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Clinical application of D-glucosamine and scale collagen peptide on canine and feline orthopedic diseases and spondylitis deformans

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ABSTRACT

We have been investigating the effect of various amino sugars, uronic acid, and collagen peptides on wound healing of experimental cartilaginous tissue damage using a rabbit model, and also testing such supplements in various of diseases in dogs and cats. In the present study, we focused on the clinical effects of orally administered D-glucosamine hydrochloride and collagen peptides on joint diseases (48 cases) including spondylitis deformans (SD, 23 cases) in dogs and cats. The collagen peptide used in the study was extracted from fish scale (SCP, MW: 800). These materials were administered at 1 g each/animal/day, mixed in dog food or cat food. Lameness was evaluated using a lameness scale of 0 to 10 (0 = normal, 10 = unable to rise). Lameness scores at the first examination were distributed from 1 to 10, however, scores fell to less than 3 by final follow-up. The simultaneous administration of D-glucosamine and SCP was very effective in various kinds of joint degeneration and SD in dogs and cats. D-Glucosamine and SCP are thought to increase proteoglycan and collagen synthesis as well as exhibit anti-inflammatory effects and trigger recovery of vascular circulation in the damaged area.

1. Introduction

In recent years, various combinations of non-steroidal anti-inflammatory drugs (NSAIDs), steroids, surgical treatment, intra-articular injection of hyarulonic acid, and oral administration of glucosamine or collagen have been selected as supportive treatments for patients with degenerative joint disease (DJD) (Leffler, Philippi, Leffler, Mosure, & Kim, 1999). Although glucosamine and collagen have a slower analgesic effect than anti-inflammatory drugs such as NSAIDs, they have low toxicity (Setnikar, Cereda, Pacini, & Revel, 1991) and are suitable for long-term administration (Qiu, Gao, Giacovelli, Rovati, & Setnikar, 1998). Clinical trials of long-term administration of glucosamine show diminished clinical symptoms of DJD (Barclay, Tsourounis, & McCart, 1998). Further, we have reported that glucosamine accelerated the healing of experimental cartilage damage (Tamai et al., 2002).

Aging results in a progressive lack of replenishment of proteoglycan and collagen, with an accompanying increase in the incidence of DJD (McDevitt & Muir, 1976). Proteoglycan is constructed from a core protein with numerous side chains of glycosaminoglycan, a polysaccharide consisting of repeated dimers of amino sugars and uronic acid (Hardingham & Fosang, 1992). In joint cartilage, the extracellular matrix consists of type II collagen, which is composed of chondroitin sulfate and keratan sulfate. Collagen has 3 bundle chains that intertwine as in the DNA helical chain structure, and its main constituting amino acids are glycine (30%) and proline (22%).

Since ancient times, we have been eating collagen as the gelatin obtained when meat is cooked. So, by experience we recognize that collagen is non-toxic and also that it has mild pain-relieving effects for DJD in stifle and/or hip joints (Deal & Moskowitz, 1999). Gelatin hydrolysate is absorbed from the intestine and accumulates in cartilage (Oesser, Adam, Babel, & Seifert, 1999). We have previously reported the synergistic effects of oral administration of collagen peptide and glucosamine on cartilaginous regeneration after experimental damage (Hashida et al., 2003).

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Table 1
Clinical cases.

Orthopedic diseases	No.	Spinal disease	No.
Hip dysplasia	17	Spondylitis deformans	23 (1)
Patella luxation	8		
Osteochondritis dissecans	4		
Anterior cruciate ligament rupture	4		
Legg–Calve–Perthes disease	4		
Elbow dysplasia	4		
Polyarthritis	3		
Tibial dysplasia	1		
Lateral collateral ligament rupture	1 (1)		
Achilles tendon injury	1 (1)		
Sub total	48 (2)		23 (1)
Total			71 (3)

The objective of the present study was to investigate the clinical effects of orally administering collagen and glucosamine to dogs and cats with various orthopedic diseases and spondylitis deformans.

2. Methods

In this prospective study, seventy-one animals (68 dogs and 3 cats) with lameness caused by orthopedic diseases and spondylitis deformans (SD) (Table 1) received simultaneous oral administration of D-glucosamine and collagen peptide. None of the animals underwent surgery and none took other anti-inflammatory medications. Cases with patella luxation of more than grade 3 or with complete rupture of the anterior cruciate ligament were not included.

