Degenerative joint disease (Osteoarthritis)
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Degenerative joint disease or osteoarthritis (OA), also known as osteoarthrosis, is the most common cause of lameness in dogs and it is estimated that 1 in 5 dogs over 1 year old (20%) is affected (Johnson et al 1997).

1. INTRODUCTION

Degenerative joint disease or osteoarthritis (OA), also known as osteoarthritis, is the most common cause of lameness in dogs and it is estimated that 1 in 5 dogs over 1 year old (20%) is affected (Johnson et al 1997).

OA can have a severe impact on quality of life and affected dogs present with joint pain, swelling and stiffness, which may worsen after exercise or after a period of inactivity. The main radiological signs include articular effusion, osteophytes at the surfaces of the joints and sclerosis of the subchondral bone.

OA is a degenerative disease that has slow dynamics of progression, characterized by the progressive degeneration of articular cartilage and the subsequent narrowing of the articular gap. OA is a complex disease that also affects the synovial membrane and subchondral bone (Figure 1).

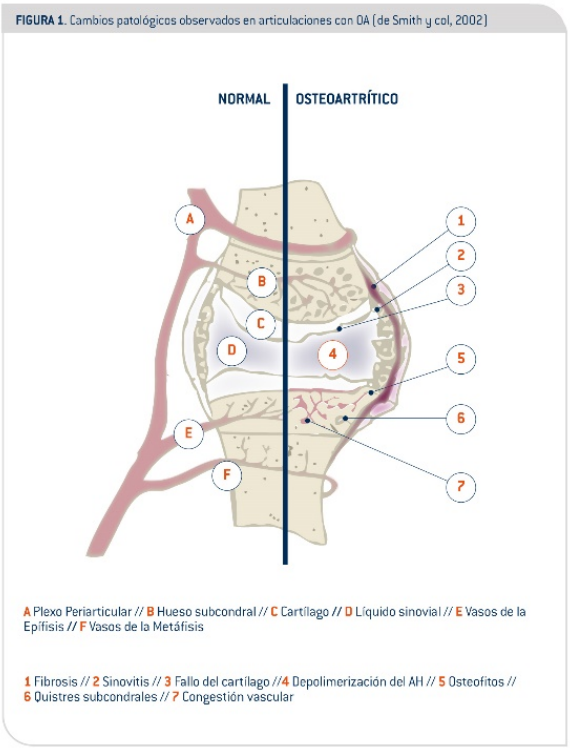


FIGURA 1. Cambios patológicos observados en articulaciones con OA (de Smith y col, 2002)

A Plexo Periarticular // B Hueso subcondral // C Cartílago // D Líquido sinovial // E Vasos de la Epífisis // F Vasos de la Metáfisis

1 Fibrosis // 2 Sinovitis // 3 Fallo del cartílago //4 Despolimerización del AH // 5 Osteofitos // 6 Quistes subcondrales // 7 Congestión vascular

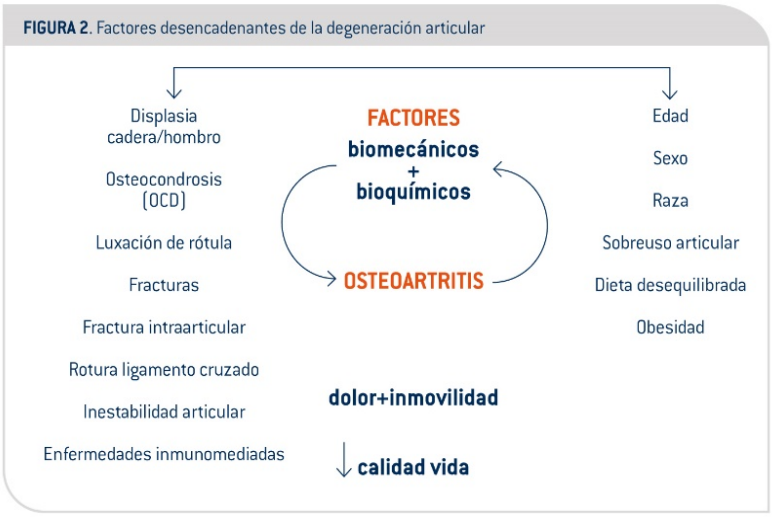
In osteoarthritic joints, pathological changes occur in the articular cartilage (loss of proteoglycans, fibrillation / erosion), the *subchondral bone (vascular congestion, structural change, sclerosis, osteophytosis) the synovial membrane (inflammation, fibrosis and abnormal synthesis of hyaluronic acid (HA)).*
All these modifications would be mediated, in part, by inflammatory processes.

