A JOINT EFFORT: OSTEOARTHRITIS AND NUTRITION

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Osteoarthritis (OA) is a common syndrome having multiple etiologies and characterized by pathologic change of the synovial or diarthrodial joint accompanied by clinical signs of pain and disability. There have been few controlled studies evaluating nutrition and arthritis in dogs although nutrition plays a role in prevention of and management of dogs and cats with OA.

In order to integrate appropriate nutritional recommendations for patient management, a two-step process is undertaken: a nutritional assessment phase (based on the “Circle of Nutrition” by the American College of Veterinary Nutrition (http://www.acvn.org)) and an analysis, interpretation, and action phase. In the assessment phase, three sets of factors are assessed: animal-specific factors, diet-specific factors, and feeding management and environmental factors. Animal-specific factors include age, physiological status, disease processes, and activity of the patient. Diet-specific factors include safety and appropriateness of diet fed and nutrients of interest. Feeding factors include frequency, timing, location, and method of feeding, and environmental factors include living space and quality of the patient’s surroundings. An important part of the assessment phase is obtaining body weight, body condition score, and muscle condition score.

Body condition score evaluates body fat. There are 2 commonly used body condition scoring systems, a 5-point and a 9-point scale. In either scale, the middle number represents “optimal condition” with a body fat content of 15-25%; higher numbers on the scale represent various degrees of over-condition and body fat content > 25% and lower numbers on the scale represent various degrees of under-condition and body fat content < 15%. The goal for most patients is a
body condition of 2.5-3.0 out of 5 or a 4-5 out of 9, which is associated with decreased health problems including musculoskeletal conditions.

Muscle condition score evaluates muscle mass, which can be independent from body fat content assessed by body condition score. Evaluation of muscle mass includes visual examination and palpation over temporal bones, scapulae, lumbar vertebrae, and pelvic bones. The scale is from 1 to 3 with 3 being well-muscled and 1 corresponding to severe sarcopenia. Sarcopenia is seen with decreased weight bearing, decrease in nerve/vascular supply, and/or aging. After collecting information from the assessment phase, information is analyzed and interpreted and an action plan is implemented; the patient undergoes repeated assessment and adjustment of the plan.

ROLE OF NUTRITION IN THE PREVENTION OF MUSCULOSKELETAL DISEASE

Prevalence of musculoskeletal disorders for all dogs at multicenter referral practices has been reported to be approximately one in four. In dogs less than one year of age, prevalence is 22%, with 20% of these possibly having a nutrition-related cause. Data is not currently available on the incidence of OA in the feline patients, but a current study has identified biomarkers that may become useful in assessment.

Developmental Orthopedic Disease (DOD)

DOD refers to a group of skeletal abnormalities (e.g. osteochondrosis dissecans, hip dysplasia, wobblers’ syndrome, ligamentous laxity, and hypertrophic osteodystrophy) that affect primarily rapidly growing, large- and giant-breed dogs. Nutrient excess (calcium and energy) and rapid growth (overfeeding and excess energy) are known risk factors for DOD in dogs that have genetic risk. Restricting food intake during growth slows growth rate without significantly reducing adult body size and is associated with decreased incidence of DOD. If a puppy’s growth is restricted with an inappropriate diet such an adult maintenance diet, other nutrient deficiencies may be created with lower this lower intake.

Dietary calcium greater than 3% on a dry matter basis is associated with increased risk despite an appropriate calcium-to-phosphorous ratio. Even if the diet contains less calcium than this, excess calcium intake can occur if owners provide supplemental calcium. Limited meal-feeding and limiting rate of growth also decrease DOD. For large- and giant-breed dogs during growth,
recommended dietary composition includes: Energy: 3.2-4.1 kcal/kg of diet (lower end of range if at risk for DOD or if clients use free-choice feeding); Crude fat: 8.5-11% on a dry matter basis; Docosahexaenoic acid: ≥ 0.02% on a dry matter basis; Protein: ≥ 27% on a dry matter basis; Calcium: 0.8-1.2% (≤ 3% on a dry matter basis) with a calcium-to-phosphorous ratio of 1.1-2.0:1.0. The diet of a DOD predisposed puppy should be evaluated to be sure these nutrient parameters are met for optimal development.

**Obesity**

Obesity can be defined as accumulation of body fat in excess of what is necessary to maintain optimum condition and health. Quantitatively, obesity is defined generally as exceeding ideal body weight by 15-20% or more. One technique that is useful in the management of clinical patients is a body condition score and muscle condition score as discussed previously. Obesity may contribute to the development and progression of OA because of excess forces placed on joints and articular cartilage, which may lead to inactivity and further development of obesity.

Current literature notes that adipose tissue is recognized as being metabolically active and pro-inflammatory; therefore, obesity may contribute to inflammation. Several studies have demonstrated a relationship between obesity and OA; however, a direct cause and effect has not been determined. A long term study was performed of 48 Labrador retrievers from 7 litters divided into 2 dietary groups. One group was fed an adult maintenance dog food and the second group was fed the same diet at 75% of the amount. Restricted fed dogs lived on average 1.8 years longer, weighed less, had better body condition scores and had longer delay to treatment of chronic disease including OA. Maintaining optimal or slightly lean body condition may be associated with lower risk of developing OA, development of less severe OA if it occurs, and delay of onset of clinical signs of OA in dogs.

A study to identify proteins with differential expression between healthy dogs and dogs with stifle joint osteoarthritis secondary to cranial cruciate ligament (CCL) disease evaluated serum and synovial fluid samples from dogs with stifle joint osteoarthritis before (n = 10) and after (8) surgery and control dogs without osteoarthritis (9). No proteins had significantly different expression between serum samples of control dogs versus those of dogs with stifle joint osteoarthritis whereas eleven proteins had significantly different expression (> 2.0-fold) between
synovial fluid samples obtained before surgery from dogs with stifle joint osteoarthritis versus those obtained from control dogs. Of these results complement component 3 was strongly expressed in all (5/5) synovial membrane samples of dogs stifle osteoarthritis and weakly expressed in 3 of 5 synovial membrane samples of dogs without arthritis. These results that the complement system and proteins involved in lipid and cholesterol metabolism may have a role in stifle joint osteoarthritis, CCL disease, or both; therefore, the consideration of the role of obesity in osteoarthritis.

ROLE OF NUTRITION IN THE TREATMENT OF MUSCULOSKELETAL DISEASE

Nutrition and Surgery

Patients undergoing surgery that are healthy and in optimal body and muscle condition require no further intervention nutritionally other than to continue feeding the current diet at the same amount and frequency.

In many instances, surgery in patients is elective; therefore, depending on the urgency of the surgical procedure, consideration should be given to weight reduction prior to surgery in patients that are obese. Reducing body weight to the optimal weight decreases anesthetic risk, improves immune function, and allows patients to more easily undergo post-surgical physical rehabilitation.

The timing of weight loss with surgery and rehabilitation should be a consideration in every orthopedic surgery patient. Assessing the patient’s weight, BCS, muscle condition score, and current activity level will be needed to optimize a nutritional program for an elective orthopedic condition. It is often easier to start these patients on a weight loss program concurrent with rehabilitation to begin weight loss, and then plan for surgical intervention. Even small amounts of weight loss can make a tremendous difference in the outcome of an orthopedic patient. This benefit may be seen from weight loss itself, but also a decrease in the pro-inflammatory state of obese patients.
Nutrition and Rehabilitation

Research into nutritional needs of patients undergoing various rehabilitation programs is non-existent. Individuals developing rehabilitation programs should have knowledge of nutrition. Rehabilitation can include simple strengthening to extensive long-term physical rehabilitation; therefore, the nutritional plan for a patient must adjunctively meet the goals set during therapy and after goals are met. Nutritional plans should be included as part of the rehabilitation therapy. Water is the most essential nutrient. During rehabilitation, excitement, fear, pain, and other stress factors affect the simplest of nutritional needs, water and electrolytes.

Energy requirements correlate to work intensity, duration, and frequency, with intensity being the primary determinant. Sprinters, such as greyhounds that are running with maximum intensity, have low energy requirements because of the short race duration and low frequency of training. These dogs use mainly carbohydrates to meet energy requirements. Studies of endurance sled dog with long durations of work are at the other extreme, requiring high energy intake. High fat diets are fed to meet these high-energy requirements. Exercise intensity has not been quantified in rehabilitation, unlike performance and working dogs. Therapy is likely an intermediate level of exercise, which has not been well defined.