Collagen peptide and D-glucosamine were provided by Kanda Giko Co. Ltd (Tottori, Japan) and Koyo Chemical Co. Ltd (Tokyo, Japan), respectively. The manufacturing process of each material is explained briefly as follows.

Collagen. This was extracted from fish scales, and was degraded by proteinase to peptides (S-collagen, Kanda Giko, Tottori). The mean molecular weight of the prepared collagen peptides was 800. The major amino acids of S-collagen are glycine (33.6%), alanine (12.6%), proline (11.0%), and hydroxyproline (8.3%) respectively. The solution of S-collagen had a pH of 4.5.

D-Glucosamine: chitin obtained from crabs was transformed into a monomer through hydrochloric acid, and the resultant D-glucosamine hydrochloride (Koyo Chemical Co., Ltd, Tokyo) was used. Purification of D-glucosamine was 100% and pH was 3.8.

D-Glucosamine and S-collagen were each administered at 1 g/animal/day, mixed with dog food or cat food. Animals were observed for 1 month to 3 years. Lameness grades were evaluated at first examination, 1 month, 2 months, 3 months, and at final follow-up using a scoring system (Table 2).

3. Results and discussion

No side effects were observed from the oral administration of D-glucosamine and S-collagen. The results of lameness scoring are shown in Fig. 1. Thirty animals had scores greater than 5 points at the first examination; however, scores had fallen in all cases to less than 3 points at the final examination.

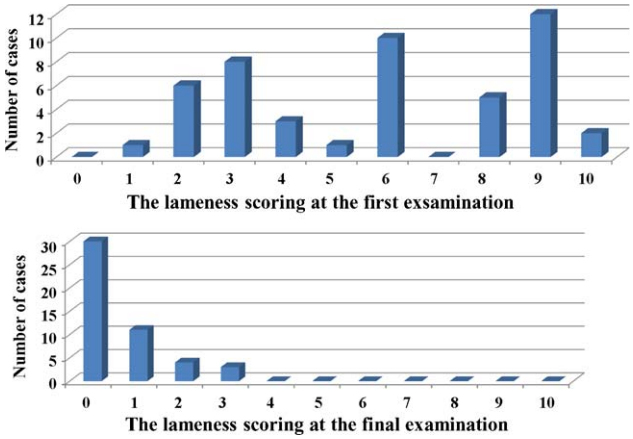

Fig. 1. Change of the lameness scoring between the first examination and the final examination.

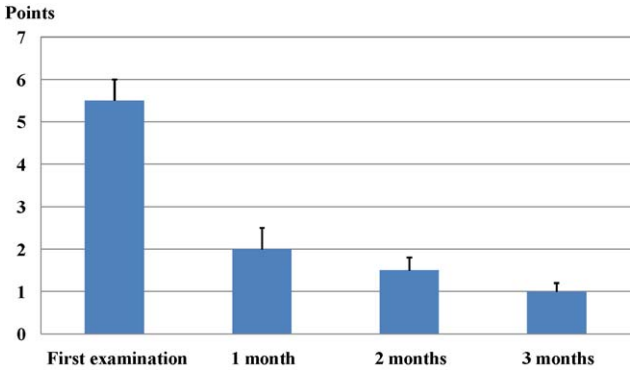

Fig. 2. The lameness scoring change in hip dysplasia. Values are significant difference among them ($p < 0.01$, $n = 17$).

A statistical analysis was performed for each orthopedic disease with more than 3 cases using Friedman test among the first examination, 1 month, 2 months, and 3 months. Significant recovery was observed in hip dysplasia ($n = 17$, $p < 0.01$, Fig. 2) and polyarthritis ($n = 3$, $p < 0.01$, Fig. 3). Significant recovery was also observed for osteochondritis dissecans (OCD) ($n = 4$, $p < 0.05$, Fig. 3), partial rupture of the anterior cruciate ligament (ACL) ($n = 4$, $p < 0.05$, Fig. 4) and grade 1 and grade 2 patellar luxations ($n = 8$, $p < 0.05$, Fig. 5); but not for elbow dysplasia ($n = 4$, Fig. 6) or Legg–Calve–Perthes disease ($n = 4$, Fig. 7). The results of high-scoring cases (more than 5 points at the first examination) are shown in Fig. 8. These cases composed 10 of hip dysplasia, 4 of partial anterior cruciate ligament rupture, one of OCD, one of tibial dysplasia, and one of lateral collateral ligament rupture (cat); significant recovery of lameness was observed ($p < 0.01$, Fig. 8). The results of the SD cases are shown in Fig. 9; these cases also showed significant recovery of lameness ($p < 0.01$, Fig. 9).

