OSTEOARTHRITIS: DEGENERATIVE JOINT DISEASE IN DOGS AND CURRENT CONCEPT OF TREATMENT

Ksenija Ilievska

Department of Surgery, orthopedics and ophthalmology
Univesrity Ss. Cyril and Methodis in Skopje,
Faculty of veterinary medicine - Skopje, Lazar Pop Trajkov 5-7, 1000 Skopje, Macedonia

Introduction

Osteoarthritis (OA), also known as a degenerative joint disease (DJD) represents a chronic, non-inflammatory, slowly progressive joint disease followed by degeneration of articular cartilage and formation of new bone tissue at the joint surface. Due to the changes in the synovial fluid and diminished cushion, osteoarthritis causes pain/soreness, stiffness, swelling of the joint and lameness. All of these symptoms occur as a result due to the changes in the synovial fluid and diminished cushion. Degenerative joint disease is the most preferred term for osteoarthritis, which indicates a pathological process that is not always associated with inflammation. Larger breeds, such as German Shepherds, Labradors, Huskies are more affected than smaller dog breeds, while as the prevalence of osteoarthritis in young dogs is significantly lower than in middleaged and older dogs.

One of the most common clinical signs in canine patients with OA is a gradual onset of unilateral or bilateral lameness. Lameness is usually followed by a reluctance to perform normal activities, joints may be swollen due to the effusion, reduced range of motion, crepitus during palpation, joint instability and pain.

Unlike the fibrous and cartilaginous type of joints, the synovial joints are made up of dense irregular connective tissue. The synovial fluid allows the joints to move freely. Coxofemoral, shoulder and elbow are one of the most affected synovial joints in canine patients with OA. Osteoarthritis in dogs and cats can be classified as primary (idiopathic) and secondary. Due to some abnormalities of the joints (osteochondritis dissecans, hip dysplasia, cruciate ligament rupture), secondary osteoarthritis is the most common type in pets.

The synovial fluid provides nutrients, lubrication and plays a role of a schok absorber for articular cartilage. The articular cartilage is composed of hyaline cartilage, an avascular tissue consisting of chondrocytes that are embedded

within an extracellular matrix of collagens, proteoglycans and non-collagenous proteins. Due to the high content of collagen type 2 in hyaline cartilage, articular cartilage on one side reduces the friction in the synovial joints but on the other side serves as a shock absorber, by distributing the pressure over the subchondral bone. Despite that, the articular cartilage is considered as an important issue in osteoarthritis, still, the synovial joint represents crosstalk between cartilage, synovium, bone, ligament, synovial fluid and fat. In every healthy joint, there is a balance between injury and repair among chondroblasts and chondroclasts, but in osteoarthritis, this balance is disrupted due to the overproduction of osteoblasts that can cause pain, swelling, and loss of joint cartilage.

Osteoarthritis has multiple causes and risk factors. As far as etiology is concerned, the current models of osteoarthritis indicate that each individual has an inherent susceptibility to osteoarthritis, although the genes that may control the susceptibility to OA have not yet been identified in dogs. Genetics, age or body weight, and obesity, on one site as systemic factors, followed by injury, instability or abnormality of the joints, are some of the predisposing factors for OA in dogs and cats. Since OA is a progressive disease, it consists of three stages. In patients with OA, catabolic processes exceed the anabolic processes in joints and regeneration of the cartilage becomes ineffective. This is one of the reasons that OA should not be seen as a static process that involves only the excessive wear and tearing of the cartilage, but also as an active process that inhibits normal cartilage regeneration that results with loss of cartilage proteoglycans and an abnormal cartilage structure.

