clinician's update™

SUPPLEMENT TO NAVC CLINICIAN'S BRIEF®

Canine Osteoarthritis

OVERVIEW, THERAPIES, & NUTRITION

NAVC
clinician's brief®
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Canine Osteoarthritis

PATHOPHYSIOLOGY

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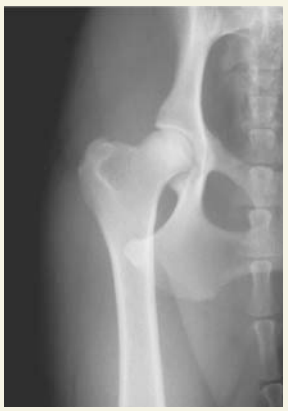
The process of local inflammation, degeneration, and mechanical dysfunction becomes a vicious cycle leading to progressive change.

Osteoarthritis (OA) is a disease characterized by joint pain, tenderness, limitation of movement, crepitus, occasional effusion, and variable degrees of local inflammation.[1] Osteoarthritis occurs when injury or cellular damage disrupts the normal homeostasis of the joint, releasing inflammatory mediators and degradative enzymes in a recurring degenerative cycle.

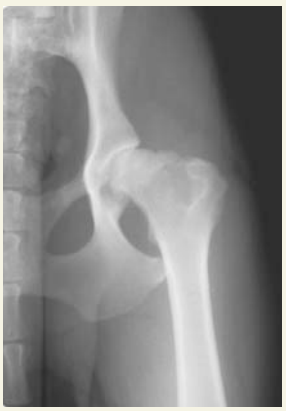
THE NORMAL JOINT

Composed of articular cartilage, subchondral bone, a synovial layer, joint capsule, and supporting ligaments and tendons, the normal joint allows for stable motion and transfer of body weight loads during walking, running, jumping, climbing, sitting, and standing. The normal joint is energy-efficient and pain free.

Chondrocytes (5%) and a mostly-water extracellular matrix make up articular cartilage. Articular cartilage is aneural, avascular, and alymphatic. Chondrocytes produce collagen and proteoglycan that are continuously modified by degradative enzymes. Collagen fibrils combine with proteoglycans to form a meshwork, providing structural support and compressive stiffness. In health, there is a normal slow turnover of the cartilage matrix.



Healthy hip joint



Arthritic hip joint

Risk Factors

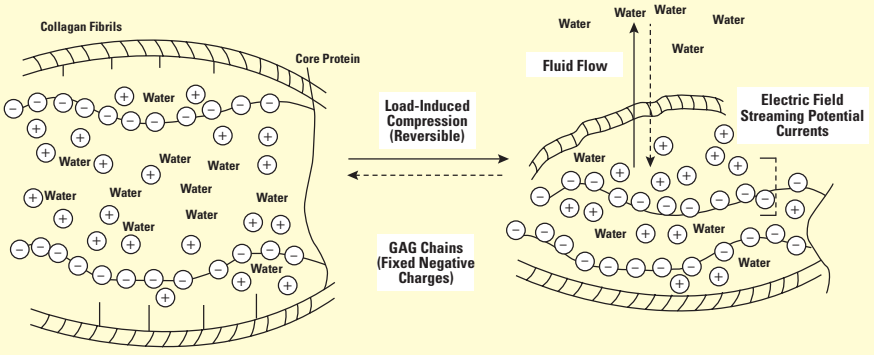
- Advanced age
- Large size
- Fast growth
- Genetic predisposition
- Working dogs, athletes
- Obesity/overweight
- Trauma

KEY POINTS

- Healthy articular cartilage consists of chondrocytes and extracellular matrix (collagen, proteoglycans, and water).
- Injury to the joint may disrupt normal homeostasis resulting in a cycle of inflammation and degradation.
- Deterioration of articular cartilage, periarticular changes, and localized inflammation lead to chronic pain and disability.

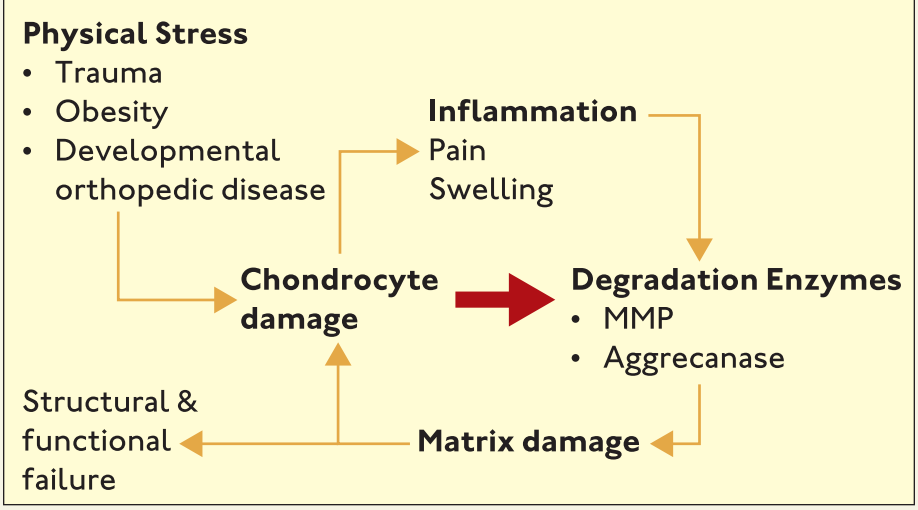
Why Cartilage Maintains its Shape When Load is Applied

