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Disease-modifying drugs in canine osteoarthritis

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Disease-modifying osteoarthritis drugs (DMOADs) or supplements are frequently provided by owners to their dog, either as part of osteoarthritis (OA) therapy or as preventative. A summary is given on the etiopathogenesis of OA followed by what currently is published on the role and efficacy of DMOADs in dogs.

ETIOPATHOGENESIS OF OA
For a good understanding of the action of different medications, a short review will be presented of the pathophysiology of OA. The difference between bone and cartilage is mainly the flexibility and therefore the water content, the lack of mineral deposition, and the structure and content of collagen. Cartilage is avascular and contains no nerves but only cells, proteoglycans, and collagen, the latter in anchored in the subchondral bone in the so-called tide-mark. The cells include chondrocytes, mature chondroblasts and cartilage resorbing chondroclasts. Proteoglycans are build out of glycosaminoglycans (GAGs) and a core protein; aggrecan is an important proteoglycan in joint cartilage with keratin sulphate and chondroitin sulphate as GAGs. About 200 aggrecan molecules are bound via a glycoprotein to a hyaluran molecule, binding a large quantity of extracellular water. Collagen molecules in cartilage are containing large amounts of hydroxyl proline and hydroxyl lysine. These molecules form a triple helix structure, bound to fibrils and these to fibres with a large strength against pull and forming a labyrinth, which holds proteoglycans in its place. GAGs are also present in tendons, ligaments, skin and blood vessels. Cartilage does not contain (blood or lymphatic) vessels, therefore loading and unloading is necessary for cartilage cell metabolism; with loading extracellular water with waste products is pressed out of the cartilage until the diameter of the pores and the increased negative covalent prevents further escape from water, whereas at unloading fresh water and nutrients enter the cartilage. During aging the length of GAGs decrease, the proteoglycan content decreases and thus the water content and the flexibility to withstand loading. Also reactive oxygen species (ROS), free radicals formed during different metabolic processes, trauma, infection and irradiation may damage GAGs. Severe cartilage damage and/or inflammation of the synovial membrane will cause the production and release of matrix metallo proteinases (MMPs) and thus of cartilage collagen breakdown (Hegemann 2003). This group of proteolytic proteinases includes a group of referred to as matrix metallo proteinases (MMP1-13). In addition, lysosomal enzymes originating from leucocytes may degenerate cartilage. Regeneration can occur in case of micro trauma, by proliferation of undamaged chondrocytes, and de novo synthesis of proteoglycans and collagen. Chondrocytes will start to produce more protein and glycosaminoglycans, although in more severe cases the de novo production will not compensate for the increased losses via the disrupted cartilage (Mastbergen et al, 2006). Severe cellular damage will lead to a scar without cells; lesions of the tide mark cause inflammation and sclerosis of the subchondral bone, and possibly the formation of a fibrotic cartilage scar with a low content of proteoglycans. Under normal circumstances MMPs will be suppressed by tissue inhibitors of MMPs (TIMPs), but in case of OA, excess of MMPs will be formed by mast cells and synovia cells under the influence of cytokines interleukin-I (IL-I) and tumour necrose factor-α (TNF α), released by synovia cells, monocytes, macrophages and T-cells. These cytokines stimulate also chondrocytes and chondroclasts to produce MMPs as soon as their surrounding cartilage has been destroyed. In addition, IL-I stimulates the release of arachidonic acid metabolites including prostaglandin from chondrocytes and synovial membrane PGE$_2$, en leukotrin B$_4$ (LTB$_4$).

THERAPY OF OA
The therapy includes adaptations, surgical corrections when (still) possible and medicaments. In short:
1. Loading of the joint - Although complete unloading will disturb circulation in the cartilage, Palmoski et al (1979) demonstrated that immobilization after cranial cruciate transaction prevented OA development, whereas a moderate exercise regimen cartilage health increased (Kiviranta et al, 1988). A significant improvement in locomotion as revealed from force plate analysis was seen in 16 client-owned dogs with clinical HD after 3 months of gage rest and with identical body weight (Hazewinkel, 1991). A significant improvement was recorded by Impellieri et al (2000) in dogs with HD, following a decrease in body weight by 11-18%. Swimming (i.e., hydrotherapy) for overweight dogs with OA, and temperature regulation of the affected joint (i.e., warm packs before exercise and cold packs after exercise) are advocated to relieve and prevent joint pain, respectively (Marcillin-Little, 2004).
2. Nonsteroid anti-inflammatory drugs (NSAIDs) have actions against cyclo-oxygenase (COX) enzymes. COX1 stimulates the production of prostaglandins (PGs) which protect the body, whereas COX2 stimulates the production of PGE, which is responsible for clinical signs like pain and hyperaemia (warm joint, overproduction of joint fluid). Selective COX2 and LOX inhibitors for dogs are available now. Effective NSAIDs with low incidence of side effects will be prescribed for a prolonged period, not to mask pain but to improve the metabolic condition of the diseased joint.

