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Orthopaedic Case Challenges Mini Series

Session 2: Osteoarthritis

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Osteoarthritis

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Diagnosis and management of osteoarthritis

Diagnosis and Staging of OA

Osteoarthritis is often not a diagnosis of sufficient accuracy in canine orthopaedics because the disease is usually secondary to a primary joint abnormality (e.g. instability, laxity, fracture). Other chapters in this textbook deal with methods to reach such diagnoses and there is often a seamless transition between the primary joint disease and the process of OA. Idiopathic OA is diagnosed when all attempts to identify an initiating cause have failed.

History

In common with other joint diseases, owners of dogs with OA may complain that their dogs show a variety of signs including reluctance to exercise, exercise intolerance, inactivity stiffness, lameness, inability to jump (up or down), and behavioural changes such as aggression. Signs may vary from very mild and intermittent to severe and persistent. External factors such as the amount of exercise and the weather may influence the severity of signs that the owner reports [1]. The tendency for most patients is for clinical signs to gradually worsen although this can be at a variable rate with interposing periods of remission and flares of disease.

There has been a recent interest in formalising the accrual of information from owners of dogs with OA. This has undoubtedly arisen because OA is usually a chronic and insidious disease and it is difficult for the veterinarian to stage the disease severity in the consultation room. In such a situation, information from the owner becomes critical but there is general nervousness on relying too heavily on information from untrained parties. Nevertheless, in recent years there have been several attempts to design and validate owner questionnaires (or clinical metrology instruments; CMIs) for canine OA such as LOAD, CBPI and HCPI [2-5]. Such questionnaires result in an aggregate score which can help the clinician to track disease progression and assess response to treatment. Some of these so-called 'clinical metrology instruments' are available [2,4,6]. Validation of such questionnaires involves assessment of validity, reliability and responsiveness [3-7].

Cats with OA may show very few signs to their owners but may typically show a reduction in activity, reluctance to jump, a reduction in maximum jump height, an unkempt appearance, and aggression. One study investigated client-selected clinical signs and those that responded to NSAID treatment in a cohort of cats with OA included: jumping up/down, playing (toys, cats), running (to food, from dog), lying down, moving up stairs, walking, sharpening claws, grooming, using the litter tray, and hunting [8]. However, as yet, there is no validated scoring system or owner completed questionnaire available for cats. Because cats tend to decide their own activity levels, there has been interest in tracking their movements with activity monitors [9]. Such an approach does show promise for using this dimension to assess treatments in a clinical research setting but, at the current time, this is not practicable in a clinical practice setting

Clinical signs of OA

Osteoarthritis in dogs is associated with a variety of clinical signs and physical examination findings including inactivity stiffness, lameness and gait alterations such as "bunny-hopping", reluctance to exercise, exercise intolerance, muscle atrophy, joint swelling, capsular and extracapsular fibrosis, joint effusion, reduced range of motion, crepitus, and pain on joint manipulation. The clinical signs are variable depending on multiple factors including the breed and demeanour of the patient, the stage of the disease, and the particular joint affected. For instance, more proximal joints are less palpable and it is not possible to feel effusion or capsular fibrosis, whereas distal joints may demonstrate such changes.

Recently, a standardised system for staging of canine osteoarthritis has been developed by an international panel of experts in orthopaedics and pain management [10]. The system, called 'Canine Osteoarthritis Staging Tool' (COAST), involves using a CMI combined with a clinical assessment of the dog and also individual joints.