Donnan Equilibrium



GAG = Glycosaminoglycan

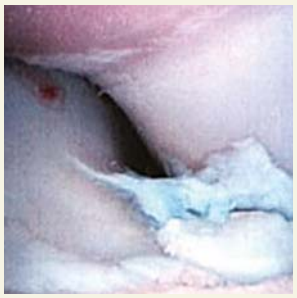
Osteoarthritis Syndrome



PROGRESSION OF OA

A disruption in the normal relationship of collagen and proteoglycans in articular cartilage is one of the first events in the development of osteoarthritis. Injured chondrocytes produce inflammatory mediators, interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α), which stimulates the production of degradative enzymes. These enzymes, metalloproteinases and aggrecanases, destroy collagen and proteoglycans faster than new ones can be produced. When collagen destabilizes and loses its ability to form crosslinks, the hydrophilic proteoglycans start absorbing water and cause cartilage to swell, reducing its compressive and tensile strength.

Healthy joint



Fragmented coronoid process

At the same time, inflammatory mediators influence the surrounding tissues. As the disease progresses, there is fibrillation and fissuring of the cartilage surface, increased subchondral bone activity and thickening, increased stiffness, and thickening of the joint capsule. Increased shear stress on already damaged tissue leads to further loss of articular cartilage. A progression of subchondral bone and joint capsule changes produces bone remodeling and osteophytes (new bone at the junction of the joint capsule and existing bone), causing further damage. Eventually, there is complete loss of cartilage with areas of osteonecrosis and severe fibrosis of the joint capsule. This severe end-stage situation could be considered "organ failure." ■

Prevalence of Osteoarthritis[2,3,4,5]

- #1 cause of chronic pain in dogs
- Affects 20% of dogs >1 year of age
- Affects quality & length of life
- 31% of dog owners say bone and joint problems are an issue for their pet
- In the "Top 10" diagnoses for dogs >7 years old
- #7 illness reported to the Veterinary Pet Insurance Co.

Osteoarthritis Clinical Signs

- Reluctance to walk, run, climb stairs, jump, or play
- Difficulty in rising from rest
- Lameness
- Stiffness
- Yelping or whimpering
- Personality changes, withdrawal
- Soreness when touched
- Lagging behind on walks
- Decreased mobility
- Aggressive behavior

Chronic Pain Management

MULTIMODAL THERAPY

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Professor of Surgery
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Athens, Georgia

Combination therapy achieves the goal of relieving pain and discomfort and improving quality of life.

KEY POINTS

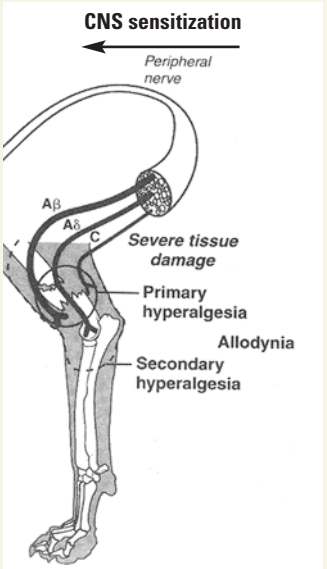
- Pain receptors and pathways become sensitized with persistent inflammation.
- Treatment plans include weight reduction, nutritional support, exercise modification/ physical therapy, and pharmacologic management.
- NSAIDs remain the most common medication for chronic pain.

MONITORING NSAID USE

- Encourage client compliance
- Ensure optimal dosing
- Adapt therapy to patient requirements
- Give lowest effective dose
- Observe for toxicity
- Screen patients for potential risk

Sources of pain in osteoarthritis are the synovium, periarticular tissues, periosteum, and subchondral bone. With chronic conditions, pain receptors and pathways become sensitized through persistent inflammation. Eventually, even minimal noxious or normal stimulations can cause pain. Interruption of the pathways to the central nervous system (CNS) is the first step in controlling chronic pain.

Although NSAIDs remain the most common medications prescribed for the treatment of osteoarthritis, they do not significantly alter the progression of the disease. Pharmacologic management is only one aspect of treatment. Several drug classes in addition to NSAIDs can be helpful and may slow early stages of OA — preventing, retarding, and in some cases reversing cartilage damage. Drug effectiveness (and side effects) can depend on individual response, so care must be taken to monitor and adapt therapy to each patient's needs. Exercise and physical therapy can also assist in ameliorating pain and restoring quality of life. Recent information stresses the role of nutritional management and the role of omega-3 fatty acids. Nutritional supplements (nutraceuticals), while still controversial, are being used with good results in combination therapy by many and are accepted by clients. ■