3. Corticosteroids suppress the phospholipase activity, with a consequent stabilisation of the blood vessel walls and of the lysosomes. The joints will be less painful and less synovial fluid is produced. It can be very useful in case of villonodular synovitis to decrease inflammation and joint pain. Since regeneration of cartilage will be decreased under the influence of corticosteroids, long-lasting or repetitive use of corticosteroids, especially of non-crystalline corticosteroids intra-articularly and at higher dosage is contraindicated. It should be used under strict guidance of a veterinarian, and can be succeeded by oral NSAIDs with special care not to use both anti-inflammatory drugs at the same time to prevent undesirable side effects.

4. Neutraceuticals - Only supplements that can administered orally to promote good health and is not a drug are considered as neutraceutical, whereas a drug is a food or non-food substance used to cure, mitigate, or prevent disease. Information about product quality, efficacy, tolerance and safety should be available during consideration of the prescription or advise to use a particular supplement (Bauer 2005).

Chondroitin sulphate. Chondroitin sulphate is the predominant glucosamine glycan (GAG) in joint cartilage and abundantly present in synovial fluid. Chondroitin sulphate increases in vitro the production of proteoglycans and as such the regeneration of cartilage (Bassleer et al 1998). It prevents synthesis of MMPs by IL-3 and thus cartilage damage when given prophylactically in rabbits. A review on efficacy of neutraceuticals in man calls for more research aimed at elucidating the working mechanisms of chondroitin sulphate (Curtis et al, 2004). In a double blind placebo controlled study in man with OA, 1200 mg chondroitin sulphate daily decreased joint swelling and/or effusion significantly (p=0.02) better than placebo, but had no effect on pain (Clegg et al, 2006). In a placebo-controlled double-blind study in dogs with OA, owners and veterinarians failed to distinguish between chondroitin sulphate or placebo supplemented dogs after 12 weeks follow-up period (Dobenecker et al, 2002).

Glucosamine. Glucosamine, an amino sugar, is naturally synthesised in the body. Glucosamine, is a precursor of GAGs, and will stimulate synthesis of GAGs, prostaglandins and collagen by chondrocytes in vitro (Bassler et al, 1992). In case of substitution of glucosamines in the medium of chondrocytes, mRNA content for aggrecan increased, and for MMPs decreased and synthesis of proteoglycan increased (Henrotin, 2001). After oral intake, 87% of the glucosamine in dogs is absorbed and for 80% metabolised in the liver, leaving less than 20% bioavailable (Setnikar et al, 1991). In rabbits with a cranial cruciate ligament rupture, 120 mg/kg body weight of prophylactic glucosamine decreased the amount of chondropathy in comparison with controls ( Couto et al, 1998), in rats with a lipopolysaccharide induced joint inflammation the induced NO-synthesis decreased by i.v. injections of glucosamine (Meininger et al 2000). In a multicenter, double-blind, placebo- and celecoxib controlled study in 1583 patients with stifle joint OA receiving 1500 mg glucosamin, 1200 mg chondroitin sulphate, or both revealed the supplementations not to reduce stifle joint pain better than placebo (Clegg et al, 2006). However in a sub-group of patients with moderate-to-severe pain, the reponse of the combination glucosamine plus chondroitin sulphate was significantly better (Clegg et al, 2006). In a study using the cranial cruciate ligament (CCL) rupture as a model, Altman et al (1989) demonstrated less cartilage swelling, less total and active metalloproteinase (MMP) and lower pathologic scores in dogs injected with 4 mg/kg bw glucosaminoglycan polysulfuric acid (GAGPS) twice weekly for 4-8 weeks, starting 4 weeks after the CCL rupture. It is suggested that GAGPS suppress proteoglycan breakdown by MMPs or by directly inhibiting MMP in cartilage, rather than by increasing synthesis of proteoglycans by chondrocytes (Altman et al, 1989). De Haan and co-workers demonstrated in a clinical (double-blind, placebo controlled) trial that 4.4 mg/kg GAGPS (i.e. every other 3-5 days) coincided with an improvement in lameness score, range of motion and joint pain and no side-effects in dogs with hip dysplasia after 8 injections, with only small improvement in the placebo group of dogs (De Haan et al, 1994). Glucosamin infusions in dogs have been reported to cause hyperglycemia, possibly due to insulin suppression by glucagons, so parenteral use in diabetic dogs can be contraindicated especially at high dosages (Bauer 2005).