Cats pose more difficulties to the clinician with respect to detection of pathological changes to joints. Some of the palpable changes observed in dogs can also be detected in cats. However the clinical examination can be more challenging in cats due to their reluctance to be held and their aversive responses to any manipulations that cause discomfort. In cats, it has been suggested that OA-associated pain can be evaluated through performance tests. Recommended activities include placing the cat down and allowing it to move across the room, encouraging the cat to jump down from a chair, and encouraging the cat to jump up to get into a carrier. Evaluating how the cat performs such tasks can, in some cases, give valuable information as to pain localisation. For example, cats are generally very willing to jump off an examination table but when they are reluctant to do so, this may be due to painful joints, especially thoracic limb joints. When a cat with elbow OA does jump, it may land very harshly, bringing its hind limbs to the ground very quickly, or landing simultaneously on its thoracic limbs, sternum and pelvic limbs [11]. Of course, compliance of the patient is essential and this can be problematic in some feline patients.

Radiology of OA
Radiographic features of OA are limited, variable and non-specific and include osteophytosis, joint effusion, subchondral sclerosis and intra-articular mineralisation. In addition, radiographic assessment of OA is not an ideal method of disease assessment because radiographs only provide information on bony changes such as osteophytosis and sclerosis, and a very limited degree of information regarding soft tissues. There is a tendency, in veterinary medicine, to concentrate on the bony changes on radiographs, particularly osteophytosis. However, the process of osteophyte formation must be understood to appreciate the limitations of such an approach.

Osteophytosis is certainly a useful marker by which to *diagnose* OA although the osteophyte is not pathogonomic since other types of arthritis may also induce their formation. However, the value of osteophytosis for *staging* the severity of OA is controversial. Studies on the post-surgical cruciate-deficient stifle joint indicate that osteophytosis often continues to progress after surgery (Elkins, Pechman et al. 1991; Vasseur and Berry 1992; Innes, Costello et al. 2004; Rayward, Thomson et al. 2004).

Management of osteoarthritis

Weight management
Overweight and obesity have already been discussed as risk factors for the development and progression of OA. However, management of obesity also has a role in treating OA. There is some evidence that reduction in obesity of dogs with clinical signs of OA can lead to improvement in clinical signs such as lameness [12,13] and there are multiple studies in human beings to show that treatment of overweight and obesity can improve symptoms [14-16]. The management of overweight and obesity is dogs is a challenging and complex area and the reader is referred to other texts and reviews for further information [17,18]. Fundamentals of weight loss programmes include client education, nutritional management (e.g. prescription diets to reduce energy intake) and exercise management (aimed at increasing energy consumption). However, in the osteoarthritic patient, it may be challenging to increase exercise without

exacerbating the clinical signs of OA. A recent development is the use of weight loss pharmaceuticals and there are now two such licensed products for use in dogs. Mitratapide is a microsomal triglyceride transfer protein inhibitor [19-21]. Dirlotapide is also a microsomal triglyceride transfer protein inhibitor but, in addition, it appears to have appetite suppression activities in dogs [22-25]. Both drugs are designed to be used in the context of a weight management programme and although there are no published trials of their use in dogs with osteoarthritis, it is likely that these agents could be useful in the management of bodyweight in arthritic patients.

Exercise

The effects of exercise on OA in dogs is largely unexplored. One study found that a short period of exercise (trotting for 1.2 km) in dogs with OA in a pelvic limb was associated with a reduction in peak vertical force in the index limb [26]. This study indicates how, in the short-term, exercise can exacerbate pain and clinical signs in dogs with OA. However, the medium to long-term benefits or otherwise of exercise programs in dogs with OA remain largely unexplored. Anecdotally and extrapolating from human medicine, it seems that regular, moderate, controlled exercise may be beneficial for OA patients.

Medical management

Non-steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most commonly used classes of pharmaceuticals in canine practice. Whilst there is a broad range of NSAIDs that are approved for use in dogs, there is a much more narrow range in cats and NSAIDs must always be used very carefully in cats. Generally, the term NSAID is restricted to those drugs that inhibit one or more steps in the metabolism of the arachadonic acid (AA) cascade. However, the mechanism of action of some of these drugs is not completely explained inhibition of AA metabolism. Structurally, NSAIDs can be broadly classified as either the salicylate or carboxylic acid derivatives including the indoles (e.g. indomethacin), propionic acids (e.g. carprofen), fenamates (e.g. mefenamic acid), oxicams (e.g. meloxicam), pyrazolones or enolic acids (e.g. phenylbutazone) and, more recently, the coxibs (e.g. deracoxib and firocoxib).