Table 2
Lameness score board.

Score	Symptom	Score	Symptom	Score	Symptom
0	Normal	4	Lame after running	8	Some steps are possible
1	Something strange in gait	5	10 m running is possible	9	Self-standing is possible
2	No lameness, but gait is clearly strange	6	10 m running is impossible	10	Unable to rise
3	Sometime lame	7	10 m walking is possible		

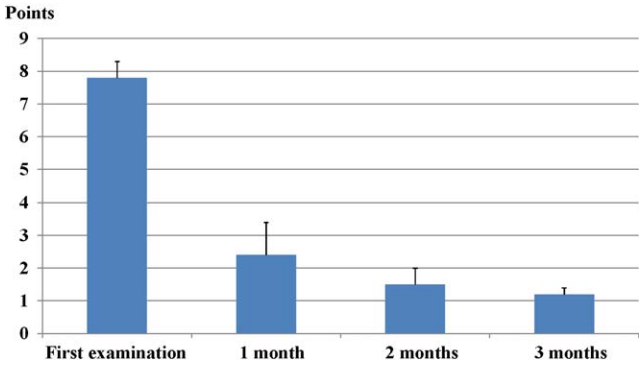

Fig. 3. The lameness scoring change in polyarthritis. Values are significant difference among them ($p < 0.01$, $n = 3$).

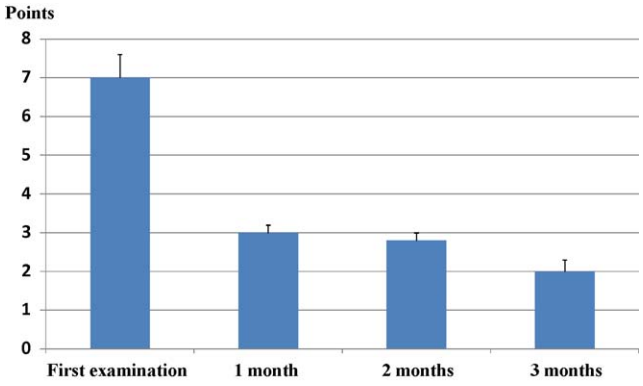

Fig. 4. The lameness scoring change in partial rupture of the anterior cruciate ligament. Values are significant difference among them ($p < 0.05$, $n = 4$).

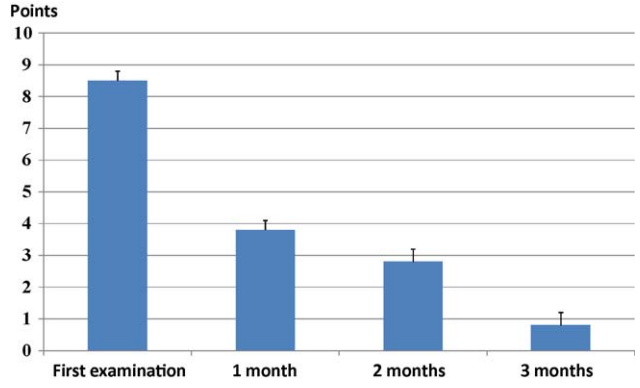

Fig. 5. The lameness scoring change in grade 1 and grade 2 patellar luxations. Values are significant difference among them ($p < 0.05$, $n = 8$)

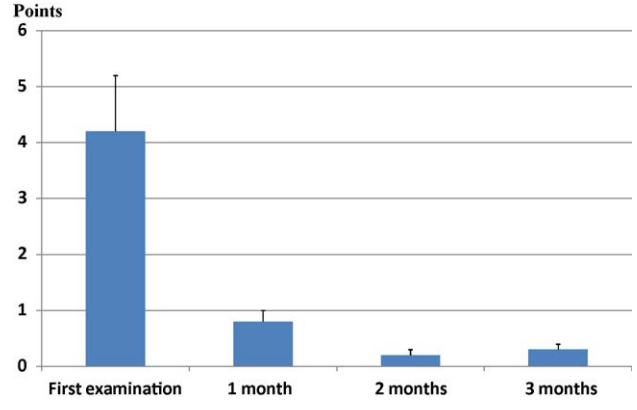

Fig. 6. The lameness scoring change in elbow dysplasia. Values are not significant difference among them ($n = 4$).

