The management of osteoarthritis (OA) in most species consists of a multimodal approach. In small animals, this involves surgically treating the primary cause if possible, reducing the patient’s weight, adapted activity combined with physical therapy, therapeutic nutrition and finally, pharmacological therapy.

As previously mentioned, in recent years innovative therapeutic modalities have emerged from both human and veterinary OA studies. This presentation will entice the nutritional approach to OA, the use of biphosphonate therapy and the use of *Brachystemma calycinum* don plant extract.

**NUTRITIONAL APPROACH**

*ω-3* polyunsaturated fatty acids

**WHAT ARE THEY?**

- Mammals synthesize fatty acids into oleic acid (Ω-9). Plants can insert a double bond and produce polyunsaturated fatty acids (PUFA). They are considered essential because mammals cannot synthesize them; they MUST be provided by food.
  - Algae in phytoplankton containing high levels of Ω-3 PUFA are ingested by fish,
- Ω-3 polyunsaturated fatty acids are synthetized from alpha-linoleic acid. The ones of interest are: docosahexanoic acid (DHA), eicosapentanoic acid (EPA) and docosapentanoic acid (DPA).

**MODE OF ACTION**

- Ω-3 PUFAs compete for arachidonic acid (AA) and replaces/decreases the amount of AA in cell membranes; Ω-3 PUFAs are not proinflammatory; EPA inhibits Matrix metalloproteases (MMPs)
- Zainal et al Osteoarthritis and Cartilage (2009)\(^1\)
  - In a model cell culture system, n-3 PUFAs were able to reduce the levels of mRNA for ADAMTS-4, ADAMTS-5, MMP-3, MMP-13, COX-2 (but not COX-1), IL-1a, IL-1b and TNF-a. Eicosapentaenoic acid (EPA) was the most effective, followed by docosahexaenoic (DHA) and then a-linolenic (ALA) acid. The n-6 PUFA, arachidonic acid (AA) had no effect.

**Efficacy**

Usually combined in therapeutic diets

- As a stand alone:
  - Several studies in the Human literature report the alleviation of clinical signs of OA and of rheumatoid arthritis with the use of fish oil
  - Fish oil alone has not been evaluated in veterinary medicine
- IN SPECIALLY FORMULATED DIETS
  - There are several reports in the literature
  - Roush et al JAVMA 2010\(^2\)
- Ingestion of the test food raised blood concentrations of omega-3 fatty acids and appeared to improve the arthritic condition in pet dogs with osteoarthritis.
  - Roush et al JAVMA 2010
  - At least in the short term, dietary supplementation with fish oil omega-3 fatty acids resulted in an improvement in weight bearing (PVF) in dogs with osteoarthritis.
  - Fritsch et al JAVMA 2010
  - Results suggested that in dogs with chronic osteoarthritis receiving carprofen because of signs of pain, feeding a diet supplemented with fish oil omega-3 fatty acids may allow for a reduction in carprofen dosage.
  - Moreau et al Osteoarthritis and cartilage 2010
  - A veterinary diet containing omega-3 PUFAs should be considered as a therapeutic modality to alleviate the clinical signs in dogs afflicted by OA as a unique treatment or as part of a multimodal approach in the management of OA.

*Green lipped mussel (GLM)*

New-Zealand green lipped mussel (*Perna canaliculis*) is a cultivated mollusk. It can reach up to 24cm in length. It contains Ω-3 PUFAs, chondroitin, glutamine.

**MODE OF ACTION**

Studies have also found that *Perna canaliculus* inhibits the 5-lipoxygenase pathway, which leads to the formation of leukotrienes, decreases the production of cytokines.

**EFFICACY**

In the Human literature
- Brien et al QJ Med 2008
  - Meta-analysis
    - The data from the two more rigorous trials, in conjunction with our re-analysis of original data suggests that GLM may be superior to placebo for the treatment of mild to moderate OA.

In the veterinary literature
- Bui et al, Veterinary Therapeutics. Spring 2001
  - The change in total arthritis score by the end of 6 weeks showed there was significant improvement ($P < .05$) in the test group versus the control group. Significant improvements were also observed in joint pain and swelling scores in the test group.

- Hielm-Björkman et al Evid Based Complement Alternat Med. 2009
  - GLM alleviated chronic orthopedic pain in dogs although it was not as effective as carprofen., GLM may be beneficial in dogs e.g. when non-steroidal anti-inflammatory drugs cannot be used.

- Servet et al J Nutrition 2006 suppl
The GLM-supplemented diet appears to be a viable option in alleviating osteoarthritic signs in dogs and could potentially help to reduce the dosage of anti-inflammatory drugs with known side effects.

