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Use of nutraceuticals and chondroprotectants in osteoarthritic dogs and cats

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Chondroprotectants and nutraceuticals have become an attractive adjunctive or alternative treatment for cats and dogs suffering from osteoarthritis (OA). OA, also commonly referred to as degenerative joint disease (DJD), is characterized by varying amounts of joint pain and dysfunction depending on the severity and course of disease. Clinical signs might initially be limited to behavioral changes, occasional stiffness, difficulty rising, or reluctance to exercise. As the condition progresses, clinical signs such as lameness, loss of joint range of motion, and muscle atrophy become readily identifiable. Clinical signs might be exacerbated by exercise, long periods of rest or recumbancy, and weather changes (particularly cold weather). Some pets show signs of a restricted, stiff gait rather than obvious lameness. This presentation is seen commonly in cats and dogs that have mild DJD or those that have multiple joints with degenerative changes. Pets might also have a history of previous joint trauma (intra-articular fracture, ligamentous injury, dislocation, and so forth), osteochondral disease (osteochondrosis, ununited anconeal process, fragmented coronoid process), or congenital deformity (patellar luxation, hip dysplasia). OA might be more frequently diagnosed in cats today because of more critical observation and greater diagnostic effort. The osteoarthritic patient can be managed satisfactorily in most situations with a combination of optimization of body condition, exercise modification, anti-inflammatory therapy, and use of chondroprotectants agents. Chondroprotectants are available as oral nutraceuticals and injectable pharmaceuticals. Presently, recommendations cannot be made regarding which chondroprotectant is best for each dog and cat afflicted with osteoarthritis. Head-to-head comparisons of these products

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have not been made, and it is not known when the different mediators of OA play an important role. Mediators of pain and degradation (prostaglandins, free radicals, metalloproteinases, serine proteases, and so forth) might change during the course of disease. It would be ideal to know what the predominant mediators were in an individual animal suffering from OA to select the best product to treat that individual patient. The best current recommendation is to use products that have well-designed experimental and clinical research evaluating efficacy and safety and products that are manufactured under the high quality standards practiced by the pharmaceutical industry.

Chondroprotectants and nutraceuticals: definition

The term chondroprotectant is applied to various compounds that are proposed to have a positive effect on the health and metabolism of chondrocytes and synoviocytes. This definition is quite broad and thus has been used to label a wide variety of veterinary products that differ considerably in their structure, function, and degree of purity. Other terms have been used to describe these types of products, including slow-acting, disease-modifying osteoarthritic agents (SADMOA), structure/disease-modifying anti-OA drug, and symptomatic slow-acting drug for OA [1–6]. Because of the great variation in nomenclature and molecular structure of these compounds, care should be taken when attempting to compare one chondroprotectant agent to another. When applicable, it is always preferable to use generic compound names rather than trade names or broad descriptive terms (eg, chondroprotectant, SADMOA, and so forth) when discussing the effects or comparing the merits of these agents. Nevertheless, the term chondroprotectant is used in this article to help bridge the information presented here with that reported elsewhere previously.

Chondroprotective agents are purported to have three primary effects:

1. Support or enhance metabolism of chondrocyte and synoviocyte (anabolic)
2. Inhibit degradative enzymes within synovial fluid and cartilage matrix (catabolic)
3. Inhibit formation of thrombi in small blood vessels supplying the joint (antithrombotic)

Many types of compounds have been purported to have chondroprotective effects, including glycosaminoglycans (GAGs), amino sugars, structural proteins, enzymes, minerals, preparations of whole tissue, and semisynthetic compounds [1,2]. These compounds are available in oral and injectable forms. Most oral chondroprotectants are classified as dietary supplements. A subset of oral chondroprotectant agents is designated as nutraceuticals. A veterinary nutraceutical has been defined by the North American Veterinary Nutraceutical Council as a nondrug substance that is

produced in a purified or extracted form and administered orally to provide compounds required for normal body structure and function with the intent of improving health and well-being [3]. Injectable chondroprotectants are drugs including glycosaminoglycan polysulfate ester, pentosan polysulphate, and hyaluronic acid.

Regulation of chondroprotectants

In the United States, dietary supplements for humans are regulated under the Dietary Supplements Health and Education Act (DSHEA). This law was enacted to permit consumer freedom to make purchasing decisions regarding supplements. Such products must be safe, but no premarketing approval is required (as is required for pharmaceuticals).

DSHEA does not apply to veterinary dietary supplements. Strict interpretation of the Food, Drug, and Cosmetic Act classifies oral veterinary compounds as foods, food additives, or pharmaceuticals. The same dietary supplements legally sold under DSHEA for human use are therefore technically unapproved veterinary pharmaceuticals when sold for animal use; however, to date the CVM has exercised regulatory discretion in the removal of veterinary dietary supplements from the market. Provided that the product is safe, poses no risk to the human food supply, and does not claim to treat, cure, prevent, or mitigate a disease, veterinary dietary supplements have not been forced to withdrawal from the market.

Chondroprotective agents administered by routes other than oral (eg, topical or injectable) are considered to be drugs and fall under the regulation of the Food and Drug Administration.

