Ultimate Hip and Joint Management

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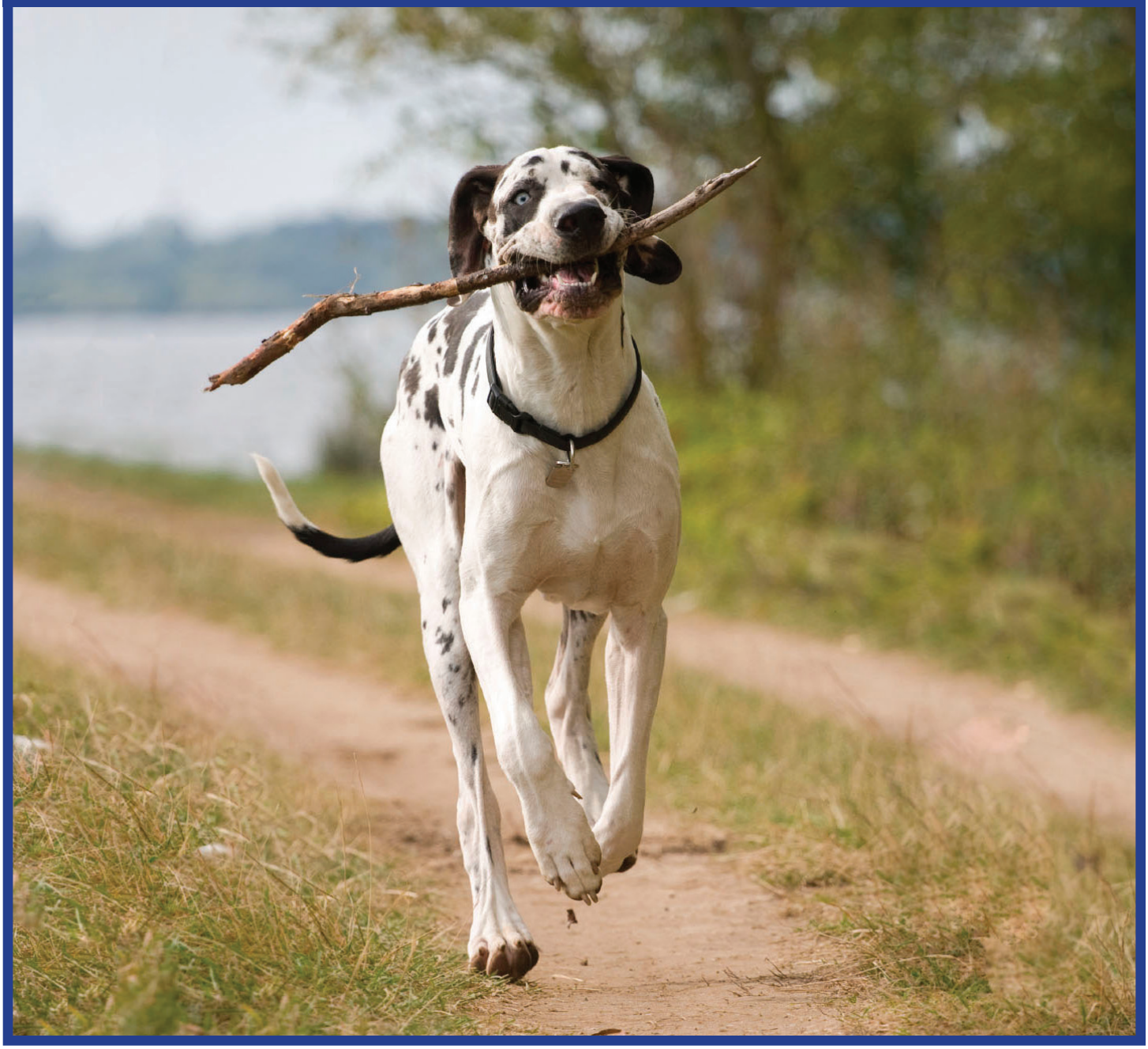


Introduction

Joint health is important and it's never too early to begin managing the care and maintenance of joints. Young active dogs as well as older dogs can have joint compromise. Reports indicate that 1 in 5 dogs have been diagnosed with osteoarthritis (1) but that does not necessarily take into account all of the dogs who have asymptomatic joint injury and degeneration. A classic example is shown in Figure 1. Because joint changes are subtle at the onset, prophylactic management is important to maintain joint integrity and to slow the progression of joint degeneration.

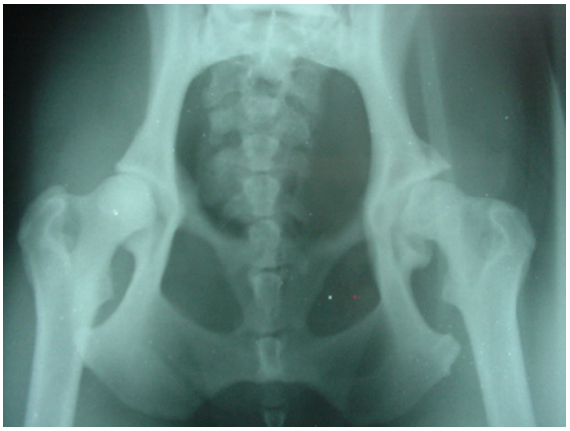


Figure 1. Five yr. old Shi Tzu admitted for vomiting and diarrhea but with significant joint degeneration.

Anatomy of Joints and Cartilage

Articular joints consist of at least two bones enclosed in a joint capsule. The joint capsule surrounds not only the ends of the articulating bones but also the articular cartilage and synovial fluid (Figure 2).

The joint capsule is composed of a tough, avascular fibrous outer sheath or stratum fibrosum and an inner layer called the stratum synovium or more commonly the synovium or synovial membrane. Fibroblasts residing in the synovial membrane produce lubricin or proteoglycan 4 and hyaluronic acid while the macrophages of the synovium are responsible for debris removal from the synovial fluid.

The synovial membrane, among other functions, secretes synovial fluid. Synovial fluid, rich in hyaluronic acid helps lubricate and minimize friction during joint movement. The synovium also plays a key role in joint maintenance and symptoms of osteoarthritis and joint degeneration.