Intensity, duration, and frequency of exercise are highly variable; therefore, it is difficult to predict energy needs of these patients. Consideration of historical exercise level combined with current patient and diet assessment may provide some insight into energy needs. In a study of well-conditioned beagles running on a treadmill, time to exhaustion correlated with fat intake, diet digestibility, and energy concentration of the diet. Increasing fat intake improves performance of dogs with extreme energy requirements.

Protein is required for structure and function, and to a lesser extent, energy. Current recommendations with exercise are to increase protein 5 to 15% regardless of the level of exercise, with dietary protein providing approximately 25% of the energy needs. Dietary protein is the most important nutrient with regard to muscle protein and exercise increases protein requirements.

Exercise combined with amino acid intake produces a greater response regarding muscle synthesis than response to individual treatments. This suggests exercise can prime the muscle
response to the anabolic effects of amino acids or exercise activates muscle synthesis, but adequate amino acid precursors are needed to increase muscle mass.

Studies have looked at specifically the branched chain amino acids: leucine, isoleucine, and valine in exercise and sarcopenia in geriatrics. Based on these studies there may be indications to use these types of specific acid supplementation in geriatrics patients being evaluated for elective orthopedic surgery. We have used branched chain amino acids supplements in geriatrics with OA that are dealing with sarcopenia when improving protein quality and quantity is not effective.

**Obesity**

Three uncontrolled clinical studies of obese dogs with OA demonstrated improvement in mobility. Results indicate that body weight reduction causes a significant decrease in lameness with a weight loss of 6.10% or more. Kinetic gait analysis supported the results with a body weight reduction of 8.85% or more. These results confirm that weight loss should be presented as an important treatment modality to owners of obese dogs with OA and that noticeable improvement may be seen after modest weight loss of 6.10 - 8.85% body weight. Weight loss is beneficial when used in combination with rehabilitation and physical rehabilitation in dogs.

In a non-blinded prospective randomized clinical trial, 29 adult dogs that were overweight or obese (body condition score of 4/5 or 5/5) having clinical and radiographic signs of OA were evaluated. All dogs underwent weight loss. One group received caloric restriction and a home-based physical rehabilitation program and the other group received an identical dietetic protocol and an intensive physical rehabilitation program including transcutaneous electrical nerve stimulation. Significant weight loss and improved mobility were achieved in both groups; however, greater weight reduction and better mobility was obtained in the group receiving intensive physical rehabilitation.

**DIETS FOR OSTEOARTHRITIS IN DOGS AND CATS**

There are several commercially available diets formulated for management of dogs with OA. These diets contain higher levels of omega-3 fatty acids and may contain chondromodulators and antioxidants. A controlled experimental study in dogs where the cruciate ligament was
transected demonstrated a beneficial effect of pre-feeding a diet containing high omega-3 fatty acids with less severe radiographic and functional joint disease. Available “joint” diets also contain antioxidants that may be beneficial in decreasing free radical induced injury with OA. Chondromodulating agents are also often included in “joint” diets. The amount of these compounds in commercial diets is less than recommended for treatment of OA; therefore, they may be beneficial in prevention or management of early disease but probably less effective in more advanced disease.

OA occurs commonly in cats; however, there is a paucity of information regarding nutrition or nutritional compounds in management. In a prospective, blinded, parallel group study evaluating a diet high in n-3 fatty acids and supplemented with green-lipped mussel extract and glucosamine/chondroitin fed to cats with OA over 9 weeks, there was an improvement in mobility of cats fed the supplemented diet and a decline in cats fed the control diet.

THE FUTURE OF NUTRITION AND OSTEOARTHRITIS IN DOGS AND CATS

Traditional nutrition research has dealt with providing nutrients to nourish populations; it now focuses on improving the health of individuals through diet. Modern nutritional research aims at health promotion, disease prevention, and performance improvement. The concept of developing nutritionally enhanced or functional food requires an understanding of the mechanisms of prevention and protection, identification of the biologically active molecules, and demonstration of the efficacy of these molecules.

The disciplines "nutrigenetics" and "nutrigenomics" have evolved. Nutrigenetics asks how individual genetic disposition affect susceptibility to diet whereas nutrigenomics addresses the inverse relationship (i.e., how diet influences gene transcription, protein expression, and metabolism). A major methodologic challenge of nutrigenomics is integrating genomics (gene analysis), transcriptomics (gene expression analysis), proteomics (global protein analysis), and metabolomics (metabolite profiling) to define a healthy phenotype. The long-term goal should be to personalized nutrition for maintenance and improvement of individual health and the prevention of disease. These major challenges for "-omics" in nutrition and health are still to be met. Some of these challenges apply to ‘–omic’ disciplines in general, and others are specific for ‘-omic’ discovery in nutrition and disease states:
Integration of gene and protein expression profiles with metabolic fingerprints is still in its early stages.

Health and wellness are poorly understood compared with our understanding of many diseases.

Omnics in nutrition may be particularly sensitive. It has to reveal many weak signals rather than a few abundant signals to detect early deviations from normal.

Metabolomic and proteomic studies in veterinary nutrition may be the future for developing nutritional interventions for diseases states in our patients. Metabolomics is the comprehensive analysis of metabolites in urine or plasma but also applicable to tissues and other biological fluids using mass spectrometry, HPLC, and other specialized techniques. The advantage of this type of research is the quantitative, noninvasive analysis of easily accessible body fluids.

To date, proteomics has been mainly perceived as a drug development platform because disease processes and treatments often manifest at the protein level. Changes in protein expression through comparative proteomics can deliver information on the mechanism of action from a therapeutic or a toxicological viewpoint. Nutritional research can use proteomics to discover biologically active food components, assess their quality and safety, and demonstrate their biologic efficacy. Proteomics has the potential to deliver biomarkers for health and comfort; reveal early indicators for disease disposition; assist in differentiating responders from nonresponders in dietary terms; and discover bioactive, beneficial food components.

Genomics and proteomic applications were applied to a large sample population of cats with degenerative joint. In this study genes and proteins from whole blood and serum were looked at to determine those that may be up- or down-regulated in DJD cats. Three pathways were specifically selected: immune function, apoptosis and oxidative phosphorylation. Identification of these key disease-associated pathways provided some early understanding of pathogenesis and diagnose of DJD in the cat. Studies similar to this will enable us to better target DJD in the cat with pharmaceutical and nutritional intervention.

A proteonomic analysis of dog serum using the canine OA surgically induced ACLT model was done to investigate new therapeutic targets and biomarkers. This study reported a proteome mapping of dog serum and an analysis of the differentially expressed proteins between before
and after ACLT. The comparison between serum from dogs before and after ACLT reveals the differential expression of suggested several proteins that could play a key role in the pathogenesis of OA. These proteins could be candidate biomarkers for diagnosis, prognosis and therapeutics. These results reinforce the similarities between dog experimental OA and human cases of OA for translational research.
Osteoarthritis (OA) is the most common form of arthritis ranking as the 6th leading cause of disability globally in the human population. In veterinary medicine OA is the most common orthopedic disease in dogs and the prevalence of musculoskeletal disorders in all dogs has been report as one in four at multicenter referral practices. Strategies to modify the inflammatory environment present within joints can include use of “nutraceuticals.” A nutraceutical is defined by the AVMA as “…micronutrient, macronutrient and other nutritional supplements” used as therapeutic agents. The AVMA Guidelines for Complementary and Alternative Veterinary Medicine states: “claims for safety and effectiveness ultimately should be proven by scientific method. Circumstances commonly require that veterinarian’s extrapolate information when formulating a course of therapy. Veterinarians should exercise caution in such circumstances.” AVMA definition and guidelines are the platform for a discussion of nutraceuticals evaluated in dogs or in vitro using canine cells. Osteoarthritis occurs commonly in cats; however, there is a paucity of research in the role of nutrition or nutritional compounds in management.