Manufacturing and quality control of chondroprotectants

The manufacturing process of chondroprotectant products varies widely. Manufacturers should apply high-quality standards similar to those practiced by the pharmaceutical industry (good manufacturing practice). The raw materials and finished product should be tested for purity and consistency by validated analytical methods to ensure the label accuracy of the product reaching the consumer. Problems with truth-in-labeling and quality control of oral chondroprotectant products have been documented [7,8]. The consumer cannot always be assured that the ingredients listed on the container are actually present in the product at the claimed concentration or purity. Presently, the results of clinical and experimental research on one product cannot be extrapolated to another similar product because of inconsistencies in manufacturing and quality control standards. Until regulation of these products improves, it is probably best to heed the recommendation found in the Arthritis Foundation's Guide to Alternative Therapies: when a supplement has been studied with good results, find out which brand was used in the study, and buy that brand.

Chondroprotectants and nutraceuticals: mechanism of action

The mechanism of action of many of these products is unknown or unproven, but some products have been substantiated with experimental and clinical trials. Dietary supplements and nutraceuticals cannot be sold under the premise of being a treatment for a medical condition, and these products cannot be marketed with the intent to diagnose, treat, cure, or prevent disease. Instead, they must be marketed as nutrients necessary for supporting or improving normal structure and function of the joint. Chondroprotective agents presumably influence cartilage metabolism by providing substrate and upregulating chondrocytes. They also appear to inhibit degradative enzymes, including metalloproteinases, serine proteases, and free radicals. Some of these products inhibit the formation of microthrombi in the periarticular vasculature, thus supporting a normal blood supply to the joint tissues. The mechanism of action of specific products, if known, is discussed in the appropriate section of this article.

The normal joint: structure and function

Diarthrodial joints are composed of a joint capsule, synovial fluid, articular cartilage, and subchondral bone. Normal joint function requires normal structure and function of these tissues. The joint capsule is composed of an outer fibrous capsule and an inner synovial membrane. The integrity of the joint capsule is important for normal gliding function, production of hyaluronic acid, and defense mechanisms. Synovial fluid is as ultrafiltrate of plasma containing the glycosaminoglycan hyaluronic acid. Synovial fluid functions include lubrication, protection (through its viscoelastic properties and participation in defense mechanisms), provision of nutrients, and removal of metabolic waste products from the cartilage. Articular cartilage is composed of hyaline cartilage. This type of cartilage has special viscoelastic properties that allow it to function at low levels of friction, which is needed to withstand the long-term forces experienced by the joint over a lifetime. Cartilage is a living tissue composed of chondrocytes embedded in an extracellular matrix composed of water, collagen, and proteoglycans. Proteoglycans are composed of small proteins, a hyaluronic acid backbone, and GAGs (keratin sulfate and chondroitin sulfate [CS]). GAGs are long chains of disaccharides. Glucosamine, a hexosamine sugar, is a precursor for the disaccharide units of GAG. GAGs play an important role in maintaining the proper concentration of water in the cartilage, which is essential for normal viscoelastic function. Chondrocytes are metabolically active cells producing collagen and proteoglycans needed for the cartilage matrix. These cells have little mitotic ability; they are not replaced when they die. Thus, it is imperative to support the health of chondrocytes. The subchondral bone plays an important role in dissipating concussive forces to the joint. This cushioning effect protects the overlying articular cartilage by decreasing the

load on the cartilage and chondrocyte. As OA progresses, the subchondral bone can become more dense, causing increased loads to be placed on the cartilage, leading to damage. Disruption of any of these components can lead to suboptimal performance, pain, and progression of osteoarthritis.

Pathophysiology of osteoarthritis

OA is characterized by a low-grade inflammatory process that leads to progressive changes in the structure and function of the joint. Joint capsular thickening and inflammation leads to pain, decreased range of motion, and decreased function. Synovial fluid alterations cause pain, a change in joint biomechanics, and a reduction in the protective mechanisms of the joint. Loss of articular cartilage leads to pain and loss of function and establishes a mechanism for perpetuating low-grade inflammation and progressive OA. Increased density of the subchondral bone affects the joint indirectly by increasing the amount of force placed on the articular cartilage.

The two broad classes of OA are primary (idiopathic) and secondary. Primary OA is often referred to as wear-and-tear joint disease owing to its insidious onset, which is thought to be caused by long-term use combined with aging. Primary OA is not associated with an identifiable predisposing cause, but this might be because of clinicians' inability to detect subtle abnormalities. Secondary OA, identified more commonly, results from an initiating cause such as joint instability, trauma, osteochondral defects, or joint incongruity.

OA is characterized by changes in the structural components of articular cartilage. The initial change involves the loss of proteoglycans from the extracellular matrix caused by increased destruction and decreased production. The breakdown and loss of collagen and chondrocytes occur as the disease progresses, leading to irreversible change.

An understanding of the pathogenesis of OA is essential to develop a rational approach to management of the condition. Although OA is usually categorized as a noninflammatory joint disease, low-grade inflammation plays an important role in its pathogenesis. Inflammation of the synovial membrane leads to extravasation of inflammatory cells, primarily mononuclear cells, from synovial capillaries to synovial fluid. Leukocytes and synoviocytes release a variety of inflammatory mediators including prostaglandins, leukotrienes, neutral metalloproteinases, serine proteases, oxygen-derived free radicals, lysosomal enzymes (proteases, glycosidases, collagenases), oncoproteins, interleukins, tumor necrosis factor (TNF), and other cytokines. The neutral metalloproteinase stromelysin is thought to be the primary factor responsible for proteoglycan degradation in degenerative cartilage. Collagenase also plays a role in the long-term destruction of cartilage in osteoarthritis. The severity of the inflammatory process appears to be enhanced compared with human counterparts, especially when observing dogs that have cranial cruciate disease (Fig. 1).