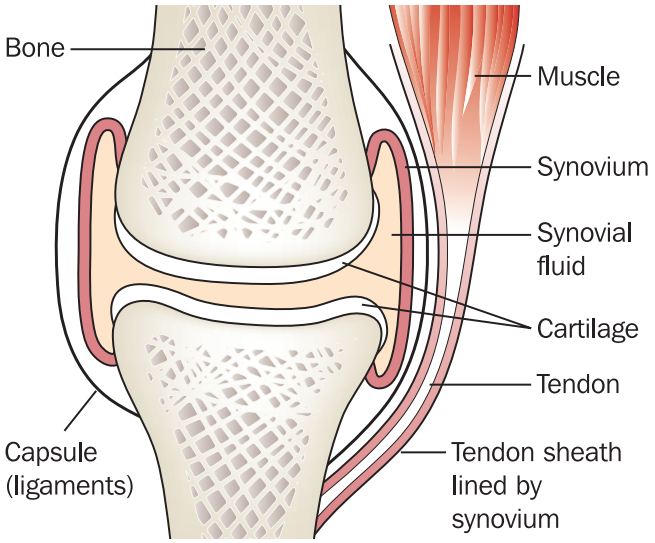


Figure 2. Joint capsule anatomy

Articular cartilage and its functions.

The articular cartilage provides a smooth gliding surface for the articulating bones and plays an important role in absorbing shock associated with weight bearing.

Table 1. Attributes of articular cartilage

Attributes of Articular Cartilage
70% Water
Contains chondrocytes or cartilage cells
Chondrocytes excrete extracellular matrix
Extracellular matrix contains proteoglycans and collagen
Cartilage is avascular in adults

The matrix is a hydrated gel of proteoglycans within a collagen framework. The collagen framework constrains the "gel" from expanding to fullpotential thus creating pressure that helps the articular cartilage function as a shock absorber. If the collagen scaffold is disrupted, the cartilage structure begins to break down leading to changes characteristic of osteoarthritis (Figure 3). In most cases, the initial disruption of collagen goes undetected and arthritic changes can occur long before clinical symptoms appear.

Chondrocytes synthesize and replace the extracellular matrix components like proteoglycans and collagen. Proteoglycans have a fast turnover rate compared with collagen. The degradation of these molecules is regulated by proteolytic enzymes called matrix metalloproteinase or MMPs (i.e.: collagenase, gelatinase etc.) also excreted by the chondrocytes. Cytokines such as interleukin-1 and tumor necrosis factor can upregulate the degradation process whereas transforming growth factor and insulin-like growth factor-1 have an opposite effect on chondrocyte metabolism.

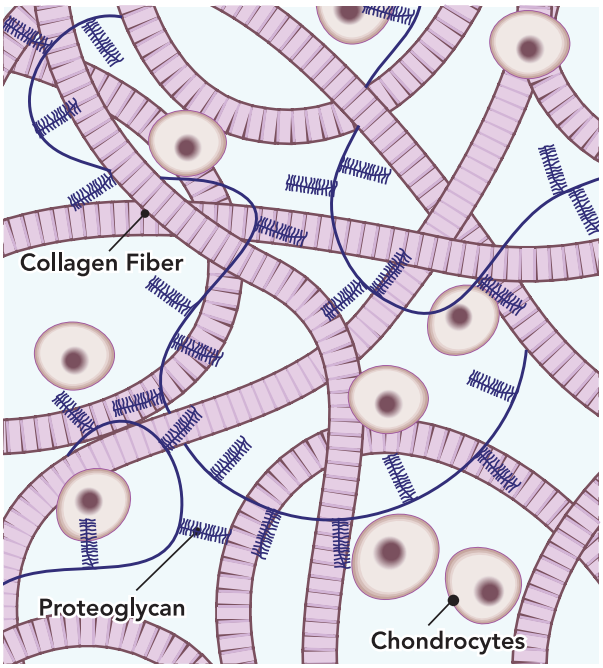


Figure 3. Normal cartilage anatomy. Collagen forms a framework that constrains the proteoglycans and helps to provide structure. Chondocytes produce extracellular matrix

A healthy joint has a balance between synthesis and degradation of cartilage components, however, when joint injury or compromise occurs, the balance is tipped toward catabolic metabolism, leading to cartilage and bone destruction. Table 2 lists the primary mediators of joint maintenance.

Table 2. Key mediators of cartilage degeneration and synthesis. Adapted from Moreland et al (2).

Mediator	Function
Nitric Oxide	Free radical
Interleukin-6 (IL-6) Interleukin-8 (IL-8) Interleukin-11 (IL-11) Interleukin-17 (IL-17) Interleukin-18 (IL-18)	Pro-inflammatory cytokines: involved in cartilage degradation
Tumor Necrosis Factor-α (TNF-α)	Inflammatory cytokine: promotes free radical synthesis inchondrocytes
Metalloproteinases (MMP)	Enzymes: degrade collagen, proteoglycans
Prostaglandin E_2 (PGE_2)	Contributes to synovial inflammation; up regulates IL-1β
Interleukin-1β (IL-1β)	Cytokine: promotes NO production; increases MMP synthesis and inhibits MMP inhibitors
Interleuk in-4 (IL-4) Interleukin-10 (IL-10) Interleukin-13 (IL-13)	Anti-inflammatory cytokines: involved in cartilage maintenance and synthesis
Transforming growth factor-1 (TGF-β1)	Stimulates proteoglycan and collagen II production; down regulates MMP
Insulin-like growth factor-1 (IGF-1)	Maintains homeostasis; stimulates production of matrix proteins; prevents degradation of proteins and delays apoptosis
Basic fibroblastic growth factor (bFGF) Bone morphogenetic protein (BMP)	Growth factors

Because adult cartilage is avascular, it relies on either diffusion from the synovium or synovial fluid "stirring" through joint loading for nutrient delivery. With joint loading, some of the water in the cartilage is squeezed out into the synovial space. When the joint is unloaded, the hydrophilic properties of the cartilage proteoglycans cause the water to be sucked back into the cartilage. As the water returns to the cartilage it brings nutrients along with it from the synovial fluid. Therefore, joint loading plays an integral role in nutrient delivery in articular joints. The amount and type of nutrients available from the synovial fluid depends on the nutrients supplied from food and supplements. Proactively providing nutrients specifically for chondrocyte metabolism will help to maintain healthy joints.

Joint Injury, Inflammation and Osteoarthritis

The etiology of osteoarthritis is complex but ultimately starts with joint injury and inflammation which begins a cascade of events leading to cartilage fibrillation and erosion, thickening of the subchondral bone and osteophytes. (Figure 4).