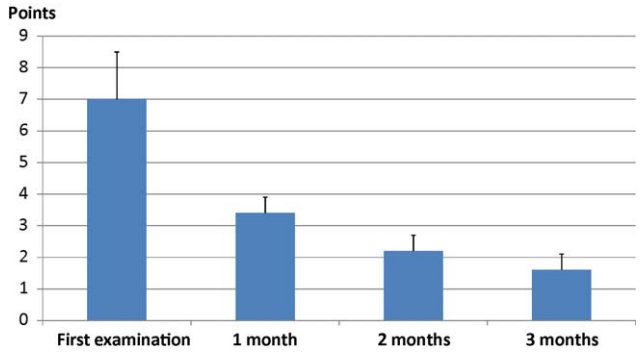

Fig. 7. The lameness scoring change in Legg-Calve-Perthes disease. Values are not significant difference among them ($n = 4$).

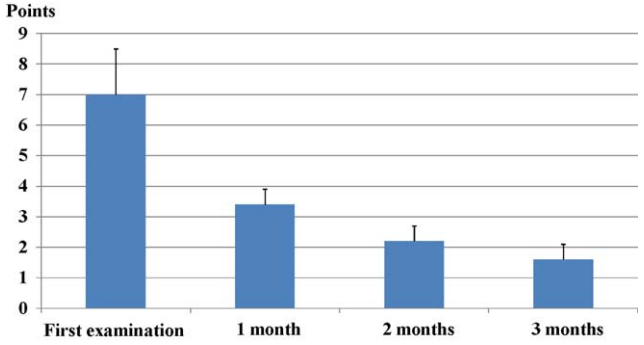

Fig. 8. The lameness scoring change in the high score cases (over 5 points). Values are significant difference among them ($p < 0.01$, $n = 17$).

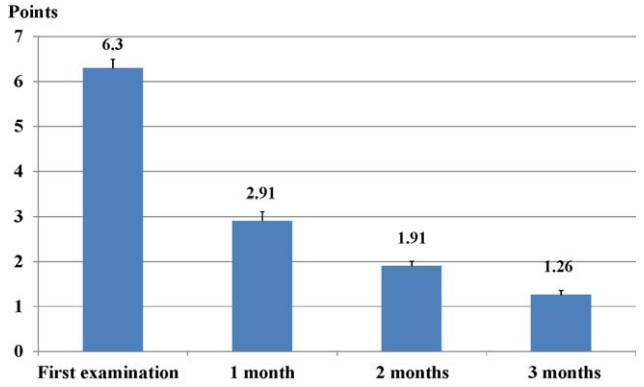

Fig. 9. The lameness scoring change in the spondylitis deformans. Values are significant difference among them ($p < 0.01$, $n = 23$).

Canine hip dysplasia (CHD) is the most common orthopedic disease in large and giant breeds of dog, and conventional treatments are triple pelvic osteotomy (Slocum & Slocum, 1992) if there is no degenerative joint abnormality, total hip displacement for hip joint degeneration (Remedios & Fries, 1995), or femoral head and neck osteotomy (Harasen, 2004). Conservative or medical treatments for CHD tend to have limited effectiveness (Johnston, 1992); however, for osteoarthritis, moderate efficacy exists for NSAIDs such as carprofen, etodolac, and pentosan polysulfate and for dietary supplements such as green-lipped mussel extract, P54FP (from Indian and Javanese turmeric), polysulfated glycosaminoglycans, and a combination of chondroitin sulfate and glucosamine hydrochloride (Aragon, Hofmeister, & Budsberg, 2007). However, the literature contains no reports of conservative treatment of CHD by administration of D-glucosamine and S-collagen in combination. In our previous experimental report (Hashida et al., 2003), D-glucosamine