Normal articular cartilage is composed primarily of 70% of water, collagen fibril, extracellular matrix, and chondrocytes. Deformation of the cartilage and increased conformity of joints are two events that occur during the normal weight-bearing. Degeneration and progressive loss of structure and function of the articular cartilage, followed by erosion and ulceration of the cartilage tissue are typical features of OA. In the beginning, cartilage matrix begins to break down due to the increased production of metalloproteinases (MMPs), enzymes that are responsible for the degradation of the extracellular matrix which results in increased friction and inflammation of the joints. During the second stage, the chondrocytes try to compensate for the damage due to the cartilage lesions and new bone growth (osteophyte), also known as bone spurs are formed. In this stage, the space between the bones is narrowed, the cartilage thins out and the cushion is lost causing grinding between the subchondral bones. The third and final stage is considered as "severe" osteoarthritis, the joint space is significantly reduced, the cartilage is almost gone and the mobility of the joint is limited (fig.1). Proper and early diagnosis of OA is crucial to prevent further damage to the cartilage.

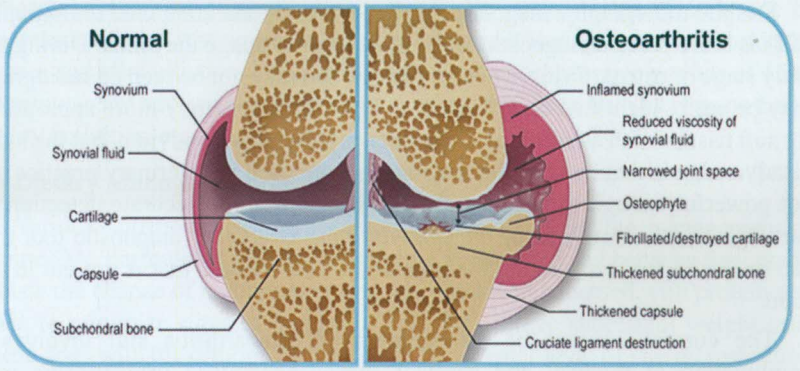

Figure 1. Comparison between normal joint and joint with OA

The pain that occurs during OA is usually chronic, and sometimes may be difficult to recognize it. To establish a proper diagnosis, the owner has a major role wich starts by observing the pain and stiffness of joints while their dog is running, walking, jumping or rising from a lying or sitting position. Radiographic evidence, patient symptoms and osteoarthritis risk factors such as age, gender, and body mass index, can all aid in predicting the risk of rapid, highly predictable joint degradation. The findings of a physical examination may include signs of pain, crepitus, joint selling and effusion, periarticular fibrosis, muscle atrophy and a decreased range of motion on the affected joints. Radiographic evidence may show the breaking down of the cartilage between bones, osteophyte formation, subchondral sclerosis, periarticular fibrosis, intraarticular mineralization and joint effusion (fig. 2). Osteophytosis is a useful marker to diagnose osteoarthritis, although they are not pathognomonic. This is one of the limitations of radiographic assessment of OA, because radiographs provide only information on the bony changes such as osteophytosis and sclerosis, with a limited amount of information regarding the soft tissues.

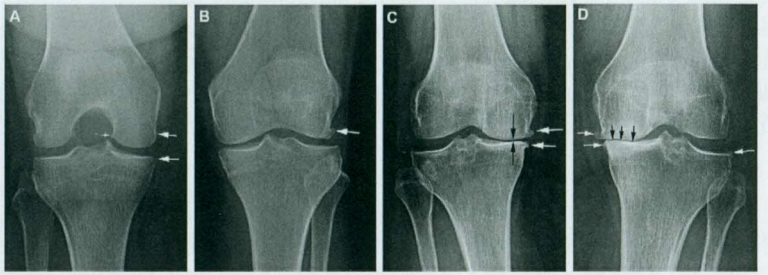

Figure 2. Radiographic features of canine osteoarthritis (OA) on the stifle joint

Despite radiography, magnetic resonance (MRI) and computed tomography (CT) is more precise diagnostic tools, often used to image the joints. During the early stage of osteoarthritis, a primary lesion that may not be seen on radiograph may be easily identified by CT. MRI, unlike CT, is generally more appropriate for soft tissues such as cartilage, ligaments, menisci, and synovium, but the main disadvantage is that most of the magnets that are used in veterinary practice are not powerful enough to have a sufficient signal to allow accurate detection of cartilage lesions. Analysis of the synovial fluid is another diagnostic tool that can be useful for categorizing the type of arthritic process that is present in the joint.