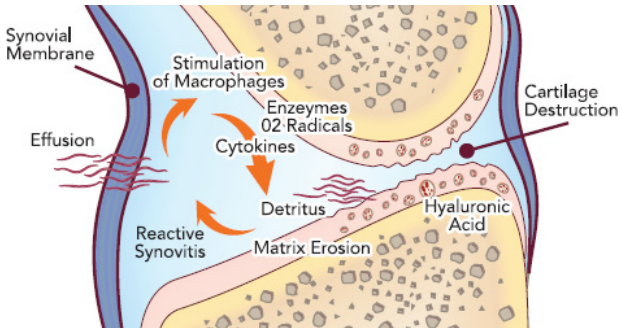


Figure 4. Initiation of joint degeneration. An injury leads to cartilage erosion and alterations in bone.

With so many dogs suffering from clinically diagnosed osteoarthritis, it seems obvious that prevention and/or amelioration of clinical symptoms is key to the dogs overall wellbeing. Cartilage has limited capacity to repair itself therefore all treatments have limitations, but combining treatments can improve patient outcomes. Prophylactic management and early intervention are very important. Table 3 lists the risk factors for joint compromise.

Table 3. Risk factors for joint compromise

Factor	Effect
Age	Older dogs have a higher incidence of symptoms
Weight	Overweight dogs are at greater risk
Genetics	Breed disposition, e.g. German Shepherd Dogs
Body size	Large breed dogs are more likely to have issues
Exercise	Intense or unusual exercise may cause joint damage
Age + Exercise + Genetic predisposition	Intense exercise in young dogs with genetic predisposition can increase the risk for early onset of joint degeneration

The goals of joint health management are:

1. Reduce inflammation and pain
2. Slow the degenerative process
3. Improve or maintain joint function

A fourfold management plan should be implemented:

1. Weight management- maintain dogs weight between 4 and 5 on a 9 point Body Condition Scale

2. Exercise modification- joint loading is important for cartilage maintenance and nutrient delivery but exercise must not cause further irritation of affected joint.

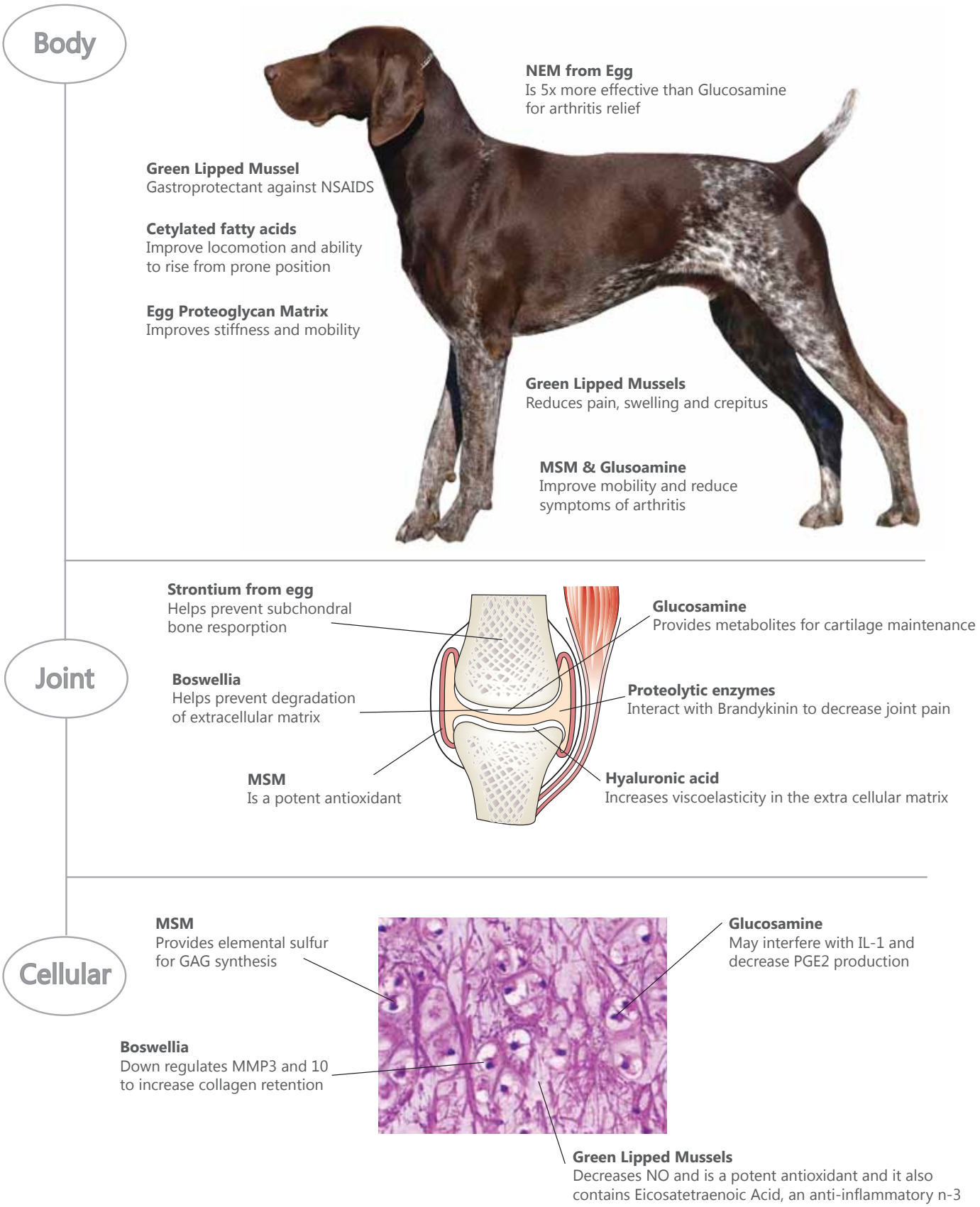
3. Drugs (non-steroidal anti-inflammatory drugs or NSAIDS, analgesics, corticosteroids)- usually prescribed for long term use to ameliorate pain and inflammation. However, patients need to be monitored for negative side effects like gastrointestinal, hepatic or kidney function compromise.

4. Dietary supplementation- a safe and effective adjunct therapy to help manage clinical symptoms of joint degeneration and to proactively maintain joint health.