USING NUTRACEUTICALS FOR OSTEOARTHRITIS IN YOUR PATIENTS
In clinical practice using nutraceuticals can be part of multimodality management of patients who have had musculoskeletal trauma, orthopedic surgery for DOD, patients at risk for DOD, and geriatric patients with OA. Understanding the physiological and pathophysiological mechanisms involved may aid in selecting individual nutraceuticals that will optimize patient
management. The concept of “cell niche” defines the unique attributes of a cell’s microenvironment that influences its development. It means understanding all the factors that the cell is exposed to or will interact with via cell to cell interactions, cell matrix interactions, autocrine and paracrine hormonal influences, growth factors, and cytokines. For OA we must consider the stem cell niche with functional and anatomical properties that permit cells to switch between resting and activated state. Progenitor cells, skeletal stem cells, osteoblasts, osteoclasts, osteocytes, chondrocytes, synoviocytes, extra cellular matrix, and bioactive factors including inflammatory cytokines, chemokines, growth factors, and hormonal influences are the individual components that comprise this unique microenvironment. Each disease state will have a specific balance of influences required to perpetuate the course of the disease, creating a unique signature or niche. Traditionally OA has been regarded primarily as a degenerative process and most often a consequence of aging. Treatments focused solely on symptomatic management rather than halting disease progression will fail as research revisits the role of inflammation in OA. The same inflammatory cytokines that drive rheumatoid arthritis have been shown in OA including IL-1, IL6, and TNFα. Studies suggest IL-1β and TNFα occupy a key role in the development of OA, with elevated levels of these cytokines or their gene expression reported in synovial tissues, synovial fluid and/or plasma. Investigating the role of an individual nutraceutical in maintaining the balance in the OA niche and attendant inflammatory milieu can be used as a regenerative strategy for bone or cartilage in OA. This requires individual patient evaluation with a complete history, current activity level, nutrition, environmental factors, laboratory test, radiographs and/or other diagnostics. This evaluation is needed to develop a working knowledge of the patient to assess the degree of inflammation and what component(s) of the OA niche can be addressed with selected therapies.

**Chondromodulating agents**

The Nutraceuticals in the studies are classified as antioxidants and chondromodulating agents that are purported to slow or alter the progression of osteoarthritis. Chondromodulating agents can be further divided into agents approved by the US Food and Drug Administration, such as parental polysulfated glycosaminoglycans such as Adequan and Pentosan, which can have label claims of clinical effect. The other type of chondromodulating agents are oral or nutritional supplements, which are not regulated, and legally cannot claim any medical benefit. These oral
nutraceuticals include glucosamine and chondroitin sulfate. Glucosamine is an amino sugar and precursor for biochemical synthesis of glycosylated proteins and sugars. Glucosamine-6-phosphate synthesized in the hexosamine pathway results in the production of UDP-N-acetylglucosamine, which is used for making glycosaminoglycans, proteoglycans, and glycolipids. Glycosaminoglycans are a major component of joint cartilage; therefore, it is believed that supplemental glucosamine may rebuild cartilage. *In vitro* studies support this claim although these studies use concentrations not achieved in serum or plasma after oral administration.

Results of studies of chondromodulants both in veterinary and human literature are mixed due to product used (glucosamine alone, glucosamine/chondroitin sulfate), dose administration, subjective and objective measurements of outcome, and length of trials. In a randomized, double blind, placebo controlled clinical trial comparing glucosamine/chondroitin sulfate to carprofen in 35 dogs with OA, carprofen treated dogs had improvement in 5 subjective measures while dogs treated with the glucosamine/chondroitin sulfate improved in 3 of 5 measures, but only after final assessment at 70 days. A 60-day, prospective, randomized, double blind, placebo controlled trial of 71 dogs comparing carprofen, meloxicam, glucosamine/chondroitin, and placebo demonstrated significant improvement in objective measurements with carprofen and meloxicam but not with the nutraceutical or placebo. Finally a large multicenter clinical trial compared an NSAID with glucosamine alone, chondroitin sulfate alone, and a glucosamine/chondroitin sulfate combination in patients stifle OA. Patients with moderate to severe stifle OA showed significant improvement in clinical function using the combination of glucosamine/chondroitin sulfate. Based on these studies and others the clinical evidence of these chondromodulants seems weak and will most likely be dependent on content, amount of disease, dosing, and length of treatment.

Another natural source of glycosaminoglycans, the New Zealand green lipped mussel (*Perna canaliculus*), is marketed for its chondromodulating effects. Numerous publications reporting the results of uncontrolled studies have been published with promising results. One randomized controlled clinical study added green lipped mussel powder to diet (0.3%) and the dogs receiving the supplemented diet vs. control had significant improvement in subjective arthritic scores.
Another randomized double blinded clinical study with 45 dogs showed improvement in mobility compared to placebo, but not as effective as carprofen. An uncontrolled study of 85 dogs with presumptive OA, using green-lipped mussel supplemental diet for 50 days showed a reduction in a composite arthritic score when compared with baseline scores on various diets the dogs were consuming. In reviewing the studies of green lipped mussel extract as beneficial in treating canine OA, results seem promising, but there are uncertainties with the scientific quality of the data published.

OTHER NUTRACEUTICALS

Omega 3 (n-3) Fatty Acids

The potential of modifying the inflammatory components of osteoarthritis using nutritional components is another approach of nutraceutical therapy. Arachidonic acid, an n-6 fatty acid, is incorporated into cell membranes and when metabolized, yields the 2 and 4 series of prostaglandins, leukotrienes and thromboxanes. These proinflammatory pathways are where conventional drugs are used to control OA inflammation. Substituting n-3 fatty acids into cell membranes may decrease inflammation with biosynthesis of eicosanoids of the 3 and 5 series, which are less proinflammatory. In addition to modulating cytokines, n-3 fatty acids have been shown to reduce expression of cyclooxygenase 2- lipoxygenase-5, aggrecanase, matrix metalloproteinase 3 and 13, interleukin 1α and 1β, and tumor necrosis factor α. Interestingly n-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been shown to decrease inflammatory exudates in tissues through production of oxygenated products called Resolvins (resolution phase interaction products) and docosatrienes.

Human studies of rheumatoid arthritis have shown beneficial effects of n-3 incorporation into diet. There is growing data showing the positive effects of n-3 fatty acids supplementation on cartilage metabolism with degradative enzymes and reducing inflammatory responses elicited by chondrocytes and joint matrix during the progression of OA. An unpublished study was performed in dogs evaluating omega 3 fatty acids and experimentally induced stifle OA. Dogs were randomly assigned to isocaloric diet groups containing 21.4% fat (dry matter basis, DMB) differing only in fatty acid composition: a diet with an n-6 to n-3 ratio of 28:1, 8.7:1(control diet) and a diet with an n-6 to n-3 ratio of 0.7:1. Dogs began the new diet 3 months prior to surgical
transection of the left cruciate ligament, were continued on the diet for 6 more months prior to surgical repair, and maintained for 12 months following repair. When compared to the high n-6 diet and control diet, the high n-3 diet was associated with lower serum cholesterol, triglycerides, and phospholipids, lower synovial concentration of prostaglandin E2, better ground reaction forces, and less radiographic changes of OA. A study of 127 dogs with OA fed a diet with a 31-fold increase in total n-3 fatty acid content and 34-fold decrease in n-6 to n-3 ratio had improved ability to rise from a resting position and play for 6 months when compared to dogs fed a control diet.

Peak vertical force values and subjective lameness parameters improved with a randomized, double blinded controlled clinical trial of 38 dogs with OA fed a high (3.5%) n-3 fatty acids for 90 days. A randomized, controlled clinical trial with 131 dogs with stable OA treated with carprofen over 12 weeks fed a diet supplemented with n-3 fatty acids provided a significantly faster carprofen dose reduction compared to a control diet. A recent study using a veterinary therapeutic diet (VTD) rich in n-3 fatty acids (total n-3 fatty acid 1.47% DMB) compared to a control diet (CTR, total n-3 fatty acid 0.18% DMB) over 13 weeks with 30 dogs with naturally occurring OA evaluated peak of the vertical oriented ground reaction force (PVF) using a force platform and activity scores provided by owners. The VTD fed dogs showed significant improvement in PVF at both week 7 and week 13 compared to CTD fed dogs. These studies provide a rationale for n-3 fatty acid supplementation or feeding diets with high n-3 fatty acid content. Recommendations for n-3 supplementation for canine OA has been reported as 310mg/(kg^{0.75}) or 1745 mg EPA + DHA per 10kg body weight for the dog.

There are now available therapeutic diets supplemented with both omega three fatty acids and glucosamine chondroitin. These diets can be used as part of an effective management program for patients with osteoarthritis. It is important to know the exact content of parental or oral glucosmaines/chondroitans if the patient is to be supplemented with these above the therapeutic diet content. It has been reported that because these nutraceuticals have a molecular structure similar to heparin; therefore bleeding may be a concern with excess levels of these products.
High levels of omega threes (N3) have been reported to cause a decrease in platelet aggregation and the NRC has an upper safe limit for EPA and DHA in dogs. It is important to know the intake of omega threes for a patient eating these therapeutic diets and know how to safely use supplements to prevent any adverse reaction such as hemorrhage. Other side effects of omega threes have been reported such as gastrointestinal upset, pancreatitis, and excess caloric intake.

