Influence of Green Lipped Mussels *(Perna canaliculus)* in Alleviating Signs of Arthritis in Dogs*

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ABSTRACT

This study evaluated the efficacy of green lipped mussel (GLM), added to a complete dry diet, for alleviating clinical signs of arthritis in dogs. A double-blind longitudinal study design was used with 31 mixed-breed dogs exhibiting varying degrees of arthritis. Each dog was evaluated by a veterinarian and joints were individually scored for degree of pain, swelling, crepitus, and reduction in range of movement. Summation of all scores for an individual dog comprised its total arthritis score. At baseline, dogs were randomly allocated to control and test groups. Both groups were fed the same base dry diet, to which 0.3% GLM powder was added for dogs in the test group. 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. Changes in joint crepitus and range of joint movement were not significantly different between the test and control groups. These findings provide strong evidence that GLM incorporated into a complete dry diet can help alleviate arthritis symptoms in dogs.

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INTRODUCTION

Arthritis is a significant problem in middle-aged and geriatric dogs, although it can occur in animals of any age. The various forms of arthritis may be broadly classified as degenerative, or inflammatory, arthropathies.[1] The most common form of joint disease in dogs is osteoarthritis (OA), a complex, progressive disease of synovial joints that is characterized by the degeneration of articular cartilage and the formation of new bone at the joint margins. Inflammation of the synovial membrane may also be present in some cases but is a variable feature throughout the course of the disease. Inflammatory joint diseases are less common than OA in dogs and include such immune-mediated arthropathies as rheumatoid arthritis (RA).

Most cases of OA in dogs occur in association with some predisposing joint disease or injury within the joint that produces focal areas of increased stress and results in accelerated turnover of the articular matrix.[2] This produces softening and weakening of the articular matrix and creates a self-perpetuating cycle of

events, which eventually result in localized cartilage erosion and exposure of the underlying bone.

Clinically, most dogs with OA ultimately present with stiffness or lameness, although structural damage may exist for some time before signs are apparent. Lameness is due to a combination of joint pain and restricted movement of the joint and may be gradual in onset or may present acutely following some minor trauma or excessive exercise. Tactical use of both steroids and NSAIDs to provide symptomatic relief has traditionally been the mainstream of conservative management of OA in dogs. However, long-term use of many of these drugs can have adverse side effects and may accelerate cartilage degeneration in both healthy and diseased joints.[3,4]

Chondroprotective agents protect cartilage from degeneration through stimulation of cartilage matrix synthesis and/or inhibition of cartilage degradation and may potentially arrest, or even reverse, progression of the disease. Parenterally administered, semi-synthetic glycosaminoglycans (e.g., polysulfated glycosaminoglycan and pentosan polysulfate) have analgesic, antiinflammatory, and chondroprotective effects and reports on their efficacy in dogs appear to be generally favorable.[3,5–7] Dietary measures also have a role in the management of both inflammatory and degenerative forms of arthritis and, where effective, can help reduce or eliminate the need for conventional drugs. Weight control is one important aspect of dietary management and, in some obese patients, may be the only measure required to control clinical signs of the disease. Furthermore, dietary factors can modify some of the underlying processes involved in arthritis, including modulation of the inflammatory response, provision of nutrients for repair, and protection against oxidative damage.

A variety of dietary supplements, including chondroitin sulfate, glucosamine, antioxidants, and omega-3 fatty acids, have been used with varying degrees of success in the management of arthritis in both human and veterinary patients.[3,8–12] Among some indigenous coastal cultures, shellfish supplements have been used as a traditional remedy for arthritis, and in recent years interest has focused on the potential benefits of a nutritional supplement prepared from the New Zealand green lipped mussel (GLM, *Perna canaliculus*).[13] Green lipped mussel is known to contain antiinflammatory components as well as a variety of other nutrients that may have a beneficial effect on joint health. Analysis has shown that GLM powder contains glycosaminoglycans, omega-3 fatty acids, amino acids, vitamins, and minerals.[14,15] It is possible that these nutrients may act synergistically to reduce inflammation, limit further cartilage degeneration, and potentially support the regeneration of damaged joint cartilage and synovial fluid.