Functional Dietary Supplements for Hip and Joint Health

Dietary supplements containing functional ingredients are a complementary component of multimodal osteoarthritis prevention and treatment. Innovative new natural ingredients are proven to be efficacious in multiple species including people and dogs (Figure 5)

Figure 5. Mode of action of ingredients in Ultimate Hip and Joint



Egg proteoglycan matrix

Egg proteoglycan matrix is a combination of eggshell calcium and natural egg membrane, NEM™. This combined ingredient provides nutrients for extracellular matrix maintenance and is reported to decrease pain and stiffness and improve joint mobility.

Egg shells contain calcium in the common form of $CaCO_3$(3) but what seems to make the calcium from eggshells more bioavailable than traditional sources of $CaCO_3$ is the protein to which eggshell calcium is bound. The "chelated" calcium is absorbed not only using active pathways with vitamin D facilitation, but also appears to have improved passive absorption in the small intestine (4).

Residual embryonic proteins like extracellular growth factors are incorporated into the eggshell matrix and are believed to have a positive effect in conjunction with $CaCO_3$, strontium and other minor minerals on bone and cartilage maintenance (5). Extracellular growth factors have been reported to regulate cytokine synthesis in damaged cartilage (6). Strontium is a natural analog for calcium and is incorporated into bone mass where it has both anabolic and antiresorptive effects on osteocytes (7), potentially slowing remodeling associated with osteoarthritis. Eggshell powder which contained egg shell membrane significantly stimulated pelvic, femur and tibia cartilage growth and cartilage weight in an in vitro model (8). In human clinical trials, egg shell powder had analgesic properties and patients reported more spontaneous physical activity after use (9).

NEM™ is the primarily fibrous protein layer found between the shell and the albumin of the egg. In addition to collagen, natural egg membrane contains glycosaminoglycans (10) such as dermatan sulfate (11) and chondroitin sulfate (11), sulfated glycoproteins like glucosamine (12), hyaluronic acid (13), sialic acid (14), desmosine and isodesmosine (15), ovotransferrin (16), lysyl oxidase (17) and _-N-acetylglucosaminidase (18). NEM™ is reported to be 5 times more effective than glucosamine or glucosamine and chondroitin combined in providing relief from osteoarthritis in humans (19).

Three clinical studies using NEM™ in humans have reported significant improvements in the symptoms associated with osteoarthritis and degenerative joint disorders. Patients reported decreases in joint pain and stiffness and increased flexibility of motion in as little as 7-10 days of treatment (19) (20) (Figure 6). Patients experiencing 50% improvement in stiffness and pain when supplemented with NEM™. (19)

The combination of eggshell calcium and NEM™ provide the metabolites required by joint tissues to maintain healthy cartilage, chondrocyte metabolite excretion like glycosaminoglycans, and to slow potential bone remodeling associated with osteoarthritis. In addition, these ingredients improve pain and stiffness as well as flexibility and range of motion. The possible mechanism for pain relief is not fully elucidated, but may be linked to the egg membrane cytokine-regulating proteins found in this ingredient. These proteins are known to regulate cartilage remodeling and ameliorate symptoms associated with joint pain.

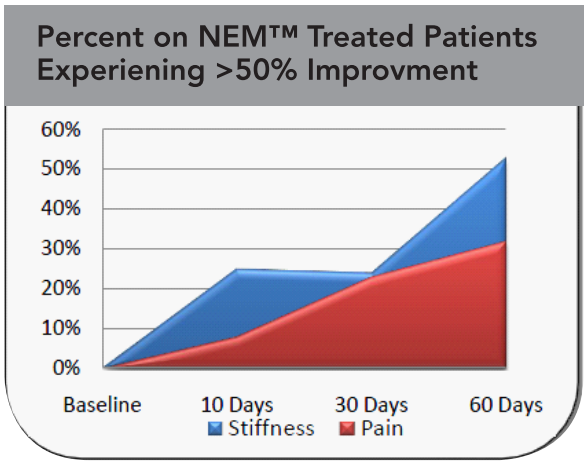


Figure 6. NEM decreases pain and stiffness scores in patients with chronic arthritis. Adapted from Winkeler et al (19).

Perna canaliculus (Green Lipped Mussels)

Green Lipped Mussels (GLM) has traditionally been used by New Zealand coastal Maori populations as a remedy for arthritis (21). In the last two decades GLM has become popular in human supplements because of their anti-inflammatory and pain relief components, high levels of chondroitin sulfate and glucosamine hydrochloride as well as a variety of other nutrients which have a proven positive effect on joint health.

Three placebo-controlled studies involving 96 arthritic dogs were undertaken wherein GLM was supplemented as a powder, incorporated into a treat or into a complete food (22). All studies had similar findings; showing that after 6 weeks, compared to the placebo, GLM was beneficial. Arthritis scores were recorded for mobility as well as pain, swelling and crepitus of individual joints and each limb. Dogs supplemented with GLM had reduced veterinarian assessed arthritic scores compared to the untreated dogs and there was a major decrease in pain score and a modest reduction in joint swelling and crepitus (Figure 7). Dogs supplemented with GLM in powder form had more dramatic decreases in arthritic score (50-70% decrease) than dogs supplemented with GLM via treat or complete diet.