The current concept of management of osteoarthritis still involves a combination of medical and surgical approaches. Since osteoarthritis is a lifelong process, owners should be prepared that the severity of OA, may increase as the dog ages. The main approach usually involves a balance between invasive and non-invasive measures, for example, exercise restriction, weight management, physical therapy with acupuncture, medical and surgical treatment. Due to the severity of the disease, most of the patients may require additional analgesia, surgery or euthanasia. There are numerous strategies on how to treat osteoarthritis in dogs and that includes five basic principles.

Weight Management

Overweight and obesity are the most important medical diseases in dogs. Recent studies suggest that approximately half of the pet dogs are either overweight or obese with many health issues. Overweight is a major risk factor for the development and progression of OA since obese dogs are less mobile and more likely to show signs of chronic pain than dogs with an ideal weight. The main reason that obese dogs are more prone to OA, is that their joints wear extra pressure that is exerted on a joint. For example, for every gained pound, three pounds of pressure is added to the knees and six pounds of pressure are added to the hips. Beagles, Dachshunds, Collies, and Labrador Retrievers, females and older dogs are more prone to obesity and therefore, a specific diet should be enforced to prevent and control body weight in dogs with osteoarthritis. Weight management should always be considered in conjunction with some other forms of medical management and surgery.

Exercise

Despite that there are very few studies about the influence of a short period of exercise on lameness, very little is known about the effects of exercise in patients with osteoarthritis. Sometimes, even a short term exercise can

exacerbate pain and clinical signs in dogs with osteoarthritis. This is one of the reasons that a resting period is very important during acute inflammatory phases and joint effusion, but generally, frequent short exercise periods of 15 to 20 minutes are advised, without some extreme activities such as chasing balls, agility activities, etc.

Dietary Management

Various nutritional treatments may be considered for the management of canine OA. Formulated weight diets should always be used because they could reduce the chance of malnutrition since they are well balanced with protein and fiber, to minimize signs of hunger in pets. To achieve successful weight loss, obese dogs with the orthopedic disease need a greater level of energy restriction as it is demonstrated in recent studies. Since measuring cups are unreliable and usually lead to overfeeding, owners are using a puzzle feeder like hollow toys or modified feed bowls because it has been shown that they can slow feed intake which can help to reduce hunger in pets.

Glucosamine, often combined with chondroitin sulfate as new methods of nutritional support, has become very popular in the treatment of osteoarthritis in dogs. The action of glucosamine is to regulate the synthesis of collagen in cartilage and to provide mild anti-inflammatory effects, while chondroitin sulfate inhibits destructive enzymes in joint fluid and cartilage. Omega-3 fatty acids are other supplements that can be added to canine diets for the management of a joint disease. If they are given at the correct dosage, omega-3 fatty acids have an anti-inflammatory effect because they can replace arachidonic acid (AA) in cell walls with eicosapentaenoic acid (EPA) which decreases pain and inflammation.

Physical Rehabilitation

Physical rehabilitation along with weight management, are cornerstones in the treatment of osteoarthritis. Strengthening, endurance, and range of motion are the primary targets of physical therapy. All the activities of physiotherapy such as aquatic physical activities – swimming and hydrotherapy, acupuncture, massages, electrotherapy, etc, should be carried out by properly trained personnel. Hot and cold packages that are often used in humans on inflamed joints, should not be applied on swollen joints because vasodilation may make this condition worse.