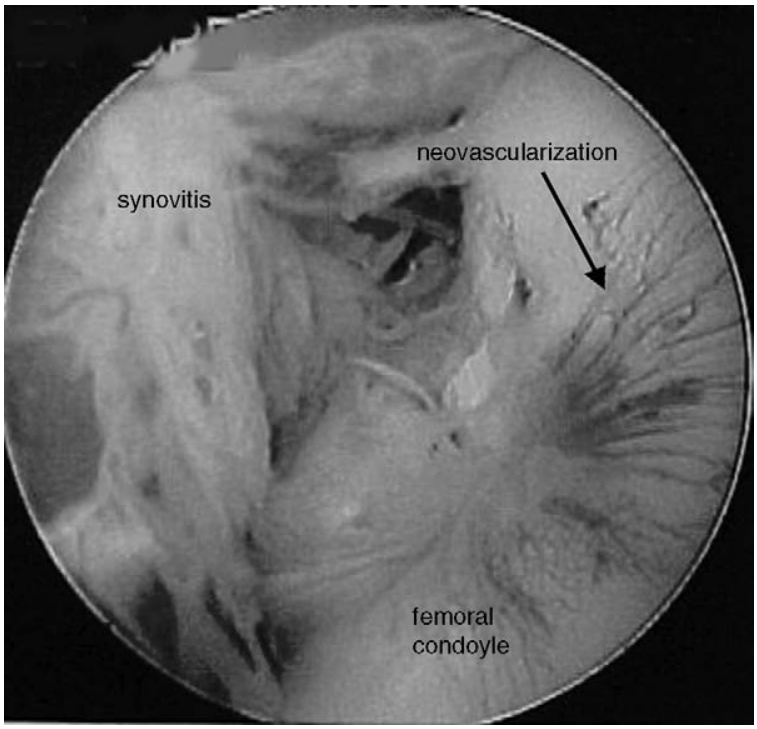

Fig. 1. Inflammation associated with OA in dogs can be progressive and severe. This dog suffered a partial tear of the cranial cruciate ligament and has been clinically lame for approximately 1 year.

Treatment of osteoarthritis

Treatment of OA might include weight loss, exercise modification, physical therapy, pharmacologic therapy, or surgery. In cases of secondary OA, the underlying cause must be identified and eliminated (if possible) to minimize the progression and long-term effects of OA, which might imply removal of an osteochondral fragment or stabilization of a stifle after rupture of a cranial cruciate ligament. Weight loss, when indicated, lessens clinical signs of OA because of decreased forces being placed on abnormal joint surfaces. Weight reduction before surgery reduces postoperative stress placed on the surgical repair. Decreased body weight has been found to be an important factor in lessening the prevalence and severity of OA in dogs that have hip dysplasia [9]. Enforced rest and restricted activity provide an opportunity for transient episodes of inflammation to resolve and decrease stress placed on the repair. Pharmacologic management of OA includes a wide variety of pharmaceuticals, most of which have gained popularity based on use in humans. Consideration should be given to drugs that inhibit the release or activity of prostaglandins, leukotrienes, neutral metalloproteases (stromelysin, collagenase), serine proteases, oncoproteins, interleukins, and TNF. Nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoid drugs are common examples. Other drugs such as chondroprotective agents not only inhibit mediators of inflammation within the joint but also might stimulate metabolic activity of synoviocytes and

chondrocytes. Such drugs include glycosaminoglycan polysulfate ester, pentosan polysulphate, and hyaluronic acid. Nutraceuticals and other dietary supplements have also become important tools in the management of OA in dogs and cats. These supplements appear to have the best effect in patients that have mild or moderate OA (Figs. 2–4). Mild OA can be treated initially with a nutraceutical and supplemented with as NSAID as needed (Fig. 5). Moderate OA is more likely to require concomitant therapy with an NSAID and nutraceutical.

Nutraceuticals

Glucosamine

Glucosamine salt supplements are most commonly found as glucosamine hydrochloride or glucosamine sulfate. Both forms are readily available, but the hydrochloride form provides more glucosamine per unit weight than the sulfate form. Another form, N-acetyl glucosamine, appears to have less activity than the hydrochloride and sulfate forms [10]. Glucosamine is commonly found in combination products containing other products including CS and manganese ascorbate. Glucosamine is an amino sugar that is a precursor to GAGs present in the extracellular matrix of articular cartilage. Normal chondrocytes have the ability to synthesize glucosamine; however, osteoarthritic cartilage appears to have a decreased ability to synthesize it [1,11]. Exogenous glucosamine stimulates the production of proteoglycans and collagen by chondrocytes in cell culture [12,13].