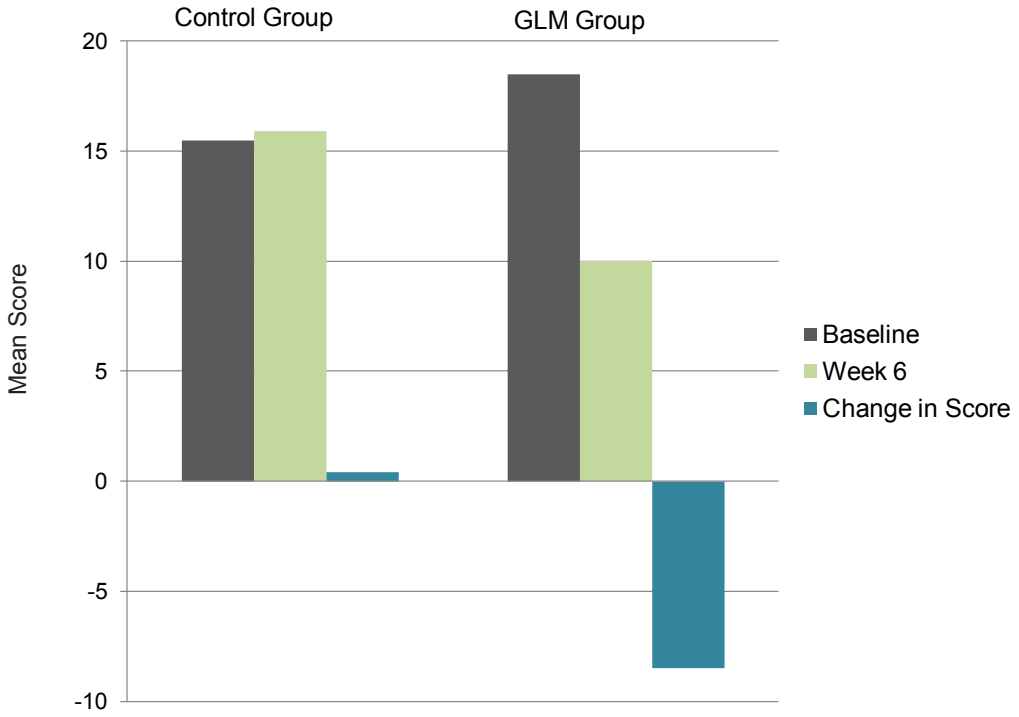


Figure 7. Changes in arthritis score in dogs supplemented with GLM. Adapted from Bierer and Bui. (22).

In a study of 45 dogs with radiographic diagnosis of osteoarthritis, GLM improved mobility and decreased both chronic pain and acute pain as reported by owner when compared to the placebo group (23). There was a 67% improvement in veterinarian assessed mobility including locomotion, walking stairs and jumping when the dogs were supplemented with GLM.

Of the many key mediators in osteoarthritis progression (Table 2), GLM has been shown to decrease the production of pro-inflammatory mediators (TNFα, IL-6) which results in decreased pain and stiffness. Glycosaminoglycans, vitamins and minerals in GLM provide nutrients for extracellular matrix maintenance and GLM has a potent antioxidant effect (decreases NO production). A unique omega-3 fatty acid called eicosatetraenoic acid is credited with many of the anti-inflammatory and analgesic effects of GLM (24). In addition, GLM may protect against the gastric upset associated with NSAIDS and act as a complement to NSAID therapy.

Boswellia serrata extract

Boswellia serrata (Indian Frankincense) is an herb which has proven anti-inflammatory and analgesic properties in humans (25) and dogs (26). It also appears to prevent degradation of extracellular matrix components and modulate both pro- and anti-inflammatory mediators (27).

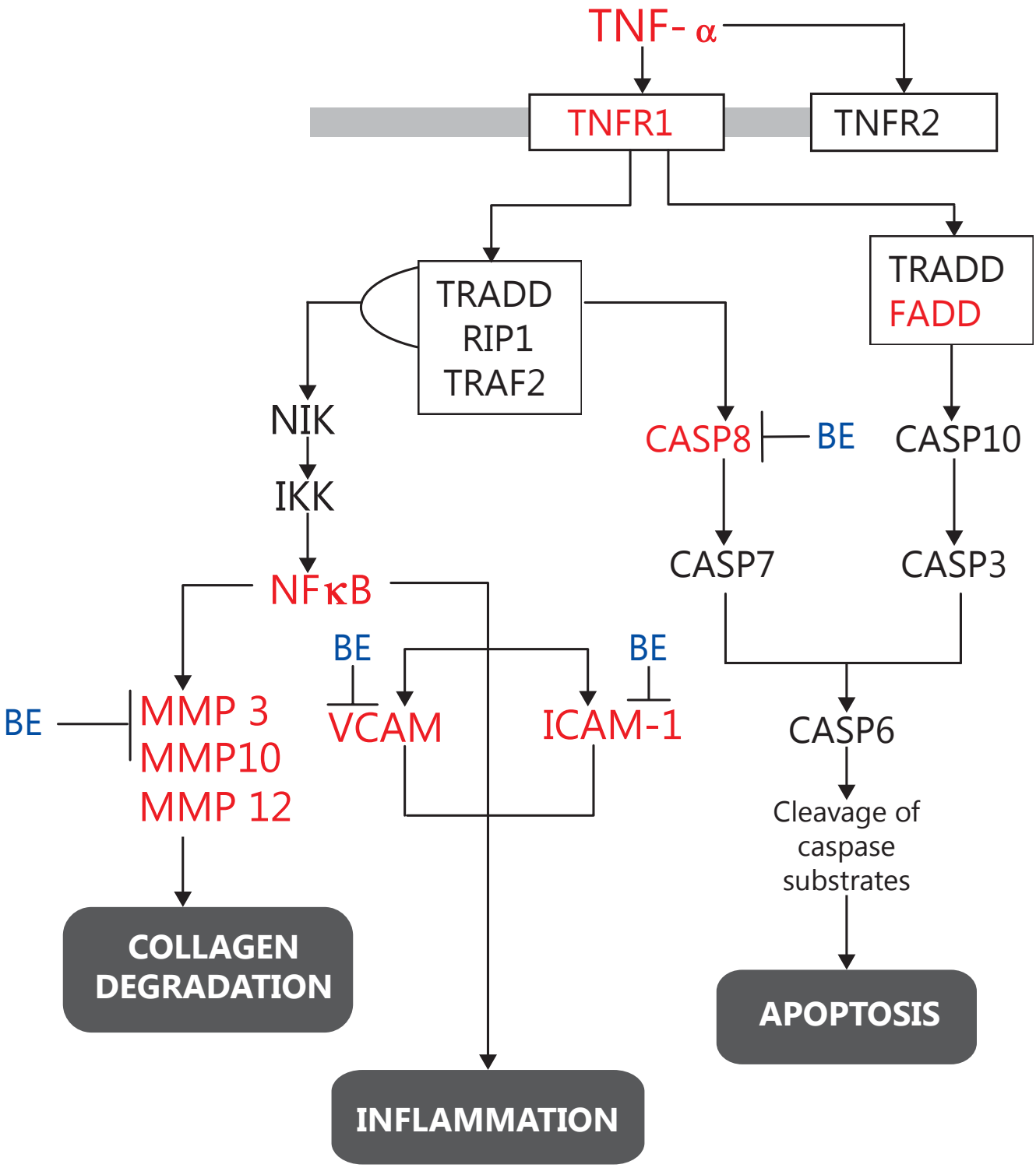
An open multicenter Swiss veterinary clinical trial, comparing conditions before and after treatment with Boswellia serrata, concluded that a standardized preparation of Boswellia can be recommended as an herbal dietary supplement providing symptomatic support in canine osteoarthritic disease (26). In dogs with manifestations of chronic joint and spinal disease, it was observed that Boswellia significantly reduced the severity and caused resolution of typical clinical symptoms in 71% of 24 dogs in the study.