Options for Osteoarthritis Pain Therapy

Class	Drug	Action
NSAID *Most common medication, effective, palliative*	• Carprofen • Etodolac • Meloxicam • Deracoxib • Tepoxalin	• COX-1 and/or COX-2 inhibitors • Combined COX & LOX inhibition
N-methyl-D-aspartate (NMDA) inhibitors	• Amantadine	• Chronic NMDA-receptor stimulation can produce a "wind-up" effect, a state of chronic CNS sensitization • In combination, may aid in prevention of chronic pain
Opioid receptor agonist	• Tramadol	• Synthetic derivative of codeine that acts on the μ-opioid receptor, facilitating the descending serotinergic system
Corticosteroids	• Hydrocortisone	• Can slow early stages of osteoarthritis • **CAVEAT** – May enhance disease progression long-term
Chondromodulating agents	• Chondroitin sulfate • Glucosamine • Hyaluronic acid • Doxycycline • Polysulfated glycosaminoglycan	• Support or enhance macromolecular synthesis and synthesis of hyaluronate • Inhibit degenerative enzymes or inflammatory mediators • Remove or prevent formation of fibrin, thrombi, and plaque
Nutritional support	• Omega-3 fatty acids (EPA)	• Controls inflammation, interrupts signal (mRNA) that prompts production of degradative enzymes
Physical therapy, exercise modification	–	• Joint manipulation, no-force activities, prosthetic devices
Weight reduction	–	• Limits opportunity for further injury

Therapy Options

PHYSICAL THERAPY FOR CANINE OSTEOARTHRITIS

Denis J. Marcellin-Little, DEDV, DACVS, DECVS, CCRP
North Carolina State University
Raleigh, North Carolina

Physical therapy treatments are aimed at addressing the secondary effects of osteoarthritis — mainly pain and loss of muscle strength — and promoting repair of damaged tissues, improving quality of life, and slowing progression of the disease. ■

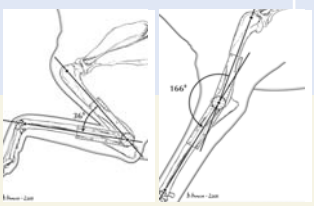
> ***Exercise and passive therapies benefit canine patients and increase the likelihood of adequate treatment.***

KEY POINTS

- Physical means can be used therapeutically to ameliorate clinical signs of osteoarthritis and improve quality of life.
- Low-impact exercises can help increase range of motion of arthritic joints.
- Low-intensity exercises are as beneficial as high-intensity exercises.[6]
- The environment can be modified to assist patient independence.
- Multimodal drug and nondrug therapies increase likelihood of adequate treatment.[7]
- Undertreatment of pain has serious negative consequences.

Physical Therapy Options*

Modality	Action	Method
Temperature	**ACUTE** **Cold** therapy decreases blood flow, inflammation, muscle spasm, and pain. Cartilage-degrading enzymes are inhibited below 30° C. Superficial ice decreases skin temperature by 16° C and joint temperature by 6° C.[8] **CHRONIC** **Heat** therapy increases blood flow, enzymatic activity, collagen extensibility, and muscle relaxation. Superficial heat increases skin temperature by 8° C and joint temperature by 2° C.[8] *In both heat and cold therapy studies, temperatures returned to pretreatment levels after three hours.*[8]	Cold can be applied with ice, gel packs, and CO_2 delivery devices. Heat can be applied with heating pads or therapeutic ultrasound.
Electrical stimulation	Transcutaneous neuromuscular electrical therapy stimulates the large cutaneous nerve fibers which transmit sensory impulses faster than pain fibers. Neuromuscular electrical stimulation may strengthen atrophied muscle fibers.	Transcutaneous electrical nerve stimulation can be delivered by handheld machines ($150 to $500 through medical supply vendors). Optimal treatment duration = ~40 minutes
Magnetic therapy	In people, pulse electromagnetic field therapy has been used to treat OA. Two studies showed benefit after 18 half-hour treatment periods. The benefits lasted for more than one month.[9]	
Acupuncture	While it may be effective as an adjunctive therapy, there are no clear proven benefits.	
Stretching	1 to 3 stretching sessions daily (10 to 15 repetitions of stretching for 20 to 40 seconds) may be beneficial in arthritic joints with limited range of motion.	
Exercises	**Isometric Exercises** - Muscle contractions without a change in muscle length or joint motion **Isokinetic Exercises** - Dynamic exercises with constant joint velocity requiring the use of a machine to control them **Isotonic Exercises** - Dynamic exercises using a constant load. This is the most practical form of exercise for companion animals **Walking or trotting** **Walking** with resistance **Sit-to-stand** exercises **Swimming**	Isotonic exercises performed at low or high intensity Resistance provided by water or elastic bands; walking on an underwater treadmill



Brenda Bunch

* Developed with Joanna Freeman, BSc PT, BSc Kine, CSCS, Animal Rehabilitation and Wellness Hospital, Raleigh, North Carolina

Nutritional Management

OPTIMAL OSTEOARTHRITIS DIET

Phillip W. Toll, DVM, MS
Associate Director,
Nutrition Technology
Pet Nutrition Center
Topeka, Kansas

Managing osteoarthritis means stopping the degradative process and the inflammatory cycle.