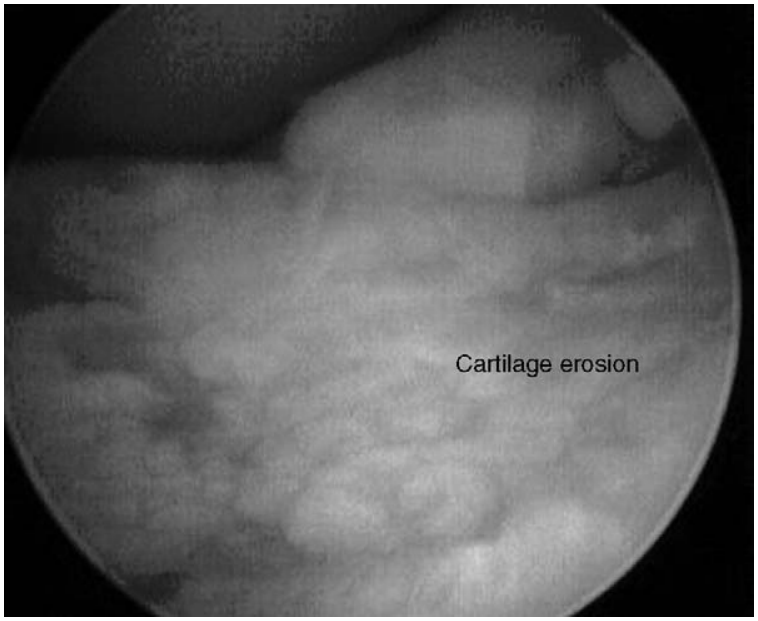

Fig. 2. Cartilage erosion is common in dogs affected by elbow dysplasia. Chondroprotectants and nutraceuticals can be used to help provide substrate for chondrocyte metabolism and potentially suppress inflammation.

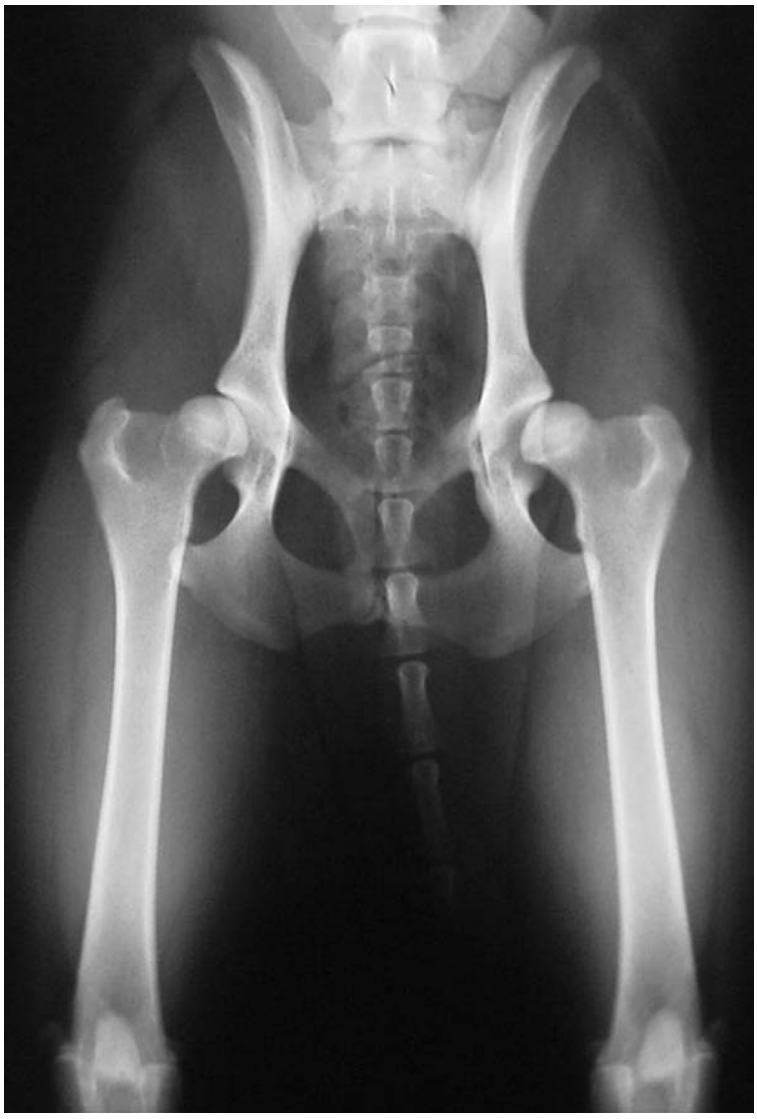

Fig. 3. Dogs and cats that have mild or moderate OA are more likely to benefit from chondroprotectant or nutraceutical therapy. This dog was diagnosed with mild bilateral OA secondary to hip dysplasia.

Glucosamine has good bioavailability when administered orally or parenterally, having good distribution to all body tissues and reaching highest concentrations in the liver, kidney, and articular cartilage [14–16]. Oral glucosamine has been shown to have an intestinal absorption rate of 87% [17]. Orally administered glucosamine sulfate has been associated with relief of clinical signs of DJD and chondroprotection in clinical and experimental studies in humans [18–21]. Although glucosamine has a slower onset of relief of clinical signs associated with DJD compared with ibuprofen, two clinical trials in humans found that it has equal long-term efficacy [18]. Oral glucosamine was found to improve clinical performance in humans who had OA [22]. Use of this product as an individual agent in animals has been proposed, but adequately controlled clinical studies have not been performed to substantiate its efficacy.