Combinations of chondroitin sulphate and glucosamins. Hulse et al (1998) reported that a combination given to dogs with OA, subjectively allowed for more normal locomotion and joint movement than untreated controls. Prophylactic provided this combination decreased inflammation in dogs with induced arthritis (Canapp et al 1999), possibly due to a modulated metabolism of the articular cartilage as was demonstrated by Johnson et al (2001) in dogs with CCL ruptures (Johnson et al, 2001).
In summary, it seems as the bioavailability of these products in dogs after oral intake is limited and is insufficient to prevent or treat OA, whereas parental application (either i.m or i.a.) seems to approach the in vitro effect. Information on the efficacy may be confused by referring to information gained by in vitro research, studies in other species, or not gained with objective, placebo controlled, double blinded studies or any studies at all.

Ω3 and Ω6 fatty acids. Leukotriens are formed out of arachidonic acid (AA; 20:4n-6) and eicosapentanit acid (EPA; 20:6n-3) originating from cellular membranes, under the influence of the enzyme 5-lipogenase. Pro-inflammatory LTB4 originetes from AA, anti-inflammatory LTB5 originates from EPA. In joints with acid (EPA; 20:6n-3) originating from cellular membranes, under the influence of the enzyme 5-lipogenase.

Ω3 coincided with a significant increase in plasma LTβ concentrations at the end of a 3-month follow-up period, although ground reaction forces did not differ between both groups of dogs (Hazewinkel et al, 1998). It can been concluded that either the period of 3 months had been too short, the Ω3 content of the food had been too low, the OA had been too severe or the efficacy too minimal. However, consumption of a diet with low Ω6: Ω3 ratio by dogs prior to cranial cruciate ligament transaction coincided with less severe clinical and radiological signs of OA (Henrotin et al, 2005).

Glucosamine sulphate and Ω3 fatty acids. In a well standardized, placebo controlled double blinded study in dogs with cartilage damage ('groove' model) force plate analysis (i.e., pain), radiological visualised osteophyte formation, histological controlled soft tissue inflammation and cartilage disruption, nor biochemical markers of cartilage regeneration revealed any beneficial effect of oral supplementation (per 25 kg dog) with 800 mg glucosamine sulphate plus 1800 mg Ω3 fatty acids to their daily ration (Frost-Christensen et al, 2006). This supplementation was provided 4 weeks before till 12 weeks following cranial cruciate rupture.

Anti-oxydantes. Antioxidants may decrease the damage of synovia cells by ROS. For this purpose vitamin A, C, and E and β-caroten can be increased (Greenwald, 1991, Kurz et al, 2002).

