explored. Primary or secondary KOA has the same pharmacological, non-pharmacological, physical therapy, rehabilitation, and surgical treatment. In 2014 Osteoarthritis Research Society International has published a guide to KOA non-surgical treatment based on the literature and scientific evidence (9). The general guidelines of the study are directed to non-surgical, non-pharmacological and physical therapy, treatment and rehabilitation, focusing on patient education and self-care. Adequate treatment modalities suitable for all patients with KOA was considered topical and oral NSAIDs (COX-2), physical therapy exercise and Duloxetine was recommended to patients with multiple arthrosis without other complications. Treatments with moderate efficacy were also considered: chondroitin, glucosamine, intra-articular infiltration with Hyaluronic Acid (HA) and TENS electroanalgesia (10). KOA treatment recommended by American College of Rheumatology was divided into two branches: non-pharmacological and pharmacological approaches. Non-pharmacological treatment includes weight loss, physical therapy exercises, thermotherapy, TENS electroanalgesia, rehabilitation, patellar Kinesio Taping®, orthopedic insoles and psychosocial programs. If no results are obtained with pharmacological treatment with: NSAIDs (COX-1 and COX-2), Acetaminophen, corticosteroids injections, HA injections, Tramadol, Duloxetine, the next step are opioids in the desire to delay surgical interventions (11). American Academy of Orthopedic Surgeons recommends, as a pharmacological treatment for KOA, administration of oral NSAIDs, local NSAIDs and Tramadol. Moreover, in 2013 they did not recommend treatments with HA intra-articular injectionos (12). European League Against Rheumatism published a clinical guide using available scientific evidence and an interdisciplinary consensus for several treatment modalities (13). The strong recommendation was: weight loss, NSAIDs, analgesics, food supplements, educating the patients using rehabilitation physical therapy exercise, intra-articular injection of steroids, topical / periarticular NSAIDs application, and opioids, intra-articular HA injection, orthopedic insoles, articular lavage and patellar Kinesio Taping® (14).