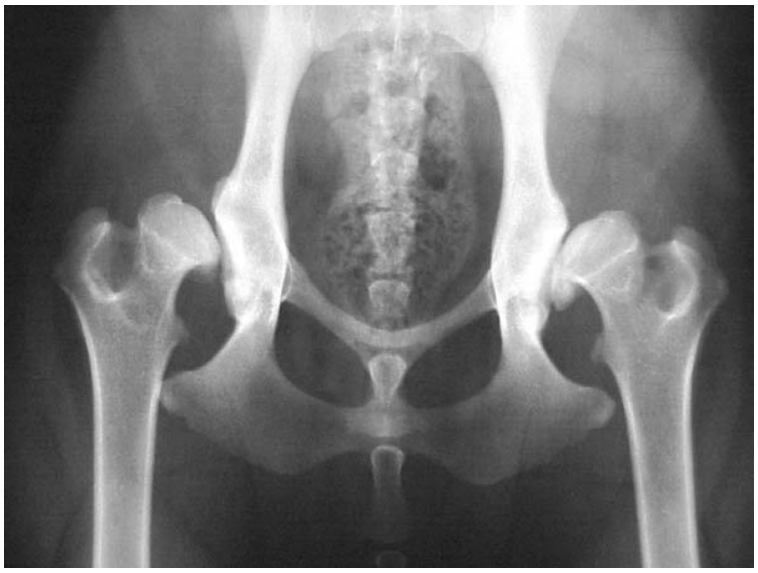

Fig. 4. This dog has severe bilateral OA of the hips secondary to dysplasia. A favorable response to nutraceuticals in this patient is less likely because of the advanced osteoarthritic condition. Nutraceuticals probably have their most beneficial effect in joints having less damage to the articular surface and a higher population of viable chondrocytes.

Chondroitin sulfate

CS is a predominant glycosaminoglycan found within the extracellular matrix of articular cartilage. Oral supplementation of exogenous CS has been advocated anecdotally for many years as a treatment for OA in humans and animals. This compound is often found in combination with other

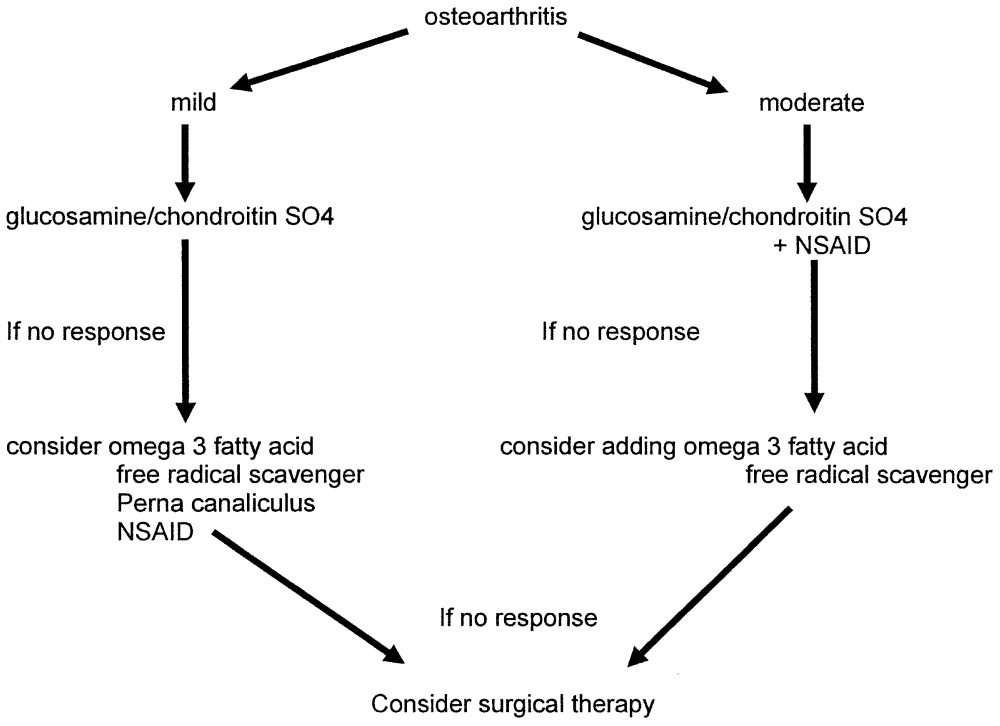

Fig. 5. Flowchart for nutraceutical usage in osteoarthritic dogs and cats.

nutraceuticals such as glucosamine and free radical scavengers. CS has been found to decrease interleukin-1 production, block complement activation, inhibit metalloproteinases, inhibit histamine-mediated inflammation, and stimulate glycosaminoglycan and collagen synthesis [4,23]. Oral absorption of CS has been reported using a variety of techniques. Some controversy exists regarding the fate of CS following oral administration. Various methods have been used to show that CS can be absorbed intestinally, but uncertainty remains regarding whether the majority of CS is absorbed intact or as a subunit of CS [4,24,25]. A highly pure, low molecular weight (LMW) form of CS has been found to have good absorption and bioavailability [14]. Clinical studies have shown improvement in clinical signs associated with OA in human patients receiving CS supplementation [5,24,25].