Green-lipped mussel. The fatty acid content of powder of the flesh part (i.e., sepatated from the shell) of the green-lipped mussel (GLM), as in use in dog food, is 34.6% saturated, 18.4% mono-unsaturated, and 47% poly-unsaturated. Of the latter, 41% is Ω3 fatty acid (mainly eicosapentaenoic and docosahexaenoic acid (EPA and DHA), and a small amount of eicosatetraenoic acid (ETA, 0.3%), as well as 5.2% Ω-6, with a ratio of Ω-6: Ω-3= 1: 10. GLM is claimed to be a 5-lipoxygenase-pathway inhibitor, whereas other suggest that green-lipped mussel may contain pharmacologically active inhibitors of prostaglandin biosynthesis (Miller et al, 1984). The latter is based on the effect of elongation of gestation period in rats, like prostaglandin synthetase inhibitors including NSAIDs. In addition GLM powder contains chondroitin and glucosamin, in a concentration of 6.9% and 0.0005% of dry matter weigh, respectively. The combination of Ω-3 poly-unsaturated fatty acids, the GAGs chondroitin and glucosamin, together with anti-oxidant micronutrients (including zinc, copper, and selenium) are claimed to have synergistic potential to limit the progression of OA. Bierer and Bui (2002) reported their findings in a double blind, randomized, controlled trial in 17 dogs given GLM supplement powder and 15 dogs given GLM supplement oil (both in a daily dosage of 1000mg when bw≥34 kg; 750 mg when bw 34-25 kg; 450 mg when bw<25 kg) and compared with 15 controls, all with OA. A non-objectivated score of arthritic signs grading from no-signs till severe was given for mobility and for all major joints individually, before the start of the study and at 6 weeks. Joint swelling, pain and crepitus were reported to improve in the GLM-powder supplemented group in comparison with the controls; the GLM-oil supplemented group were only significantly different in joint pain and crepitus scores. In none of the groups with GLM supplementation significant effects were observed with regard to mobility (scores for lameness in walking, trotting, and climbing stairs) or improvement of the range of motion in all major joints.

In addition, Bierer and Bui report a dose-response on alleviating arthritic score in 4 groups of dogs, i.e. 12 control animals, 11 dogs receiving 50% GLM powder dose, 12 dogs 100% GLM powder dose, and 12 dogs 200% GLM powder dose. All three dosages resulted in a similar improvement in total arthritic score, and all significantly different from controls. The highest anti-inflammatory activity in GLM was found in the poly-unsaturated free fatty acid fraction of the powder, possibly the ETA by blocking both the COX as the lipoxygenase (LOX) pathway. No gastrotoxic effects of platelet aggregation has been found in in vitro studies with GLM, therefore it is thought that the action is less directed to COX-1 than to COX-2. The GAGs in GLM may help to regenerate cartilage or to decrease proteoglycan breakdown (Altman et al, 1989). A recent review of published control studies in man over the last 35 years concludes that it is still uncertain if GLM powder is of particular benefit in the management of patients with arthritis, despite some early enthusiastic reports of the benefits (Cobb et al, 2006). This is in line with the results as described by Dobe-
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necker et al (2002), who evaluated double-blinded three groups of dogs with OA supplemented for 12 weeks with chondroitin sulphate (n=21), GLM extract (n=18), or placebo (n=19) with questionnaires, and could not demonstrate a beneficial effect of the supplements regarding lameness or pain. The varying responses in these and other trials have been suggested to be due to the lack of stabilizing processes, avoidance of heat during opening of the mussels and during the processing of the diets, the ratio of omega-3 to omega-6 FA (i.e., the effect of the background diet), the purity and dosage of the product, and the significant placebo effect (Curtis et al, 2004, Cobb et al, 2006, Dobenecker et al, 2002). The strong influence of the latter by the awareness of the owner concerning OA of their pet and the necessity to adapt the dog’s life style is the experience of most veterinary surgeons evaluating therapies (Marcellin-Little, 2004), perhaps not as high as in human studies (~60%, Clegg et al, 2006). Dobenecker et al describe that some symptoms improved even more in the placebo group than in supplemented groups, and conclude that studies in assessing the efficacy of chondroprotectiva must therefore be carried out placebo-controlled, double blinded (Dobenecker et al, 2002), and preferably with objective measures. Other supplements are under study (Curtis et al, 2004) including green tea and herbal extracts. As can be learned from the findings above, provided preliminary information should be considered with care. Results should be gathered in the target species (i.e., the dog) and not in small laboratory animals, in man, or in in vitro studies. Both dosage, duration and route of the DMOAD should be taken into account. Since most of these products are not pharmaceuticals, neither purity nor content is per se under strict control, although the package or information material may suggest otherwise. The daily intake, together with the food, can have practical advantages, i.e., client compliance is greater and the supplement will get its chance for long term effects. However, parenteral application has its advantage to overcome biological inavailability, used only when (still) indicated or stopped and replaced by other prescriptions or modalities when not effective.

Double blind studies are a necessity, and the use of objective measures (e.g. force plate, determination of relevant markers) make multi-centric trials possible to learn more about the efficacy of these and future nutraceuticals.