These findings in the canine seem to be consistent with observation in humans. A randomized double-blind placebo-controlled crossover study has been conducted to assess the efficacy, safety and tolerability of Boswellia in 30 patients of osteoarthritis of knee for 8 wks. All patients receiving drug treatment reported significant decrease in knee pain, increased knee flexion and increased walking distance. The frequency of swelling in the knee joint was significantly decreased (25).

An in vitro study indicated that Boswellia prevented degradation of glycosaminoglycans in various tissue (28) helping to maintain cartilage integrity. Approximately 30% of TNFα inducible genes related to inflammation were regulated by Boswellia. Figure 8 illustrates the Boswellia sensitive TNFα signaling pathways. Boswellia has a direct positive effect on collagen retention by down-regulating MMP-3 and MMP-10 synthesis and preventing untimely apoptosis or cell death in in-vitro human cell line models (27). Vascular cell adhesion molecule (VCAM) is a potent promoter of inflammation by recruiting leukocytes to areas of inflammation. Boswellia prevented expression of this molecule, thereby prevented inflammation.

The lipoxygenase (LOX) pathway generates a new class of arachidonic acid oxygenation products called the leukotrienes which mediates inflammation. Unlike prostaglandins, some of which play important roles as biological regulators, the action of the LOX products appears to be exclusively of a pathological nature (29). Thus, the anti-lipoxygenase effects of Boswellia are likely to have therapeutic implications. In addition, in vitro studies indicate that Boswellia upregulates IL-4 and IL-10 potent inhibitors of inflammation (30). Boswellia switches off many pro-inflammatory cytokines and mediators and promotes the expression of anti-inflammatory cytokines as well as promoting cartilage maintenance resulting in decreased pain and stiffness and improved joint mobility.

Figure 8. TNF signaling pathways and Boswellia intervention. Blue BE indicates where Boswellia has a joint sparing effect and red indicated a degredation process. Adapted from Roy et al. (27).



Cetylated fatty acids

Cetylated fatty acids are naturally occurring fats reported to improve mobility and locomotion and increase joint flexibility. In an open label clinical trial, 75% of dog owners reported improvements in clinical symptoms associated with joint disease (31). Most notably, more than 50% of dogs were described to have an improved walking gait and flexibility and were better able to rise from a sitting or lying position. Owners also stated that the dogs suffered less pain and stiffness after 30 days of treatment with cetylated fatty acids. In humans supplemented with oral cetylated fatty acid there was a significant improvement in knee joint flexion and mobility and decreased pain and stiffness (32).

The mechanism by which cetylated fatty acids improve joint mobility is not well elucidated but may be due to the incorporation of cetylated fatty acids into the cell membranes of affected joints resulting in cell membrane stability. In addition, it is postulated that myristoleic acid found in cetylated fatty acids may inhibit 5-LOX which would decrease inflammation.

Methyl sulphonyl methane (MSM)

Methyl sulphonyl methane (MSM) is a natural occurring sulfur compound best known for its antioxidant properties, however, as more research is completed with MSM, other benefits are beginning to emerge, such as improvement in arthritis scores including pain and swelling. Studies with humans and horses show significant decrease in oxidative stress associated with exercise (33) (34). MSM is an organic source of sulfur and as such is a vital component of powerful antioxidants such as N-acetyl cysteine and reduced glutathione. Damage from oxidative stress can often lead to pain and inflammation. The results of several animal studies have indicated that with MSM supplementation, joint pain was significantly reduced and mobility enhanced(35) (36). There was a decrease in nitric oxide, lipid hydroperoxides, and glutathione peroxidase, tranferase and reductase in horses administered MSM before an exercise bout including a jumping exercise (34).

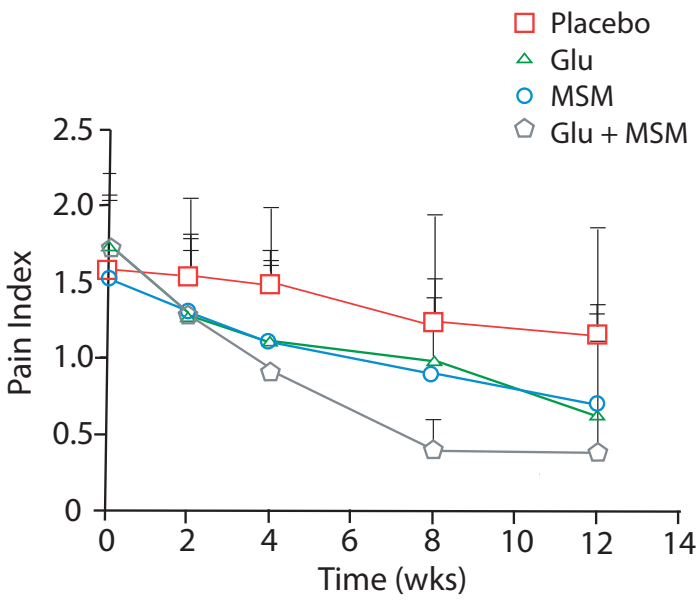


Figure 9. The effect of four treatments on pain index in humans. The four treatments were glucosamine (Glu); MSM; a combination of glucosamine and MSM (Glu+MSM) and placebo. Adapted from Usha et al. (37)

In three human clinical trials, MSM supplementation resulting in improved pain, swelling and functionality scores (37)(38) (39)(Figure 9 and 10). In addition, overall arthritis scores were reduced after four weeks of supplementation. MSM efficacy was improved when combined with other supplements (37), in particular glucosamine. Increases in serum sulfate may partially explain the therapeutic effects of supplements like MSM and glucosamine.

Glucosamine HCl

Glucosamine is a well-accepted natural supplement used in several species to help manage joint health. It is a common constituent of glycosaminoglycans in the cartilage matrix and synovial fluid and a precursor in the biosynthesis of many connective tissue macromolecules. Glucosamine exerts various pharmacological effects on the articular cartilage and joint tissue. Many clinical trials in multiple species have demonstrated its symptom-modifying and radiographic effects in patients with joint compromise or osteoarthritis (40).