KEY POINTS

- Risk of osteoarthritis and other diseases increases with age.
  - Dogs 1 year of age or older are at risk for osteoarthritis.
  - Middle-aged dogs are at risk for obesity.
- Distribution of weight in very old dogs is bimodal — some are too fat and some are too thin.
- A successful nutritional profile for osteoarthritis should target older dogs and their common issues.

Most dogs are at risk for several diseases as they age and more than 50% of dogs 10 years of age or older have osteoarthritis.[2] Because it is too painful to exercise normally, osteoarthritis may increase the risk of obesity — a major concern for dogs with osteoarthritis as it increases stress on joints.

Managing the Osteoarthritis Cycle

- Stress
  - Correct abnormal forces (weight, conformation)
  - Strengthen cartilage matrix
- Inflammation
  - Medications
  - Omega-3 fatty acids
- Degradation
  - EPA
- Cartilage matrix damage
  - Chondroprotectives (glucosamine & chondroitin)

HEALTH ISSUES FOR AGING DOGS

Risk of kidney disease and osteoarthritis increases steadily from youth and older dogs are also at risk for cognitive decline. Obesity can start as a problem in young dogs and continue into later years or it can develop in an arthritic dog that can no longer exercise normally. The cycle of inflammation, degradation, and chondrocyte damage in osteoarthritis can be promoted by joint stress because of excess body weight. Obesity also increases the likelihood of other diseases in addition to osteoarthritis. A diet with a senior nutrient profile is a good place to start to treat and prevent the infirmities of old age in the dog.

WEIGHT MANAGEMENT

Because energy requirements depend on activity levels, reducing arthritis pain and inflammation will provide exercise benefits for maintaining appropriate body weight in an arthritic dog. If the patient is only slightly overweight, a food designed to disrupt the cycle of inflammation may increase activity, which in turn allows weight to remain constant or normalize. Foods with increased levels of omega-3 fatty acids, in particular eicosapentaenoic acid (EPA), reduce the degradative enzymes that cause cartilage damage. Most overweight dogs can benefit from eating a therapeutic food specially formulated for the amelioration of arthritis signs, at least until their joints are better. As their activity levels increase, patients can be reevaluated to see if a weight loss program with more restrictive calorie levels is warranted. ■

Hill's® Prescription Diet® Canine j/d™

	Dry	Canned
Energy, kcal/kg	3704	4190
Protein, %	20.1	19.6
Fat, %	14.3	19.3
Total omega-3, %	3.51	4.24
EPA, %	0.44	0.85
Omega-6:Omega-3	0.7:1	0.7:1
Carnitine, mg/kg	351	319
Vitamin E, IU/kg	851	698
Glucosamine & Chondroitin	Included	Included

Optimal Osteoarthritis Diet

- Senior nutrient profile
- High omega-3 fatty acids
- High ratio of omega-3 to omega-6 fatty acids
- High level of EPA
- High level of α-linolenic acid
- Chondroprotectives (glucosamine & chondroitin)
- Carnitine
- Antioxidants

Canine Cartilage

PHYSIOLOGY OF CARTILAGE TURNOVER — A MODEL SYSTEM[10]

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School of Biosciences & Cardiff
Institute of Tissue Engineering & Repair
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The breakdown of cartilage is performed by the cartilage proteinases — aggreganase (ADAMT-4 & -5), collagenase, and metalloproteinase (MMP-13). In osteoarthritis, these proteinases are important in cartilage proteoglycan catabolism and release. When proteoglycans and collagen are released, monoclonal antibody testing (e.g., Western Blot) can be used to evaluate the metabolites. This has enabled the creation of a model culture system for drug or nutraceutical evaluation. ■

Cartilage is in a constant state of turnover. When the system becomes pathologic (osteoarthritis), the degradation process outstrips the synthesis of new matrix.

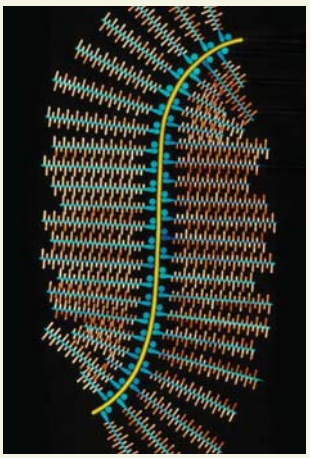
KEY POINTS

- In normal adult cartilage, there is a balance (homeostasis) between synthesis and degradation of cartilage matrix.
- In pathologic cartilage (arthritis), degradation outstrips synthesis.
- Adult cartilage matrix turnover is relatively slow compared with that of other tissues and organs. Normal adult cartilage turnover is measured in years (1 to 2). Normal cartilage proteoglycan turnover is measured in months (80 to 100 days).
- Cartilage turnover is performed by proteolytic enzymes called matrix proteinases (aggrecanases, collegenases, and gelatinases), which are active in the extracellular matrix.
- Cartilage degradation starts with loss of cartilage aggrecan followed by loss of cartilage collagens, resulting in loss of ability to resist compressive forces during joint movement.
- This lab has developed models that mimic canine cartilage degradation in the arthritic state. These models can be used to test the potential benefit of dietary supplementation in canine osteoarthritis.

