FEED RIGHT Nutritional strategies can help prevent and manage osteoarthritis in dogs, giving veterinarians and owners a variety of ways to care for their patients and pets.

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NUTRITION NOTES

Nutrition and Osteoarthritis: What Do We Know?

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Osteoarthritis is a common problem among dogs and increases with age. Nutrition can be one tool for preventing and managing osteoarthritis in dogs. This article discusses the role of 4 nutritional approaches that are used to prevent or treat this disease. The value of some approaches remains uncertain, and research is ongoing. This article summarizes current research findings and provides references for more in-depth review.

DIET

The role of nutrition in development of musculoskeletal disease in growing dogs has been recognized for decades. Developmental orthopedic disease (DOD) refers to a group of skeletal abnormalities that affect primarily fast-growing, large, and giant breed dogs. Risk factors among dogs already at genetic risk are nutrient excess (calcium and energy) and rapid growth (overfeeding and excess energy in diet).[1-5] Increased risk for DOD has been associated with dietary calcium >3% on a dry matter basis, despite an appropriate calcium-to-phosphorous ratio.[2] Another cause of excess calcium intake is client-provided treats and/or calcium-containing supplements. For example, 2 level teaspoons of calcium carbonate (10 to 15 antacid tablets) added to a large breed puppy's daily intake doubles the calcium intake. Diets formulated for growth of large and giant breed dogs contain less energy and calcium and higher protein than growth diets for smaller dogs. Commercial diets for puppies at risk for DOD display the following statement from the Association of American Feed Control Officials (AAFCO): "[Pet food name] is formulated to meet the nutritional levels established by the AAFCO Dog Food Nutrient Profiles for growth/all life stages *including* growth of large-size dogs (70 lbs or more as an adult)." In addition, prevention of DOD in dogs has been associated with restricted food intake during growth, which slows the rate of growth without reducing adult body size.[6,7]

WEIGHT CONTROL

Obesity is the condition of having accumulated body fat that negatively affects health, including increased risk for osteoarthritis. Obesity can result in osteoarthritis because of the excess forces placed on joints and articular cartilage, which may lead to inactivity and further weight gain. Thus, a vicious cycle ensues. But perhaps more clinically relevant, adipose tissue is metabolically active and pro-inflammatory; therefore, obesity may contribute to inflammation.[8-12] The negative effects of excess weight may be obvious in an obese dog, especially when obesity-related disease is

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present, but should not be overlooked in an overweight but otherwise clinically healthy dog.

Body Condition Score

Assigning a body condition score (BCS) and muscle condition score is essential for preventing the conditions of being overweight (BCS 6-7/9) or obese (BCS 8-9/9). Quantitatively, obesity is defined as exceeding ideal body weight by 30% or more.

Risk for Osteoarthritis

Several studies have demonstrated a relationship between overweight and obese dogs and osteoarthritis;[9] however, a cause and effect has not been found.[13,14] A long-term study of 48 dogs fed the same diet found that those fed 25% less quantity experienced longer delay to development of chronic disease, including osteoarthritis.[15] They also weighed less, had better BCS, and lived an average of 1.8 years longer. Maintaining optimal or slightly lean body condition may lower risk of developing osteoarthritis, reduce the severity of osteoarthritis, and delay onset of clinical signs of osteoarthritis in dogs.

Mobility

Other studies have shown improved mobility after weight loss among obese dogs with osteoarthritis.[16,17] In these studies, improvement was noticed after modest weight loss of at least 6% body weight.

Additional Therapy

Weight loss may have additional value for dogs when combined with rehabilitation and physical therapy. One clinical trial evaluated 29 adult dogs that were overweight or obese (BCS of 4/5 or 5/5) and had clinical and radiographic signs of osteoarthritis.[18] All dogs were fed the same diet; however, those that received intensive physical therapy, including transcutaneous electrical nerve stimulation, obtained greater weight reduction and better mobility than those that received home-based physical therapy.[18]

