Int. J. Morphol.,
35(3):870-876, 2017.

Role of Hyaluronic Acid in the Homeostasis and Therapeutics of Temporomandibular Joint Osteoarthritis

Rol del Ácido Hialurónico en la Homeostasis y Terapéutica de la Osteoartritis de Articulación Temporomandibular

Veronica Iturriaga[1,2,3]; Bélgica Vásquez[4]; Carlos Manterola[5,6] & Mariano del Sol[5]

ITURRIAGA, V.; VÁSQUEZ, B.; MANTEROLA, C. & DEL SOL, M. Role of hyaluronic acid in the homeostasis and therapeutics of temporomandibular joint osteoarthritis. *Int. J. Morphol., 35(3)*:870-876, 2017.

SUMMARY: The aim of this study was to perform a literature review regarding the role of hyaluronic acid (HA) in the homeostasis and therapeutics of temporomandibular joint (TMJ) osteoarthritis (OA). The TMJ has characteristics that give it special adaptation and recovery abilities, where HA plays a fundamental role in helping to maintain joint homeostasis, which is affected in pathological processes like OA. OA is a chronic degenerative multi-factor disease that can affect all the components of the synovial joints, causing degradation of the articular cartilage, extracellular matrix and breakage in the HA molecules. HA is a non-branched linear polysaccharide with viscosupplementation, anti-inflammatory, lubrication and pain relief effects; it also activates the intrinsic repair processes of the cartilage and normalizes the endogenous production of HA by the synoviocytes. In recent years, the therapeutic use of HA has shown evidence that supports its application in TMJ OA, improving viscosupplementation capacity, acting at the cellular and molecular levels, reducing various inflammatory mediators and improving the reparative characteristics. Its use has been studied in animal models and in humans. However, no consensus has been reached in terms of concentrations, dose, application frequency or molecular weight to be used.

KEY WORDS: Hyaluronic acid; Osteoarthritis; Temporomandibular joint; Temporomandibular disorders; Viscosupplementation.

INTRODUCTION

The temporomandibular joint (TMJ) is classified as a synovial joint, condylar, ellipsoid or bicondylar, and presents two main axes of movement, making it one of the most complex joints in the body (Vasconcellos *et al*., 2007).

Among the diseases that can affect the TMJ are inflammatory-degenerative disorders like osteoarthritis (OA), which is one of the most significant pathologies affecting this joint, and is known as temporomandibular joint disorder (TMD) (Manfredini *et al*., 2010; Güler *et al*., 2011). OA is a chronic degenerative multi-factor disease that can affect all components of the synovial joints (Kim *et al*., 2001; Uchôa de Rezende & Constantino de Campos, 2012), where hyaluronic acid (HA) plays an important role in the disease adaptation process.

It has been suggested that HA presents properties that could maintain the internal homeostasis of the TMJ, helping it to adapt to different pathologies, producing the viscosupplementation phenomenon. Currently exogenous HA (EHA) is being used as an alternative therapy, and there is evidence that would support its use in TMJ OA.

The aim of this study was to perform a literature review regarding the role of HA in the homeostasis and treatment of TMJ OA.

Characteristics of the temporomandibular joint. The human TMJ is composed of the condylar process of the mandible, the mandibular fossa and the articular tubercle of the squamous part of the temporal bone (Vasconcellos *et*

[1] Departamento de Odontología Integral del Adulto, Universidad de La Frontera, Temuco, Chile.
[2] Programa Doctorado en Ciencias Médicas, Universidad de La Frontera, Temuco, Chile.
[3] Becario CONICYT, PFCHA/ Doctorado Nacional/2015-21151352.
[4] Facultad de Ciencias de la Salud. Universidad de Tarapacá. Arica, Chile.
[5] Centro de Estudios Morfológicos y Quirúrgicos (CEMyQ), Universidad de La Frontera, Temuco, Chile.
[6] Departamento de Cirugía, Universidad de La Frontera, Temuco, Chile.
Funding: This research was financed by CONICYT through national doctoral scholarships. CONICYT, PFCHA/ Doctorado Nacional/ 2015-21151352.

al.). The two bones are separated by a concave-convex articular disk formed by fibrous and dense connective tissue with intertwined bundles of collagen devoid of blood vessels or nerve fibers at its core (Vasconcellos *et al*.; Okeson, 2008). The joint capsule has a synovial inner layer, which is responsible for the secretion of synovial fluid (SF), contributing to the lubrication of the TMJ (Vasconcellos *et al*.).