Measuring Progressive Cartilage Degeneration in Osteoarthritis

Glycosaminoglycan (GAG) that has been released by proteoglycan catabolism can be measured in canine synovial fluids (SF). They increase early in osteoarthritis (OA) and then decrease with progressive cartilage degeneration.

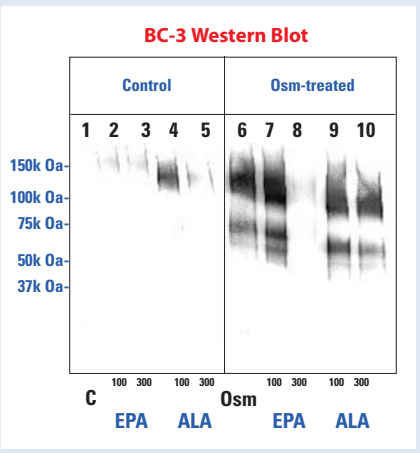
GAG	Normal SF	Early Elbow	Early Stifle	Late Stifle
Mean (SD)	22.8 (30.7)	31.6 (16.0)	48.4 (21.5)	8.9 (3.0)
Median	10.5	27.1	51.6	8.2
Range	2.2 - 83.6	11.0 - 74.1	21.1 - 69.2	5.5 - 15.3



Aggrecan proteoglycan model showing large macromolecular aggregates of aggrecan monomers. Aggrecan binds water strongly and becomes entrapped by the larger collagen fibrils in cartilage tissue to form a meshwork that maintains tension and high osmotic pressure, enabling the joint to function normally.

In Vitro Model

Canine articular cartilage is harvested from stifle joints, the cells incubated for 72 hours, then cultured for 4 days with catabolic agents or control. Using Western Blot (shown), chondrocytes are exposed to catabolic agents to determine which cause cartilage degeneration.



EPA = Eicosapentaenoic acid; ALA = α-Linolenic acid

This analysis (using mAb BC-3 that detects aggrecanase-generated degradation products) shows evidence for some weak aggrecanase activity in control cultures that have been either untreated or exposed to EPA or ALA. In contrast, in cultures exposed to inflammatory cytokines such as oncostatin-M (Osm-treated, lane 6) that induce increased cartilage degradation, there is evidence for a large increase in aggrecanase activity. However, this increased activity is reduced when cultures are exposed to EPA (OSM-treated lanes 7 & 8; but not effected by ALA exposure, lanes 9 & 10).

Canine Cartilage

FATTY ACID METABOLISM & INFLAMMATION

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Pet Nutrition Center
Topeka, Kansas

EPA controls the production of the degradative enzyme, aggrecanase, at the gene level.

KEY POINTS

- Fatty acids are an important part of cell membranes.
- Omega-3 fatty acids were able to reduce inflammation in dog chondrocytes.
- Omega-3s are incorporated into canine cartilage in ~3 days.
- When the omega-3 fatty acid EPA replaces arachidonic acid (AA) in cell membranes, the inflammatory cascade is decreased.
- Dog chondrocyte membranes selectively store EPA and not other omega-3 fatty acids.
- EPA is the only omega-3 fatty acid that decreases aggrecan degradation, preventing fragmentation of GAGs.
- EPA turns off signal mRNA that prompts production of degradative enzymes.

Dog chondrocyte membranes selectively store EPA and not other omega-3 fatty acids, positively moderating pathologic canine cartilage catabolism. Food with high levels of omega-3 fatty acids also decreases inflammation and helps improve clinical signs of OA — especially difficulty in rising from a resting position, walking, running, and playing. ■

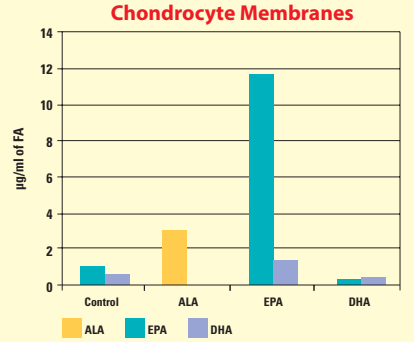
Polyunsaturated Fatty Acids (PUFAs)

Omega-3 (n-3) Fatty Acids	Omega-6 (n-6) Fatty Acids	Omega-9 (n-9) Fatty Acids
• α-Linolenic Acid (ALA) – Leafy green vegetables, flaxseed, canola oil • Eicosapentaenoic Acid (EPA) – Fish oil • Docosahexaenoic Acid (DHA) – Fish oil	• Linoleic Acid (LA) – Soy, corn, safflower oils • Arachidonic Acid (AA) 20:4 n-6 – Animal Fat	• Oleic Acid (OA) – Olives, olive & canola oil – Walnuts • Eicosatrienoic Acid (ETA) – Animal Fat, Fish oil

IV GRADE* STUDY 1 OMEGA-3 FATTY ACIDS IN CANINE IN VITRO CHONDROCYTE MEMBRANE

- Chondrocytes were enzymatically released (explants) from canine articular cartilage and then cultured for 24 hours in serum-free Dulbecco's Modification of Eagle's Medium (DMEM).
- Monolayers were then cultured for 3 to 6 days in serum-free DMEM with either 100 µg/ml PUFA, 300 µg/ml PUFA, or no PUFA.
- Fatty acids were extracted and the amount of PUFA that was incorporated into chondrocyte membranes was evaluated with gas liquid chromatography.