**Hyaluronic acid in knee osteoarthritis**

HA (C\(_{33}\)H\(_{54}\)N\(_2\)O\(_{23}\)) is a natural carbohydrate found in the human body, with a molecular weight 846,786 g / mol. HA is an amorphous, glassy substance and is part of the class of glycosaminoglycans or acid mucopolysaccharide compounds, with the effect of filling the extracellular spaces between the collagen fibers. HA behavior in biological structures is to attract water, lubricate intracellular structures and give "volume", forming a gelatinous matrix with which the elastin and collagen fibers are coagulated and aligned together (15).
HA is present in most connective tissues and especially in synovial fluid (16). HA degradation is a step-by-step process that can occur through enzymatic or non-enzymatic reactions. A reduction in molecular HA weight by degradation or slowing of synthesis affects physical and chemical properties such as tissue volume, viscosity and elasticity. HA is a molecule found in abundance in the knee joint and especially in synovial fluid, but also in articular cartilage. The knee joint is a harsh bio-mechanical environment because it is avascular, aneural and alimphatic, where the synovial fluid serves as a lubricant with special rheological properties. Synovial fluid also has the property of clearing free radicals and regulating intracellular activity and proteins binding. Progression of KOA is closely related to the loss of synovial fluid lubrication function. This process is a consequence of depolimerization of endogenous HA with high molecular weight (6500-10900 kDa) and his transformation in a low molecular weight (2700-4500 kDa). HA with low molecular weight leads to a synovial fluid with much reduced mechanical and visco-elastic properties. Injection of a high molecular weight exogenous HA may be used in the KOA to limit the loss of properties of synovial fluid due to endogenous depolimerisation of natural HA. Exogenous HA does not replace or restore endogenous HA but its presence in the joint induces an improvement in the symptoms of KOA over a period of several months (17). This is possible due to the synthesis of glycosaminoglycan and/or synthesis of proteoglycan, thus synovial fluid maintaining its visco-elastic properties. Exogenous HA has also an important antiinflammatory effect which, through secondary mechanisms, will reduce pain. FDA-approved (Food and Drug Administration) HA injected products have various physico-chemical characteristics that make a product more efficient/competitive than the other. The molecular weight is the main element targeted by clinicians, and this can range from 500 up to 6000 kDa (17). As a general rule, the higher the molecular weight, the longer the therapeutic efficacy. The source of animal and non-animal HA origin is another criteria for the selection, along with the molecular structure (linear, crosslinked or in combination), degree and crosslinking method, the concentration that can range between 0.8 - 30 mg/ml, and dose of injected volume (0.5 - 0.6 ml).
NSAID’s side effects (26). KOA is a surgical end-wear disease. Intra-articular HA injection in the knee opens new horizons and new possibilities to limit the progression of the disease, thus treating the causes of joint damage. It is known that HA only lasts 2-3 days in the joint, however its chondroprotective effects are seen over the several weeks post-injection (27). HA provides the synthesis of extracellular matrix proteins such as collagen type II and increased proteoglycan and glycosaminoglycan synthesis (28,29,30). HA reduces proteoglycan loss in cartilage and apoptosis of chondrocytes (28). Intra-articular HA stimulates the endogenous synthesis of HA ensuring joint lubrication (31). Also, by decreasing local production of cytokines, HA reduces the degradation of joint and decreases the generation of pain mediators (28). By binding to CD44 nociceptors, HA reduces prostaglandin and cyclooxygenase (COX-2) production, and by activating opioid receptors, alleviates pain through modification of pain pathways (31). Therefore, HA has shown efficacy in the treatment of KOA by its anti-inflammatory, chondroprotective and analgesic effects. A conducted study made in 2015 by the European Society of Sports Traumatology, Knee Surgery, Arthroscopy was conducted to assess the effectiveness of recovery through therapeutic exercise in combination with injected HA in moderate KOA. The study was prospective, randomized trial controlled, blinded, with three patient groups over a 6-month period. Group 1 only received HA injected two weeks, Group 2 only performed individualized exercise up to 20 sessions in one month. Group 3 simultaneously received both types of treatment in combination. The evaluation was done using the WOMAC scale and active motion domain (AROM), patients passing through successive series of assessments at 1, 3 and 6 months after the treatment session. All patient groups experienced improvements from one month after treatment, and group 3 experienced a significant improvement over the first group. In the second group from the second to the sixth month of treatment, WOLMAC score was modified, showing the symptoms worsening (stiffened joint, pain and the gradual loss of mechanical function). From the AROM evaluation perspective, there were no differences between groups during the 6 months of monitoring. The authors conclude that HA injected therapy combined with adapted medical exercise has greatly improved pain one month after treatment. Improving knee function and limiting KOA progression with injected HA is due to the counterbalance of the negative effect of inflammatory mediators that are involved in chronic synovitis, cartilage destruction in bone remodeling and soft tissues (32). A multicenter study was conducted in the United States, to determine the effectiveness of physical therapy associated with the injection of HA to treat and recovery KOA, from the perspective of clinical utility and costs. The combined therapy program for recovery KOA, was composed by HA injectable and therapeutic physical exercises that included: muscle toning, flexibility exercises and proprioception. The design of the study was to track 553 patients with symptomatic KOA for 8 weeks in 27 USA specialized centers, patients who had undergone previous but not effective pharmacological treatments. Physical therapy was performed under the guidance of physiotherapists throughout the 2-3 sessions in an week. The result was quantified by reducing the knee pain by 59% in all evaluated patients. The WOLMAC score was improved with values ranging from 44% to 51%, with patients experiencing a significant reduction in specific symptomatology, even in KL3-KL4 stages. The combined therapy program is said to be cost-effective ratio over 2 years of monitoring, clearly delaying the surgical treatment of the knee. The authors believe that rehabilitation through physical therapy programs and HA injections acts through a synergistic handler using different therapeutic mechanisms that can limit the progression of KOA in the medium term and with a good cost-effectiveness ratio (33). 

For the future
Clinical studies and meta-analyses have sometimes reported contradictory results on the safety and effectiveness of HA injections for KOA. Due to these confounding results, KOA treatment and rehabilitation guidelines differ from one author to another and from one society to another, sometimes uncertain recommendations are made and often objectionable. From the perspective of side effects, when compared to corticosteroids and saline solution, HA does not appear to have higher side effects. Controlling the symptoms on medium and long term in mild and moderate KOA, HA provides better and more stable outcomes than corticosteroids.
and rehabilitation physical therapy improve the function of knee. The clinical response differs from one solution to another, rheological parameters also can differ, and the assessment of the product classes has to be done individually, because the universal evaluation may not be adequate. Physical therapy rehabilitation programs optimized on patient are much more effective than general - homemade treatment programs and in combination with TENS electroanalgesia, VAS and WOLMAC score are improved. However, additional research is needed on the HA's chondroprotective mechanisms, in larger group samples and longer periods of observation, in order to clarify the therapeutic effects and the safety of HA for widespread use. It would also be interesting to study various ways of controlling the evolution of the disease and its side effects. Exploiting the potential of HA's treatments with different molecular compositions in combination with physical therapy, clinicians could improve the KOA's overall treatment guidelines. More in-depth studies would be required based on a clear and homogeneous methodology, taking into account rheological behavior, molecular weight, injected amount, HA origin, disease status, comorbidities and combinations with other drugs. Nevertheless, the quality of these studies could be influenced by data processing method and that should be homogeneous and the collection, processing, analysis, data interpretation and generation of conclusions should be in consensus. More comprehensive studies are needed, in which HA injected therapy in particular could be studied alongside, rehabilitation physical therapy, TENS, LED, LASER, cold-warm therapy, ultrasound, TECAR, etc.

References