Covering the bone tissue of the condyle and mandibular fossa on the joint surface, there is a 2 mm-thick layer of dense fibrous tissue that serves to absorb pressures and distribute them across the surface (Wurgaft & Montenegro, 2003). This joint surface has four different histological areas that give the TMJ distinctive properties (Hansson *et al*., 1977). The surface layer, called the joint or fibrous area, is formed by fibroblasts and has dense fibrous connective tissue with fibers strongly bound to support the forces of movement. Contrary to what occurs in most synovial joints, which are covered by hyaline cartilage, creating an advantage in terms of repair, sensitivity to aging and support for the forces of movement (Wurgaft & Montenegro; Okeson). The second layer, called proliferative or cellular, is very thin and is located mainly in the lateral areas of the condylar surface, near the synovial capsule and membrane. It is composed of undifferentiated mesenchymal tissue giving the articular cartilage the chance to proliferate, allowing the TMJ to respond to functional demands and loads. In cases of prolonged mandibular immobilization, it has been noted that this layer can be lost, making joint tissue neoformation and recovery impossible (Wurgaft & Montenegro). The authors cited, report that the third fibro cartilaginous layer is formed by a cartilaginous matrix, chondrocytes in its lagoons and type I collagen fibers, some intertwined, others radially, providing increased resistance to lateral and compression forces. The thickness of this layer varies depending on its position, it is thicker in areas subjected to greater pressure, and thinner in areas further from the working space. Finally, the fourth calcified layer is the deepest and is formed by chondroblasts, chondrocytes and osteoblasts distributed throughout the articular cartilage. In this layer, the chondrocytes give rise to the osteoblasts from inside the bone and are the ones charged with synthesizing the collagen, proteoglycans, glucoproteins and enzymes that form the extracellular matrix. This is how a mesh of collagen, proteoglycans and HA is formed which attracts water and aids in supporting joint loads, keeping the internal and external joint pressures in balance (Wurgaft & Montenegro; Okeson).

In some pathologies, such as condylar hyperplasia, a variation has been noted in the size and definition of these layers, in addition to differences in the type of collagen fibers and cellularity involved (Vásquez *et al*., 2016). On the other hand, Oyanguren *et al*. (2010), studied the amount and distribution of collagen and elastic fibers, finding a relationship with the functional role of joint tissues where they are found.

Temporomandibular joint osteoarthritis. TMJ OA is a slow, progressive and debilitating heterogeneous condition that can cause pathological changes on the joint surfaces (Kim *et al*.; Uchôa de Rezende & Constantino de Campos). Clinically, it is characterized as presenting joint pain, a reduced range of mandibular movement, a crackling noise and functional difficulty (Okeson). In terms of imaging, OA can be detected through tomographies like computed tomography or cone beam computed tomography and magnetic resonance (López López *et al*., 2005). Imaging features to be found include erosion, sclerosis, the presence of osteophytes and flattening of the surfaces (Güler *et al*.).

Histopathological characteristics include a progressive degeneration of the articular cartilage (Cledes *et al*., 2006), fibrillation and erosion of the articular surfaces, proliferation of chondrocytes, eburnation of the articular cartilage, synovitis, changes and exposure in the subchondral bone and formation of osteophytes at the articular margin (Cledes *et al*.; Güler *et al*.). The imbalance occurs between the process of synthesis and degradation within the chondrocytes, which leads to the loss of cartilaginous tissue. As a result, over time a degenerative process of the joint surfaces occurs, characterized by degradation of the cartilaginous matrix and synthesis inhibition of its components, leading to joint deterioration and pain in advanced stages (Güler *et al*.). It has been suggested that this inflammatory reaction could contribute to the development and progression of the pathology (Hirota, 1998).

High levels of inflammatory mediators in the SF of patients with TMD have been detected, such as disk displacement and OA (Quinn & Bazar, 1990; Shafer *et al*., 1994; Fu *et al*., 1995). Among the most recognized inflammatory mediators are arachidonic acid derivatives, related enzymes and some cytokines (Uchôa de Rezende & Constantino de Campos). Cytokines like interleukin-1b (IL-1b) and tumor necrosis factor a (TNF-a) can affect bone resorption, the proliferation of SF and cause the destruction of the cartilage (Hirota). These cytokines are derived from monocytes, synovial fibroblasts and epithelial cells, which can stimulate the production of arachidonic acid metabolites like some prostaglandins (Hirota), directly and indirectly increasing joint damage, producing a vicious circle where disintegration of the cartilage occurs due to changes in the HA of the SF (Xinmin & Jian, 2005).