Studies have demonstrated beneficial effects of GLM in human subjects with both RA and OA.[16] The effects of GLM in alleviating clinical signs of arthritis in dogs, however, have not been widely documented. A series of preliminary studies has shown that dietary supplementation with freeze-dried GLM powder helped reduce arthritic signs in dogs.[17] Oral supplementation with a glycosaminoglycan preparation derived from GLM was found to reduce lameness and pain in a high proportion of arthritic dogs after 8 weeks of treatment.[15] Furthermore, heat processing of GLM into a food product has been shown to result in a significant loss of activity, but studies have demonstrated that efficacy was retained when the powder was incorporated into a semi-moist treat using a special, low-temperature process.[18] The study presented here was designed to determine whether freeze-dried stabilized GLM powder would alleviate chronic signs of arthri-

tis in dogs when incorporated into a complete dry diet using a method designed to retain activity of the supplement.

MATERIALS AND METHODS

Animals and Housing

Thirty-one mixed-breed dogs of both sexes (neutered and spayed), ranging in age from 8 to 13 years and exhibiting chronic signs of lameness for 4 months to several years, were identified for the study at an animal sanctuary. Dogs exhibiting acute signs of lameness for less than 4 months and dogs thought to have been injured recently were excluded from the study. The dogs were housed outdoors in groups of 10 and had the same exposure to sunlight. Ambient temperature ranged from 30°F to 100°F during summer and fall. All dogs were examined by a veterinarian for general health at baseline, and blood biochemistry and complete blood cell counts were analyzed to determine the health status of the animals before they were included in the study.

Diet and Feeding

All dogs were adapted to a nutritionally complete and balanced adult dry diet for at least 6 weeks prior to the baseline measurements. At the start of the trial, all dogs were switched to either a control or test diet. Dogs were fed once a day (between 8 AM and noon) and had free access to tap water. Feeders carefully observed the dogs to verify consumption of the meal each day.

Test Substance

Both the test and control diets were produced using the same base recipe as the diet used during the adaptation period. Pulverized, freeze-dried, whole-flesh GLM was obtained from a research facility (MacLab, Surrey Hills, VIC, Australia) and was added to the test diet at an inclusion level of 0.3% GLM. The GLM was added to the test diet during processing, using a proprietary low-temperature inclusion system. Dogs were fed the diet at levels to maintain their body weight throughout the trial. The GLM powder contained 40% to 50% protein, 20% to 30% complex carbohydrates, 10% to 12% fat, and vitamins and minerals.

Test Design

The study used a double-blind longitudinal test design. A total arthritis score for each dog was determined by summation of the scores for the following parameters: mobility, degree of joint pain, swelling, crepitus, and reduction in range of movement. Mobility was calculated as the average of the individual visual scores for lameness in walking, trotting, and climbing stairs. Joint pain, swelling, crepitus, and reduction in range of movement were assessed via palpation. The joints of each limb (carpus, elbow, and shoulder joints for the front limbs and tarsus, stifle, and hip joints for the rear limbs) were examined individually and were each given a separate score. All scoring used the following scale: 0 (no signs), 1 (mild), 2 (moderate), 3 (marked), and 4 (severe). Therefore, for each parameter assessed by palpation, the maximum score was 48 (maximum score of 4 × 3 joints/limb × 4 limbs). The maximum mobility score was 4, (i.e., [4 + 4 + 4]/3 parameters), making the maximum total arthritis score possible for each dog 196 (48 + 48 + 48 + 48 + 4). Dogs were then randomly allocated to two groups, with each group containing equivalent baseline mean total arthritis scores (Table 1).

Scoring Validation

Prior to the study, 20 dogs with varying degrees of lameness were selected for validation of the scoring method explained above. All dogs, in random order, were assessed by a veterinarian each day for 3 consecutive days. Daily scores for each dog over the 3 days were then

TABLE 1. Group Allocation

Group	*No. of Dogs*	*Diet Fed*	*Duration*
Control	17	Dry base	6 wk
Test	14	Dry base + GLM*	6 wk

*GLM = green lipped mussel powder.

TABLE 2. Improvement in Total Arthritis Score after 6 Weeks of Feeding a Complete Dry Diet with or without Green Lipped Mussel Powder

	Percentage of Dogs Showing Improvement (Number Improved/Total in Group)	
Reduction in Total Arthritis Scores*	*Control*	*Test*
<0% (increased score)	59% (10/17)	7% (1/14)
No change	6% (1/17)	7% (1/14)
<20%	35% (6/17)	14% (2/14)
20%–29%	0% (0/17)	21% (3/14)
30%–39%	0% (0/17)	21% (3/14)
40%–49%	0% (0/17)	21% (3/14)
≥50%	0% (0/17)	7% (1/14)

*Total arthritis score for each dog was determined by summation of scores, on a 0 to 4 scale (0 = least severe and 4 = most severe) for the following parameters: mobility, degree of joint pain, swelling, crepitus, and reduction in range of movement.

compared and were found to be consistent; thus, this scoring method and veterinarian scorer were used throughout the trial.