2. RISK FACTORS

Canine OA is usually secondary to musculoskeletal disorders (dysplasia, joint instability with a genetic component) where the mechanical effect on the joint is the causative agent. Overweight and age clearly accelerate its evolution (FIGURE 2). All joints may be affected (hip, shoulder, elbow, wrist ...).

3. ETIOPATHOGENESIS

It is important to consider OA as a "generalised disease of the joint" (cartilage, subchondral bone and synovial capsule) instead of as a "cartilage disease" (FIGURE 1) and note that although it is often classified as a non-inflammatory disease, studies indicate that inflammation (of the synovia and the cartilage) plays an important role in the pathogenesis of OA, as reflected in their symptoms (joint effusion, joint stiffness, pain ...) (FIGURE 2).



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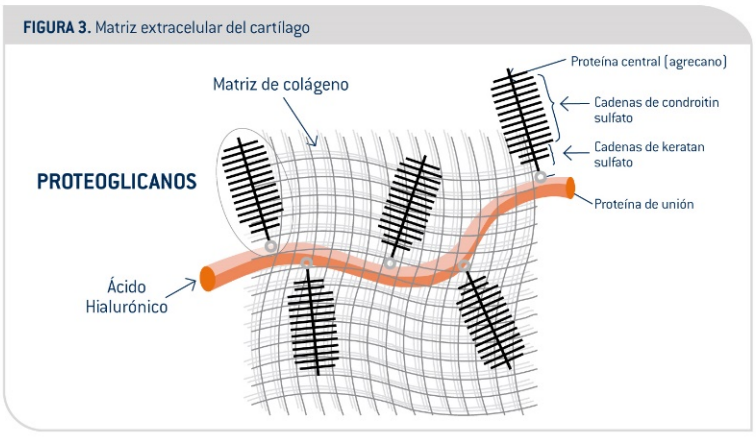
3.1 THE ROLE OF CARTILAGE: ENDOCHONDRAL REACTIONS

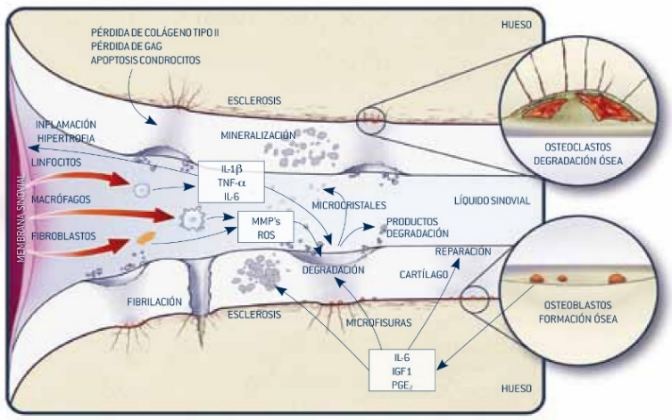
The hyaline cartilage consists of chondrocytes in an extracellular matrix (EM) consisting mainly of type II collagen and specific proteoglycans (known as aggrecans).
Glycosaminoglycans (GAGs) that are sulphated, such as chondroitin sulphate as (CS) are attached to cartilage aggrecan and help give support against forces of compression. Hyaluronic acid (HA) is also present and is responsible for the viscoelasticity and lubricating properties of synovial fluid (FIGURE 3).



OA is characterized by a loss of articular cartilage componen ts, mainly collagen type II and aggrecans, due to an imbalance between breakdown of the cartilage matrix and its repair. Depending on the stage of OA, the chondrocyte phenotype underg oes changes that make it a hypertrophic chondrocyte in an early stage, and later into a cell like a macrophage or apoptotic cell. In this way, it contributes to cartilage hypertrophy (as an attempt to repair) and subsequently to its degradation and mineralization.

In a more advanced stage of disease there is fragmentation, degradation and a net loss of cartilage, suggesting that the process of cartilage repair has been temporary and not effective (FIGURE 4).

FIGURA 4. Cambios bioquímicos en la degeneración articular



The degradation of articular cartilage is due to an **imbalance** between **breakdown** and **repair** of the extracellular matrix of the cartilage.

3.2. **THE ROLE OF THE SYNOVIAL MEMBRANE IN LESIONS OF THE CARTILAGE**

The synovial membrane is the lining of the joint capsule and it covers the joint structure, except for the cartilage itself. Synovial inflammation is characterized by the infiltration of macrophages, T lymphocytes and neutrophils, and by vascularization and hyperplasia of the synovial membrane (FIGURE 4).