Additionally, a decomposition of the HA is produced, reducing its concentration and molecular weight in the joint, which in turn produces a change in the nature of the SF (Balazs *et al*., 1967; Dahl *et al*., 1985). Viscosity and molecular barrier functions are also weakened, preventing protection of the articular proteoglycan matrix, making it difficult to inhibit the inflammatory process (Goldberg *et al*., 1991; Xinmin & Jian). It has been suggested that HA modifies the flow of the SF through the joint. Although, it has been reported that the flow of SF is reduced in OA, most of the measurements indicate that there is a faster elimination of HA and proteins in the joints with synovitis than in joints with OA (Brandt *et al*., 2000).

Hyaluronic acid and its role in joint homeostasis. HA is a non-branched linear polysaccharide comprised of several units of glucuronic acid disaccharides and N-acetylglucosamine (Brandt *et al*.; Kim *et al*.). It is synthesized by synoviocytes, fibroblasts and chondrocytes present in the connective tissue of all mammals (Brandt *et al*.). In addition, it is the largest natural component of SF and an important component of the articular cartilage (Xinmin & Jian).

In physiological conditions, HA plays an important role in maintaining intra-articular homeostasis (Manfredini *et al*., 2010). Its action stems from the ability of the polysaccharides to connect to each other when they are in solution, forming a network that provides a high degree of viscosity to the SF (Brandt *et al*.; Xinmin & Jian), thereby obtaining a "cushioning" effect in the support of loads. In addition, it has anti-inflammatory and lubricant effects, relieves pain, activates intrinsic repair processes of the cartilage and normalizes the endogenous production of HA by the synoviocytes (Manfredini *et al*., 2010). Its metabolic activity also facilitates the nutrition of the joint disk and cartilage in vascular areas (Coronado *et al*., 2015).

In situations where rapid mandibular movements occur, elasticity is the main property that SF possesses, but in slow mandibular movements viscosity becomes the main characteristic (Xinmin & Jian). This is important because viscosity helps joint lubrication and occurs often with HA.

Hyaluronic acid as a therapeutic alternative. In recent years, intra-articular infiltration of EHA has been gaining ground in the treatment of TMJ OA as a viscosupplementation method (Manfredini *et al*., 2010). From the biochemical point of view, this molecule is a drug in the glycosaminoglycan group. However, in physiological conditions it is found in the form of salt, as sodium hyaluronate or hyaluronan; its properties can vary in relation to its molecular weight and shape (Uchôa de Rezende & Constantino de Campos).

Under in vitro conditions, HA presents a variety of effects on cell and joint damage (Brandt *et al*.). These include inhibition of prostaglandin E2, synthesis of inerleukin-1 (Yasui *et al*., 1992; Tobetto *et al*., 1992), and protection against the disintegration of proteoglycans and cytotoxity induced by oxygen free radicals. In addition, it affects leukocyte adhesion, proliferation, migration and phagocytosis (Ghosh *et al*., 1995); it directly influences the control mechanism of monocyte activation; in the cartilage it has been seen to suppress degradation of the cartilaginous matrix by fibronectin fragments (Homandberg *et al*., 1997; Williams *et al*., 1997; Brandt *et al*.).

Animal studies have shown that EHA infiltration has positive effects on joint pain reduction and OA (Armstrong, 1994; Sakakibara *et al*., 1994; Gosh *et al*.; Neo *et al*., 1997; Shimizu *et al*., 1998). Although its mean life is 13 to 30 hours, the intra-articular application yields persistent benefits (Bertolami *et al*., 1993; Sato *et al*., 2001; Uchôa de Rezende & Constantino de Campos), and increases the molecular weight and amount of HA synthesized by the synovia (Brandt *et al*.; Uchôa de Rezende & Constantino de Campos). It is proposed that the positive effects are due to direct and indirect consequences of viscosupplementation (Uchôa de Rezende & Constantino de Campos), as this compensates for the viscosity of the SF that has decreased as a result of OA (Xinmin & Jian); therefore, EHA infiltration could improve the rheological properties of the HA, modulate the joint inflammation, promote a better distribution of forces, stabilize the extracellular matrix, stimulate the proliferation of chondrocytes, regulate the production/degradation of type II collagen and avoid sensitization of pain receptors in joints with OA (Kim *et al*.; Uchôa de Rezende & Constantino de Campos). In addition, it would reduce the gene expression of cytokines and enzymes associated with OA, and would cause the decrease in prostaglandins and concentration of metalloproteinases (Uchôa de Rezende & Constantino de Campos).