ANTI-INFLAMMATORY SUPPLEMENTS

Degenerative osteoarthritis involves an inflammatory component, which might be modified by the addition of nutritional components, specifically omega-3 (n-3) fatty acids, to the diet. Eicosanoids derived from n-6 fatty acids, for the most part, have vasoactive and pro-inflammatory effects. Arachidonic acid (an n-6 fatty acid) is incorporated into cell membranes and when metabolized yields prostaglandins, leukotrienes, and thromboxanes of the 2 and 4 series. Many drugs used to treat degenerative osteoarthritis inhibit conversion of arachidonic acid to these eicosanoids. Metabolism of n-3 fatty acids yields eicosanoids of the 3 and 5 series, which are less vasoactive and less pro-inflammatory. Substituting an n-3 fatty acid in the membrane may decrease these responses. In addition to modulating cytokines, n-3 fatty acids reduce expression of cyclooxygenase-2, lipoxygenase-5, aggrecanase, matrix metalloproteinases 3 and 13, interleukin-1α and -1β, and tumor necrosis factor α.[19-23] Novel oxygenated products, called resolvins (resolution phase interaction products), and docosatrienes (generated from n-3 fatty acids), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) have been identified as resolving inflammation in exudates and tissues,[24-26] including the tissues involved in osteoarthritis.[27-32]

One study of 18 dogs with experimentally induced and surgically repaired transection of the left cranial cruciate ligament found that consumption of a high n-3 diet was associated with lower serum concentrations of cholesterol, triglycerides, and phospholipids; lower synovial concentration of prostaglandin E2; better ground reaction forces; and fewer radiographic changes of osteoarthritis compared with consumption of a high n-6 diet or a control diet.[33,34] Synovial membrane fatty acid composition mirrored the fatty acid composition of the diets consumed. Studies of dogs with osteoarthritis found associations between high n-3 diets and improved ability to rise from a

resting position and play,[35] improved peak vertical force values and subjective improvement in lameness and weight bearing,[36] and the ability to tolerate more rapid reduction of carprofen dosage,[37] compared with dogs fed control diets. A study of 48 dogs that underwent tibial plateau-leveling osteotomy for cranial cruciate ligament disease found that those fed a commercial diet with increased n-3 fatty acids had lower synovial inflammatory cytokine concentrations than did dogs fed a maintenance diet, with or without receiving postoperative rehabilitation therapy. Decreased progression of osteoarthritis was noted for dogs fed the increased n-3 diet and for dogs that underwent rehabilitation in this[38] and in another[39] study.

Dosages

Supplements given to dogs with osteoarthritis are often underdosed. Giving n-3 fatty acid supplements or feeding diets containing increased n-3 fatty acid levels to dogs with osteoarthritis is beneficial when the appropriate doses of EPA and DHA are delivered. When administering n-3 fatty acids, use the sum of EPA (a 20-carbon n-3 fatty acid) and DHA (a 22-carbon n-3 fatty acid) rather than the total amount of n-3 fatty acids. Recommended dosage is up to 175 mg of the sum of EPA and DHA per kilogram of body weight. A more accurate dosage is based on metabolic body weight: 310 mg of the sum of EPA and DHA per kilogram of body weight raised to the 0.75 power.[40] The National Research Council safe upper limit is approximately 200 mg of the sum of EPA and DHA per kilogram of body weight or 370 mg of the sum of EPA and DHA per metabolic body weight.

Initially high dosages of n-3 fatty acids often result in diarrhea. Therefore, we often start with 600 to 900 mg of the sum of EPA and DHA per kilogram of body weight for a few weeks and then increase slowly to 1200 to 1700 mg of the sum of EPA and DHA per kilogram of body weight.

Although flaxseed is often recommended as a source of n-3 fatty acids (because it contains α-linolenic acid), it is not a good source of n-3 fatty acids in dogs because dogs can convert less than 10% of α-linolenic acid to EPA.[40]

CHONDROMODULATING AGENTS

Chondromodulating agents are purported to slow or alter progression of osteoarthritis. They are used for dogs with osteoarthritis when cartilage damage is present but before fibrocartilage has developed. Beneficial effects of chondromodulating agents may include a positive effect on synthesis of cartilage matrix and hyaluronan as well as an inhibitory effect on catabolic enzymes in osteoarthritic joints.[41] These agents may also be beneficial when used prophylactically for dogs prone to osteoarthritis. Chondromodulating compounds fall into 2 categories: Food and Drug Administration-approved agents that can have label claims of clinical effects (e.g., polysulfated glycosaminoglycan) and products considered to be nutritional supplements, which legally cannot claim any medical benefits (e.g., glucosamine and chondroitin sulfate). Although many of these products are administered as supplements or alternative treatments, some (e.g., glucosamine and green-lipped mussel) are incorporated into pet foods.