Arthritis Assessment

Six weeks after initiating control and test diets, visual and physical assessments for arthritis signs were carried out and arthritis scores were determined for each dog, as before treatment.

Statistical Analyses

The change from baseline to 6 weeks after treatment was determined for all variables monitored: mobility, joint pain, swelling, crepitus, re-

duction in range of movement, and total arthritis scores. One-way analysis of variance (ANOVA) was used via the non-equal Tukey's test to assess differences between the groups for these variables. Significance was declared at $P < .05$. Data are expressed as group means ± SD.

RESULTS

At baseline, mean scores for all the parameters assessed were not significantly different between the control and test groups. After 6 weeks, 50% (7 of 14) of the dogs in the test group demonstrated a 30% or greater reduction in total arthritis scores (indicating an improvement), including four dogs (29% of the group) demonstrating improvement of 40% or greater, and one dog (7%) showing 50% or greater improvement (Table 2). Overall, 12 of 14 dogs supplemented with GLM were determined to have improved total arthritis scores, one dog had no change, and one dog had an increased total arthritis score (Figures 1 and 2).

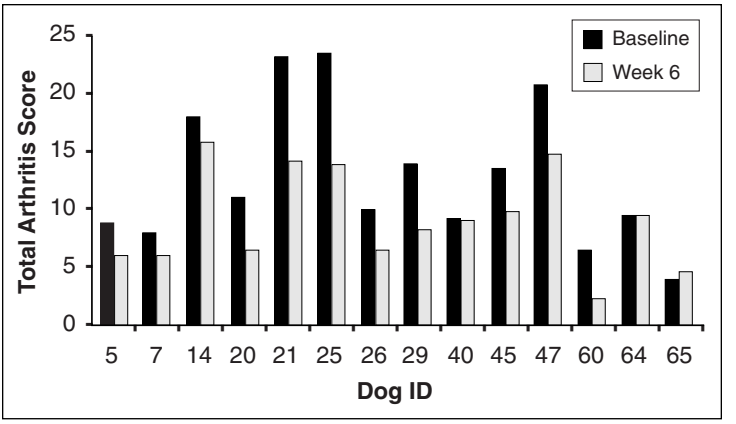

Figure 1. *Total arthritis scores for individual dogs in the test group, which was fed a diet supplemented with green lipped mussel powder for 6 weeks.*

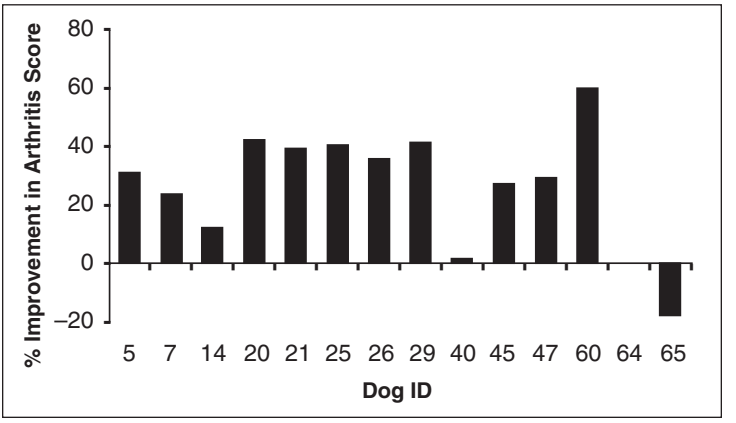

Figure 2. *Percentage improvement in total arthritis scores for dogs in the test group, which was fed a diet supplemented with green lipped mussel powder for 6 weeks.*

Total arthritis scores for 10 of the 17 control dogs increased by 1% to 9% (i.e., their condition worsened) after 6 weeks (Figures 3 and 4). Six control dogs had improved total arthritis scores, with the greatest improvement being 17.6%, and one dog had no change in total arthritis score after 6 weeks. The mean change in total arthritis score from baseline to Week 6 was significantly greater ($P < .05$) for the test group than for the control group (Figure 5).