With respect to the origin of EHA preparations, they can be of avian or non-avian origin (Uchôa de Rezende & Constantino de Campos; Brandt *et al*.). In the first case, they are derived from rooster comb and in the second from bacteria like Streptococcus zooepidermicus. The latter pose the least potential of an allergen (Uchôa de Rezende & Constantino de Campos). Examples of preparations of avian origin would be Synvisc® or Synvisc®oneTM, and of non-avian origin Suprahyal®.

Application of EHA: Studies on humans. Manfredini *et al*. (2010) conducted a systematic review, finding seven publications where EHA was used in the treatment of patients with TMJ OA. In these publications, all reported a marked

improvement in the measured variables (ranges of movement and pain). After application of EHA in patients with TMD, there was a significant reduction in inflammatory cytokines like IL-1β and TNF-α (Hirota), avoiding progression of the pathology. Iturriaga *et al*. (2017) performed a systematic review in which the effect of the EHA was assessed in the regulation of inflammatory mediators in TMJ OA in humans, finding that its effect also extends to the plasminogen activation system and to nitric oxide. The authors indicated that HA not only acts as a viscosupplement, mechanically reducing the friction, but can also play a role as an inflammatory mediator in the osteoarthritic process by regulating the proteolytic activation of the plasminogen activation, avoiding the release of proinflammatory mediators, reducing the activation of metalloproteinase proforms and modulating neurotransmission and vasodilatation processes.

Manfredini *et al*. (2010) found that the application of a single infiltration of EHA showed better results than the use of metacarbamol plus paracetamol (Oliveras-Moreno *et al*., 2008; Manfredini *et al*., 2010). Positive effects were also found in comparison with patients without treatment (Bjørnland *et al*., 2007; Møystad *et al*., 2008); and no differences were found with the short-term use of intra-articular corticosteroids (Guarda-Nardini *et al*., 2005; Manfredini *et al*., 2010). However, the use of corticosteroids can present some adverse effects such as progression of the disease and condylar resorption (Wenneberg *et al*., 1991; El-Hakim *et al*., 2005), whereas the application of EHA does not show any major adverse effects (Li *et al*., 2012; Grossmann *et al*., 2013). According to Uchôa de Rezende & Constantino de Campos, the minimum adverse effects described were related to the infiltration procedure, such as effusion, joint pain, burning and joint erythema, which are all temporary.

There is no consensus in the literature regarding the concentrations, dosage and application frequency of EHA in humans. The most frequently used concentrations are 1 %, 0.5 % and 1.5 %, with the first being the most frequent (Coronado *et al*.). In terms of dosage, applications of 0.5 ml, 0.7 ml, 1 ml and 2.6 ml can be found, and with respect to the frequency, the most frequently used protocols are single infiltration or, weekly infiltration for five weeks, which have been extrapolated mainly from knee procedures. In the case of the knee joint, the only medication that has shown benefits with a single infiltration is Synvisc®oneTM, unlike the other hyaluronates, which must be infiltrated once a week for 3-5 weeks (Uchôa de Rezende & Constantino de Campos).

Few studies describe molecular weight. Generally, it may be said that most of the preparations present a higher molecular weight than human HA. However, they can be divided into: EHA of low molecular weight, 0.5-1 x 106 Da, such as Hyalgan® or Suprahyal®; EHA of intermediate molecular weight, 1.8 x 106 Da, Viscoseal®; and EHA of high molecular weight, 6 x 106 Da, Synvisc® or Synvisc®oneTM (Balazs & Denlinger, 1993).

Guarda-Nardini *et al*. (2012) compared the effects of EHA of low and intermediate molecular weight in TMJ OA in humans, finding no statistically significant differences: Both were beneficial with respect to different symptoms. On the other hand, a study conducted on humans compared six TMJ infiltration protocols prior to arthrocentesis with different infiltration rates and molecular weight. Pain when chewing, mouth opening and joint noise were compared, and no statistically significant differences were found between the groups. However, the protocol of a weekly infiltration of EHA of low molecular weight for five weeks showed slightly better results than the rest, suggesting further study is required (Manfredini *et al*., 2012).

In relation to the physicochemical effects of EHA, it is suggested that the higher the molecular weight the more positive the effect; however, some authors hypothesize that excessive molecular size (between 1-6 x 10^6 Da) would prevent the HA from moving from the intra-articular environment to the intercellular environment in such a way that it would not be able to act on synoviocytes and chondrocytes, which is why products with a molecular weight between 0.5-1 x 10^6 would be the most effective (Uchôa de Rezende & Constantino de Campos). Manfredini *et al*. (2012), reported severe pain with the infiltration of EHA of high molecular weight, despite other in vivo results indicating a direct relation between molecular weight and analgesia (Uchôa de Rezende & Constantino de Campos).