3.3. THE ROLE OF SUBCHONDRAL BONE IN OA

Remodelling of the subchondral bone is an important feature in OA and it is unclear if it precedes or follows changes to the cartilage. Its main manifestations are: sclerosis, fissures, vascularization and the occurrence of osteophytes.

OA presents itself with osteoblasts of a different phenotype, associated with increased bone turnover and the secretion of biochemical factors involved in the remodelling of bone tissue, which could contribute to the remodelling of the overlying cartilage (FIGURE 4).

Inflammation of the synovial membrane contributes significantly to the **onset of pain**, joint inflammation and cartilage degradation.

At the present time, the treatments being used for osteoporosis are also being studied for the treatment of OA (Henrotin et al, 2005 and 2009, Sutton et al, 2009; Abramson and Attur, 2009).

4. THE EFFECTS OF DIET ON THE EVOLUTION OF OA

The management of OA usually involves a multimodal approach, with short-term treatment for an improvement in the symptoms (pain, lack of mobility), and long-term treatment intended to modify the joint structure, with the aim of slowing /stabilizing any injury to the cartilage, bone or synovium (FIGURE 5).

Subchondral bone remodelling is an important feature of OA, and it is unclear whether it is a consequence or cause of the degeneration of cartilage.

4.1 CHONDROITIN SULPHATE AND GLUCOSAMINE

Chondroitin sulphate (CS) and glucosamine are well known and are recommended as a treatment of OA in both humans and animals. Glucosamine is the precursor of the glycosaminoglycans, structural units of proteoglycans (aggrecans), and between them they form the basic structure of articular cartilage. Chondroitin sulphate is the predominant glycosaminoglycan within the cartilage matrix (FIGURE 3) and is a natural component of other body tissues such as tendons, bones and vertebral discs.

Using diet, it is possible to combine nutrients aimed at changing the various joint structures (bone, cartilage, synovial membrane) that are affected by OA and to modify the pathological biochemical pathways (anti-inflammatory, antioxidant) to help slow the progression of the disease and relieve clinical signs

A clinical double-blind, randomized, controlled study in dogs with OA has been shown that oral supplementation of glucosamine and chondroitin sulphate improves signs of pain and severity of disease from day 70 (Mc Carthy et al, 2007).

A positive effect on postoperative conditions (unilateral cross section cruciate ligament in 16 dogs) from feeding a combination of glucosamine and chondroitin sulphate has also been shown (Johnson et al, 2001).

In vitro studies demonstrated that a combination of glucosamine and CS protects against cartilage degradation via the inhibition of various enzymes and mediators involved in cartilage degradation (MMP-3, MMP-9, MMP-13, MMP-14, cathepsin-b, IL-1, COX-2, PGE 2, NF-kB), increasing the production of cartilage and increasing the synthesis of endogenous hyaluronic acid.

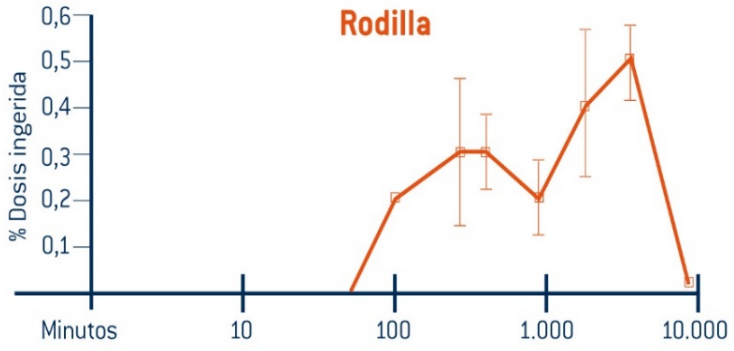
4.2 HYALURONIC ACID (HA)

HA is also a glycosaminoglycan, but is un-sulphated. It is present in synovial fluid and in the extracellular matrix of cartilage and is responsible for the viscoelastic and lubricating properties of synovial fluid (FIGURE 3). In osteoarthritis, the concentration of HA is reduced and the viscoelastic property of the liquid is compromised, increasing susceptibility of cartilage damage (Figure 1). Intra-articular treatment with HA (visco-supplementation) is widely accepted as a way to reduce joint pain in osteoarthritis, with beneficial effects both on function and patient global assessment.

It has been demonstrated *in vitro* that HA induces synoviocytes to secrete more endogenous AH and reduces the production of PGE2 and MMP-1, but increasing the biosynthesis of collagen and receptor expression of IGF-1.
The oral bioavailability of HA of high molecular weight, has been demonstrated in rat models and also in dogs. Despite its high molecular weight, orally administered HA is absorbed through the small intestine and has a high affinity for tissues, including joints and skin (Balogh et al, 2008) (FIGURE 6).