Medical Treatment

Up till today, there is no treatment that can completely cure dogs affected with OA. Since OA in dogs usually develops secondary to other orthopedic problems, the underlying problem should be corrected as soon as possible.

Drugs that are used for medical treatment in pets with OA, can be classified into two categories: symptom and structure-modifying agents.

Symptom modifying agents includes drugs that are designed to modify clinical signs and to treat and relieve pain associated with osteoarthritis. The second group, structure-modifying agents are less available for dogs and they are designed to retard, stop or reverse the pathologic changes that occur in articular cartilage, but this is currently not possible because in veterinary medicine, there are no fully validated methods to assess the status of articular cartilage in patients.

Non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen (paracetamol)/codeine, oral opioids (buprenorphine, tramadol), amantadine, gabapentin, and corticosteroids are mostly used symptom-modifying drugs in pets to manage osteoarthritis, in order relieve the pain associated with the condition.

• ***Non-steroidal anti-inflammatory drugs (NSAIDs)***

Nonsteroidal antiinflammatory drugs are one of the most commonly used anti-inflammatory and analgesic agents, but in the long term dogs treated with these drugs may have some adverse effects in the form of gastrointestinal, kidney, liver and cardiovascular damage. Compared with cats, a broad range of NSAIDs have been approved for use in dogs. To reduce the production of prostaglandin, NSAIDs inhibit the cyclooxygenase (COX) enzyme.

COX 1 (constitutive) and COX 2 (inducible) are two main forms of COX that exist, although a third-class COX 3, has been identified and may be the target for paracetamol (acetaminophen). The main difference between COX-1 and COX-2 is that COX-1 is expressed in almost all tissues for the maintenance of normal physiological functions, on the other hand, COX-2 tends to increase during inflammation under influence of pro-inflammatory cytokines. Today, NSAIDs have been developed to be more selective for COX 2 to allow analgesia to occur with less common side effects especially gastrointestinal irritation and ulceration, nausea, diarrhea, and renal papillary necrosis. The most common anti-inflammatory drugs used for the treatment of OA are presented in table 1. Naproxen, indomethacin, ibuprofen are especially dangerous and they should not be used in pets.

Table 1. Most common anti-inflammatory drugs used for the treatment of OA in dogs

	RIMADIL	DERAMAXX	ETOESIC	METACAM	PREVICOX
Generic name	Carprofen	Deracoxib	Etodolac	Meloxicam	Firocoxib
Mechanism of action	COX 2 >COX 1	COX 2 >COX 1	COX 2 >COX 1	COX 2 >COX 1	COX 2>COX 1
Dosage	2.2 mg/kg, q12hr or 4.4 mg/kg q24hr, or as needed for prevention or treatment of pain	3-4 mg/kg, q24hr for up to 7 days, 1-2 mg/ kg, q24hr for chronic pain or as needed for prevention or treatment of pain	10-15 mg/ kg, q24hr or as needed for prevention or treatment of pain	0.1 mg/kg, q24hr with food; a "loading dose" of 0.2 mg/ kg may be given on the first day	5 mg/kg, q24hr
Side effects	Gastric ulceration, vomiting, anorexia, liver disease, possible kidney effects	Gastric ulceration, vomiting, anorexia, possible kidney or liver disease; avoid in dogs with KKS	Gastric ulceration, vomiting, anorexia, possible colitis, possible kidney or liver disease	Gastric ulceration, vomiting, anorexia, possible colitis, possible kidney or liver disease	Vomiting, diarrhea, anorexia, lethargy, pain, somnolence, hyperactivity

• ***Acetaminophen (paracetamol)/ Codein***

Acetaminophen should not be prescribed for cats, because it is extremely toxic, but it can be used safely in dogs when given at the correct dosages (10 to 15 mg/ kg for every 8 or 12 hours). The treatment with acetaminophen for management of pain should be used only for five days and not in conjunction with NSAIDs. Acetaminophen does not produce renal or gastric injury in dogs when prescribed at commonly recommended dosages and was used in dogs in combination with codeine, as a rescue medication in a double-blind placebo-controlled trial, with no report of adverse events. Codeine, also known as methylmorphine, is a natural alkaloid found in the opium poppy and it was first isolated in 1932. Codeine is a prodrug because it is metabolized in vivo to the primary active compounds morphine and in the US it's regulated by the Controlled Substances Act.