Application of EHA: Studies on animals. On the other hand, in vivo studies on animals are frequently used to study pathological mechanisms and the development of new therapies in TMJ AO. A review by Coronado *et al*. found four studies on the topic, which used different animal species, such as rabbits, rats and sheep. In general, the species used depends on the aim of the study. Rats are linked mainly to the study of the nervous system and nociception, rabbits to TMD models such as disk or inflammatory disorders, and sheep to surgical procedures (Herring, 2003).

As mentioned, the rabbit presents some advantages when studying inflammatory disorders of the TMJ. The rabbit has similarities with the characteristics of the human TMJ in terms of its anatomy and movements, mainly the laterality that gives it a mobility not found in other animals (Savalle *et al*., 1990; Güler *et al*.). In addition, it is a

manageable animal like the rat, but unlike the rat, the rabbit has a high rate of bone and joint turnover, which makes it possible to observe joint physiological and pathological processes more quickly, this being an advantage when studying inflammatory disorders of the TMJ. Likewise, it is preferable for the subjects to be male to avoid a hormonal influence on the metabolism of the articular cartilage and bone (Güler *et al.*).

In summary, Coronado *et al.*, mentioned that the most reported application frequencies in animal models, are the single doses of EHA and a weekly dose for five consecutive weeks. In relation to the concentration, the most used was EHA at 1 %; however, the doses vary among species. According to the authors, in rabbits the concentrations can fluctuate between 0.1 ml and 0.5 ml, 0.12 ml in rats and 1 ml in sheep. The molecular weight of the EHA was not reported in any of the studies reviewed (Coronado *et al.*). Based on what was previously indicated in animal models, there is also no consensus regarding the different EHA infiltration protocols, since to date no comparison has been made among them. Table I shows a summary of the physiological and therapeutic properties of hyaluronic acid.

Table I. Physiological and therapeutic role of hyaluronic acid in the temporomandibular joint.

Physiological role of hyaluronic acid
Provides a high degree of viscosity to the sinovial fluid.
Has anti-inflammatory effects.
Increases joint lubrication.
Contributes to pain relief in pathological processes.
Activates intrinsic cartilage repair processes.
Stimulates endogenous production of hyaluronic acid.
Facilitates the nutrition of the disc and articular cartilage.
Therapeutic role of hyaluronic acid
Offers visco-supplementation to the joint.
Inhibits PGE_2, IL-1, TNF-α and metalloproteinases.
Decrease the cytotoxicity given by oxygen free radicals.
Decreases the degradation of proteoglycans.
Affect the adherence, proliferation, migration and leukocyte phagocytosis.
Prevents sensitization of joint pain receptors.
Increases the molecular weight and amount of endogenous hyaluronic acid.
Improves rheological properties of endogenous hyaluronic acid.

CONCLUSION

The TMJ is one of the most complex joints in the body, presenting unique features that afford it great adaptive and reparative capacity. TMJ OA is a frequent pathology that produces an imbalance in joint homeostasis, causing degradation of the cartilage and extracellular matrix, inhibition of the synthesis of the joint components, an increase in inflammatory mediators in the SF and breakage in the hyaluronic acid molecules, thereby reducing their concentration and molecular weight. The use of EHA has provided evidence that supports its application in TMJ OA; however, there is insufficient evidence comparing different application protocols in humans and animal models, which encourages further research into its advantages and applications.

ITURRIAGA, V.; VÁSQUEZ, B.; MANTEROLA, C. & DEL SOL, M. Rol del ácido hialurónico en la homeostasis y terapéutica de la osteoartritis de articulación temporomandibular. *Int. J. Morphol., 25(3)*:870-876, 2017.

RESUMEN: El objetivo de este estudio fue realizar una revisión de la literatura respecto del rol del ácido hialurónico (AH) en la homeostasis y terapéutica de la osteoartritis (OA) de la articulación temporomandibular (ATM). La ATM presenta características que le confieren propiedades de adaptación y recuperación especiales, donde el AH juega un rol fundamental ayudando a mantener la homeostasis articular, la cual se ve afectada en procesos patológicos como la OA. La OA es una enfermedad multifactorial crónica degenerativa que puede afectar a todos los componentes de las articulaciones sinoviales, generando degradación del cartílago articular, matriz extracelular y quiebre de las moléculas de AH. El AH es un polisacárido lineal no ramificado que presenta efectos de viscosuplementación, antiinflamatorios, lubricantes, en el alivio del dolor, permite además, activar procesos intrínsecos de reparación del cartílago y normalizar la producción endógena de AH por parte de los sinoviositos. En los últimos años el uso terapéutico del AH ha presentado evidencia que sustenta su aplicación en OA de ATM mejorando la capacidad de viscosuplementación, actuando a nivel celular y molecular, disminuyendo diversos mediadores inflamatorios y mejorando las características reparativas. Su uso se ha estudiado en modelos animales y en humanos, sin embargo no existe consenso en cuanto a concentraciones, dosis, frecuencias de aplicación y peso molecular a utilizar.