NSAIDs have been used to treat the chronic pain of OA (OA) since aspirin was first marketed in 1899. Their popularity is due to their rapid efficacy for palliating the painful symptoms associated with this condition, although in a minority of patients the use of these agents may be associated with adverse events, which are occasionally serious. Nevertheless, a systematic review of management of canine OA concluded that there was the strongest evidence for efficacy for certain NSAIDs [27]. As NSAIDS have developed, pharmaceutical companies have strived to produce an NSAID that optimises efficacy and diminishes the incidence of adverse events, particularly adverse events affecting the gastrointestinal system, through a greater understanding of basic pharmacology. In addition, the realisation that OA is often associated with a need for long-term treatment has brought innovations in the field of drug delivery and pharmacokinetics. This review will focus on these newer developments in NSAIDs for use in dogs with OA.

Phospholipids are released from the cell membrane when cell damage occurs. When oxygen reacts with the polyunsaturated fatty acid (PUFA) eiscosanoids, such as prostoglandins and leukotrienes, and oxygen free radicals are synthesised. The most important of these PUFAs, arachadonic acid (AA) is produced by the action of phospolipase A_2 on cell membrane phospholipid. Metabolism of AA via the cyclooxygenase (COX) pathway generates an unstable

endoperoxide prostaglandin G_2 which is converted to prostaglandin H_2, the precursor of all prostoglandins and thromboxanes, with the release of toxic oxygen free radicals. Various enzymes act on PGH_2 to produce thromboxane A_2 and B_2, Prostoglandin (PG) E_2, PGF_2 and PGI_2 (prostacyclin). PGE_2 is considered to be the predominant eicosanoid associated with inflammatory conditions. PGE_2 concentrations have been demonstrated to be elevated in synovial fluid from OA joints and PGE_2 is associated with vasodilation, increased vascular permeability, and oedema. In addition, PGE_2 decreases the nocioceptive threshold, thereby enhancing pain response to other stimuli. These stimuli may include chemical substances such as bradykinin, histamine, and serotonin, which are also associated with the inflammatory response, or mechanical stimulation in the form of pressure or motion. PGE_2 also modifies both T-cell and B-cell function in part by inhibition of IL-2. The ability to decrease PGE_2 formation is therefore viewed as a desirable event in decreasing pain associated with OA.

Advances in the early 1990s showed the presence of two isoforms of COX [28,29]. Put simply, COX-1 is considered to be the constitutive form as it produces PGs that are important for normal physiologic function and are produced by many tissues, including gastrointestinal cells, platelets, endothelial cells and renal cells. COX-2 is considered to be an inducible form of the enzyme, the expression of which is tightly controlled under basal conditions, but is dramatically upregulated in the presence of inflammation. Proinflammatory cytokines such as TNF and IL-1 stimulate the expression of COX-2 in many cells, such as synovial cells, endothelial cells, chrondrocytes, osteoblasts, monocytes and macrophages. Thus, most NSAIDs have their major action by blocking PG synthesis, by binding to and inhibiting COX; this action is both dose and drug dependent and the major therapeutic and toxic effects of NSAIDs have been correlated extensively with this effect. Recent data have confirmed that synovial and subchondral bone tissue from canine hips with OA have increased COX-2 expression compared to healthy controls [30].