FIGURA 6. Absorción del hialurónico oral

Presencia de hialurónico radioactivo en la articulación de la rodilla tras la administración de ácido hialurónico vía oral en rata. (Balogh L, 2008)

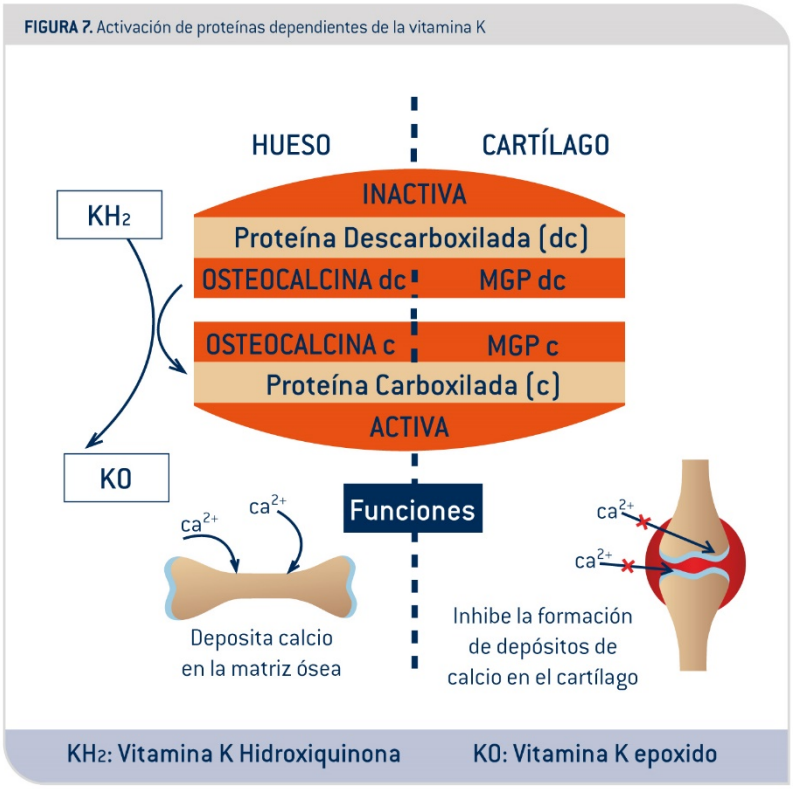


In a clinical double-blind, controlled study with human patients having knee OA, it was shown that oral HA reduces joint effusion, pain and the severity of OA faster than paracetamol, and significantly improved the quality of life of the patients, with effects observed after following one month of treatment.

The combination of **glucosamine** and **chondroitin sulphate** stimulate cartilage metabolism **by inhibiting its degradation, reducing the clinical symptoms**, both in patients with **osteoarthritis** and for **post-surgical conditions.** Well tolerated by dogs when administered for prolonged periods of time, this makes it an attractive combination for modifying both the "structure" and "symptoms".

4.3 VITAMIN K

Vitamin K is a fat-soluble vitamin essential for carboxylation or activation of several proteins that are involved, not only for blood coagulation, but also for stimulation and/or inhibition of calcification of bone, cartilage and blood vessels. The common property of all vitamin K-dependent proteins is their high affinity for calcium, which is essential for them to perform their functions. Osteocalcin and matrix GLA protein (MGP) are proteins dependent on vitamin K. Osteocalcin is synthesized in the bone and is involved in mineralization. MGP is synthesized by the cartilage and vascular endothelium, acting as an inhibitor of calcification. Therefore one of the functions of the vitamin K is to regulate the balance of mineralization processes in bones, cartilage and blood vessels (FIGURE 7).



Recent studies in the human population have shown that low levels of vitamin K are associated with lower bone mineral density (BMD) and increased risk of fractures (Feskanich et al, 1999; Tsugawa et al, 2008; van Summeren et al. 2008). It has also been shown that a daily supplement of vitamin K increases bone mineral density in postmenopausal women with osteoporosis (Iwamoto et al, 2001). In addition, an epidemiological study showed the relationship between low vitamin K and the prevalence of osteoarthritis in humans (Neogi et al, 2006).

It has been demonstrated that hyaluronic acid of high molecular weight administered ORALLY is absorbed in the small intestine and deposited in the joints. Its supplementation significantly improves the quality of life of patients with symptoms of OA.