**Zeel®**

Zeel® is an over-the-counter preparation that has been evaluated in 2 controlled studies in dogs. This is a highly diluted proprietary formulation of herbs, metabolites, minerals, and antioxidants. In a study of 68 dogs greater than one year of age diagnosed with OA, it was compared with carprofen in a multicenter, prospective, observational open-label cohort study in 12 German veterinary clinics. In another study in dogs (n=44), greater than one year of age diagnosed with OA, it was compared with carprofen and a placebo. Clinical signs and several measures of OA improved significantly with treatment in both studies; however, in one study, it was not as effective as carprofen. The composition of the products and the dosage of Zeel® differed between the two studies, which confounds interpretation of results.

**Boswellia serrata**

Boswellia, also known as Boswellin or Indian frankincense, comes from the Indian *Boswellia serrata* tree. Resin from the bark of this tree is purported to have anti-inflammatory properties derived primarily from 3-O-acetyl-11-keto-β-boswellic acid (AKBA), which inhibits 5-lipoxygenase and matrix metalloproteinases, and decreases tumor necrosis factor α and interleukin 1β. Boswellia resin has been shown to improve clinical signs and pain in humans in controlled studies. Boswellia resin has been evaluated in 24 dogs in an open multi-center study. Improvement in clinical signs, lameness, and pain was found in 17 of 24 dogs.

**Avocado/Soybean Unsaponifiables**

Avocado/soybean unsaponifiables (ASU) are composed of the unsaponifiable fractions of avocado and soybean oils in a 1/3 to 2/3 proportion. ASU has anti-OA properties by inhibiting interleukin-1 and stimulating collagen synthesis in cartilage cultures. Human clinical trials have shown some beneficial effects of ASU on clinical symptoms of OA, but conflicting data in other
studies found no long term benefits. In one study of dogs, OA was induced by anterior cruciate ligament transection. Dogs then received placebo or ASU (10 mg/kg/24h). The size of macroscopic lesions of the tibial plateau, severity of cartilage lesions, synovial cellular infiltration, and inducible nitric oxide synthase were decreased significantly and there was reduced loss of subchondral bone volume and calcified cartilage thickness in the group receiving ASU.

**S-adenosyl l-methionine (SAMe)**

S-adenosylmethionine (SAMe) is a co-substrate involved in transmethylation, transsulfuration, and aminopropylolation reactions, which occur primarily in the liver. In controlled trials of humans with osteoarthritis, SAMe is as effective as non-steroidal anti-inflammatory drugs and better than placebo in reducing pain and in improving function with a lower likelihood of side-effects; however, no difference with a non-steroidal anti-inflammatory drug was found in one study. A systematic review was inconclusive and was hampered by inclusion of small trials of questionable quality.

A six week RCCT of 33 dogs blocked by body condition score were assessed using pressure platform gain analysis, examinations score, goniometry, and Canine Brief Pain Inventory (CBPI). Data collected did not support the use of SAMe as a single treatment for reducing clinical signs of OA.

**EVALUATING NUTRACEUTICALS**

The AVMA defines nutraceuticals as micronutrients, macronutrients and other nutritional supplements used as therapeutic agents. They are often called dietary supplements and defined as a concentrated form of a presumed bioactive substance used to enhance health in dosages exceeding those obtainable from normal foods. Regardless of definition, nutraceuticals and dietary supplements have little regulation as compared to the pharmaceutical industry.

Guidelines we use to evaluate these products include:

- National Animal Supplement Council (NASC) [http://www.nasc.cc/](http://www.nasc.cc/)
- Consumerlab.com
- Do you know the manufacturer?
- Are there studies on efficacy and safety?
- Products should have lot # and expiration date
- Guaranteed analysis
• Recent reviews include
  • Vanderweerd, et al, JVIM 2012;26:448
  • Bartges & Raditic in Physical Therapy & Rehabilitation. Millis & Levine. New release

**USING THERAPEUTIC DIETS FOR OSTEOARTHRITIS**

Therapeutic diets can be a safe starting point for using nutraceuticals to treat OA in veterinary patients. A recent review of the nutraceuticals and OA in horses, dogs, and cats found the evidence of efficacy poor with the exception of diets supplemented with n-3 fatty acids. Knowing the exact formulations and specific nutrients of concern in these diets allows for better application of these diets. When nutraceuticals are used with these diets, the total intake of at least n-3 fatty acids should be determined. Potential adverse effects of n-3 fatty acids includes altered platelet function, gastrointestinal adverse effects, altered immune function, nutrient-drug interactions, lipid peroxidation and weight gain. Adverse effects are less likely with glucosamine intake, but the potential for coagulopathies may exist.

**INTEGRATING DIET, SUPPLEMENTS, AND NUTRACEUTICALS IN YOUR PRACTICE:**

• Can you supplement a dog with N3 supplements if they are on a therapeutic joint diet?
• Can you supplement a dog with glucosamine/chondroitans if they are eating a therapeutic diet?
• Can you use a therapeutic joint diet in a DOD puppy?

What supplements do I use? Example cases:
• How would I manage a CCL patient with surgery? Without surgery?
• How do you manage a young dog with OCD?
• How do you manage a dog with elbow dysplasia, hip dysplasia, bilateral luxating patellas and CCL?
• How do you manage a geriatric dog? Geriatric cat?
**USING THERAPEUTIC JOINT DIETS: (Raditic, Bartges 2013)**

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<td>3.3</td>
<td>2.0</td>
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<tr>
<td>ALA</td>
<td>mg/100kcal</td>
<td>563</td>
<td>585</td>
<td>-</td>
<td>694</td>
<td>491</td>
<td>1.97</td>
</tr>
<tr>
<td>EPA</td>
<td>mg/100kcal</td>
<td>122</td>
<td>70</td>
<td>96</td>
<td>126</td>
<td>202</td>
<td>32</td>
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<tr>
<td>Total n3</td>
<td>mg/100kcal</td>
<td>308</td>
<td>218</td>
<td>250</td>
<td>951</td>
<td>1011</td>
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<tr>
<td>Glucosamine</td>
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<td>51.3</td>
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<td>27.0</td>
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<td>2.64</td>
<td>Not Added</td>
<td>18.6</td>
<td>9.14</td>
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<td>Kcal</td>
<td></td>
<td>307</td>
<td>324</td>
<td>408</td>
<td>356</td>
<td>498</td>
<td>296</td>
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</table>
Use of Omega 3 in clinical practice: EPA + DHA = 170 - 1745mg/10 kg (22lb)

Table 1—Approximate dosages of EPA and DHA recommended as adjunctive dietary treatment for various clinical disorders in dogs.

<table>
<thead>
<tr>
<th>Clinical disorder</th>
<th>Dosage (mg/kg0.75)*</th>
<th>Approximate EPA and DHA dose for a 10-kg (22-lb) dog (mg)†</th>
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<tbody>
<tr>
<td>Idiopathic hyperlipidemia</td>
<td>120</td>
<td>675</td>
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<tr>
<td>Kidney disease</td>
<td>140†</td>
<td>790</td>
</tr>
<tr>
<td>Cardiovascular disorders</td>
<td>115</td>
<td>645</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>310†</td>
<td>1,745</td>
</tr>
<tr>
<td>Inflammatory or immunologic (atopy or IBD)</td>
<td>125</td>
<td>700</td>
</tr>
<tr>
<td>NRC recommended allowance22</td>
<td>30</td>
<td>170</td>
</tr>
<tr>
<td>NRC safe upper limit</td>
<td>370</td>
<td>2,080</td>
</tr>
</tbody>
</table>

*Calculated on a metabolic BW basis; if BW is recorded in pounds, it must first be divided by 2.2 to convert it to kilograms for use in this equation. †Values have been rounded to the nearest 5 mg. ‡Dosage may be increased (depending on the severity and chronicity of the disorder) up to the NRC safe upper limit.

Bauer, JE JAVMA 2011
An adverse reaction to food is defined as a clinically abnormal response attributed to an ingested food substance, and may be further categorized as immunologic or non-immunologic in nature. Food allergy is an immunologically mediated, reaction to ingested food. This is different than food intolerance, which is a non-immunologically mediated adverse reaction including toxic reactions, pharmacological reactions, metabolic reactions, and idiosyncratic reactions.