and S-collagen combination treatment significantly affected not only cartilaginous tissue and subchondrial bone regeneration, but also normal cartilage thickening within 1 month after administration. We believe this is why high lameness scores fell quickly at the 1 month follow-up examination in the present study. An additional mechanism is thought to be the anti-inflammatory effects of D-glucosamine (Hua, Suguro, Hirano, Sakamoto, & Nagaoaka, 2005; Yomogida, Hua, Sakamoto, & Nagaoka, 2008) and collagen (McDevitt & Muir, 1976). The cartilaginous tissue and subchondrial bone regeneration and the anti-inflammatory effects are thought to effectively relieve pain and allow the recovery of suitable joint movement. This allows animals to recover normal gait by self-rehabilitation, prompting muscle recovery. The normalized gait will in turn increase blood supply to the bones and the joints.

Why was the current therapy not significantly effective for elbow dysplasia or Legg–Calve–Perthes disease? We noted a trend toward improved scores in these conditions as duration of treatment increased, but this did not reach significance. The data might be influenced by the distribution of lameness degree at the first examination. In elbow dysplasia, particularly where there is fragmentation of the coronoid process, prevention of osteoarthrosis of the elbow joint is difficult despite conservative or surgical treatment (Temwichitr, Leegwater, & Hazewinkel, 2009). Legg–Calve–Perthes disease is a painful disease because of severe morphological and pathological changes in the hip joint with accompanying inflammatory reaction (Mickelson, McCurnin, Awbrey, Maynard, & Martin, 1981). Hence, even if no significant improvement in lameness score occurred, D-glucosamine and S-collagen are likely to have decreased inflammation and prevented further cartilaginous damage.

SD is a degenerative disease of the spine characterized by the presence of one or more osteophytes. It is important to decrease the incidence and severity of spondylosis in order to enhance longevity and welfare of dogs and cats with SD (Carnier, Gallo, Sturaro, Piccinini, & Bittante, 2004). Severe spondylosis causes back stiffness, lameness, change of gait, and pain. Moreover, SD can affect multiple sites at each vertebra as it can affect any of the vertebral joints. Surgical treatment for DJD of the canine cervical spine has been reported (Trotter, 2009); however, there are no reports of surgical treatment for multiple DJD or of effective medical treatment. The present findings that supplementation of D-glucosamine and S-collagen could produce significant recovery from lameness might suggest a similar effect on vertebral joint disease, owing to the same mechanism.

In the present study, animals with all degrees of hip dysplasia recovered their gait and exhibited normal activity. The most important point was that all owners achieved satisfactory responses for their pets, which were able to return to normal activity and appeared happy. Moreover, the treatment is economical and non-invasive. Conventional treatment with NSAIDs and cage rest has a limited duration because of obvious side effects such as gastrointestinal ulceration (Aftab et al., 2010). The present treatment had no apparent side-effects and can be used long-term, appearing to be safe in animals from 8 months to 7 years of age.

Simultaneous administration of D-glucosamine and collagen peptide appears to be very effective for CHD and SD, allowing the possibility of prolonged maintenance without side effects.

4. Conclusion

Oral administration of D-glucosamine and collagen peptide in various orthopedic diseases and SD in dogs and cats was effective. No side effects were observed. We therefore recommend the long-term administration of D-glucosamine and collagen peptide in dogs and cats with these conditions.

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References

Aftab, A. R., Donnellan, F., Zeb, F., Kevans, D., Cullen, G., & Courtney, G. (2010). NSAID-induced colopathy. A case series. *Journal of Gastrointestinal and Liver Diseases*, *19*, 89–91.

Aragon, C. L., Hofmeister, E. H., & Budsberg, S. C. (2007). Systematic review of clinical trials of treatments for osteoarthritis in dogs. *Journal of American Veterinary Medical Association*, *15*, 514–521.

Barclay, T. S., Tsourounis, C., & McCart, G. M. (1998). Comment: Glucosamine:selecting appropriate study exclusion criteria. *Annals of Pharmacotherapy*, *32*, 1371–1372.

Carnier, P., Gallo, L., Sturaro, E., Piccinini, P., & Bittante, G. (2004). Prevalence of spondylosis deformans and estimates of genetic parameters for the degree of osteophytes development in Italian Boxer dogs. *Journal of Animal Science*, *82*, 85–92.