A key building block of cartilage, glucosamine is derived from both endogenous biosynthesis and diet, is metabolized into the much larger matrix components of glycosaminoglycans (GAGs) including chondroitin sulfate and hyaluronic acid (Figure 11). Except for hyaluronic acid, GAGs are found covalently attached to proteins in the form of proteoglycans.

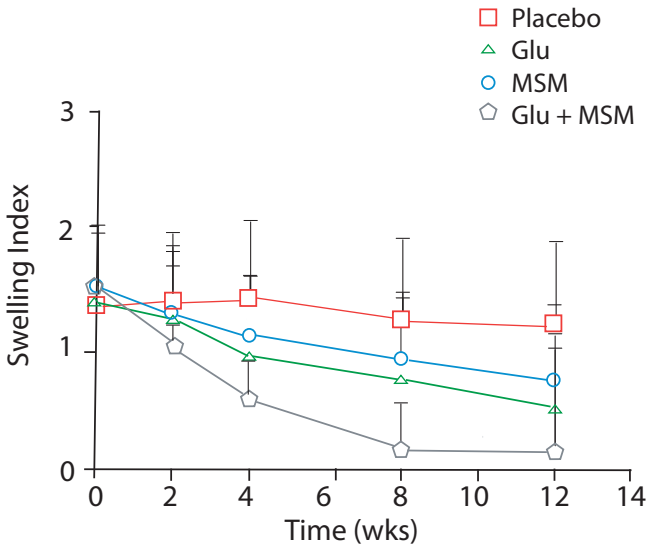


Figure 10. The effect of four treatments on swelling index in humans. The four treatments were glucosamine (Glu); MSM; a combination of glucosamine and MSM (Glu+MSM) and placebo. Adapted from Usha et al. (37)

Over the last three decades, an increasing body of evidence supports the use of glucosamine for osteoarthritis. Overall, glucosamine alone or in combination has been shown to improve symptoms of osteoarthritis including pain and weight bearing and to prophylactically provide nutrients needed for joint maintenance. Data from peer-reviewed journals on the effects of oral supplementation with glucosamine are summarized in Table 4.

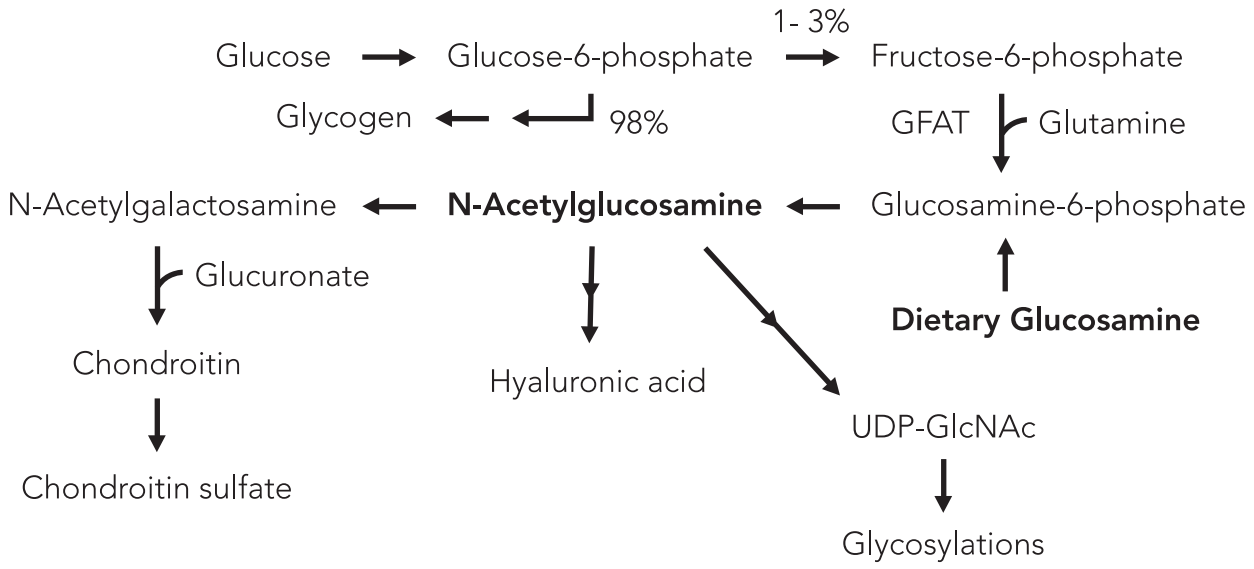


Figure 11. The biosynthesis of glucosamine

The mechanism by which glucosamine decrease clinical symptoms is not well described but may take a multi-pronged approach including: providing glucosamine for biosynthesis; decreasing MMP production; interfering with IL-1 stimulation of PGE_2 ; and by decreasing glycosaminoglycan loss from injured joints (40). Glucosamine hydrochloride appears to be used more specifically at the joint level than other sources of glucosamine in the dog (49)(50).

Overall, glucosamine hydrochloride is a ubiquitous chondroprotectant that improves clinical symptoms of osteoarthritis in dogs with long term use.