Dogs fed the test diet with GLM for 6 weeks did not show a significant improvement in walk, trot, or climbing stair scores as compared with controls (data not shown). Furthermore, the change in mean mobility score was not significantly different between the test and control groups after 6 weeks of treatment (Figure 6). Mean joint pain and joint swelling scores were significantly improved ($P < .05$) in the

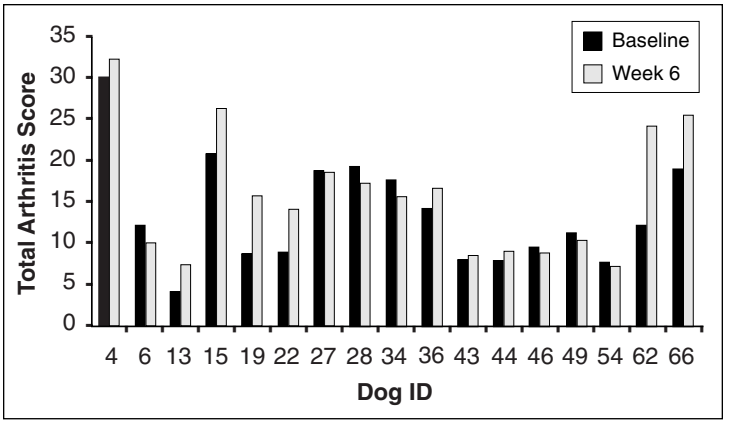

Figure 3. *Total arthritis scores for individual dogs in the control group, which was fed a standard dry diet with no supplementation for 6 weeks.*

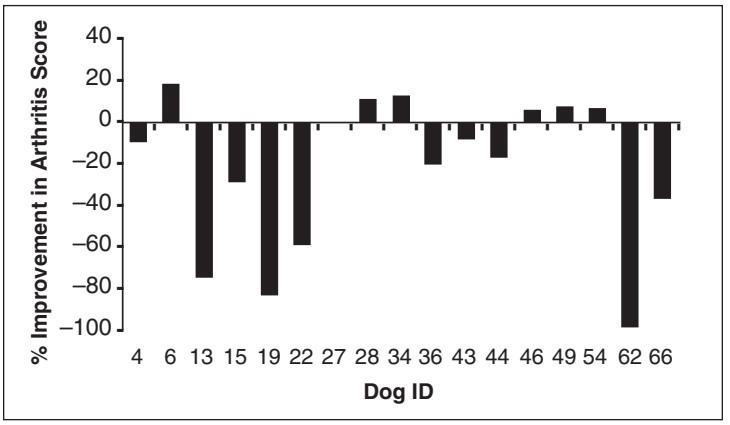

Figure 4. *Percentage improvement in total arthritis scores for dogs in the control group, which was fed a standard dry diet without supplementation for 6 weeks.*

test group, as compared with the control group, after 6 weeks of treatment. Joint pain (Figure 7) and swelling scores (Figure 8) in the control dogs worsened when compared with their baseline scores.

At the start of the study, 8 dogs in the control group were affected with joint crepitus, and 6 dogs in the test group were affected. After 6 weeks of treatment, 3 of the 8 control dogs showed improvement in joint crepitus, and 3 of the 6 affected dogs receiving GLM in the diet showed improvement (data not shown). The mean change in joint crepitus score, however, was not statistically significant at 6 weeks between the groups (Figure 9). Significant differences were not observed in range of joint movement scores between the test and control groups after 6 weeks of treatment (Figure 10).

DISCUSSION

Clinical studies of the use of GLM in humans with RA and OA have provided conflicting results. In one study, administration of freeze-dried GLM extract for 3 to 6 months was effective in reducing pain and stiffness in 68% of rheumatoid patients and 40% of osteoarthritic patients.[16] Conversely, no significant improvements were observed in patients with RA when the same product was administered in other studies over 6 to 12 weeks or for 6 months.[19,20]

Results of the present study support earlier findings that GLM is effective in reducing clinical signs of arthritis in dogs[17,18] and demonstrate that its efficacy is present even when processed into a dry complete product. After 6 weeks of feeding the GLM diet, total arthritis scores were significantly improved in the test group (demonstrated by a ≥30% reduction in scores for 50% of the dogs) compared with none of dogs in the control group exhibiting

this degree of improvement. Significant improvements in joint pain and joint swelling scores also were observed in the dogs fed GLM powder in the diet as compared with the control group at 6 weeks. However, the change in scores for joint crepitus, reduction in range of joint movement, and mobility were not significantly different between the two groups. In previous studies, joint crepitus was significantly improved after feeding GLM for 6 weeks either top-dressed on food as a powder or given in a semi-moist treat.[17,18] It is possible that the significant improvements in crepitus could not be detected in this study because of the low number of dogs in each group that actually exhibited this sign at the onset of the study.