Glucosamine and Chondroitin Sulfate

Glycosaminoglycans are a major component of joint cartilage and glucosamine is a glycosaminoglycan precursor; therefore, supplemental glucosamine may help rebuild cartilage.[42-48] However, data concerning the clinical effects of glucosamine-chondroitin sulfate on osteoarthritis are conflicting.[49-59] In a clinical trial comparing glucosamine hydrochloride and chondroitin sulfate with carprofen in 35 dogs with osteoarthritis, the carprofen-treated dogs showed improvement in 5 subjective measures while dogs treated with glucosamine-chondroitin sulfate showed improvement in 3 of 5 measures but only at the final assessment.[60] A 60-day trial of 71 dogs with osteoarthritis assessed subjective and objective measures comparing carprofen, meloxicam, glucosamine-chondroitin, and placebo.[61]

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Results indicated that objectively measured variables improved significantly for dogs that received carprofen and meloxicam but not for those that received glucosamine-chondroitin or placebo. Subjective findings of veterinarians agreed with findings of objective evaluation, but subjective assessment by clients identified improvement with meloxicam only.[61] On the basis of these results, reviews have concluded that the clinical evidence of benefit of glucosamine and chondroitin sulfate in dogs with osteoarthritis is weak.[49-51]

Many dog foods formulated and marketed for adult dogs, geriatric dogs, and growing large breed dogs contain glucosamine and chondroitin sulfate, but the exact amounts are often not readily available. In terms of evaluating glucosamine and chondroitin sulfate inclusion in a manufactured dog food, questions have arisen over whether these agents are bioavailable and in enough quantity to provide benefit. These compounds are not recognized as essential by AAFCO and thus are not included in dog nutrient profiles. They are considered "generally regarded as safe" ingredients.

Green-Lipped Mussel

New Zealand green-lipped mussel (*Perna canaliculus*) is a rich source of glycosaminoglycans, although its proposed benefit is thought to be from its anti-inflammatory effects.[62] Research findings have been discrepant, possibly because of differences in product stabilization. A stabilized lipid extract more effectively inhibits inflammation than a nonstabilized extract.[63] Early studies, which used nonstabilized products, found no beneficial effect of green-lipped mussel on arthritis. By 1986, dried mussel extracts stabilized with a preservative became available, and addition of green-lipped mussel to the diet was associated with significant improvement in subjective arthritis scores,[64] reduced joint swelling and joint pain,[65] improved mobility (but not as much as dogs that received carprofen),[66] and improved clinical signs (but not musculoskeletal scores)[67] compared with dogs that received placebo. However, although systematic reviews of agents used to treat osteoarthritis in dogs found the data regarding the benefits of green-lipped mussel extract in dogs to be promising, uncertainties existed relating to the scientific quality of the data and no definitive relationship has been proven between clinical improvements and the therapy.[50,51]

In summary, 4 nutritional approaches may help prevent or treat osteoarthritis in dogs.

- Diets aimed at preventing developmental orthopedic disease may help prevent later development into osteoarthritis.
- Weight loss for overweight and obese dogs not only decreases the mechanical wear and tear on joints but decreases systemic inflammation that accompanies osteoarthritis.
- Omega-3 fatty acids (specifically EPA and DHA) beneficially modulate the inflammatory response.
- Chondromodulating agents maintain cartilage integrity and facilitate repair of damaged cartilage. TVP

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Dr. Raditic consults, lectures, and publishes on the use of nutrition and integrative veterinary therapies. She earned her DVM degree at Cornell College of Veterinary Medicine. While in small animal practice, she completed a nutrition residency and become a Diplomate of the American College of Veterinary Nutrition. She later became a professor for the Nutrition and the Integrative Medicine services at the University of Tennessee College of Veterinary Medicine. As an integrative practitioner, veterinary nutritionist, and academician, she offers unique perspectives on the role of clinical nutrition, supplements, and integrative care for companion animals.

Mirataz™
(mirtazapine transdermal ointment)

For topical application in cats only. Not for oral or ophthalmic use.

CAUTION: Federal law (USA) restricts this drug to use by or on the order of a licensed veterinarian.

Before using this product, please consult the product insert, a summary of which follows:

INDICATION: Mirataz™ is indicated for the management of weight loss in cats.

DOSAGE AND ADMINISTRATION: Administer topically by applying a 1.5-inch ribbon of ointment (approximately 2 mg/cat) on the inner pinna of the cat's ear once daily for 14 days. Wear disposable gloves when applying Mirataz™. Alternate the daily application of Mirataz™ between the left and right inner pinna of the ears. **See Product Insert for complete dosing and administration information.**

CONTRAINDICATIONS: Mirataz™ is contraindicated in cats with a known hypersensitivity to mirtazapine or to any of the excipients. Mirataz™ should not be given in combination, or within 14 days before or after treatment with a monoamine oxidase inhibitor (MAOI) [e.g. selegiline hydrochloride (L-deprenyl), amitraz], as there may be an increased risk of serotonin syndrome.