PALABRAS CLAVE: Acido hialurónico; Osteoartritis; Articulación temporomandibular; Trastornos temporomandibulares; Viscosuplementación.

REFERENCES

Armstrong, S.; Read, R. & Ghosh, P. The effects of intraarticular hyaluronan on cartilage and subchondral bone changes in an ovine model of early osteoarthritis. *J. Rheumatol., 21(4)*:680-8, 1994.

Balazs, E. A.; Watson, D.; Duff, I. F. & Roseman, S. Hyaluronic acid in synovial fluid. I. Molecular parameters of hyaluronic acid in normal and arthritis human fluids. *Arthritis Rheum., 10(4)*:357-76, 1967.

Balazs, E. A. & Denlinger, J. L. Viscosupplementation: a new concept in the treatment of osteoarthritis. *J. Rheumatol. Suppl., 39*:3-9, 1993.

Bertolami, C. N.; Gay, T.; Clark, G. T.; Rendell, J.; Shetty, V.; Liu, C. & Swann D. A. Use of sodium hyaluronate in treating temporomandibular joint disorders: a randomized, double-blind, placebo-controlled clinical trial. *J. Oral Maxillofac. Surg., 51(3)*:232-42, 1993.

Bjørnland, T.; Gjaerum, A. A. & Møystad, A. Osteoarthritis of the temporomandibular joint: an evaluation of the effects and complications of corticosteroid injection compared with injection with sodium hyaluronate. *J. Oral Rehabil., 34(8)*:583-9, 2007.

Brandt, K. D.; Smith, G. N. Jr. & Simon, L. S. Intraarticular injection of hyaluronan as treatment for knee osteoarthritis: what is the evidence? *Arthritis Rheum., 43(6)*:1192-203, 2000.

Cledes, G.; Felizardo, R.; Foucart, J. M. & Carpentier, P. Validation of a chemical osteoarthritis model in rabbit temporomandibular joint: a compliment to biomechanical models. *Int. J. Oral Maxillofac. Surg., 35(11)*:1026-33, 2006.

Coronado, L.; Iturriaga, V.; Bornhardt, T. & Fuentes, R. Evaluación de los protocolos de aplicación de ácido hialurónico en procesos degenerativos óseos de la articulación temporomandibular. una revisión de la literatura. *Av. Odontoestomatol., 31(2)*:77-84, 2015.

Dahl, L. B.; Dahl, I. M.; Engström-Saurent, A. & Granath, K. Concentration and molecular weight of sodium hyaluronate in synovial fluid from patients with rheumatoid arthritis and other arthropathies. *Ann. Rheum. Dis., 44(12)*:817-22, 1985.

El-Hakim, I. E.; Abdel-Hamid, I. S. & Bader, A. Tempromandibular joint (TMJ) response to intra-articular dexamethasone injection following mechanical arthropathy: a histological study in rats. *Int. J. Oral Maxillofac. Surg., 34(3)*:305-10, 2005.

Fu, K.; Ma, X.; Zhang, Z. & Chen, W. Tumor necrosis factor in synovial fluid of patients with temporomandibular disorders. *J. Oral Maxillofac. Surg., 53(4)*:424-6, 1995.

Ghosh, P.; Holbert, C.; Read, R. & Armstrong, S. Hyaluronic acid (hyaluronan) in experimental osteoarthritis. *J. Rheumatol. Suppl., 43*:155-7, 1995.

Goldberg, R. L.; Huff, J. P.; Lenz, M. E.; Glickman, P.; Katz, R. & Thonar, E. J. Elevated plasma levels of hyaluronate in patients with osteoarthritis and rheumatoid arthritis. *Arthritis Rheum., 34(7)*:799-807, 1991.

Grossmann, E.; Januzzi, E. & Iwaki FIlho, L. The use of sodium hyaluronate in the treatment of temporomandibular joint disorders. *Rev. Dor., 14(4)*:301-6, 2013.

Guarda-Nardini, L.; Cadorin, C.; Frizziero, A.; Ferronato, G. & Manfredini, D. Comparison of 2 hyaluronic acid drugs for the treatment of temporomandibular joint osteoarthritis. *J. Oral Maxillofac. Surg., 70(11)*:2522-30, 2012.