Deal, C. L., & Moskowitz, R. W. (1999). Nutraceuticals as therapeutic agents in osteoarthritis. The role of glucosamine, chondroitin sulfate, and collagen hydrolysate. *Rheumatic diseases clinics of North America*, *25*, 379–395.

Harasen, G. (2004). The femoral head and neck ostectomy. *Canadian Veterinary Journal*, *45*, 163–164.

Hardingham, T. E., & Fosang, A. J. (1992). Proteoglycans: Many forms and many functions. *FASEB Journal*, *6*, 861–870.

Hashida, M., Miyatake, K., Okamoto, Y., Fujita, K., Matsumoto, T., Morimatsu, F., Sakamoto, K., & Minami, S. (2003). Synergistic effects of D-glucosamine and collagen peptides on healing experimental cartilage injury. *Macromolecular Bioscience*, *3*, 596–603.

Hua, J., Suguro, S., Hirano, S., Sakamoto, K., & Nagaoaka, I. (2005). Preventive actions of a high dose of glucosamine on adjuvant arthritis in rats. *Inflammation Research*, *54*, 127–132.

Johnston, S. A. (1992). Conservative and medical management of hip dysplasia. *Veterinary Clinics of North America: Small Animal Practice*, *22*, 595–606.

Leffler, C. T., Philippi, A. F., Leffler, S. G., Mosure, J. C., & Kim, P. D. (1999). Glucosamine, chondroitin, and manganese ascorbate for degenerative joint disease of the knee or low back: A randomized, double-blind, placebo-controlled pilot study. *Military Medicine*, *164*, 85–91.

McDevitt, C. A., & Muir, H. (1976). Biochemical changes in the cartilage of the knee in experimental and natural osteoarthritis in the dog. *Journal of Bone and Joint Surgery*, *58*, 94–101.

Mickelson, M. R., McCurnin, D. M., Awbrey, B. J., Maynard, J. A., & Martin, R. K. (1981). Legg–Calve–Perthes disease in dogs: A comparison to human Legg–Calve–Perthes disease. *Clinical Orthopedics and Related Disease*, *157*, 287–300.

Oesser, S., Adam, M., Babel, W., & Seifert, J. (1999). Oral administration of (14)C labeled gelatin hydrolysate leads to an accumulation of radioactivity in cartilage mice (C57/BL). *Journal of Nutrition*, *129*, 1891–1895.

Remedios, A. M., & Fries, C. L. (1995). Treatment of canine hip dysplasia: A review. *Canadian Veterinary Journal*, *36*, 503–509.

Setnikar, I., Cereda, R., Pacini, M. A., & Revel, L. (1991). Antireactive properties of glucosamine sulfate. *Arzneimittelforschung*, *41*, 157–161.

Slocum, B., & Slocum, T. D. (1992). Pelvic osteotomy for axial rotation of the acetabular segment in dogs with hip dysplasia. *Veterinary Clinics of North America: Small Animal Practice*, *22*, 645–682.

Tamai, Y., Miyatake, K., Okamoto, Y., Takamori, Y., Sakamoto, H., & Minami, S. (2002). Enhanced healing of cartilaginous injuries by glucosamine hydrochloride. *Carbohydrate Polymers*, *48*, 369–378.

Temwichitr, J., Leegwater, P. A., & Hazewinkel, H. A. (2009, July 27). Fragmented coronoid process in the dog: A heritable disease. *Veterinary Journal* (Electric publication).

Trotter, E. J. (2009). Cervical spine locking plate fixation for treatment of cervical spondylotic myelopathy in large breed dogs. *Veterinary Surgery*, *38*, 705–718.

Qiu, G. X., Gao, S. N., Giacovelli, G., Rovati, L., & Setnikar, I. (1998). Efficacy and safety of glucosamine sulfate versus ibuprofen in patients with knee osteoarthritis. *Arzneimittelforschung*, *148*, 469–474.

Yomogida, S., Hua, J., Sakamoto, K., & Nagaoka, I. (2008). Glucosamine suppresses interleukin-8 production and ICAM-1 expression by TNF-alpha-stimulated human colonic epithelial HT-29 cells. *International Journal of Molecular Medicine*, *22*, 205–211.