Combination products

The combination of high-purity glucosamine hydrochloride, LMW CS, and manganese ascorbate (GCM) might be the most commonly used nutraceutical combination in osteoarthritic companion animals (Cosequin, Nutramax Labs) [26]. The effects of the individual components are described below. The combined action of glucosamine and CS is synergistic [27]. This combination has been described as a preferential substrate and stimulant of proteoglycan biosynthesis, including hyaluronic acid and CS [4]. CS appears to inhibit degradative enzymes associated with OA, including metalloproteases and collagenases. These degradative enzymes break down the cartilage and hyaluronan in synovial fluid. Manganese is a cofactor in the synthesis of GAGs and its supplementation might aid in cartilage matrix synthesis. Manganese is also necessary for the synthesis of synovial fluid. It is possible that manganese might also have antioxidant properties. Overdose safety studies have been conducted in the dog, cat, and horse and no persistent abnormality in hematology, serum chemistry, or hemostatic parameters were observed [23,28,29]. No known side effects of clinical significance have been seen in the cat or dog.

Clinical and experimental studies support the use of GCM in combination or as individual components. Leeb et al performed a meta-analysis of the clinical efficacy of CS in humans [30]. Sixteen published studies were examined, with seven trials of 372 patients selected for the meta-analysis. All selected studies were randomized, double-blinded designs in parallel groups; however, rescue medication (analgesics or NSAIDs) were permitted, which is typical of human clinical studies of OA. CS was shown to be significantly superior to placebo with respect to the Lequesne index (a validated, subjective assessment of pain associated with OA). Patients showed at least a 50% improvement in study variables in the CS group compared with placebo. A double-blind clinical study in horses showed GCMs efficacy for treatment of DJD associated with navicular disease [31]. Administration of GCM to dogs that had experimentally induced OA by way of transection of the cranial

cruciate ligament showed increased concentration of OA markers, indicative of cartilage matrix synthesis [32]. Glucosamine, CS, and manganese ascorbate might act as signaling molecules for upregulation of the genes for aggrecan and collagen II, not just as substrates for cartilage production [33]. This combination has also been found to suppress the inflammatory affects of chemically induced acute synovitis and experimental immune-mediated arthritis [34,35].

The fate of orally administered CS appears to be affected by the molecular weight of the molecule. LMW CS is absorbed in approximately 2 hours and accumulates in the serum over time, having an estimated bioavailability of 200% [14,36]. Glucosamine hydrochloride is also absorbed in less than 2 hours, but it does not accumulate over time [14]. Orally administered glucosamine has been found to be absorbed readily, and it reaches highest concentrations in articular cartilage [14]. A recent study showed good bioavailability of glucosamine and CS after oral dosing [36].

Mixed glycosaminoglycan products

Most oral GAGs or glucosamine products are available as single- or multiple-ingredient products. Most of the glycosaminoglycan products contain CS or mixed GAGs. Different glucosamine salts are available. Much controversy exists regarding the necessary purity, concentration, and type of glycosaminoglycan or glucosamine product necessary to provide beneficial effects to cartilage. The New Zealand green-lipped mussel (GLM; *Perna canaliculus*) is known to contain GAGs, omega-3 fatty acids, amino acids, vitamins, and minerals [37]. This product is available as a sole dietary supplement or as an additive in canine diets. *Perna canaliculus* is purported to have mild anti-inflammatory and chondroprotective actions, but these effects have not been substantiated unequivocally in humans and animals. Beneficial effects have been purported in one study in humans suffering from rheumatoid arthritis and OA. A recent study in dogs found improvement in joint pain and swelling in arthritic dogs fed a complete diet containing 0.3% GLM [37]. No effect was seen on joint crepitus, range of motion, or mobility scores. Although the study concluded that a GLM supplemented diet could alleviate symptoms of arthritis in dogs, several points about the study can be questioned. The dogs used in the study were not definitively diagnosed as having OA. Joint swelling, which is not a consistent finding in osteoarthritic joints, was significantly improved; however, joint mobility, range of motion, and crepitus, commonly associated with OA, showed no improvement. Additionally, control dogs showed a marked worsening in joint pain and swelling over the 6-week period of the study, which is inconsistent with dogs selected for a chronic, slowly progressive condition such as OA. This study also included a subjective scoring system with parameters added across joints for a total score within the animal. It is difficult to envision that certain scores, such as the measurement of joint

swelling of the hip and shoulder, could be obtained accurately or consistently. The validity of the scoring system can be questioned. Further study is warranted before unequivocal acceptance of this substance as a chondroprotective agent or nutraceutical useful in osteoarthritic dogs.

Free radical scavengers

Another class of nutraceutical that has been promoted to reduce inflammation is the free radical scavengers such as superoxide dismutase (SOD), bioflavonoids, glutathione, and dimethylsulfoxide (DMSO). Oxygen-derived free radicals (superoxide, hydrogen peroxide, hydroxyl radical) are thought to play a role in the progression of DJD through their ability to damage cells by oxidative injury. Oxidative injury leads to depolymerization of hyaluronic acid, destruction of collagen, and decreased production of proteoglycans [38–40]. Superoxide dismutase and glutathione are endogenous antioxidants present in mammalian cells that inhibit production of oxygen free radicals. This enzyme acts to stabilize phagocyte cell membranes and lysosomes and reduce superoxide radical levels in tissues, with a resultant decrease in free radical generation. The efficacy, bioavailability, and safety of many oral antioxidants are unknown. This product might also have potential manufacturing or storage problems, which might lead to less active ingredient being available to the pet than is labeled on the product. A recent study found discrepancies in certificate of analysis and labeled contents in six SOD products [8]. Since this study several new products have become available that might have resolved this problem.

