

Fish oil decreases matrix metalloproteinases in knee synovia of dogs with inflammatory joint disease

Rodney A. Hansen^{a,*}, Mary A. Harris^b, G. Elizabeth Pluhar^c, Tatiana Motta^d, Sean Brevard^e, Gregory K. Ogilvie^f, Martin J. Fettman^e, Kenneth G.D. Allen^b

^aDepartment of Health Promotion and Human Performance, Weber State University, Ogden, UT 84408, USA

^bDepartment of Food Science and Human Nutrition, Colorado State University, Fort Collins, CO 80523, USA

^cDepartment of Veterinary Clinical Sciences, College of Veterinary Medicine, University of Minnesota, St Paul, MN 55108, USA

^dDepartment of Biomedical Sciences, Cornell University, Ithaca, NY 14853, USA

^eDepartment of Clinical Sciences, Colorado State University, Fort Collins, CO 80523, USA

^fAngel Care Cancer Center, California Veterinary Specialists, Carlsbad, CA 92008, USA

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Abstract

This study was designed to determine whether dietary fish oil affects the expression and activity of matrix metalloproteinases (MMP), tissue inhibitors of MMP-2 (TIMP-2) and urokinase plasminogen activator (uPA) in synovial fluid from dogs with spontaneously occurring stifle (knee) instability in a single hind limb resulting from acute cranial cruciate ligament (CCL) injury. Two groups of 12 dogs were fed diets from 1 week prior to surgery on the affected knee to 56 days post-surgery. The fish oil and control diets provided 90 and 4.5 mg, respectively, of combined eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)/kg body weight per day. Plasma and synovial fluid, from both surgical and nonsurgical knee joints, were obtained at start of the diet (−7), surgery day (0) and 7, 14, 28 and 56 days post-surgery. Plasma total EPA and DHA were significantly increased, and plasma total arachidonic acid (AA) was significantly decreased by the fish oil diet. In synovial fluid from the nonsurgical knee, fish oil treatment significantly decreased proMMP-2 expression at Days 7 and 14, and proMMP-9 expression at Day 56, and uPA activity at 28 days and significantly increased TIMP-2 expression at Days 7 and 28. There were no differences in MMP expression or activity, TIMP-2 expression and uPA activity in the surgical joint synovial fluid at any time throughout the study. These results suggest that dietary fish oil may exert beneficial effects on synovial fluid MMP and TIMP-2 equilibrium in the uninjured stifle of dogs with unilateral CCL injury.

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1. Introduction

Osteoarthritis (OA) is a degenerative inflammatory joint disease characterized by breakdown of articular cartilage. The breakdown of articular cartilage involves endogenous enzymes that degrade the constituents of the connective tissue matrix. Matrix metalloproteinases (MMP) are a family of enzymes that mediate the breakdown of the extracellular matrix of connective tissue [1]. Overproduction of MMP or underproduction of tissue inhibitors of metalloproteinases (TIMP) plays a major role in the pathogenesis and progression of joint instability and OA [1].

The regulation of MMPs occurs by three mechanisms: enzyme expression, posttranslational activation and inhibition of enzyme activity by binding to tissue inhibitors [2]. MMP expression is up-regulated by certain mediators including inflammatory eicosanoids [3] and cytokines [4]. MMPs are expressed in inactive proforms, and proteolytic activation of pro MMPs occurs in the extracellular matrix [2]. Urokinase plasminogen activator (uPA) is a key agent in the proteolytic activation of MMP in the articular cartilage of arthritic joints [5]. The process involves proteolytic cleavage of plasminogen to plasmin that subsequently cleaves pro-MMP to active MMP [6].

Tissue inhibitors of metalloproteinases form noncovalent complexes with activated MMP in a 1:1 molar ratio, which inhibits the catalytic activity of the enzyme [1]. TIMPs are

* Corresponding author. Tel.: +1 801 626 7748.

E-mail address: rhansen@weber.edu (R.A. Hansen).

Table 1
Composition of the diet

Ingredient	g/kg diet
Brewers rice	450.0
Soybean meal	120.0
Canola meal	50.0
Chicken, whole carcass	160.0
Catfish meal	200.0
Yeast	20.0
Fat component ^a	70.0
Vitamin mix	0.75
Vitamin C	0.14
Vitamin E	0.2
β -Carotene	0.05
Mineral mix	3.0
Potassium chloride	5.0
Sodium chloride	2.5
Choline chloride	1.24
Taurine	0.52

^a Control diet contained 35.0 g beef tallow plus 35.0 g safflower oil/kg diet. Fish oil diet contained 35.0 g beef tallow plus 35.0 g menhaden oil/kg diet.

present in both tissues and fluid compartments and are produced by a variety of cell types including chondrocytes [7]. The suppression of MMP has been recognized as a key target in the treatment of OA [8]. There has been much interest in the development of pharmacologic MMP inhibitors [1]. However, the pharmacological inhibition of MMP with the broad-spectrum MMP inhibitor Marmistat caused tendonitis in its Phase III clinical studies [9].