This concept of COX-1 “good” and COX-2 “bad” greatly oversimplifies a very complex situation. It is important to note that COX-2 is constitutively expressed in the kidney and brain and mediates a cytoprotective effect in damaged or inflamed gastrointestinal mucosa. There is no clear delineation between beneficial and inflammatory PGs and their respective pathways. Nevertheless, much of the current literature is based on the hypothesis that a NSAID that selectively inhibits COX-2 without affecting COX-1 will allow analgesia without the common side effects of COX-1 inhibition. Methods of establishing COX-1 and COX-2 activity have relied on in vitro exposure of cell systems to increasing concentrations of the NSAID and subsequent measurement of the levels of enzyme activity. The amount of drug necessary to inhibit 50% of activity of each enzyme was recorded and expressed as a ratio of COX-2:COX-1.

A drug that inhibits COX-2 at a lower concentration than the concentration necessary to inhibit COX-1 is probably safer because COX-2 PGs (inducible) are more likely than COX-1 PGs (constitutive) to be inhibited at concentrations studied. Care is required to not over-interpret these ratios because the use of different cell systems precludes direct comparison of the data obtained in various studies. Also species differences exist in relative sensitivity of COX-1 versus COX-2 among NSAIDs and the relative safety of a NSAID for one species should not be interpreted as safety for others; data in the target species is therefore preferred. In the late 1980s and early 1990s, prior to the discovery of COX-2 several new NSAIDs had been developed with improved safety profiles; these were later discovered to be COX-2 selective (e.g. carprofen, meloxicam).

Prostaglandin-receptor inhibition

Recently, we have seen the introduction of a new NSAID, grapiprant, which is from the piprant class of NSAIDs, as opposed to the COX inhibitors. Grapiprant specifically targets the EP4 receptor, a mediator of pain and inflammation in joints. Grapiprant appears to have a good safety profile with respect to gastrointestinal safety.

Other actions of NSAIDs
NSAIDs also appear to alter cellular and humoral immune responses and may suppress inflammatory mediators other than prostoglandins and leukotrienes. Studies have shown that NSAIDs alter the inflammatory response by inhibiting activation of neutrophils and thus the release of inflammatory cellular enzymes such as collagenase, elastase, and hyaluronidase. These appear to be the result of interference with protein interactions within plasma membranes and by disruption of the response of inflammatory cells to extracellular signals by affecting signal transduction proteins. The extent of inhibition of neutrophil activation varies with the individual drug.

The peripheral anti-inflammatory activity of NSAIDs appears to correlate somewhat poorly with the analgesia that they provide, and has led to the search for other modes of action. A central mechanism has been proposed and supported by the provision of analgesia by the intrathecal administration of extremely low doses of NSAIDs. Suggested mechanisms of central activity by NSAIDs include inhibition of PG synthesis, interaction with a central opioid mechanism, interaction with central serotonin activity, or interference with an excitatory amino acid such as glutamine in the central nervous system.

Effects of NSAIDs on joint tissues
Because NSAIDs may be used for prolonged periods, there has been interest in the effects these drugs may have on the metabolism of joint tissues. Even if these effects are small, over a long treatment period, these effects may be cumulative. Studies have shown inhibition of proteoglycan synthesis when cartilage explants are incubated with certain NSAIDs in vitro whereas other NSAIDs have caused stimulation of synthesis. In addition, certain NSAIDs have been demonstrated in vitro to decrease the OA associated degradation of cartilage extracellular matrix molecules. It has further been suggested that effects on subchrondral bone may be important in this process of disease modification in OA and certain NSAIDs have been studied in this regard. Conflicting results have been obtain in long-term studies involving human beings with regard to the effects on progression of OA between groups treated with pure analgesics and those treated with NSAIDs. The clinical implication of many of these findings for veterinary patients remains unresolved.

Adverse effects of NSAIDs

All NSAIDs can induce undesirable and potentially life-threatening adverse events. Without a placebo control group in a study, it is impossible to know the true effect of a NSAID (experimental event rate) over and above the background rate (control event rate) of such adverse events in canine OA populations. A recent systematic review of long-term (28 days or more) use of NSAIDs reported experimental event rates of 0-0.31 but there are few control event rates with which to reference these figures [31].