HUMAN WARNINGS: Not for human use. Keep out of reach of children. **Wear disposable gloves when handling or applying Mirataz™ to prevent accidental topical exposure.** After application, dispose of used gloves and wash hands with soap and water. After application, care should be taken that people or other animals in the household do not come in contact with the treated cat for 2 hours because mirtazapine can be absorbed transdermally and orally. However, negligible residues are present at the application site and the body of the cat at 2 hours after dosing. In case of accidental skin exposure, wash thoroughly with soap and warm water. In case of accidental eye exposure, flush eyes with water. If skin or eye irritation occurs seek medical attention. In case of accidental ingestion, or if skin or eye irritation occurs, seek medical attention.

PRECAUTIONS: Do not administer orally or to the eye. Use with caution in cats with hepatic disease. Mirtazapine may cause elevated serum liver enzymes (See **Animal Safety** in the product insert). Use with caution in cats with kidney disease. Kidney disease may cause reduced clearance of mirtazapine which may result in higher drug exposure. Upon discontinuation of Mirataz™, it is important to monitor the cat's food intake. Food intake may lessen after discontinuation of mirtazapine transdermal ointment. If food intake diminishes dramatically (>75%) for several days, or if the cat stops eating for more than 48 hours, reevaluate the cat. Mirataz™ has not been evaluated in cats < 2 kg or less than 6 months of age. The safe use of Mirataz™ has not been evaluated in cats that are intended for breeding, pregnant or lactating cats.

ADVERSE REACTIONS: In a randomized, double-masked, vehicle-controlled field study to assess the effectiveness and safety of mirtazapine for the management of weight loss in cats, 115 cats treated with Mirataz™ and 115 cats treated with vehicle control were evaluated for safety. The vehicle control was an ointment containing the same inert ingredients as Mirataz™ without mirtazapine. The most common adverse reactions included application site reactions, behavioral abnormalities (vocalization and hyperactivity), and vomiting. **See Product Insert for complete Adverse Reaction information.** To report suspected adverse events, for technical assistance or to obtain a copy of the SDS, contact Kindred Biosciences, Inc. at 888-608-2542. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at **http://www.fda.gov/AnimalVeterinary/SafetyHealth**.

EFFECTIVENESS: The effectiveness of Mirataz™ (mirtazapine transdermal ointment) was demonstrated in a randomized, double-masked, vehicle-controlled, multi-site field study involving client-owned cats of various breeds. Enrolled cats were ≥ 1 year of age and had existing documented medical history of ≥ 5% weight loss deemed clinically significant. The most common pre-existing conditions included renal insufficiency, vomiting, and hyperthyroidism. Some cats had more than one pre-existing condition. Cats were randomized to treatment groups in a 1:1 ratio of Mirataz™ to vehicle control. A total of 230 cats were enrolled and received either Mirataz™ (115 cats) or a vehicle control (115 cats) containing the same inert ingredients without mirtazapine. The cats were 2.8-24.6 years of age and weighed 2.1-9.2 kg. The dosage was a 1.5-inch ribbon (approximately 2 mg/cat) mirtazapine or vehicle ointment administered topically to the inner pinna of the cat's ear. A total of 177 cats were determined to be eligible for the effectiveness analysis; 83 cats were in the Mirataz™ group and 94 cats were in the vehicle control group. The primary effectiveness endpoint was the mean percent change in body weight from Day 1 to the Week 2 Visit. At Week 2, the mean percent increase in body weight from Day 1 was 3.94% in the mirtazapine group and 0.41% in the vehicle control group. The difference between the two groups was significant ($p<0.0001$) based on a two-sample t-test assuming equal variances. A 95% confidence interval on the mean percent change in body weight for the Mirataz™ group is (2.77, 5.11), demonstrating that the mean percent change is statistically different from and greater than 0.

STORAGE: Store below 25°C (77°F). Multi-use tube. Discard within 30 days of first use.
HOW SUPPLIED: Mirataz™ is supplied in a 5 gram aluminum tube.
MANUFACTURED FOR:
Kindred Biosciences, Inc.
1555 Bayshore Highway, suite 200
Burlingame, CA 94010

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