DMSO, which is used as a topical agent when treating musculoskeletal problems, has the ability to penetrate most tissues, including skin [41]. Topical application of 20 mL/day of medical-grade DMSO (70–90% solution) every 6 to 8 hours for up to 14 days has been recommended to treat local inflammation [41]. Side effects with topical use are minimal but include a garlic odor to the breath.

Superoxide dismutase is an endogenous antioxidant present in mammalian cells that inhibits production of oxygen free radicals. This enzyme acts to stabilize phagocyte cell membranes and lysosomes and reduce superoxide radical levels in tissues, with a resultant decrease in free radical generation [39–41]. The efficacy of exogenous superoxide dismutase is unknown. One author recommends giving 5 mg subcutaneously for 6 days in the dog followed by alternate day therapy for 8 days [2,41]. The manufacturer recommends giving 2.5 mg/kg subcutaneously five times per week for 2 weeks for treatment of spondylitis or disc disease.

Bioflavanols are also purported to have strong antioxidant properties. Grape seed meal has a rich source of bioflavanols. Bioflavanols are purported to scavenge free radicals, alleviate inflammation induced by oxidative damage, and inhibit degradative enzymes released by oxidative cells [42–45]. One double-blind, randomized study in dogs found

improvement in clinical signs attributable to hip OA in dogs supplemented with a product containing bioflavanoids, SOD, and glutathione [42]. Other clinical studies have reported improvement in function and decreased pain in osteoarthritic dogs and horses [43–45]. These studies also reported improvement after 2 to 3 weeks of product administration. Bioflavanols are available commercially, usually in combination with glucosamine and hydrolyzed collagen or with an assortment of other antioxidants including selenium, vitamin E, and superoxide dismutase.

Methyl-sulfonyl-methane

Methyl-sulfonyl-methane (MSM) has been suggested as an agent for management of pain, inflammation, and as an antioxidant [46]. The rationale behind its use, according to the manufacturer and others, is the possibility of a dietary sulfur deficiency. MSM is a white, crystalline, water soluble, odorless, tasteless compound that is sold as a supplement. It is actually a metabolite of industrial-grade DMSO. MSM is found naturally in certain foods, but it is destroyed during processing. DMSO is a byproduct of the wood pulp processing industry and is also available in a medical grade, which is approved only for the treatment of interstitial cystitis in the United States. Radiolabeled sulfur from MSM has been found in amino acids (methionine and cysteine) of proteins in guinea pigs following experimental oral administration. There are no controlled experimental or clinical studies available to support the use of MSM for management of OA in dogs. Companies supplying MSM base their claims of relief of pain and inflammation on results of studies conducted with DMSO. Little is known about safety of the product. Sold in capsules for human use, MSM is available in powder form, tablets, and capsules for use in horses and small animals. Manufacturer recommendations for dosage should be followed. Its use cannot be recommended at this time, however, because of the previously mentioned lack of studies and knowledge about safety.

Omega-3 fatty acids

Omega-3 fatty acids have gained popularity recently for their potential use in pets that have DJD. These products are available naturally in fish and plant sources and commercially as nutraceutical supplements. Omega-3 fatty acids are desaturated in the body to produce eicosapentaenoic acid, which is an analog of arachidonic acid. Prostaglandins, thromboxanes, and leukotrienes are produced from these compounds through the action of cyclo-oxygenase and lipoxygenase. The products resulting from arachidonic acid metabolism are proinflammatory, proaggregatory, and immunosuppressive compared with the metabolic byproducts of eicosapentaenoic acid, which are less inflammatory, vasodilatory, antiaggregatory, and not immunosuppressive. The use of omega-3 fatty acids could theoretically benefit dogs and cats

suffering from DJD by decreasing inflammation and reducing the occurrence of microthrombi; however, objective data are lacking to attest to this product's efficacy. The ideal ratio of N6:N3 fatty acids for canine diets is controversial; the current recommendation is between 10:1 and 5:1. A recent study reported lower PGE_2 and reduced clinical and radiographic signs of OA in experimental dogs undergoing cranial cruciate ligament transection while being fed a diet low in N6 fatty acids [47]. Future studies would be useful to evaluate the role of fatty acid therapy in osteoarthritic patients more critically.

Chondroprotectants

Polysulfated glycosaminoglycan

Chondroprotection is achieved by the inhibition of various destructive enzymes and prostaglandins associated with synovitis and DJD. Polysulfated GAGs (GAGPS) have been found to inhibit neutral metalloproteinases (stromelysin, collagenase, elastase), serine proteases, hyaluronidase, and a variety of lysosomal enzymes [40,48–51]. GAGPS have also been discovered to inhibit PGE_2 synthesis, generation of oxygen-derived free radicals, and the complement cascade [48,49]. Protection of articular cartilage has also been seen on gross and histologic examination in numerous experimental studies [50–52]. GAGPS have also been found to stimulate anabolic activity in synoviocytes and chondrocytes. Chondrostimulatory effects are characterized by increased synoviocyte secretion of hyaluronate and enhanced proteoglycan, hyaluronate, and collagen production by articular chondrocytes [53–57]. GAGPS also have anticoagulant and fibrinolytic properties that facilitate clearing of thrombotic emboli deposited in the subchondral and synovial blood vessels [40,57,58]. While the majority of experimental and clinical studies support the premise that GAGPS possesses properties of chondroprotection and chondrostimulation, some studies have found that GAGPS have no beneficial effect or a detrimental effect on cartilage metabolism [40,57].