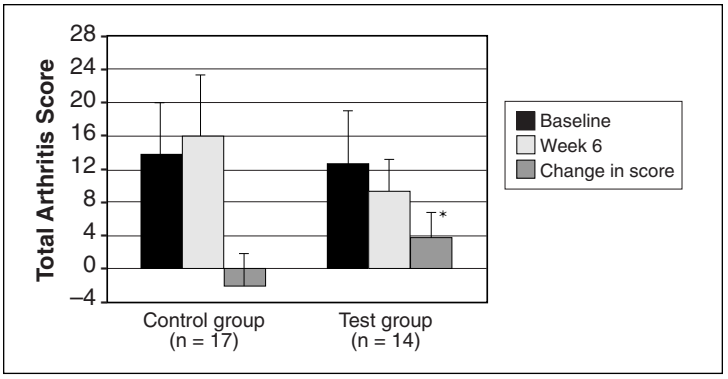

Figure 5. *Total arthritis scores and change from baseline to Week 6 (mean ± SD) for dogs fed either a standard diet (control group) or a diet supplemented with green lipped mussel powder (test group) for 6 weeks. *Change from baseline significantly greater for test group than for control group* (P < *.05).*

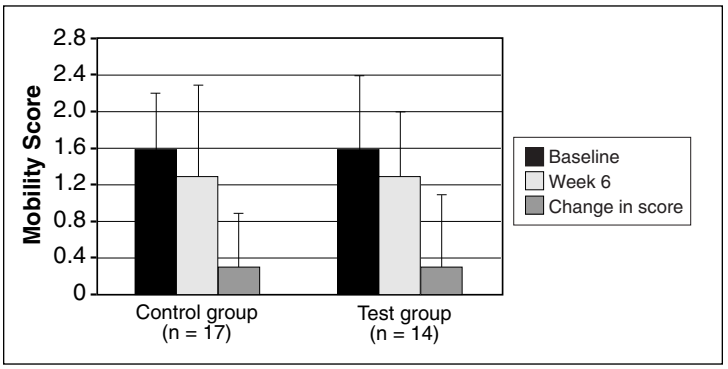

Figure 6. *Mobility scores and change from baseline to Week 6 (mean ± SD) for dogs fed either a standard diet (control group) or a diet supplemented with green lipped mussel powder (test group) for 6 weeks.*

Mobility scores, including scores for walk, trot, and climbing stairs, were not significantly improved in this study after feeding the GLM-enhanced diet for 6 weeks. The reasons for this are unclear, but it may be a reflection of the objective method of assessment used in this study. Handlers who were familiar with the animals commented that mobility and general well-being were noticeably improved, although improvements may not have been sufficient to register on mobility scores. In previous studies, dogs supplemented with GLM in a semi-moist treat showed a significant improvement in trot scores that was positively correlated with reductions in both joint pain and joint swelling.[18]

Scores for range of joint movement were not significantly improved after 6 weeks of feeding the GLM diet. However, scores in this study represented an average of scores for each major joint of each limb, and it is possible that including scores for unaffected or marginally affected joints in some legs may have masked any significant improvement in individual joints

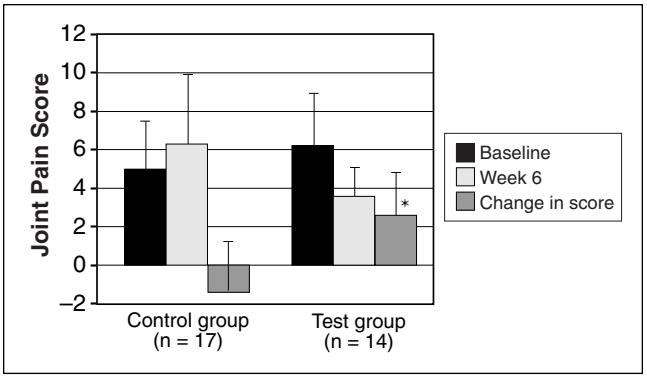

Figure 7. *Joint pain scores and change from baseline to Week 6 (mean ± SD) for dogs fed either a standard diet (control group) or a diet supplemented with green lipped mussel powder (test group) for 6 weeks. *Change from baseline significantly greater for test group than for control group* (P < *.05).*