The most common clinical signs of toxicosis in published studies have been inappetance, vomiting, and diarrhoea. However, the true incidence of gastrointestinal toxicity in dogs treated with NSAIDs is unknown. NSAIDs induce gastric damage through local and systemic effects. The systemic adverse effects of NSAIDs are associated with the inhibition of endogenous prostaglandin production. The natural mechanisms for gastric mucosal protection from gastric acid secretions are threefold; 1) secretion of a bicarbonate rich mucous, 2) gastric epithelial cell apical membrane and cytosolic bicarbonate, and 3) increased blood flow which readily releases bicarbonate and acts as a sink for gastric acid quickly neutralising and removing any excess acid. A rich blood flow is also important for epithelial repair by restitution and replication. Endogenous PGE_2 is important in maintaining the gastric mucosal layer, the quality of gastric mucus, mucosal blood flow, and the production of gastric acid.

Risk factors for gastrointestinal toxicity in human beings include old age, concurrent administration of other medications, previous evidence of gastrointestinal bleeding or ulcer disease, and the presence of other disease. In elderly patients changes that might contribute to

decreased drug clearance and increased susceptibility to NSAID toxicity include decreased albumin levels, decreased hepatic and renal function, decreased metabolic rate, and changes in volume distribution. The effect of aging on an individual's ability to metabolise NSAIDs is highly variable. However it would appear prudent to err on the side of caution initially, dosing at the low end of the recommended range and making adjustments as necessary.

Nearly all NSAIDs are able to impair platelet activity due to impaired prostaglandin (thromboxane) synthesis, a COX-1 selective action. In addition to their antiplatelet effects, selected NSAIDs (e.g. phenylbutazone) have also been associated with bone marrow dyscrasias. Gastric bleeding is the most common sign of bleeding problems in part because of the ulcerogenic properties of these drugs. Prostocyclin (PGI_2) which is mediated by COX-2 plays a role in the prevention of thrombosis within vascular channels, this could be expected to be a possible effect of COX-2 selective drugs.

In the kidney, vasodilatory and tubuloactive prostoglandins are protective, ensuring that medullary vasodilation and urine output continue during states of renal arterial vasoconstriction. PGE2 and PGI2 (COX-1 and COX-2) have important roles in maintaining renal blood flow and ion transport within the nephron. Any loss of this protective function becomes important in patients with compromised renal function. Predisposing factors associated with "analgesic nephropathy" include geriatric patients suffering from cardiac, renal, or liver disease, patients in hypovolemic states including shock and dehydration, and patients receiving nephrotoxic (e.g. aminoglycosides) or nephroactive (e.g. diuretics) drugs.

Other analgesics for osteoarthritis

Amantadine
Amantadine is a N-methyl d-aspartate (NMDA) receptor antagonist. In human beings, chronic pain has been shown to be associated with sensory disturbances similar to those found with neuropathic pain. In addition, experimentally it has been established that the NMDA receptor is involved in the neurobiological changes underlying these sensory disturbances in prolonged inflammatory pain. Amantadine was first recognized as an antiviral agent and was later found to be useful in treating Parkinson's disease. Although initially thought to be caused by effects on the dopaminergic system, its effectiveness in treating nervous system disorders appears to result predominantly from its inhibition of NMDA responses. The analgesic effect of amantadine in dogs with chronic OA pain was investigated in a study comparing dogs treated with meloxicam alone compared to dogs treated with meloxicam and amantadine (3–5 mg/kg once daily per os) [32]. The results indicated some benefits of amantadine treatment over and above treatment with meloxicam alone, as measured by veterinarian lameness score and owner questionnaires, after 42 days of treatment. To date, this represents the only study on the use of amantadine for treatment of canine OA.