A clinical study in hip dysplastic dogs found the greatest improvement in orthopedic scores at a dose of 4.4 mg/kg (2 mg/lb Adequan) given intramuscularly every 3 to 5 days for eight injections [59]. Use in cats has also been reported at the same dose. Another study found that twice-weekly intramuscular administration of 5.0 mg/kg GAGPS from 6 weeks to 8 months of age in growing pups that were susceptible to hip dysplasia resulted in less coxofemoral subluxation [60]. The longevity of relief provided by GAGPS is unknown. Most studies have evaluated its effect in the short-term only. Anecdotal reports of duration of amelioration of clinical signs range from days to months. It is also not known whether the complete series of injections are needed when clinical signs return or whether a shorter regimen would suffice.

Side effects of GAGPS in dogs include short-term inhibition of the intrinsic coagulation cascade and inhibition of platelet aggregation when given at

doses of 5 mg/kg or 25 mg/kg intramuscularly [1,61]. GAGPS has also been found to inhibit neutrophils and complement, which might predispose to infections, especially when injected intra-articularly under contaminated conditions [62,63]. GAGPS has been reported to cause sensitization reactions in humans, but this effect has not been reported in dogs.

Pentosan polysulphate (Cartrophen-Vet, Biopharm Australia, Sydney, Australia) is a polysaccharide sulfate ester (mean molecular weight 6000 Daltons) prepared semisynthetically from beech hemicellulose [64]. The drug is approved for use in dogs and horses in Australia and is used in a similar manner as Adequan for relieving clinical symptoms of DJD. Pentosan polysulphate can be administered intra-articularly, intramuscularly, subcutaneously, or orally. The recommended dose for intra-articular use is 5 to 10 mg per joint weekly as necessary. The intramuscular or subcutaneous dose in dogs is 3 mg/kg once weekly for 4 weeks. This regimen can be repeated as necessary. A double-blind study evaluating the efficacy of this product for treatment of DJD in dogs found this dose to be ideal [64]. This dose has also been used anecdotally in cats. Oral calcium pentosan polysulphate given at a dose of 10 mg/kg weekly for 4 weeks then repeated every 3 months was found to reduce the presence of cartilage breakdown products in osteoarthritic cartilage [65].

Sodium hyaluronate has been touted to promote joint lubrication, increase endogenous production of hyaluronate, decrease prostaglandin production, scavenge free radicals, inhibit migration of inflammatory cells, decrease synovial membrane permeability, protect and promote healing of articular cartilage, and reduce joint stiffness and adhesion formation between tendon and tendon sheaths [66,67]. The molecule lines the synovial membrane and acts like a sieve, preventing bacteria and inflammatory cells from reaching the synovial compartment by steric hindrance [66,67]. The actions of exogenous and endogenous hyaluronan appear to be similar. Presently, sodium hyaluronate is generally recommended for mild to moderate synovitis and capsulitis rather than DJD. The drug appears to have a chondroprotective effect, but it is unclear whether this is a direct effect or a result of its effect on the articular soft tissues. Sodium hyaluronate is administered intra-articularly or intravenously. Hyaluronate was used in experimental dogs at a dose of 7 mg per joint intra-articularly once weekly with success in slowing DJD [66,67].

Chondroprotectant use during the postoperative period and physical rehabilitation

Rehabilitation programs are developed to improve function and decrease pain in dogs and cats that have musculoskeletal compromise (or following orthopedic surgery). Rehabilitation can involve many physical modalities designed to improve strength, flexibility, and coordination. Chondroprotectants can be used concurrently to accelerate and enhance recovery possibly by several mechanisms:

1. Pain relief to increase willingness of patient to perform rehabilitation exercises
2. Reduction of degradative and inflammatory enzymes might help protect cartilage
3. Stimulation of synovial fluid, proteoglycan, and collagen production to promote cartilage matrix repair

Agents that reduce the expression of inflammatory mediators or upregulate normal chondrocyte expression might provide a microenvironment favorable for optimal cartilage and connective tissue homeostasis. A recent study evaluated the effect of a nutraceutical on intra-articular graft ligamentization dogs undergoing unilateral cranial cruciate ligament transection. Cosequin appeared to have two primary effects in this study: (1) return of the joint capsule/reconstructed CCL complex to a more physiological state, and (2) reduction in the severity of OA in operated joints [68]. Translation following transection of reconstructed CCLs from the Cosequin group was similar to the control, which suggested preservation of a more normal physiologic joint capsule. Dogs not receiving Cosequin had less translation after resection of the reconstructed CCL, suggesting joint capsule thickening and fibrosis. OA was less in dogs receiving Cosequin subjectively as judged by morphologic observation and with mean modified Mankin scores.

Limb immobilization can be performed postoperatively as adjunctive support to restrict use, reduce pain, treat open wounds, or control swelling. Whatever the indication, immobilization of joints can have adverse effects on joint health. Joint immobilization reduces synovial fluid production and leads to proteoglycan depletion because of decreased loading. The changes seen are similar to those observed in OA cartilage. Chondroprotectant treatment might help reduce deleterious effects on the joint during periods of immobilization. Immobilization should be limited to the shortest possible time to improve the chances of joint recovery.

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