CONNECTIVE TISSUE RESEARCH
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Evaluation of cytokines in protective effect of docosahexaenoic acid in experimental achilles tendinopathy rat model induced with type-1 collagenase

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ABSTRACT

Background: We aimed to investigate the effectiveness of docosahexaenoic acid (DHA) as a treatment for Achilles tendinopathy (AT) induced with type-I collagenase in rats and compare it with collagen.

Methods: The AT model was induced with type I collagenase, and animals were randomly assigned to groups. Group 1:AT, Group 2: Collagen (7.2 mg/kg/day), Group 3:DHA (300 mg/kg/day), and Group 4:DHA (100 mg/kg/day). Right tendons of Group1 were used as a healthy control (HC). Oral treatments were applied for eight weeks. Serum tumor necrosis factor-alpha(TNF-α), matrix metalloproteinase-13 (MMP-13), and interleukin-1 beta(IL-1β) concentrations were determined by ELISA. Tendon samples were taken for histopathological evaluation and examined immunohistochemically with antibodies specific for Col1A1, TNF-α, MMP-13, IL-1β, and nitric oxide synthase-2(NOS-2). The ultimate tensile force (UTF) yield force(YF) and stiffness were measured by biomechanical assessments.

Results: UTF,YF and stiffness values were increased in all treatment groups compared to the AT control, a significant increase was found in Group 2 ($p < 0.05$). There was severe degeneration of tendon cells in the AT control. The tendon cells in samples from Groups 2-3 were less degraded, and this was statistically significant ($p < 0.05$). TNF-α, MMP-13, IL-1β, and NOS-2 expressions were significantly higher in the AT control compared to the HC. In all treatment groups, their concentrations were lower than in the AT control. Serum TNF-α, MMP-13, and IL-1β levels were lower in all treatment groups (Especially in Group3 ($p < 0.001$)) compared to Group1.

Conclusion: The efficacy of high-dose DHA as a treatment for AT was investigated from biochemical, histopathological, and biomechanical perspectives. The results showed that DHA could be an alternative treatment compound to collagen.

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Introduction

The Achilles is the largest and strongest tendon in the human body[1]. Achilles tendinopathy (AT) is a condition that occurs with palpation tenderness, edema, activity-related pain, and disability[2], and the incidence of spontaneous rupture of the Achilles tendon is quite high[3]. It is claimed that repetitive mechanical loads cause degenerative changes in the tendon, leading to rupture of the Achilles tendon[4]. Tissue edema, leukocyte infiltration, dead tissue phagocytosis, and an inflammatory phase produced by humoral mediators occur after tendon damage[5]. The proliferative phase starts with the production of type III collagen. In the remodeling phase, inflammation and scar tissue formation are gradually reduced and maturation and tissue reorganization are increased[6]. The current treatment approach for achilles tendon rupture is two main approaches: operative and conservative. First, conservative treatments are applied as NSAIDs, collagen protein, and physiotherapy. If these methods are not successful, operative treatment may be applied. In addition, both types of treatment were reported to have failed to fully recover from Achilles tendon rupture even two years later[7].

In the pathogenesis of tendinopathy, oxidative stress and apoptosis are believed to have a role[8,9]. Oxidative stress induced by reactive oxygen species (ROS) can lead to tendinopathy via the apoptotic death of

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