• ***Opioids (tramadol)***

Tramadol is also a very popular therapy in dogs, although there is little evidence of its efficacy in OA. Unlike, NSAIDs, tramadol is not licensed for use in dogs or cats in the UK. The main disadvantage of tramadol is metabolization, after which the only one from eight parts is active in the dog but only for a short (one to two hours) period.

• ***Gabapentin and amantadine***

Gabapentin and amantadine are drugs that are designed to manage chronic pain. Amantadine works by acting on the N-methyl-D-aspartate (NMDA) receptor and reduces the prolonged inflammatory pain associated with the chronic disease while gabapentin works on the g-aminobutyric acid (GABA) receptor and is thought to reduce neuropathic pain. At first, amantadine was recognized as an antiviral agent but later was found to be useful in treating Parkinson's disease. Until now, the effect of amantidine in dogs with chronic pain was investigated in only one study. Gabapentin is originally developed for the treatment of epilepsy and is widely used in human patients to relieve pain. Gabapentin is not licensed for use in dogs or cats. Despite that, the exact mechanism of action is still unknown, but its therapeutic action on neuropathic pain is thought to involve voltage-gated N-type calcium ion channels. The recommended dosage starts with 10 mg/kg administered per os on every 8 hours in dogs and 5 mg/kg per os in cats.

• ***Corticosteroids***

These drugs are one of the most used and misuses in veterinary practice. In general, corticosteroids as an oral tablet are used for stress response, immune system issues, inflammation, nutrient metabolism and maintaining electrolyte levels in the blood. But, the use of corticosteroids for OA is still controversial. Similar to NSAIDs, steroids can inhibit the production of arachidonic acid, which can stop the inflammation and production of prostaglandins. The mechanism of action of corticosteroids is to depress chondrocyte metabolism and alter cartilage matrix, so the use of these drugs in the management of OA is restricted as long-acting intraarticular injection of methylprednisolone acetate. The intraarticular injection may provide rapid alleviation of clinical signs, without inducing a systemic response.

• ***Surgical management***

A combination of medical and conservative treatment in most patients with osteoarthritis is still the best option in patients with OA, but those with

severe functional deficits may be candidates for surgical management. As a less invasive method, arthroscopy unlike in human medicine where is a relatively routine procedure, in veterinary practice due to the lack of information for the management of canine osteoarthritis, is not recommended. To minimize the pain and to save the function of the limb, several surgical procedures are available. Arthroplasty, joint replacements (hip, stifle and elbow) and arthrodesis (elbow, stifle and shoulder) are currently the most commonly performed surgical procedures in pets with OA. Total hip replacement is currently the most commonly performed surgery with good to the excellent function of the joints, achieved in more than 90 percent of cases. In case, where is not possible to perform a total joint replacement, arthrodesis may be a suitable alternative. Amputation or euthanasia, as the last option is performed in some extreme cases where the welfare of the animal is impaired and treatment options have failed.

Despite the conventional treatment for osteoarthritis, a lot of studies recently put an accent on regenerative medicine, an experimental treatment - use of mesenchymal stem cells (MSCs) and platelets rich plasma (PRP) in small animal cases. Regenerative medicine is a new discipline that aims to develop biologic, cell-based therapies to repair or to replace injured or eroded tissues, for example, cartilage. At the current time, for these techniques, a harvest of autologous adipose tissue and extraction of stromal cells is the involve and stromal cells in a form of suspension is injected, intraarticularly after the extraction.