ADVERSE REACTIONS AND FOOD HYPERSENSITIVITY.
Throughout life, animals are exposed to a great variety of potential dietary allergens. However, after a variable period of time, some animals may develop an immune response against a particular foodstuff that activates one or more immunopathogenic pathways. After development of this response, subsequent ingestion of this foodstuff results in clinical signs. These dietary antigens do not normally cause problems because the intestinal mucosa forms a barrier that limits absorption of macromolecules, but this mechanism is imperfect. There is evidence that antigens are absorbed through both normal and abnormal gut. Indeed, antibodies to food allergens, usually IgG, are often demonstrable in normal individuals, but they do not result in clinical disease. Upon initial presentation of the antigen to the gut mucosa, there is generally an immune response involving IgA. This reduces the amount of antigenic material that is absorbed. Immune complexes of antigen and IgA antibody are transported across
hepatocytes, into bile, and re-circulated to the intestine. This local IgA response may be followed by a transitory systemic immune response, but immunologic tolerance follows. Thus, there is an apparent paradox of a vigorous local immune response followed by a systemic tolerance.

Absorption of macromolecules can be altered in either direction by local immunity. Decreased uptake has been demonstrated experimentally following oral or parenteral immunization in rats, and increased absorption occurs in IgA-deficient human beings. Absorption is also enhanced by vasodilatation in the gut mucosa, such as that resulting from a local allergic reaction. In this case, the patient becomes caught in an immunological vicious circle because local hypersensitivity reactions favor access of allergens that in turn heightens the antibody response.

**PATHOPHYSIOLOGY OF FOOD HYPERSENSITIVITY:**
Factors that lead to development of hypersensitivity to ingested antigens are speculative. Those most frequently implicated are heat- and acid-stable glycoproteins with molecular weights of 18,000-30,000 Daltons. Hypersensitivity reactions involved in food allergies have been shown to involve types I, III, and IV reactions. Some studies indicate that IgE is implicated in some instances and the reactions involved include both the classic, immediate Type I reaction and the late-phase IgE-mediated reactions. The factors that determine the extent of absorption of allergens by the intestine are not fully understood, although local vasodilation is clearly facilitatory. Once local vasodilation is stimulated by local reactions, the cycle feeds on itself. What initiates the original immunologic reaction is not clear. Certainly, if clinical or subclinical gastrointestinal disease occurs which alters mucosal integrity, absorption of antigenic proteins may occur which may initiate the processes. Inflammatory mediators involved in food allergy may include interleukins, platelet activating factor, histamine and cytokines.

**Food Allergy**
Clinical signs of food allergy relate primarily to dermatologic and gastrointestinal. Dermatologic signs often include pruritis, erythema, and secondary pyoderma. Gastrointestinal signs may include vomiting and/or diarrhea, flatulence, perianal fistulae, and anorexia. Other potentially associated disorders include cholangiohepatitis/cholangitis, feline asthma, idiopathic epilepsy, and feline urinary tract disease.
Most basic food ingredients have potential to induce an allergic response, although proteins cause the majority of reactions. Dietary components reported to cause food sensitivity in dogs and cats include: cow’s milk, beef, mutton, pork, chicken, rabbit, horse meat, fish, eggs, oatmeal, wheat, corn, soy, rice flour, potatoes, kidney beans, canned foods, cod liver oil, dry food, pet treats, and food additives.

**Treatment of food allergy:**

*Elimination diets and dietary challenges.* The most useful and reliable aid in diagnosis of dietary sensitivity is the procedure of feeding a restricted or elimination diet followed by dietary challenge with a test meal. Elimination diets must be individualized based on the previous dietary exposure. A detailed study of the animal’s diet will allow identification of foods that have not been fed before, and that could be used to formulate a nutritionally balanced elimination diet that will “hypo-allergenic”. If it is not possible to formulate a suitable elimination diet, then a restricted diet may be used that contains only one or two potential allergens, preferably ones that the animal has not eaten in the preceding month. Many homemade diets that are used as elimination diets are not complete and balanced (e.g. cottage cheese and rice, or chicken and rice). Supplementation with vitamins and minerals is encouraged, but avoid use of supplements that contain potentially offending foodstuffs (e.g. beef or pork). It is tempting to use commercially prepared “hypoallergenic diets” during the diagnostic period for owner convenience and to ensure feeding of a complete and balanced diet. This may be effective, but approximately 20% of dogs diagnosed as food hypersensitive when fed a home-cooked lamb and rice diet manifested clinical signs of allergic dermatitis when fed the commercially prepared lamb and rice diet. Gastrointestinal signs may subside in 3-5 days, but if it chronic in nature; it may take 4-6 weeks. Once clinical improvement is noted, it is advised to attempt to identify the offending antigen by introducing foodstuffs to the elimination diet

*Protein hydrolysates.* Because proteins with molecular weights over 18,000 Daltons are incriminated as being antigenic, modification of proteins to compounds having lower molecular weight may be of benefit. Protein modification is a process that alters the physical characteristics of protein molecules, presumably reducing the antigenicity and rendering them less able to elicit an immune response. By reducing the average weight of the protein molecule, this process can result in a protein that may be truly hypoallergenic. To be effective, it must reduce the molecular weight of the protein below 18,000 Daltons. Recently, several
commercially available diets containing protein hydrolysates have been introduced including Exclude, DVM Pharmaceuticals, Hill’s Prescription Diet z/d, and Purina’s CNM HA-Formula. Anecdotally, these diets appear to be effective as elimination diets, and they have the advantage of being complete and balanced. These diets may be used long-term, but cost more.

*Homemade and raw diets.* Homemade diets allow promote control over ingredients and truly novel ingredient diets may be formulated. Because some dietary ingredients may become antigenic due to processing, feeding a whole ingredient or raw food diet means there is no processing. Additionally, homemade diets are typically more digestible and smaller quantities may be fed.

Nutrition consults
- The ACVN ([http://www.acvn.org](http://www.acvn.org))
- Michigan State 517 / 432 – 7782
- North Carolina State 919 / 513 - 6871
  [http://www.cvm.ncsu.edu/vhc/vhwc/nutrition/](http://www.cvm.ncsu.edu/vhc/vhwc/nutrition/)
- Ohio State 614 / 292 – 1221
  [http://www.vet.osu.edu/nssvet.htm](http://www.vet.osu.edu/nssvet.htm)
- Tufts University 08 / 839 – 5395 ext 84 696
- UC Davis 530 / 752 – 1387
  [http://www.vmth.ucdavis.edu/vmth/services/nutrition/nutrition.html](http://www.vmth.ucdavis.edu/vmth/services/nutrition/nutrition.html)
- University of Missouri [http://www.vmth.missouri.edu/clin_nu.htm](http://www.vmth.missouri.edu/clin_nu.htm)
- University of Tennessee 865 / 974 – 8387 utvns@utk.edu
- Veterinary Information Network ([http://www.vin.com](http://www.vin.com))

*Management of food hypersensitivities.* If the client has been cooperative, the presumptive food antigen has been identified. If this has occurred, or if it is not possible to identify the antigen, then long-term management procedures should be instituted. First, the diet is gradually changed from a home-prepared elimination diet to a commercially prepared diet of selected protein. This not only provides a nutritionally balanced and complete diet, but also is more convenient for owners. There are many single protein source diets available including diets that contain duck, venison, lamb, rabbit, and kangaroo. If the animal continues to do well,
It must be emphasized to the owner to not give table scraps or treats, and to not switch the diet even if clinical signs have not recurred.

Inflammatory bowel disease (IBD) is an immune mediated disease which is not due to food allergy and/or intolerance. It is an idiopathic disorder associated with persistent or recurrent GI signs, characterized by histologic evidence of inflammation with no discernible cause, but it is not due to infectious, neoplastic, or metabolic disease. We will include it in this discussion as an idiopathic immunological disease of the gut and the current pathogenic theories are as follows:

1. Development of defect in mucosal barrier, increased gut permeability, and hypersensitivity response to antigens
2. Aberrant immunological responses to luminal antigens - defects in GALT suppressor function
3. Intestinal microbiome and the innate immune system
   a. Pattern recognition receptors (PRRs) and Pathogen-associated molecule patterns (PAMPs)

It is becoming more evident that the adaptive immune system and T cells play crucial roles in development in IBD. And a dysregulated immune response to components of the commensal (nonpathogenic) flora may play an important role in induction and perpetuation of chronic intestinal inflammation. In the human literature Toll-like receptors (TLR) are up regulated in human IBD and recent studies have shown that TLR2 are higher in dogs with severe IBD and TLR2 is also with associated canine chronic enteropathy clinical activity score (CCECAI). There has been demonstrated a dysbalance between Enterobacteria & Clostrial sp. in IBD dogs similar to human studies. Flagellin, a bacterial protein considered a biomarker in human IBD has been shown as an antigen marker for IBD found in dogs. There also is a genetic predisposition being identified especially in the German shepherd.