Gabapentin
Gabapentin is a gamma-aminobutyric acid (GABA) analogue. It was originally developed for the treatment of epilepsy, and currently gabapentin is widely used in human patients to relieve pain, particularly neuropathic pain. Gabapentin is not licensed for use in dogs or cats. Its exact mechanism of action is unknown, but its therapeutic action on neuropathic pain is thought to involve voltage-gated N-type calcium ion channels. Gabapentin's most common adverse effects in adult human beings include dizziness, drowsiness, and peripheral edema although these mainly occur at higher doses and in elderly patients. Gabapentin is excreted by the kidneys, and patients with renal insufficiency may require less frequent dosing because of slower elimination. Although rare, there are several cases of human hepatotoxicity reported.

There is wide dose range for gabapentin, and therefore it should be given to effect starting at a low dose. Tapering of the dose is important because stopping the drug abruptly may lead to rebound pain that may be severe. Recommended dosing schedules are to start with 10 mg/kg administered orally every 8 hours in dogs and 5 mg/kg administered orally in cats and to ramp up or taper down to effect (dosage range: 5–25 mg/kg) [33]. There are no published peer-reviewed studies on the use of gabapentin in dogs and cats but there are some data from experimental models of OA in rodents [34] and some anecdotal reports of use in dogs and cats.[33,35,36]

Paracetamol

Acetaminophen is a well-established centrally-acting analgesic for the treatment of OA in human patients [37-39] but is much less widely used in animals [40]. It **should not be prescribed to cats** under any circumstances because it is extremely toxic in this species but it can be used safely in dogs given at the correct doses (10-15mg/kg every 8 or 12 hours). The mechanism of action of acetaminophen is still unclear. Some data suggest a central inhibitory action on a COX-1 splice variant [41]. Other proposed mechanisms of action for acetaminophen involve pathways that may also be affected by other drug categories. Descending inhibitory pain pathways are mediated by serotonin and data indicate that acetaminophen can stimulate the inhibitory pain pathway mediated by serotonin, and this can be blocked by serotonin antagonists. These data suggest that acetaminophen may directly activate serotonin receptors [42]. However, interactions with opioidergic systems and nitric oxide containing pathways may also be involved.

One advantage of acetaminophen may be its safety profile. Acetaminophen has not produced renal or gastric injury in dogs when prescribed at commonly recommended doses for dogs and evidence of toxicity was not observed in dogs until doses of 100 mg/kg were exceeded [43].

Reports of the use of acetaminophen in dogs are scarce. It was administered to dogs, in combination with codeine, as a rescue medication in a double-blind placebo controlled trial in osteoarthritic dogs with no adverse events reported [40]. Acetaminophen is not licensed for use in dogs in the majority of countries and clinicians should be aware of regulations on the use of unlicensed drugs in their country before prescribing acetaminophen.

Codeine

Codeine, or methylmorphine, is a natural alkaloid found in opium poppy and was first isolated in 1932. Codeine is considered a prodrug, since it is metabolised *in vivo* to the primary active compounds morphine and codeine-6-glucuronide. Approximately 5-10% of codeine is converted to morphine, with the remainder either free, conjugated to form codeine-6-glucuronide (~70%), or converted to norcodeine (~10%) and hydromorphone (~1%). In the United States, codeine is regulated by the Controlled Substances Act. It is a Schedule II controlled substance for pain-relief products containing codeine alone or more than 90 mg per dosage unit. Tablets of codeine in combination with aspirin or acetaminophen (paracetamol/Tylenol) made for pain relief are listed as Schedule III.

There are no published reports of the isolated use of codeine in OA in dogs or cats but it was used as a rescue analgesic, in combination with acetaminophen, in a clinical trial for canine osteoarthritis in the UK with no adverse events reported [40].

Anti-nerve growth factor antibodies

Nerve growth factor is an important mediator of joint pain and many studies confirm it as a target for the alleviation of joint pain. In the last decade, we have seen the development of monoclonal antibodies for dog and cat, to block the action of NGF. Clinical trials have shown the efficacy of such an approach in cats and dogs [44-46].