References

1. Aragon C. L., Hofmeister E. H,, Budsberg S.C. (2007). Systematic review of clinical trials of treatments for osteoarthritis in dogs. J Am Vet Med Assoc, 230:514
2. Bland S.D. (2015). Canine osteoarthritis and treatment: a review. Veterinary Science Development, 5:593, 84-89
3. Bhathal A. Spryszak M., Louizos C., Frankel G. (2017). Glucosamine and chondroitin use in canines for osteoarthritis: A review. Open Veterinary Journal, Vol. 7(1): 36-49
4. Davis M. (2015). Practical management of canine osteoarthritis. Vet times, 1-16
5. Innes J. F., Costello M., Barr F. J., Rudorf H., Barr A.R.S. (2004). Radiographic progression of osteoarthritis of the canine stifle joint: a prospective study. Veterinary Radiology and Ultrasound 45, 143-148
6. Marshall W. G., Bockstahler B. A., Hulse D. A., Carmichael S. (2009).

A review of osteoarthritis and obesity: current understanding of the relationship and benefit of obesity treatment and prevention in the dog. Vet Comp Orthop Traumatol; 22: 339–345 doi:10.3415/VCOT-08-08-0069

7. Norlund E. (2017). Pain management in dogs with osteoarthritis. Veterinärprogrammet, examensarbete för kandidatexamen Delnummer i serien: 2017:61, Upsala
8. Pettitt R.A., German A.J. (2015). Investigation and management of canine osteoarthritis. In Practice, Canine Mobility, 1-8, doi:10.1136/inp.h5763
9. Sanderson R.O.,1, Beata C.,, Flipo R.M.,, Genevois J.P.,, Macias C., Tacke S., Vezzoni A., Innes J.F. (2009). Systematic review of the management of canine osteoarthritis. Vet Rec 164:418
10. Tobias K. M. and Johnsgton S.A. Veterinary surgery small animals. ELSEVIER

MESENCHYMAL STROMAL CELLS IN VETERINARY MEDICINE: AN OVERVIEW ON THEIR BIOLOGICAL FEATURES AND CLINICAL APPLICATIONS

Luisa Pascucci

Department of Veterinary Medicine, University of Perugia

Basic Biological Features

Mesenchymal Stromal Cells (MSC) have generated great excitement in the last decades as potential protagonists of cell-based therapies in human and veterinary medicine. Friedenstein and colleagues described for the first time this population of bone marrow stromal cells that were able to adhere to the plastic culture substrate, giving rise to colonies of fibroblast-like proliferating elements. MSC were then isolated from numerous tissue sources demonstrating their ubiquitous distribution in vivo. MSC are defined by several key characteristics: they strongly adhere to plastic surface in culture, display a high proliferation potential, and are multipotent as they exhibit adypocytic, osteoblastic and chondroblastic trilineage differentiation potential in vitro.

Concerning MSC immunophenotypic profile, according to the position paper of the Internation Society of Cell Therapy (ISCT), MSC express antigens such as CD90, CD73, CD105 and lack the typical hematopoietic antigens (CD45, CD34, CD14) and HLA-DR surface molecules.

MSC display immunosuppressive and immune-modulatory properties: they are well tolerated when infused in immunocompetent animals and, through mechanisms involving both direct cell to cell contact and production of soluble factors, they can induce an immunosuppressive environment. Additionally, MSC produce a plethora of bioactive molecules involved in their biological action. MSC modulate the inflammatory response and tumour progression. Finally, their capacity to deliver genes and to uptake and release drugs has enhanced the spectrum of prospective therapeutic applications.

The Secretome: A Switch from Differentiation to a Paracrine Mechanism

The integration of MSC at the site of injury and their differentiation into the damaged tissue elements was initially considered the mechanism driving the regeneration process. Nowadays, a focus on secretome has shown that MSC also act through a paracrine mechanism. In fact, they secrete a broad spectrum