Guarda-Nardini, L.; Masiero, S. & Marioni, G. Conservative treatment of temporomandibular joint osteoarthrosis: intra-articular injection of sodium hyaluronate. *J. Oral Rehabil., 32(10)*:729-34, 2005.

Güler, N.; Kürkçü, M.; Duygu, G. & Cam, B. Sodium iodoacetate induced osteoarthrosis model in rabbit temporomandibular joint: CT and histological study (part I). *Int. J. Oral Maxillofac. Surg., 40(11)*:1289-95, 2011.

Hansson, T.; Oberg, T.; Carlsson, G. E. & Kopp, S. Thickness of the soft tissue layers and the articular disk in the temporomandibular joint. *Acta Odontol. Scand., 35(2)*:77-83, 1977.

Herring, S. W. TMJ anatomy and animal models. *J. Musculoskelet. Neuronal Interact., 3(4)*:391-4, 2003.

Hirota, W. Intra-articular injection of hyaluronic acid reduces total amounts of leukotriene C4, 6-keto-prostaglandin F1a, prostaglandin F2a and interleukin-1b in synovial fluid of patients with internal derangement in disorders of the temporomandibular joint. *Br. J. Oral Maxillofac. Surg., 36(1)*:35-8, 1998.

Homandberg, G. A.; Hui, F.; Wen, C.; Kuettner, K. E. & Williams, J. M. Hyaluronic acid suppresses fibronectin fragment mediated cartilage chondrolysis: I. *In vitro. Osteoarthritis Cartilage, 5(5)*:309-19, 1997.

Iturriaga, V.; Bornhardt, T.; Manterola, C. & Brebi, P. Effect of hyaluronic acid on the regulation of inflammatory mediators in osteoarthritis of the temporomandibular joint: a systematic review. *Int. J. Oral Maxillofac. Surg., 46(5)*:590-5, 2017.

Kim, C. H.; Lee, B. J.; Yoon, J.; Seo, K. M.; Park, J. H.; Lee, J. W.; Choi, E. S.; Hong, J. J.; Lee, Y. S. & Park, J. H. Therapeutic effect of hyaluronic acid on experimental osteoarthrosis of ovine temporomandibular joint. *J. Vet. Med. Sci., 63(10)*:1083-9, 2001.

Li, P.; Raitcheva, D.; Hawes, M.; Moran, N.; Yu, X.; Wang, F. & Matthews, G. L. Hylan G-F 20 maintains cartilage integrity and decreases osteophyte formation in osteoarthritis through both anabolic and anti-catabolic mechanisms. *Osteoarthritis Cartilage, 20(11)*:1336-46, 2012.

López López, J.; Chimenos Küstner, E.; Blanco Carrión, A.; Reselló Llabrés, X. & Jané Salas, E. Diagnóstico por la imagen de los trastornos de la articulación craneomandibular. *Av. Odontoestomatol., 21(2)*:71-88, 2005.

Manfredini, D.; Piccotti, F. & Guarda-Nardini, L. Hyaluronic acid in the treatment of TMJ disorders: a systematic review of the literature. *Cranio, 28(3)*:166-76, 2010.

Manfredini, D.; Rancitelli, D.; Ferronato, G. & Guarda-Nardini, L. Arthrocentesis with or without additional drugs in temporomandibular joint inflammatory-degenerative disease: comparison of six treatment protocols*. *J. Oral Rehabil., 39(4)*:245-51, 2012.

Møystad, A.; Mork-Knutsen, B. B. & Bjørnland, T. Injection of sodium hyaluronate compared to a corticosteroid in the treatment of patients with temporomandibular joint osteoarthritis: a CT evaluation. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod., 105(2)*:e53-60, 2008.

Neo, H.; Ishimaru, J. I.; Kurita, K. & Goss, A. N. The effect of hyaluronic acid on experimental temporomandibular joint osteoarthrosis in the sheep. *J. Oral Maxillofac. Surg., 55(10)*:1114-9, 1997.

Okeson, J. P. *Tratamiento de Oclusión y Afecciones Temporomandibulares*. 6th ed. Barcelona, Elsevier, 2008.

Oliveras-Moreno, J. M.; Hernandez-Pacheco, E.; Oliveras-Quintana, T.; Infante- Cossio, P. & Gutierrez-Perez, J. L. Efficacy and safety of sodium hyaluronate in the treatment of Wilkes stage II disease. *J. Oral Maxillofac. Surg., 66(11)*:2243-6, 2008.