PUFA Incorporation Into Chondrocyte Membranes



RESULTS

- Incorporation of omega-3 PUFAs into canine chondrocyte membranes required much longer (>3 days) than in bovine or human cells (12 to 24 H).
- No difference was found between 3- and 6-day exposure to PUFAs for incorporation in monolayer.
- At doses and times tested, EPA, ALA, and AA were incorporated into canine chondrocyte membranes.
- None of the PUFAs had a detrimental effect on chondrocyte metabolism after 3 to 6 days' incubation as determined by media lactate.

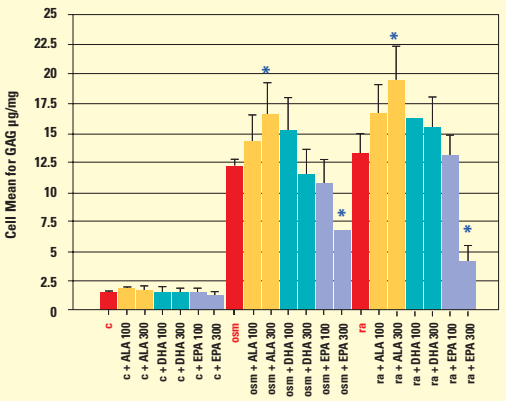
IV GRADE* STUDY 2 PUFA MODULATION OF IN VITRO CANINE CARTILAGE DEGENERATION

- Chondrocyte explants were cultured for 5 days in serum-free DMEM with or without 100 or 300 µg/ml PUFAs.
- 50 ng/ml oncostatin M (OSM) or 10^{-6} M retinoic acid (RA) was added to cultures.
- Release of proteoglycans was measured.

RESULTS†

- EPA (300 µg/ml) significantly decreased OSM & RA-induced glycosaminoglycans (GAGs).

Proteoglycan Release From Cartilage



*See page 10 for study grade explanation.
†In another, larger study, when cells derived from donor dogs were maintained on a standard diet for 6 months prior to collection, results were even better.[11]

University Clinical Trials

OMEGA-3 FATTY ACID EFFECTS ON FORCE PLATE ANALYSIS & CLINICAL SIGNS[12]

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Manhattan, Kansas

Metabolism of omega-3 fatty acids produces eicosanoids that are not as inflammatory as eicosanoids produced from omega-6 fatty acids.

KEY POINTS

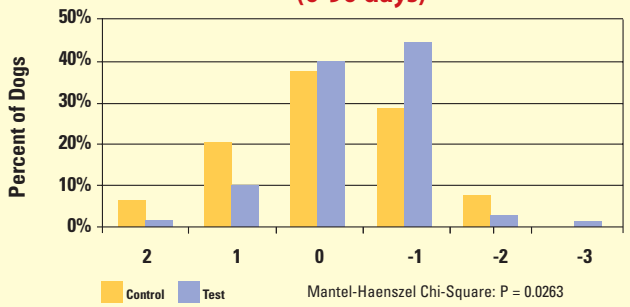
- A high level of omega-3 fatty acids are beneficial for osteoarthritic joints.
- Metabolism of omega-3 fatty acids produces eicosanoids that are less potent inflammatory mediators than those produced by omega-6 fatty acids.
- Force plate analysis is an objective method of measuring limb ground reaction forces.
- Dogs with OA that were fed Hill's® Prescription Diet® Canine j/d™ were 7.48 times more likely to have improved peak vertical force (PVF) than dogs fed the control food.
- In a similar study with NSAIDs, dogs were only 3.3 times more likely to have improved PVF.[13]

Nutritional management using a food with a high level of omega-3 fatty acids helped improve clinical signs of osteoarthritis in dogs as measured by clinical examination and analysis of ground reaction forces. ■

I GRADE UNIVERSITY FORCE PLATE CLINICAL TRIALS

A 90-day prospective, randomized, double-masked, controlled study at Kansas State University and University of Florida

Change in Combined Assessments (0-90 days)



ELIGIBLE DOGS

- 38 client-owned dogs completed the trial
- >1 year of age
- ≥25 pounds
- Free of systemic disease
- Radiographic evidence of osteoarthritis
- Clinical signs of lameness
- Consuming AAFCO standard dry food

FOODS TESTED

- 22 dogs received test food (Hill's® Prescription Diet® Canine j/d™)
- 16 dogs received control food

CLINICAL EVALUATION PARAMETERS

- Lameness
- Weight bearing
- Range of motion
- Reluctance to stand on limb with contralateral elevation
- Pain on palpation of affected joint

GROUND FORCE ANALYSIS

Lameness analyses using a computerized biomechanical force plate were conducted at the beginning of the study, 45, and 90 days after feeding the control food or the test food. Five valid force plate trials were obtained for each dog for the most severely affected and contralateral limbs. All forces were normalized with respect to body weight. Data from valid trials for each limb were averaged to obtain a mean value for each time period. The key parameter measured was peak vertical force (PVF).