Clinical signs include waxing and waning clinical signs including weight loss, appetite changes, mucoid feces, abdominal pain, tenesmus, hematochezia, increased frequency of defecation and the “finicky eater.” It is almost diagnoses by exclusion as response to treatments are transient. There is a failure to respond to elimination diets and dietary challenges with no pathognomonic
laboratory findings. A diagnostic work up must be done to rule out other causes of these clinical signs to include:

- Rectal cytology: Histoplasmosis
- Fecal analysis: enteric parasites
- Fecal culture: Salmonella, Campylobacter
- Fecal toxin assays: Clostridium

And before diagnosing IBD it is recommended to treat as follows:

- Fenbendazole 50 mg/kg PO for 5 days
  - Repeat in 3 weeks and 3 months
- Elimination diet
  - Minimum 3-4 weeks
  - Antibiotic responsive diarrhea
- Treat for 14 days
  - Tetracycline
  - Tylosin
  - Metronidazole (?)

Final diagnosis is the intestinal biopsy via endoscopy or surgical. Gross lesions are seen in 50% of dogs and 42% of cats. Multiple biopsy sites should be obtained regardless of visual assessment with endoscopy or surgery. The classification of IBD is then anatomical and histological.

The treatments of IBD are presented as follows:

1. Diets and Nutrients of Concern
2. Conventional medications for treatment of IBD
   a. Antibiotics
      i. Tylosin: 10-20 mg/kg q 8 h for 21 days, 20-40 mg/kg q 12 h, tapered to lowest effective dose, 40-80 mg/kg/day po (cats).
      ii. Metronidazole: 10-20 mg/kg q 12 h for 10-14 days, then q 24 h for 10-14 days; 10 mg/kg po q 12 h or 25 mg/kg/day po for 5 days (cats)
      iii. Enrofloxacin: 10-20 mg/kg PO q24h
      iv. Oxytetracycline: 10-20 mg/kg q 8 h
   b. Immunosuppressive drugs
      i. Glucocorticoids – either systemic (e.g. prednisone: 1-2 mg/kg PO q24h or divided q12h) or topical (e.g. budesonide: 3 mg/m2 q24-48h (dogs), 1
mg/cat PO q24h (cats)). Glucocorticoids are often very effective if eosinophilic component.

ii. Azathioprine – a purine analog that is immunosuppressive. Used primarily in dogs and has been reported that cats are very sensitive to toxicity. There may be a lag phase between initiation and response; however, newer data suggests that it is not necessarily more than 1 week or so. In dogs, there are a couple of protocols: 2 mg/kg PO q24h x 2-4 weeks, then either 1 mg/kg PO q24h or 2 mg/kg PO q48h, then 1 mg/kg PO q48h until decide to stop. It can be used indefinitely if patient tolerates. May induce bone marrow suppression, liver disease, and pancreatitis.

iii. Chlorambucil – an alkylating agent also used as a chemotherapeutic drug. Dosages include: Dogs: 6 mg/m2 PO q48h for 2-4 weeks then taper or 0.25-0.33 mg/kg PO q72h for 2-4 weeks then taper; Cats: 2 mg/cat PO q48h for 2-4 weeks then taper or 2 mg/cat PO q72h for 2-4 weeks then taper. Can be myelosuppressive.

iv. Cyclosporin A – inhibits T cell function; therefore, may be more effective with lymphocytic IBD. Dose: 5 mg/kg PO q24h. May be associated with renal and liver toxicity, myelotoxicity, and increased infections.

v. Mycophenolate – also a purine analog. Dosage: Dogs: 10-20 mg/kg PO q12h; Cats: 10 mg/kg PO q12h. Seems to be well tolerated. Main side effects are GI signs.

c. Motility modifiers

   i. Loperamide (Imodium): 0.1 - 0.2 mg/kg q8 - 12h PO (dog), 0.08 – 0.16 mg/kg q24h PO (cat – cautiously);

   ii. Diphenoxylate (Lomotil): 0.05 – 0.2 mg/kg q8 - 12h PO (dog), 0.05 – 0.1 mg/kg q12h PO

d. Anti-emetics- Appetite stimulants

   i. Ondansetron (Zofran): 0.5-1 mg/kg PO q12-24h

   ii. Dolasetron (Anzemet): 0.5 mg/kg SC, PO q24h.
iii. Mirtazapine (Remeron): 15 – 30 mg PO q24h (dog), 1.875 – 3.75 mg PO q72h (cat)

e. Anti-inflammatories

i. Sulfasalazine: 20-30 mg/kg q 8-12 h, 10-25 mg/kg q 8 h for 6 weeks, then taper; 10-20 mg/kg po q 8-24 h for up to 10 days (cats)

ii. Olsalazine: 10-15 mg/kg q 8-12 h, 5-10 mg/kg q 8 h for 6 weeks, then taper. Side-effects may include KCS due to the sulfa drug

f. Pancreatic enzymes- EPI patients and patients with malassimilation

Integration of complimentary therapies for IBD patients

1. Probiotics- As a general rule: “more is better” – more bugs of more types in more numbers- see below product information

2. Omega 3 fatty acids

   i. Dose is based on the amount of EPA and DHA in the product not the total amount of omega-3 fatty acids

3. Digestive enzymes- plant vs. animal base

4. L- Glutamine and Arginine

5. Specific Vitamin and Minerals- B12, B complex, Vitamin A, D, Cu, Fe, Zn, Se

6. Fiber sources

   a. Soluble vs. insoluble

   b. Fermentable vs. non fermentable

7. Bismuth, charcoal, clay

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<tr>
<th>Product</th>
<th>Amount</th>
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<td>FortiFlora</td>
<td>10 M / g (pouch)</td>
<td>Entoerococcus faecium SF68</td>
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<td>ProstoraMAX</td>
<td>100 M / g</td>
<td>Bifidobacterium animalis</td>
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<td>ProViable KP</td>
<td>500 M / g</td>
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<tr>
<td>ProViable DC</td>
<td>5 B / capsule</td>
<td>Enterococcus faecium, Streptococcus thermophilus,</td>
</tr>
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</table>
Lactobacillus acidophilus, Lactobacillus bulgaricus, Lactobacillus casei, Bifidobacterium bifidum, Lactobacillus plantarum

**Culturelle**

10 B / capsule
(manufactured with 30 B)

Lactobacillus GG

**VSL #3**

450 B / packet
112 B / capsule

Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus bulgaricus, Streptococcus thermophilus

**CANINE ATOPIc DERMATITIS (AD): CAN DIET BE USED TO IMPROVE THE AD PATIENT?**

Canine atopic dermatitis is a multifaceted disease determined by a combination of genetic and environmental factors. The accepted the definition of atopy as “a genetically predisposed tendency to develop IgE-mediated allergy to environmental allergens.” Environmental proteins include pollens, molds, dusts, danders, mites and in some cases insects, chemicals, and foods. AD affects the immunologic response, skin barrier function, and nerve function.

The pathophysiology of AD is better understood. It involves percutaneous exposure and absorption of allergens through an epidermis that may have a defective barrier function. Naïve Langerhans cell captures and internalizes allergens then they are processed, packaged and presented to naïve T-helper cells (Th0) cells in the draining lymph node. Dendritic cells will activate T-helper cells which produce cytokines such as IL-4 and IL-13. These cytokines can stimulate B cells to become plasma cells which then produce allergen-specific IgE. Now there is allergen specific IgE also enter into the circulation and other tissues and bind to cells.

**FOOD INTOLERANCE- NON-IMMUNOLOGICAL**
An immunological food reaction involves hypersensitivity with food allergies being an immunologically mediated, reaction to ingested food. **Food intolerance** is a non-immunological abnormal physiological response to a food item, and may involve, toxic, pharmacological, or metabolic reactions or dietary idiosyncrasies, in which the animal is unable to digest or otherwise process a dietary component. Examples of food intolerance include lactose intolerance, gluten intolerance, reaction to vasoactive amines in diet, reactions to histamine-containing foods or foods that stimulate histamine release, reactions to foods that contain opiates, food additives, and toxic reaction to food substances.