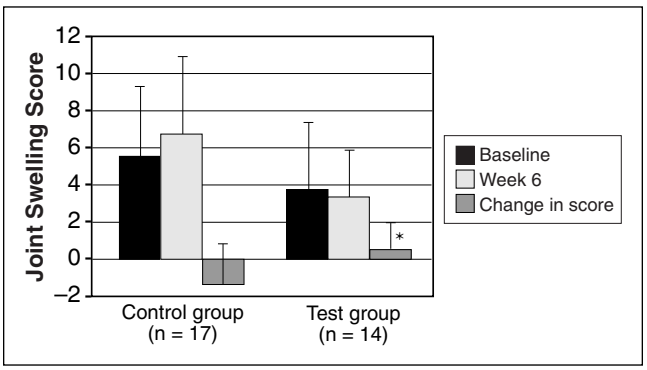

Figure 8. *Joint swelling scores and change from baseline to Week 6 (mean ± SD) for dogs fed either a standard diet (control group) or a diet supplemented with green lipped mussel powder (test group) for 6 weeks. *Change from baseline significantly greater for test group than for control group* (P < *.05).*

that were severely affected. Moreover, the initial severity of arthritis and the extent of the existing joint pathology were not recorded in these dogs. It is possible that extensive physical changes, such as bony proliferation or joint capsular thickening, may physically limit the degree of movement of a joint and, hence, mobility. These changes are unlikely to be affected by GLM supplementation or, indeed, by any other form of medical therapy. It should be emphasized that there is no known cure for OA and that any treatment is aimed at alleviating symptoms and, possibly, delaying progression of the disease.

Joint pain and joint swelling scores were significantly reduced after feeding the GLM diet for 6 weeks. The mechanism by which this is achieved is not fully understood but may be due in part to a reduction in the synovial inflammatory response. Antiinflammatory activity of the freeze-dried mussel extract has been identified in studies of rats with carrageenan-induced paw edema, although in one study the effect was only observed following intraperitoneal administration of the extract.[21] In another study, however, orally administered freeze-dried GLM not only had modest antiinflammatory activity that reinforced the therapeutic activity of some NSAIDs but also markedly reduced the gastric ulceration that is often induced by these drugs.[22]

The antiinflammatory activity of GLM has been attributed to a variety of pharmacologically active agents. Inhibition of prostaglandin biosynthesis, as indicated by delayed parturition and retarded fetal development, was reported in rats following oral administration of freeze-dried GLM extract.[23] Malformations, however, were not observed in rat fetuses. Many NSAIDs are believed to exert their antiinflammatory effect through inhibition of prostaglandin biosynthesis and have a similar effect on reproductive function. In another study, an antihistaminic principle in freeze-dried GLM was identified as lysolecithin.[24] More re-

cently, freeze-dried GLM was reported to reduce carrageenan-induced and trauma-induced inflammation in rats following both oral and parenteral administration, and an active component was shown to be present in the glycogen fraction of the mussel.[25] The compound was found to suppress neutrophil emigration, possibly by blocking carbohydrate receptors on neutrophils or endothelial cells.

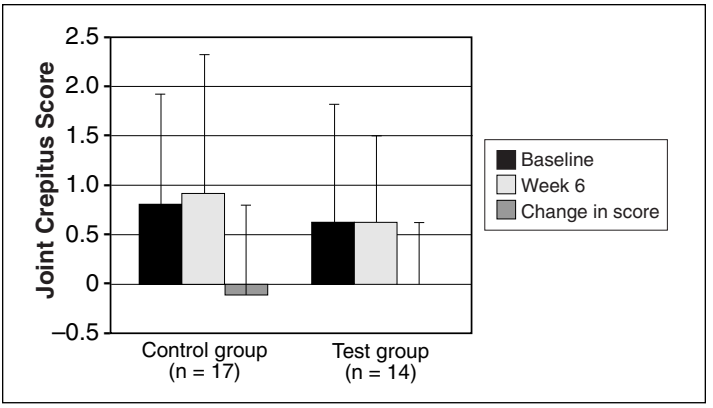

Figure 9. *Joint crepitus scores and change from baseline to Week 6 (mean ± SD) for dogs fed either a standard diet (control group) or a diet supplemented with green lipped mussel powder (test group) for 6 weeks.*