CLINICAL RESULTS

A significantly greater percentage of dogs consuming the test food were evaluated as improved versus those consuming the control food. Also, at the end of the 90-day trial, more dogs in the test food group had a reduction in pain when the joint was palpated.

GROUND FORCE ANALYSIS RESULTS

There was no significant change in mean peak vertical force (PVF) in the control group. Mean PVF increased significantly in the lame leg (5.35%) in the dogs consuming the test food. Dogs with OA fed test food were 7.48 times more likely to have improved PVF on the lame leg (82% of dogs improved over the course of the study) than dogs fed the control food (31% improved over the study). In a study of dogs with osteoarthritis given carprofen, dogs were only 3.3 times more likely to have improved their PVF as the dogs receiving placebo.[13]

Evidence-Based Medicine

THE ROLE OF NUTRITION IN OSTEOARTHRITIS — 3 CLINICAL STUDIES

Timothy A. Allen, DVM, DACVIM
Director & Chief Medical Officer
Pet Nutrition Center
Topeka, Kansas

Evidence-based medicine (EBM) is the integration of the best research evidence and clinical expertise.[1-4] Using the scientific method for clinical decisions requires a systematic, rigorous, disciplined approach to evaluating research and recognizes that not all studies are equal. By considering the total body of knowledge, better therapeutic decisions can be made. ■

Clinical trials for Hill's® Prescription Diet® Canine j/d™ included 4 Grade I studies.* This is the only food developed for the management of osteoarthritis utilizing this level of research.

KEY POINTS

- Evidence-based medicine applies the best available evidence using a systematic approach.
- Clinical trials for Prescription Diet® Canine j/d™ included 3 Grade I studies.
- Study 1 – Dogs with OA in 6-month feeding trial showed improved ability to rise from rest, walk, run, and play.
- Study 2 – Serum EPA levels increased in 3-month dose-titration feeding trials and dogs with OA improved.
- Study 3 – In a 3-month trial, 43% of dogs with OA consuming Canine j/d were able to sustain decreased NSAID doses.
- Study 4* – In 90-day university force plate clinical trials, dogs fed high omega-3 Canine j/d were 7.48 times as likely to improve.

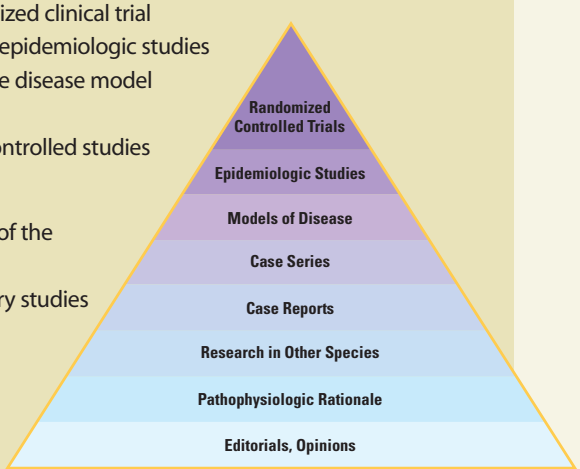
Study Grades† in Evidence-Based Medicine

Grade I
Well-designed, properly randomized and controlled clinical trial that utilizes patients with naturally occurring disease.
- Prospective studies

GRADE II
Well-designed and controlled laboratory studies in the target species with naturally occurring disease.

GRADE III
Evidence obtained from one of the following
- Well-designed nonrandomized clinical trial
- Cohort- or case-controlled epidemiologic studies
- Studies using an acceptable disease model
- Case series
- Dramatic results from uncontrolled studies

GRADE IV
Evidence obtained from one of the following
- Bench-top in vivo laboratory studies
- Opinions based on clinical experience
- Descriptive studies
- Studies conducted in another species
- Pathophysiologic justification
- Reports of expert committees



Evidence-Based Clinical Nutrition Pyramid

†Quality of evidence guidelines are adapted from the U.S. Preventive Services Task Force.

*See also: Roush university study, page 9 of this supplement.

STUDY 1 OMEGA-3 FATTY ACIDS IN CANINE OSTEOARTHRITIS[15]

I GRADE

- Prospective; 6-month feeding period
- Randomized, controlled
- Double masked (pet owner and veterinarian)
- Multicenter (18 general practices, 131 dogs)
- Data collected at 0, 6, 12, and 24 wk

RESULTS

- Dogs fed the test food had significantly improved ability to rise from a resting position, run, and play at 6 wk.
- Improvements were seen in walking at 12 and 24 wk compared to control dogs.
- Serum EPA levels were significantly higher in dogs fed the test food at 45 days.