**OTHER ADVERSE FOOD REACTIONS**

**Food components**

Hazardous food components encompass dietary components that are present in the food. These may be components that should be present, but are present in an unbalanced manner, or components that should not be present. **Nutrient imbalances** may occur when there is a problem in the formulation or manufacture of a diet, or if the owner supplements a complete and balanced diet with an incomplete and unbalanced food or supplements. Examples of excesses include hypervitaminosis A (raw liver or cod liver oil) and hypervitaminosis D (recent food recall). Examples of toxicity associated with ingestion of foodstuffs include onion poisoning, which causes a Heinz body hemolytic anemia in cats, and chocolate toxicity, which causes vomiting, diarrhea, and central nervous system disease due to theobromine. Raisins and grapes have been associated with acute renal failure in dogs. Examples of deficiencies include generic foods that may be unbalanced, fat deficiency, and vitamin and trace element deficiencies. Pet foods contain many **food additives** from antioxidants, to humectants in semi-moist food, to coloring agents. These are approved by the FDA for inclusion in pet foods and are similar to additives used in human foods. Occasionally, food may become **contaminated**. This may occur if the manufacturer uses contaminated foodstuffs or the food may become contaminated after production. **Mycotoxins** are a rare problem in pets; however, there have been sporadic reports of mycotoxin-containing foodstuffs being used in the manufacture of dog food resulting in disease and death. Pet foods may become contaminated if **mold** is allowed to grow. This should not occur in pet foods, but if the food becomes moist or if the fat becomes rancid, it may occur. Occasionally, food may become “spoiled” and bacterial contamination may occur. Such organisms as Salmonella, Campylobacter, and Botulism have been reported. Lastly, ingestion of
animal tissues containing residues of toxic substances may result in disease. For example, if a
cat eats a mouse that has been killed using a warfarin-like rodenticide, the cat may develop a
hemorrhagic disease due to the vitamin-K-dependent coagulation factor inhibition.

**Mechanical injuries**

Food may sometimes contain something that causes mechanical injury to the animal or the animal may
ingest such an item. An example is a dog that ingests a bone, which becomes lodged in the esophagus
or a cat that ingests a needle with a string attached.

**Poisonous plants and animals**

It occurs occasionally \ in small animals. For example, ingestion of Easter Lilies results in renal failure in
cats.

**Metals and minerals**

Lead and zinc toxicity may occur with ingestion.

**Food associated illness and toxicity**

Recognizing food-associated illness can be difficult as often cases present sporadically with no
apparent connection. Recognizing clusters of cases geographically (e.g. regionally) or during the
same time period (e.g. animals in same household) is important. Take a good diet history from
the owners. Introduction of a new food or a new bag of food, poor palatability or acceptance of
the food by the pet(s), and pets eating the same food whether in the same household or different
households may provide clues to problems with diet. Keep in mind that animals may present
with similar clinical signs and histories but consuming different diets and/or snacks/treats.
Discuss cases with your colleagues as they may be having similar experiences that can support
your concerns.

**Reporting potential adverse reactions:**

- Contact the manufacturer – they should be willing to listen and take information as well
  as answer questions as to whether other complaints have occurred
- FDA Center for Veterinary Medicine:
  www.fda.gov/AnimalVeterinary/default.htm
- Complaints:
  www.fda.gov/AnimalVeterinary/SafetyHealth/ReportaProblem/ucm182403.htm
- Questions & Answers
- AVMA: [http://www.avma.org](http://www.avma.org) – specifically, this link for reporting adverse events with
drugs vaccines, and pet food:
  www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm295445.htm
It is important to gather as much information as possible and to save as much as possible. Document the product name, type of food, manufacturer/distributor information, and date code/best buy code. Keep a copy of the packaging if you can. If the owner has a copy of the purchase receipt, it helps. Retain samples of the food; keep at least 4 cans or pouches of canned or semi-moist food and 1 kg of dry food. Do not send all of the samples for analysis – keep or have the owner keep some. Have the owner document consumption of the food by pet(s) with as much detail as they can recall. Keep good records including signalment, clinical signs, and test results. If a pet dies, perform a necropsy or have a necropsy performed. Make sure to tell the diagnostic lab performing the necropsy of your suspicion of toxicity. Save tissue and fluid samples, if possible. Document all communications with the manufacturer and with FDA/AVMA. If other pets may have been exposed, test them. Keep good records and samples of suspect food.

**Jerky treats:**

It is unknown at this time what in these treats is causing problems in the pet and most recently human adverse food reactions.

As of May 16, 2014:

- 4,800 complaints of illness in pets - chicken, duck, or sweet potato jerky treats
  - nearly all imported from China
- 5,600 dogs, 24 cats, 3 people, & include >1,000 dog deaths
- 60% of the cases GI/Hepatic, 30% Renal/Urinary, 10% (neurologic, dermatological, immunologic)
- 15% of renal/urology- tested positive for Fanconi syndrome

[http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm360951.htm](http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm360951.htm)

- Oct 22, 2013 [FDA Releases Progress Report on Jerky Pet Treat Investigation](http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm360951.htm)
- [FDA Voice: Help Us Find Out Why Jerky Treats Are Making Pets Sick](http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm360951.htm)
- Jan 09, 2013 [FDA CVM Update on Jerky Treats](http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm360951.htm)
- [FDA Voice: Is It Something My Pet Ate?](http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm360951.htm)
- Nov 18, 2011 [FDA Continues to Caution Dog Owners About Chicken Jerky Products](http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm360951.htm)
- Dec 19, 2008 [Preliminary Animal Health Notification - Chicken Jerky Products for Dogs](http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm360951.htm)
- Sept 26, 2007 [FDA Cautions Consumers about Chicken Jerky Products for Dogs](http://www.fda.gov/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/ucm360951.htm)
ADVERSE FOOD REACTIONS: REACTION FROM CONSUMERS

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Objectives:

1. Understanding obesity and the pro-inflammatory state
2. Understanding fat as endocrine gland
   a. Metabolic syndrome in people
   b. Is there a veterinary metabolic syndrome?
3. Maillard reaction and advanced glycation end products (AGE)
   a. Is it ideal for pets to consume the same diet through out life?

What if there was a disease that affected 30-45% of dogs & cats in the US that was associated with decreased activity, dermatitis, cardiac disease, diabetes mellitus, hypertension, GI problems and cancer. It was associated with deaths and shortened life spans, but was easy to diagnose and treat. This disease does exist and it is obesity seen on a daily basis in general practice. Obesity defined as follows:

- Quantitative: 15-20% above ideal BW
- Functional: Accumulated fat impairs health or function
- General: Excessive fat accumulation in relationship to body mass
- But it is known that distribution also important
To treat this epidemic in veterinary medicine simple we can nutritional assessment as outlined below:

1. JAAHA; 2010 July/August, Volume 46; Page 285
2. Screening evaluation
   a. Done on all patients
3. Extended evaluation
   a. Done if nutritional risk factors are identified
4. Body condition scoring
5. Muscle condition scoring

Another part of understanding the obesity crisis in our patients is how pet diets contribute to this disease. We need to realize that reading and understanding pet food labels is not simple and there is not a great deal of useful information for you as a veterinarian to determine which diets are superior. The ingredient lists and guaranteed analysis to not give you complete insight into the quality of the diet. Understanding the AAFCO life stage statement can be useful, but has its limitations. Keeping up to date on pet food recalls and industry changes are problematic in today’s busy practice.

From a nutritionists stand point, this is problematic when we are trying to determine the ideal diet to feed a patient for optimal health. The pet food industry reports in 2013 about $56 billion in expenditures and has grown annually despite the economy. Another problem with pet diets is the high simple carbohydrate content ranging from 30 – 60% on a dry matter basis (DM). Pet diets are highly processed using heat and pressure then coated with flavor enhancers, vitamin, minerals, and preservatives to produce a product that is not only complete and balanced, but is stable for shipping with a long shelf life. Dry kibble diets especially can be problematic as they are energy dense diets and easily over fed containing only about 10% moisture. The AAFCO diets that are labelled complete and balanced for all life stages can be problematic when fed to more sedentary adult or senior pets. It is also problematic that the kcals per cup are not yet part of the legal labelling required pet diets.

**Obesity and Metabolic syndrome:**

It is now well established that body fat can no longer be considered an inert tissue or dead weight in human and animal patients. It is now known to be a metabolically active tissue and obesity is a pro-inflammatory state. The number and concentration of inflammatory markers is HIGHLY
correlated with the degree of obesity in several species. We should no longer report a patient “healthy but obese.”