Oyanguren, F. R.; Wurgaft, D. R. & Montenegro, R. M. A. Histological and histochemical evaluation of collagen and elastic fibers in human TMJ tissue. *Int. J. Odontostomat., 4(3)*:277-84, 2010.

Quinn, J. H. & Bazar, N. G. Identification of prostaglandin E2 and leukotriene B4 in the synovial fluid of painful, dysfunctional temporomandibular joints. *J. Oral Maxillofac. Surg., 48(9)*:968-71, 1990.

Sakakibara, Y.; Miura, T.; Iwata, H.; Kikuchi, T.; Yamaguchi, T.; Yoshimi, T. & Itoh, H. Effect of high-molecular-weight sodium hyaluronate on immobilized rabbit knee. *Clin. Orthop. Relat. Res., (299)*:282-92, 1994.

Sato, S.; Oguri, S.; Yamaguchi, K.; Kawamura, H. & Motegi, K. Pumping injection of sodium hyaluronate for patients with non-reducing disc displacement of the temporomandibular joint: two year follow-up. *J. Craniomaxillofac. Surg., 29(2)*:89-93, 2001.

Savalle, W. P.; Weijs, W. A.; James, J. & Everts, V. Elastic and collagenous fibers in the temporomandibular joint capsule of the rabbit and their functional relevance. *Anat. Rec., 227(2)*:159-66, 1990.

Shafer, D. M.; Assael, L.; White, L. B. & Rossomando, E. F. Tumor necrosis factor-alpha as a biochemical marker of pain and outcome in temporomandibular joints with internal derangements. *J. Oral Maxillofac. Surg., 52(8)*:786-91, 1994.

Shimizu, C.; Yoshioka, M.; Coutts, R. D.; Harwood, F. L.; Kubo, T.;

Hirasawa, Y. & Amiel, D. Long-term effects of hyaluronan on experimental osteoarthritis in the rabbit knee. *Osteoarthritis Cartilage, 6(1)*:1-9, 1998.

Tobetto, K.; Yasui, T.; Ando, T.; Hayaishi, M.; Motohashi, N.; Shinogi, M. & Mori, I. Inhibitory effects of hyaluronan on [14C]arachidonic acid release from labeled human synovial fibroblasts. *Jpn. J. Pharmacol., 60(2)*:79-84, 1992.

Uchôa de Rezende, M. & Constantino de Campos, G. Viscosupplementation. *Rev. Bras. Ortop., 47(2)*:160-4, 2012.

Vasconcellos, H. A.; Sousa, E. M. A. & Cavalcante, M. L. T. M. H. Temporomandibular joint classification: functional and anatomic aspects. *Int. J. Odontostomat., 1(1)*:25-8, 2007.

Vásquez, B.; Olate, S.; Cantín, M.; Sandoval, C.; Fariña, R. & del Sol, M. Histopathological analysis of unilateral condylar hyperplasia: difficulties in diagnosis and characterization of the disease. *Int. J. Oral Maxillofac. Surg., 45(5)*:601-9, 2016.

Wenneberg, B.; Kopp, S. & Gröndahl, H. G. Long-term effect of intra-articular injections of a glucocorticosteroid into the TMJ: a clinical and radiographic 8-year follow-up. *J. Craniomandib. Disord., 5(1)*:11-8, 1991.

Williams, J. M.; Plaza, V.; Hui, F.; Wen, C.; Kuettner, K. E. & Homandberg, G. A. Hyaluronic acid suppresses fibronectin fragment mediated cartilage chondrolysis: II. *In vivo. Osteoarthritis Cartilage, 5(4)*:235-40, 1997.

Wurgaft, R. & Montenegro, M. A. *Desarrollo y Estructura de la Articulación Temporomandibular.* Santiago de Chile, Editorial Servimpres Ltda., 2003.

Xinmin, Y. & Jian, H. Treatment of temporomandibular joint osteoarthritis with viscosupplementation and arthrocentesis on rabbit model. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod., 100(3)*:e35-8, 2005.

Yasui, T.; Adatsuka, M.; Tobetto, K.; Hayaishi, M. & Ando, T. The effect of hyaluronan on interleukin-1 alpha-induced prostaglandin E2 production in human osteoarthritic synovial cells. *Agents Actions, 37(1-2)*:155-6, 1992.

Corresponding author:
Veronica Iturriaga
Departamento de Odontología Integral Adulto
Facultad de Odontología
Universidad de La Frontera
Avenida Francisco Salazar 01145
Temuco
CHILE

E-mail: veronica.iturriaga@ufrontera.cl

Received: 08-04-2017
Accepted: 16-06-2017