STUDY 2 DOSE-TITRATION EFFECTS OF OMEGA-3 FATTY ACIDS FED TO OSTEOARTHRITIC DOGS[16]

I GRADE

- Prospective; 3-month feeding period
- Randomized, controlled (3 dietary treatments – dose titration)
  - Dry food EPA values of 0.5%, 1.2%, or 1.7% dry matter basis (DMB)
  - Canned food EPA values of 0.4%, 0.9%, or 1.4% DMB
- Double masked (veterinarian and pet owner)
- Multicenter (28 general practices, 177 dogs)
- Data collected at 0, 3, 6, and 12 wk

RESULTS

- Pet owner evaluations – All foods resulted in significant improvement in pet owner evaluations. There were no statistically significant differences.
- Clinician evaluations – Dogs consuming the highest concentrations displayed the greatest improvements. Progression of disease was reduced in the highest EPA level group.

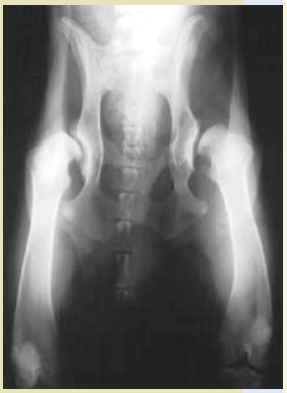
Hill's® Prescription Diet® Canine j/d™ Clinical Trials

General inclusion criteria

- Dogs >1 year old
- Consuming dry food
- Clinical diagnosis of OA
- Radiographic evidence of OA
- Otherwise healthy
- Consistent dosing of medications and/or supplements

General exclusion criteria

- Acute traumatic injury
- Systemic illness
- Planned surgery during the study
- Recent intraarticular injection or arthrocentesis



Radiograph of osteoarthritis

STUDY 3 PROSPECTIVE 3-MONTH FEEDING PERIOD[17]

I GRADE

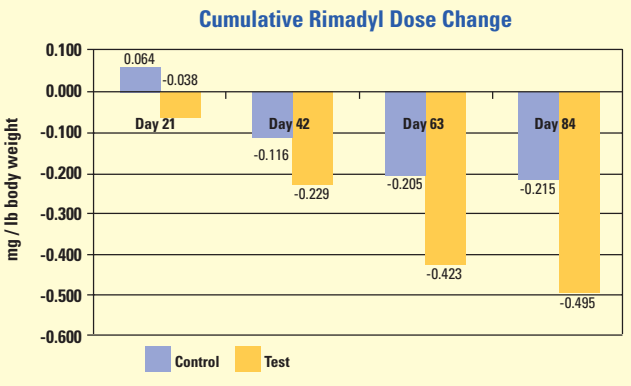
Objective: *Determine whether a therapeutic food alters NSAID dose required to control clinical signs in dogs with OA*

- Randomized, controlled (drug/dietary treatment)
- Double masked (veterinarian and pet owner)
- Multicenter (35 general practices, 193 dogs)
- Standardized drug-dose period
- Examination and dose adjustments at 3, 6, and 12 wk

RESULTS

- Pet owners reported a decrease in severity on 10 of 15 parameters during the first 21 days of feeding Canine j/d.
- Pet owners observed significantly greater pain reduction in dogs consuming the therapeutic food compared to the control food.
- NSAID dose reduction was possible for 43% of dogs consuming the therapeutic food compared to 32% of dogs eating the control food (significantly greater reduction in the dogs eating the therapeutic food).
- NSAID dose increases were needed in 11% of dogs consuming the control food compared to 2% of dogs consuming the therapeutic food.

Therapeutic Food and Drug in Dogs with Osteoarthritis



Hill's® Prescription Diet® Canine j/d™ Highlights

Osteoarthritis is the most common form of canine joint and musculoskeletal disease, affecting up to 20% of dogs over age one.[2] The concept of managing arthritic dogs with nutritional supplementation of omega-3 fatty acids is relatively new in veterinary medicine. Canine j/d is the only clinically proven nutritional product for management of dogs with arthritis. EBM (evidence-based medicine) Level 1 research showed that dogs with osteoarthritis run better, play better, and rise more easily on Canine j/d. They also experience less stiffness and more ease of movement, including walking better and climbing stairs more easily.

- Clinically proven to reduce pain in dogs with osteoarthritis.[12,16]
- Helps dogs with OA walk, run, play, and climb stairs more easily.[16,17]
- 82% of dogs fed Prescription Diet® Canine j/d™ experienced improvement in weight-bearing ability as measured by limb peak vertical force.[12]
- EPA, an omega-3 fatty acid component, works to turn off the genes that cause cartilage damage.[10]
- Prescription Diet® j/d™ has highest levels of EPA.[18]
- Contains highest[18] levels of omega-3 fatty acids and lowest[18] levels of omega-6, helping to reduce inflammatory mediators that cause inflammation.
- Contains appropriate levels of nutrients for long-term feeding for both adult and senior dogs

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*This summary is based on presentations by Drs. Steven C. Budsberg, Bruce Caterson, Denis J. Marcellin-Little, and William D. Schoenherr at the **NAVC 2005 Symposium, Canine Osteoarthritis** as well as additional presentations by Drs. Spencer A. Johnston, Philip W. Toll, James K. Roush, and Tim A. Allen at the **Hill's Canine j/d™ Symposium** in Orlando, Florida, also included here. Additional data on file at Hill's Pet Nutrition, Inc.*