Table 4. Summary of Glucosamine Studies

Objective	Subjects	Dose, Method of Administration & Duration	Results	Ref
Clinical evaluation of bovine cartilage product for osteoarthritis	19 dogs with prior history of pain or lameness were treated	Treats containing concentrated glycosaminoglycans from bovine trachea	18 out of 19 dogs were viewed as positive by their owner, and 16 of the 19 dogs showed positive improvement when scored by the veterinarian	(41)
Determine if glycosaminoglycan polysulfate (PSGAG) protects articular cartilage	14 mature beagles	2 mg/kg, 2-3 times/wk; subcutaneous; 23 weeks	Histological evaluation showed PSGAG provided some protective effect	(42)
Measure chondroprotective activity in dog serum	13 beagles under 1 yr. of age	400 mg chondroitin sulfate, 500 mg glucosamine hydrochloride, 76 mg manganese ascorbate, twice daily; oral; 30 days	Serum GAGs were elevated 37%; glucosamine incorporation into cartilage increased significantly, proteolytic degradation decreased	(43)
Evaluate effects of glucosamine hydrochloride/chondroitin sulfate and glucosamine/chondroitin/S-adenovsyl-L-methionine on chemically induces synovitis in dogs	32 adult mixed-breed dogs	500 mg glucosamine, 400 mg chondroitin sulfate, 10 mg manganese, 66 mg ascorbate, 3 times daily; oral; 69 days	21 day prior treatment with glucosamine/chondroitin had a significant protective effect against chemically induced synovitis	(44)
Test if intramuscular injections of glycosaminoglycan polysulfates mitigates signs of hip dysplasia in growing pups	30 Labrador retriever pups from 4 litters	2.5-5.0 mg/kg glycosaminoglycan polysulfates, twice weekly; intramuscular; from 6 weeks to 8 months	Data indicated that early treatment of susceptible pups with glycosaminoglycan polysulfates reduced signs of incipient hip dysplasia	(45)
Determine if practitioners perceived clinical efficacy and safety of oral chondroprotective agent	3,080 practitioners from 2 groups received mail survey; 82% (2,524) responded	Clients administered the glucosamine with chondroitin sulfate	Majority of responders indicated some level of improvement	(46)
Roundtable discussion with practitioners on methods of treating canine osteoarthritis	Six veterinary practitioners		All six practitioners stated some use of chondroprotective agents	(47)
Randomized double blind positive control trial to assess the efficacy of glucosamine/chondroitin sulfate for the treatment of osteoarthritis in dogs	35 dogs	475 mg/g glucosamine hydrochloride;350 mg/g chondroitin sulfate;50 mg/g N-acetyl-d-glucosamine ; 50 mg/g ascorbate; 30 mg/g Zn sulfate or 1 g or mannitol as placebo daily	Dogs treated with glucosamine mix had statistically improved pain, weight bearing and severity of condition at after 70 days of supplementation compared to placebo	(48)
Trace the fate of oral glucosamine administration via labeled glucosamine	2 dogs	500 mg/kg/dog or 250 mg/kg/dog 13C-Glucosamine HCl for 14 days	A dose dependent increase of 13C-Glucosamine HCl in chondrocytes of treated dogs	(49)

Hyaluronic Acid

Hyaluronic acid is a polysaccharide composed of repeating disaccharide units and belongs to the group of glycosaminoglycans but unlike chondroitin sulfate or keratin sulfate, hyaluronic acid is not sulfonated (Figure 12). It is widely distributed but mainly localized to the extracellular matrix and body fluid. Hyaluronic acid contributes to the viscoelasticity of the fluid and elasticity in connective tissues which absorb mechanical stress, for example, between cartilage and cartilage surfaces (51). In clinical studies, hyaluronic acid has been shown to improve mobility, slow the degeneration of cartilage and have an analgesic effect (52). High molecular weight hyaluronic acid enhances the synthesis of chondroitin and keratin sulfate as well as other proteoglycans (53).

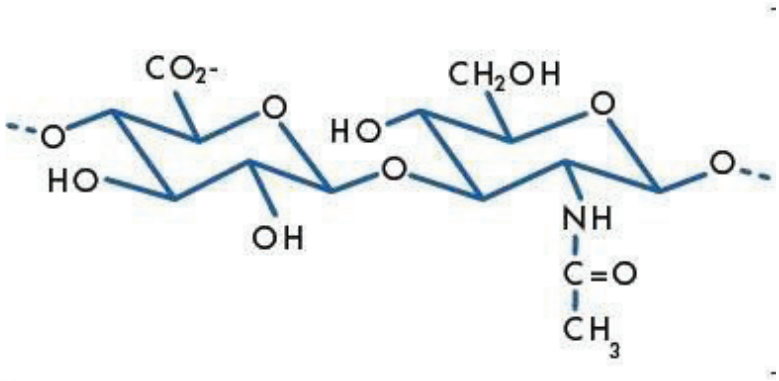


Figure 12. Composition of Hyaluronic acid.

In an in vitro model of canine osteoarthritis, a reduced amount of glycosaminoglycans release was found in hyaluronate-treated joints compared with an increased release in untreated joints (54) which may explain the increased mobility and decreased cartilage degeneration found in clinical studies. Hyaluronic acid has been shown to suppress inflammation in articular joints in vitro. Hyaluronic acid inhibits IL-1β induced MMP production (55) and specifically inhibits aggrecanase expression in a human chondrocyte model. In a canine model, TNFα and its receptor were not evident in atrophied articular cartilage treated with hyaluronic acid by immunostaining but were observed in untreated cartilage (56). Based on in vitro studies, hyaluronic acid has an important role in helping to preserve and protect articular cartilage.

Hyaluronic acid administered orally was detected in the target joints and vertebrae of dogs and therefore, oral administration is an alternative to intracellular administration of hyaluronic acid (57). In humans, intra-articular administration is only suggested if oral administration of hyaluronic acid or NSAIDS would not be tolerated. Hyaluronic acid concentration changes during the initial stages of osteoarthritis and supplementation with hyaluronic acid may ameliorate clinical signs of inflammation, pain and decreased mobility through a variety of inhibiting mechanisms at the cellular level.

Enzymes

Oral hydrolytic enzymes are used widely in Europe for human and animals and are reported to be fibrinolytic, anti-edematous, anti-inflammatory and analgesic. The anti-inflammatory effect of oral hydrolytic or proteolytic enzymes appears to be quite complex and involve several different mechanisms including the cleavage of proteins in the complement protein cascade. The analgesic properties are thought to be the result of enzymes direct influence on pain mediators such as bradykinin as well as indirect effects through its anti-inflammatory actions which reduce pain (58). In addition, proteolytic enzymes engage the macrophages of the synovium and improve debris removal (58).

Proteolytic enzymes were equal to the NSAID diaclofenac in three double blinded randomized studies (n= 193) and a single blind randomized study (n= 50) in humans which evaluated arthritis pain in the knee and hip. Joint pain and stiffness were reduced and function improved with the supplementation of proteolytic enzyme blend (59) (60) (61) (62).

Summary

Each of the natural ingredients detailed here have positive benefits for joint health based on a plethora of peer-reviewed scientific studies. In many cases, some ingredients contain multiple components which have proven efficacy, for example egg proteoglycan matrix and GLM both contain glycosaminoglycans and glucosamine within a complex matrix. The synergistic combination of ingredients results in a holistic approach to maintain joint integrity and health before permanent injury and to decrease or minimize clinical symptoms associated with osteoarthritis or joint degeneration.

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