Rialland P et al CJVR. 2012
Effects of a green-lipped mussel-enriched diet on pain behaviours and functioning in dogs with clinical osteoarthritis.

Plasma concentrations in DHA and EPA were significantly higher at D90 when compared to D0 ($p < 0.001$ and $p = 0.016$, respectively)

The GLM-enriched diet modified gait in OA dogs in that the PVF significantly increased (2.5%) over the 60-day period when GLM was introduced after a standardised control diet

**BIPHOSPHONATES**

Biphosphonates are a class of drugs that are known to prevent the loss of bone mass. They are mainly used in the treatment of several bone conditions including osteoporosis, Paget’s disease and in bone metastases. Their use in osteoarthritis has been recently investigated.

- Shirai et al J orthop res, 2011
  - ALN/ACLT group had mild cartilage degeneration compared with that of the ALN/sham group. Immunohistochemical analysis showed that ALN suppressed the expression of matrix metalloproteinase-13, interleukin-1b, type-X collagen, vascular endothelial growth factor, and receptor activator of nuclear factor kB ligand in OA cartilage. ALN had a chondroprotective effect in an experimental rabbit model of OA.

  - ALN plays an important role in cartilage protection in OA joints that is associated with the improvement of subchondral bone quality through reduction of subchondral bone resorption. ALN could be potentially used as a disease-modifying strategy to limit the progression of OA.

- Jones et al ART 2010
  - Bisphosphonate and NSAID therapy may be an effective disease-modifying drug regimen if administered early after the initial injury.

Tiludronate is a non-nitrogenous, sulphured biphosphonate. It possesses high affinity for bone mineral, interferes with cell energy metabolism (ATP) thus inhibiting osteoclastic activity. It has recently been investigated in canine OA models

- Moreau et al, Arthritis research and therapy 2011
  - A better functional outcome was observed in TLN dogs than OA placebo controls. Tiludronate treatment demonstrated a positive effect on gait disability and joint symptoms. This is likely related to the positive influence of the treatment at improving some OA structural changes and reducing the synthesis of catabolic and inflammatory mediators.
• Pelletier et al, 2011, Journal of Rheumatology.\(^{15}\)
  o Our findings indicate that in dogs with ACL transection, ECS greatly prevents development of cartilage volume loss. Treatment with TA provided an additional benefit of reducing the development of OA lesions.

• Interestingly, Moreau’s paper lead to an editorial by Walsh DA and V Chapman in *Arthritis Research & Therapy* (2011)\(^{16}\). The title was: “Biphosphonates in osteoarthritis.”
  o Synovitis and subchondral bone turnover are associated with pain in OA. Bisphosphonates provide tools for investigating these pathogenic mechanisms and also may have therapeutic potential. Translating preclinical findings into new treatments or human osteoarthritis requires a critical appraisal and refinement of animal models, identification of those pathogenic mechanisms that are amenable to intervention, and pharmacological targeting of those mechanisms in the right people at the right time.

Tiludronate is homologated in Europe and Australia for bone spavin and navicular disease. Could it have other indications in equine OA?

**BRACHYSTEMMA CALYCINUM D DON (BCD)**

Non-steroidal anti-inflammatory drugs (NSAID) are commonly used in the management of OA.\(^{17-18}\) NSAIDs are reported to have the most frequent and serious life threatening side-effects.\(^{19}\) The use of alternatives must be explored. It has been reported that natural products are better tolerated.\(^{20}\) *Brachystemma calycinum* D don (BCD) is a plant originating from southwestern China, in the region of the Himalayas. It has been used in traditional Chinese medicine to relieve rheumatic pain, numb limbs and aches. The active compounds are cyclic peptides called Brachystemins F1 through F4.

In an experimental model of canine OA,\(^{21}\) BCD decreased the severity of macroscopic and histopathological scores; decreased key inflammatory & catabolic factors namely MMP-13, iNOS, PAR-2 and improved gait disability (PVF). In the recent literature, 3 studies have investigated the role of PAR-2 in osteoarthritis: One confirmed the in vivo implication of PAR-2 in the development of OA in a murine model,\(^{22}\) a second\(^{23}\) confirmed its role in the mediation of inflammation in OA and a third\(^{24}\) proposed that PAR-2 inhibition is a potential therapeutic target of the disease.

In a double blinded, randomized placebo-controlled trial, *Brachystemma calycinum* D don effectively improved the limb impairment and enhanced the locomotor activity in dogs afflicted by naturally-occurring OA.\(^{25-26}\) This clinical trial provides interesting and new information about the potential of BCD as an OA therapeutic.

**SELECTED REFERENCES**