Nutritional management of OA

Over the last three decades, there has been considerable interest in the effect of nutrients or nutritional supplements on the symptoms, signs and pathology of OA [47]. Nutritional supplements can be delivered in two forms, either as a 'nutraceutical' or a 'functional food'. A nutraceutical is effectively any substance that is a food or part of a food, which provides medical or health benefits, including the prevention and treatment of disease [48].

Examples of nutraceuticals include the heteropolysaccharides chondroitin sulphate (CS), glucosamine sulphate (GS) and glucosamine hydrochloride (GHCl), essential fatty acids particularly n-3 polyunsaturated fatty acids (PUFA) and antioxidant sugars (vitamin C). These supplements may also be incorporated in to functional foods to be delivered as complete diets for dogs and cats. It is imperative that veterinarians consider the evidence-base around each of these different molecules and the temptation to lump them all together as "good" or "bad" should be avoided. Just as pharmaceuticals and evaluated critically, so should nutritional supplements.

Chondroitin sulphate (CS)

Chondroitin sulphate shows approximately 5% bioavailablility in dogs after a single dose [49]. Studies of the distribution of orally-adminstered CS in dogs have disagreed as to the fate of the molecule. Labeling with H_3 has demonstrated distribution to articular cartilage in dogs [50]. However, labelling with C_{14} in a 3-month-old dog showed no distribution to articular cartilage although there was uptake in physeal cartilage [51]. The implication from these results is that oral chondroitin sulphate may not reach the articular cartilage intact and there is some degree of depolymerisation. Furthermore, six hours after oral administration of tritiated CS to rats, the majority of radioactivity in articular cartilage was from oligosaccharides, monomer and tritiated water [52].

The effects of CS on tissues and cells have also been investigated. *In vitro* studies of the actions of CS on human neutrophils have shown antichemotactic activity, a reduction in phagocytic activity, reduced lysosomal enzyme release, and reduced membrane damage [53]. With respect to synovial tissues, CS has been shown to have a stimulatory effect on cultured human chondrocytes [54].

In experimental animals, CS has been demonstrated to have anti-inflammatory effects. In particular, CS was shown to reduce oedema formation in a rat carrageenin model [53] although this effect was not as potent as ibuprofen or indomethacin. CS was also shown to reduce neutrophil and macrophage infiltration [53]. However, these experiments did not assess these activities in synovial joints but in soft tissues.

A systematic review of management of canine OA found no published studies for the use of CS alone for the treatment of canine OA [27]. In addition, a recent systematic review of management of human hip and knee OA concluded that effect sizes for pain relief from chondroitin sulphate had diminished since the previous review (2006) and there was greater heterogeneity of outcomes and more evidence of publication bias [55]. In summary, there is insufficient evidence to recommend the use of chondroitin sulphate for the management of canine or feline OA at the current time.

Glucosamine sulphate and glucosamine hydrochloride

Glucosamine has been used for the symptomatic relief of osteoarthritis for some time. Oral glucosamine sulphate is 90% absorbed and is a prodrug for glucosamine [56]. In addition, it diffuses into articular tissues [57]. There are some data which suggest that glucosamine might influence chondrocyte metabolism. Exogenous glucosamine has been shown to stimulate proteoglycan synthesis *in vitro* [58,59]. Specifically, glucosamine appears to stimulate the

production of monomeric proteoglycan capable of assembling into large PG aggregates. Glucosamine has also been demonstrated to increase aggrecan core protein mRNA. It has been suggested that glucosamine acts through increasing GAG synthesis which in turn stimulates proteoglycan core protein production. However, a recent study of canine chondrocytes in three dimensional culture demonstrated detrimental effects of glucosamine on cell viability and GAG production. Glucosamine has also been demonstrated to have weak anti-inflammatory effects in a variety of animal models of inflammation.