Recent studies in dogs with CCL rupture have shown an increase in synovial fluid MMP-2 and -9 and cathepsin S expression [10], and increased MMP-3 activity and production of sulfated glycosaminoglycans [11]. Immature cross-links between sulfated glycosaminoglycans have been demonstrated in the ruptured ligaments of dogs with CCL rupture, and ligament rupture was associated with increased pro-MMP-2 expression [12]. Increased degradation of collagen in ruptured ligaments has also been demonstrated in dogs with CCL rupture [10]. In dogs with osteoarthritic joints, synovial fluid MMP-2 and MMP-9 activities were dramatically increased compared to dogs with healthy joints [13]. In CCL rupture in dogs and anterior cruciate ligament rupture in humans, inflammatory mediators up-regulate the expression of ligament proteases such as cathepsin [14].

N-3 fatty acids have been shown to have an effect on MMP expression in vitro [15]. Linolenic acid and eicosapentaenoic acid (EPA) long-chain n-3 polyunsaturated fatty acids (LC n-3 PUFA) suppress expression of MMP-3 (stromelysin) and MMP-13 in human OA cartilage explant cultures [15]. LC n-3 PUFA were postulated to suppress the production of cytokines, inflammatory pathways mediated by cyclooxygenase-2, and MMP expression [15]. EPA inhibits ultraviolet-induced MMP-1 expression in human dermal fibroblasts [16].

The effect of LC n-3 PUFA supplementation on MMP regulation has not been investigated in an in vivo model.

Furthermore, no studies have addressed the effect of LC n-3 PUFA on the activators and inhibitors of MMP in vivo. This study was designed to investigate the effects of a diet supplemented with LC n-3 PUFA on the production and activity of canine MMP and TIMP-2 production in a model of joint inflammation secondary to instability in dogs.

Cranial cruciate ligament (CCL) injury is a common cause of hindlimb lameness in dogs typically leading to stifle OA [17]. The joint instability is often treated surgically by a tibial plateau leveling osteotomy (TPLO) procedure that limits cranial tibial thrust and slows OA progression [17,18]. Dogs with unilateral CCL injury treated by a TPLO provide an excellent in vivo model to test the efficacy of a fish oil diet in altering MMP expression and activity, TIMP expression and uPA activity in both the injured (surgery) knee and the nonsurgical knee, which may experience increased stresses as a result of decreased weight bearing on the injured limb.

2. Methods and materials

2.1. Animals and diets

Dogs are susceptible to CCL injury, which results in stifle (knee) instability [19,20]. Larger dogs typically undergo a surgical procedure to stabilize the joint, such as TPLO. Although CCL rupture may occur bilaterally, in most cases surgery is performed on a single limb at a time as was the case in this study. This afforded an ideal model to examine the in vivo effect of n-3 fatty acid supplementation on MMP regulation in a severely inflamed, acute (surgical) and a minimally to moderately stressed, chronically affected (nonsurgical) stifle in an individual dog.

Dogs presenting with hindlimb lameness at the Colorado State University Veterinary Teaching Hospital were evaluated for stifle (knee) instability. Twenty-four dogs presenting with stifle instability in a single hindlimb resulting from CCL injury, with or without secondary meniscal injury, were enrolled in this study. The Colorado State University Animal Care and Use Committee approved all procedures. Informed consent was obtained in writing from owners before their dogs were enrolled in the study. All dogs were patients at the Colorado State University Veterinary Teaching Hospital and treated within a 380-day period.

Dogs varied by breed and had a body weight of 34.7 ± 1.8 kg (mean $\pm$ S.E.M.). Dogs were randomly assigned to one of two diet treatment groups of 12 dogs: an experimental fish oil-based maintenance diet with high levels of EPA and DHA, and a control safflower oil-based

Table 2
Diet analysis, g/kg as fed

Protein	278.5
Carbohydrate	429.0
Fat	126.5
Ash	82.6
Moisture	83.4
kcal/kg	3968.5

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