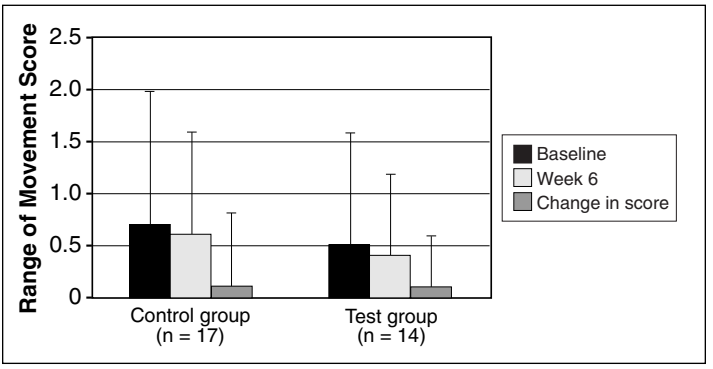

Figure 10. *Range of movement scores and change from baseline to Week 6 (mean ± SD) for dogs fed either a standard diet (control group) or a diet supplemented with green lipped mussel powder (test group) for 6 weeks.*

Since 1986, stabilized dried mussel extract of a more standardized quality has become available, with superior efficacy than earlier versions of the powdered extract. A lipid-rich extract of stabilized GLM has been shown to be a potent but relatively slow-acting anti-inflammatory agent, with the highest antiinflammatory activity being found in the polyunsaturated fatty acid (PUFA) component of the mussel.[13,26] *In vitro* studies have shown that the lipid extract of GLM suppressed leukotriene B_4 biosynthesis by stimulated human neutrophils and prostaglandin E_2 production by activated human macrophages. Both leukotriene B_4 and prostaglandin E_2 are important mediators in the inflammatory sequence. Much of this anti-inflammatory activity was associated with a novel omega-3 PUFA, eicosatetraenoic acid (ETA), which appears to act as dual inhibitor of arachidonic acid oxygenation by both the cyclooxygenase (COX) and 5-lipoxygenase pathways. Unlike many NSAIDs, however, the lipid extract was found to be nongastrotoxic and did not affect platelet aggregation, suggesting that it may selectively block the proinflammatory COX-2 pathway rather than the physiologically important COX-1 pathway.

Dietary omega-3 PUFAs can potentially modify immune and inflammatory responses by competing with arachidonic acid and other omega-6 PUFAs for incorporation into cell membrane phospholipids, thereby reducing

the production of proinflammatory arachidonic acid metabolites following cell membrane injury. Eicosapentaenoic acid and docosahexaenoic acid are omega-3 PUFAs commonly found in fish oils. These acids have been associated with clinical benefits in some cases of inflammatory or autoimmune disease, such as RA.[9,27]

In previous studies, the lipid extract of GLM, which has a relatively high proportion of ETA, was found to be less effective than the freeze-dried GLM powder in alleviating signs of arthritis in dogs.[17] It is likely that most, if not all, dogs in this earlier study had OA, in which inflammation is a variable feature. Although freeze-dried GLM powder contains less omega-3 PUFAs than the lipid extract, it also contains a variety of other nutrients, including complex proteins, glycosaminoglycans, vitamins, minerals, and amino acids, that may have a beneficial effect on joint health. Glycosaminoglycans, including chondroitin sulfate and hyaluronic acid, are long, unbranched carbohydrates that are major components of cartilage matrix and synovial fluid. Dietary supplementation with glycosaminoglycans, particularly chondroitin sulfate, may help stimulate cartilage matrix production; inhibit degradative enzyme activity in cartilage; and prevent thrombus, plaque, and fibrin formation in synovial and subchondral blood vessels.[28,29] Oral supplementation with a glycosaminoglycan preparation derived from GLM was found to reduce lameness and pain in a high proportion of arthritic dogs after 8 weeks of treatment.[14]

CONCLUSION

Results of this study provide strong evidence that GLM, incorporated into a complete dry diet, can help alleviate arthritic symptoms in dogs, although the mechanism for its beneficial effect remains unclear. Further studies will help determine whether dietary supplementation with GLM can reduce or eliminate the need for conventional medical therapy in arthritic dogs. Where concurrent drug therapy is required, the reported gastroprotective action of GLM may be of additional clinical benefit.

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