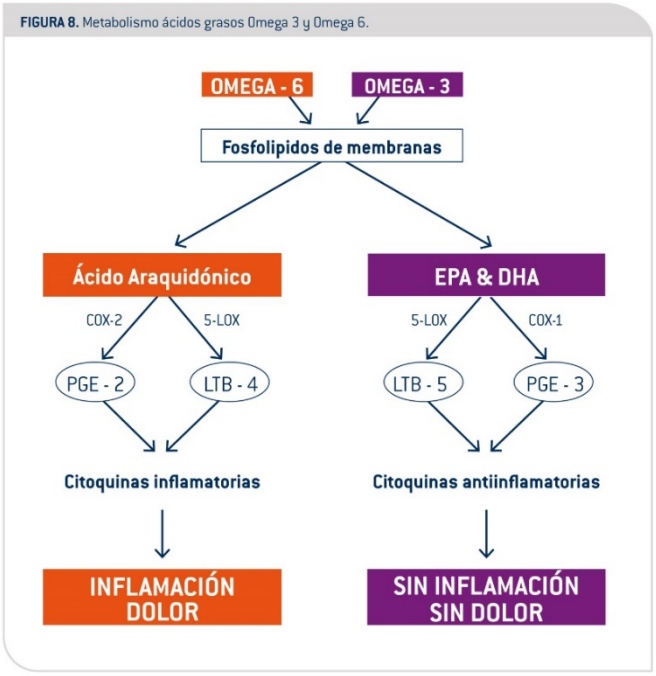
Data from a study by Affinity Petcare in dogs with OA showed greater carboxylation of MGP where there were high plasma levels of vitamin K (> 1 ng/ml) than in those dogs with low levels of vitamin K (<1 ng/ml). These results indicate a low level of calcification in the cartilage of dogs with high circulating vitamin K levels.

Vitamin K intake prevents bone loss, reduces risk of fracture and incidence of osteoarthritis by increasing bone mineralisation, the formation of bone /cartilage and the inhibition of cartilage calcification.

4.4 OMEGA-3 FATTY ACIDS

An increased consumption of omega-6 fatty acids in the diet causes an increase in the generation of pro-inflammatory metabolites from arachidonic acid (AA) (FIGURE 8). It has been found that the pro-inflammatory metabolites of AA play an integral role in the pathophysiology of OA.
It has been demonstrated that a high intake of Omega-3 fatty acids may have beneficial effects on degenerative cartilage metabolism. Omega-3 fatty acids can reduce serum concentrations and activity of the proteoglycan degrading enzymes, COX-2 and LOX-5 and induction of inflammation by cytokines.

Data from a study by Affinity Petcare in dogs with OA showed less **cartilage calcification** activity with high levels of **Vitamin K**



4.5 ANTIOXIDANTS

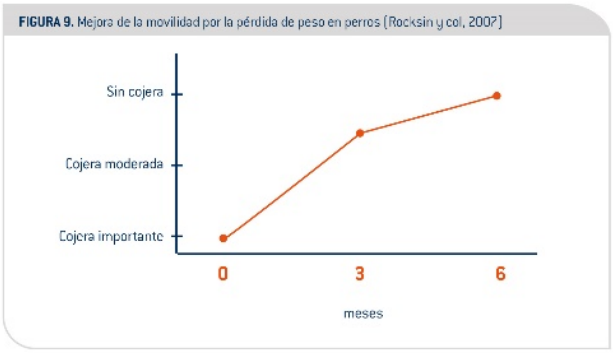
The articular cartilage degradation in OA results from a combination of mechanical stress, inflammatory mediators and biochemical factors, mainly metallo-proteinases and pro-oxidant molecules (reactive oxidant species or ROS). The main ROS involved in the pathogenesis and progression of OA are nitric oxide (NO), peroxynitrite (ONOO-) and superoxide anion radicals (O2-). These factors are involved in cartilage degradation.

Antioxidants act at the joint level, inhibiting oxidative enzymes and neutralizing the harmful effects of free radicals on tissues, interrupting the chain reaction these initiate.

4.6 ENERGY RESTRICTION

Traumatic or degenerative disorders (OA, humeral condylar fractures, rupture of the anterior cruciate ligament, intervertebral disc disease), are clearly more frequent in obese dogs (Edney and Smith, 1986, Brown et al, 1996, Smith et al, 2001; Lund et al, 2006). The excessive weight of obese dogs increases the mechanical stress on joints and hastens the onset of osteoarthritis. Body fat and excess weight also influence the metabolism of cartilage and bone, affect hormone secretion, and affect inflammatory processes involved in OA (Blum et al, 1992, Larsonet al, 2003, Smith et al, 2006).

Rocksin et al (2007, showed that it is very beneficial to use diets formulated for weight reduction on obese dogs with OA and lameness (FIGURE 9).



A **reduction in body weight** in obese dogs with osteoarthritis **reduces pain** in the joints by reducing degenerative processes.

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