Meta-analyses in human patients suggest that there may indeed be symptom-modification from use of glucosamine in human OA [60] but there is concern that there is likely publication bias towards positive results and more studies are required to confirm therapeutic effects. There is a lack clinical trials of glucosamine alone in veterinary species [27]. In addition, a recent updated systematic review of management of human hip and knee OA concluded that effect sizes for pain relief from glucosamine had diminished since the previous review (2006) and there was greater heterogeneity of outcomes and more evidence of publication bias [55].

Essential Fatty Acids

The essential fatty acids are a particular group of polyunsaturated fatty acids (PUFAs), that contain more than one carbon-carbon double bond within their structure The two principle essential fatty acids are linoleic acid (18:2 n-6 LA) and α-linolenic acid (18:3 n-3 LnA), the n-designation referring to the position of the double bond relative to the omega carbon atom (the methyl carbon at the distal end of the chain). Arachidonic acid (eicosatetraenoic acid), an n-6 fatty acid, and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), n-3 fatty acids, may be derived from dietary LA and LnA respectively, via desaturation and elongation. The essential fatty acids are components of cell membranes, are involved in lipid transport and serve as precursors to the eicosanoid hormone family which regulate inflammatory processes.

The n-3 and n-6 fatty acids compete for incorporation into phospholipids and as substrates for cyclo-oxygenases (COX) 1 and 2 and 5-lipoxygenase. While the metabolism of both types of fatty acids leads to eicosanoid production, a higher proportion of n-6 fatty acid within cell membranes is believed to promote the production of the inflammatory prostaglandins, leukotrienes and thromboxanes. Arachidonic acid, in particular, is a precursor of pro-inflammatory eicosanoids. While many studies have reported the potential anti-inflammatory and therapeutic effects of n-3 fatty acids in rheumatoid arthritis (RA), a disease that is associated with extensive inflammation of the synovium and cartilage, there have been relatively few studies that indicate the role of an n-3 to n-6 imbalance in the pathogenesis of OA.

An association between lipid composition and tissue pathology in OA articular cartilage was demonstrated in a study by Lippiello et al. 11 [61]. Specifically, the study indicated that the severity of OA cartilage lesions is linked to a higher proportion of the n-6 fatty acid, arachidonic acid. Two of the local eicosanoid hormones produced from n-6 fatty acids, prostaglandin E_2 (PGE_2) and leukotriene B_4, are considered key mediators of inflammation in OA and, consistent with the previous study, it has been shown that the PGE_2 levels produced spontaneously by OA cartilage are highly elevated.

Recent studies have addressed the efficacy of a functional food containing high concentrations of EPA in dogs with OA and using peak vertical force (PVF) as the primary outcome variable [62]. Improvement in peak vertical force values was evident in 82% of the dogs in the test-food group, compared with 38% of the dogs in the control-food group. Another study using the same diet, this time using semi-objective outcomes measures, found that, according to owners, dogs

fed the test food had a significantly improved ability to rise from a resting position and play at 6 weeks and improved ability to walk at 12 and 24 weeks, compared with control dogs [63].

Mesenchymal stem cell therapies for OA

Mesenchymal stem cells (MSCs) are multipotent stem cells that can differentiate into a variety of cell types including chondrocytes and osteoblasts. In the past decade or so, there has been a surge of interest in the use of MSCs to repair damaged connective tissues. This discipline, known as regenerative medicine, aims to develop biologic, cell-based therapies to repair or replace injured or eroded tissues such as cartilage. At the current time, techniques offered commercially for OA in dogs involve harvest of autologous adipose tissue and extraction of the stromal cells. The stromal cells in suspension are then injected intra-articularly after extraction [64,65]. A proportion of these stromal cells will be mesenchymal stem cells. The mode of action of such procedures is unclear at the current time and may involve soluble factors released by the stromal cells or actions of the cells themselves. Early clinical trials, including one placebo-controlled trial, suggest some efficacy in dogs with OA of the hip and elbow although outcomes measures to date have been semi-objective [64,65].

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