There are studies of over 50 adipokines defined as hormones and factors secreted by adipose in multiple species including dogs and cats. They are essential to normal metabolism regulating energy, glucose, lipid metabolism and playing a role in inflammation, immune, and angiogenesis. The most well-known adipokines are leptin and adiponectin in healthy and obese patient populations.

In the obese patient it is known that there is insulin resistance, leptin resistance, and adiponectin is decreased. It has also been shown that there exits an increased secretion of TNFα and IL-6, resulting in a pro-inflammatory state in body tissues. In human metabolic syndrome, insulin resistance and obesity are key, but the syndrome includes a pro-inflammatory state, risk factor for chronic diseases, genetics, hormonal changes, physical inactivity and accelerated aging.

Human metabolic syndrome can be defined as any three of the five traits:

- Abdominal obesity (waist circumference)
- Impaired fasting glucose (insulin resistance)
- Hypertension
- Hypertriglyceridemia
- Low HDL (“good”) cholesterol

**Veterinary metabolic syndrome:**

Verkest in The Vet J (2014) defined metabolic syndrome (MS) as elevated triglycerides (TG), low HDL, elevated blood pressure (BP), elevated blood glucose (BG), and excess waist circumference. He compared this to the definition of human metabolic syndrome where risk factors include for morbidity & mortality include: atherosclerosis, cardiac disease, type 2 DM and stroke. Using this analysis, definitions and comparison it was concluded there is not a defined veterinary metabolic syndrome.

Tvarijonaviciute et al in BMC (2012) defined MS complex cluster of ‘metabolic risk factors’ predispose to develop secondary diseases. It was also noted that equine MS well described & known risk factor for laminitis, reproduction and BP. The study assessed 35 dogs before and after weight loss to look at a diagnostic criteria defined as canine obesity-related metabolic
dysfunction (ORMD) to include BCS, BP, fasting TG, cholesterol and glucose. Included were measurements with DEXA, adiponectin, fasting insulin, and C reactive protein. The results reported were that 20% of obese dogs were ORMD having abnormal ORMD measurements. It was concluded that MS in obese dogs is less than what has been reported in obese humans where 50–60% have MS. Results showed Obese dogs with ORMD had two times less adiponectin, two times more insulin; therefore, up to 1/3rd obese dogs do suffer from ORMD characterized by hypoadiponectin and hyperinsulinaemia.

Based on these and other studies we consider these diseases as having a known pro-inflammatory state or potential for ORMD.

1. Hyperadrenocorticism
   a. Concurrent dermatitis, UTI, PU/PD, gastroenteritis
2. Pancreatitis
3. Hyperlipidemia
4. Chronic stress colitis
5. Feline urological diseases
6. Osteoarthritis
7. Chronic cystitis
8. Triaditis
9. Diabetes mellitus

**How a nutritionist treats the pro-inflammatory:**

If you consider obesity and metabolic syndrome as part of chronic disease states in your patients there are novel, yet simple therapies that become part of your treatment plan. This is where we probably gain more on the management of many chronic diseases as thoughtful nutritionists.

1. Weight loss, exercise – increase lean body mass
2. Decrease simple carbohydrate intake
   a. Homemade, raw, therapeutic diets
   b. Treats- real foods
3. Branched chain amino acids
4. Supplements
   a. Omega three fatty acids, vitamins, antioxidants
What we see clinically when we treat the pro-inflammatory state (ORMD or veterinary metabolic disease) in our patients:

1. Improves many symptoms in patients with multiple disease processes
2. Improves results in patients on medications with side effects
3. Improvement of quality of life in chronic disease states and hospice patients
4. Prevention of disease states- endocrine, GI, dermatological, orthopedic

**Pet food safety and Salmonella:**

Because pet diets are made from meat base proteins sources, there are quality controls required with federal and state regulations to assure the final product is safe. Quality control measures can often exceed human food safety standards because few human foods contain animal source protein mixed with other ingredients. Recently the FDA (July 2013) released the following statement changing prior safety regulations for dry foods:

“FDA maintains a zero-tolerance policy for Salmonella in pet food because it can pose risks to human health when people who are “at-risk” (children, the elderly, and individuals with compromised immune systems) come into direct contact with contaminated pet food.”

“FDA also withdrew an earlier Compliance Policy Guide that covered only dry dog food. Dry dog food is now included in the scope of the new CPG. FDA continues to have a zero-tolerance policy with regard to Salmonella in **dry dog food**, as well as other pet foods.”

**Maillard reaction products (MRP) and Advanced Glycation End (AGE) products:**

Despite the ongoing quality control measures for pet diets, there is another less known issue with pet diets that are made from animal products. In human studies, there is a critical evaluation of the chemical reaction between protein building blocks, amino acids (especially lysine) and simple glucose, called the Maillard reaction. This reaction is responsible for the browning in foods and adds flavor to even our own diets and results in Maillard reaction products (MRP). It is known that high heat and other food processing techniques drives this reaction. Further reactions continue with storage or even after consumption to produce what are now known as Advanced Glycation End Products (AGE).
AGE can cause glycation of structural and functional proteins of body tissues. In human food processing AGE’s are being looked at for their role in immunological and degenerative disease states as well as neoplasia. Studies have shown AGEs are mediators of oxidative stress (OS) and reactive oxygen species (ROS). An accumulation of AGEs in tissues may increase OS and long term impair organ function. Elevated oxidative state increases risk for chronic diseases (cancer, cardiovascular diseases, cataracts, CRD & degenerative disorders as damage to cell constituents (DNA, proteins, lipids, etc.) and cell structures occur. The levels of AGEs are being studied for their role in aging and chronic disease morbidity. This is why human nutritionist may not agree on the ideal food pyramid, but they do agree in a “wide variety of FRESH foods” is dogma.

It is known that AGEs are recognized by the immune system as strong B-cell epitopes and are sufficiently stable to be absorbed intact. Absorbed AGEs either directly or indirectly as modified antigens can evoke a Th2 response to generate IgE antibodies. This can provoke allergic sensitization and subsequent immune reactions. AGEs are known to enhance allergenic potency of diets. Is there a role or MRP and AGEs in pet diets in disease states such as food allergy, IBD and other chronic diseases.

The effects of the Maillard reaction is well known in pet diets as the amino acid lysine, is considered limiting in pet diets. Much research has provided manufacturers information to ensure adequate levels of lysine as the Maillard reaction proceeds in pet food processing. The amount of early (and advanced) MRP in pet foods may originate from three sources:

- ingredients may already contain early MRP due to processing
- processing conditions
- lysine may react during coating & storage

Interestingly elevated levels of AGE in tissue proteins in dogs were observed for a number of diseases. In a recent study the question is being hypothesized that the daily intake of thermally processed foods could provide an additional peak load of AGE that may exceed capacity to protect against AGE in pet diets.

This information on MRP and AGE in pet diets deserves more research and consideration in disease management in our patients. Many of the “miracles” of raw fed patients may be due to the low MRP and AGE content of these diets. It is interesting to note when a client states “the old dog or cat back when we were children, that never visited the vet and ate what we ate lived to
be 18 years old and was never sick.” We have all heard these claims, understanding the role of MRP and AGE in pet diets, which most pets eat their entire life may be problematic. Despite complete and balanced pet diets, preventative health care programs, vaccinations for infectious disease and proactive dentistry why are we not seeing our patients living longer?

Regardless of the lack of direct evidence, it does seem counterintuitive to recommend our patients eat the same diet for its entire life time. In human nutrition it has not been put forth the concept of eating the same diet every day and a diet that is highly processed albeit complete and balanced. Example cases and patient management will be discussed.

**Questions for a Pet Food Company:**
1. Do you have a Veterinary Nutritionist or some equivalent on staff in your company? Are they available for consultation or questions?
2. Who formulates your diets and what are their credentials?
3. Which of your diet(s) is AAFCO Feed Trial tested? Which diet(s) have been AAFCO Nutritional Analyzed?
4. What specific quality control measures do you use to assure the consistency and quality of your product line?
5. Where are your diets produced and manufactured? Can this plant be visited?
6. Can you provide a complete product nutrient analysis of your best-selling canine and feline pet food including digestibility values?
7. Can you give me the caloric content per can or cup?
8. When was the last time one of your products had a recall or voluntary recall? What was it caused by and what measures did you do to correct the problem?