WHAT TREATMENT OF TENDINOPATHY: INFLAMMATION OR DEGENERATION?

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ABSTRACT

Tendinopathy is a common clinical problem in many occupational settings, including athletes. It is characterized by pain in the tendon and impaired performance. Chronic tendon pathology is difficult to treat. The intrinsic pathogenetic mechanisms underlying tendinopathy remain unclear, with much debate whether inflammatory or degenerative hypothesis has the prominent role. Overuse and microruptures of tendon fibres may be considered as the initial disease factors. Several molecules are expressed, some of which promote the healing process, while others, including inflammatory cytokines act as disease mediators.

In this systematic review we present information relating to the effectiveness and safety of the following treatments of tendinopathy: corticosteroid injections, non-steroidal anti-inflammatory drugs (oral and topical), autologous whole blood injections, physiotherapy, eccentric exercise therapy, extracorporeal shock wave therapy, iontophoresis, dermoelectroporation, low-level laser therapy, manipulation, orthoses (bracing), platelet-rich plasma injections, pulsed electromagnetic field treatment, surgery, ultrasound, cryotherapy, heat treatment, sclerosant injection, acupuncture.

Key words: tendinopathy, inflammation, degeneration, treatment.

INTRODUCTION

Tendons are tissues that connect muscle to bone. They transmit the forces generated by muscle to bone, resulting in joint movement. Tendon disorders – tendinopathies are frequent clinical problem for much morbidity both in sport and the workplace and they are often reason for musculoskeletal pain consultation. The term tendinopathy description an overuse pathological condition in and around tendon. It is characterized by pain in the tendon and impaired performance. Usually tendinopathy occurs in major tendons such as the Achilles, patellar, rotator cuff, forearm extensor tendons and in any other tendon.

The terms “tendinosis”(degenerative changes), “tendinitis”or “tendonitis” (inflammatory process) should only be used after histopathological examination (1).

The incidence of tendinopathy is rising in developed world because of increased participation in recreational sports. Despite the magnitude of the disorder, high-quality scientific data on etiology and available treatments have been limited. Repetitive exposure in combination with intrinsic factors such as genetics and metabolic disorders is a risk factor for development of tendinopathy. The pathogenetic mechanisms underlying tendinopathy remain unclear, with much debate whether inflammatory or degenerative hypothesis has the prominent role. Increasing evidence points towards an early inflammatory infiltrate and associated inflammatory cytokine production in human and animals models of tendon disease. IL-21R is present in early human tendinopathy mainly expressed by tenocytes and macrophages (2). These data suggest that early human tendon injury has an inflammatory, which may provide novel targets in the treatment of tendinopathies. Chronic tendon pathology is difficult to treat.

HISTOPATHOLOGY AND PATHOPHYSIOLOGY

Normal tendon is brilliant white in color and has a firm fibroelastic texture. Immature tendon cells are tenoblasts and as they age, become elongated and transform into tenocytes. Tenoblasts and tenocytes lying within a network of extracellular matrix (ECM), between the collagen fibres, along the
long axis of the tendon. Tenocytes synthesize collagen and all components of the extracellular matrix.

Macroscopically, tendinopathic tendon is grey or brown, and is soft, thin, fragile and amorphous (3).

Inflammatory and degenerative changes are found very often coexist in adjacent areas of pathological samples (4). Histologically degenerative changes classified as hypoxic, hyaline, mucoid or mixoid, fibrinoid and fatty are found in 90% of biopsy specimens taken from symptomatic parts of the tendon (5, 6). The collagen fibers show unequal and irregular crimping and degenerated type I collagen fibers are sometimes replaced by calcification or by of lipid cells. Injured tendons have a type III collagen, which is deficient of cross-links between tropocollagen units (7). The role of inflammation is still debated, and studies support, that inflammation may play a role in the acute tendinopathy (8,9). It has been that an inflammatory process may be related to the development of chronic tendinopathy (10). The absence of inflammatory cells in or around the lesion does not mean that inflammatory mediators are not implicated in tendinopathies (8,9.). Endothelial and mast cells, platelets, macrophages and leukocytes express and respond to a network of inflammatory mediators such as interleukins (IL-1β, IL-6, IL-21), prostaglandin E2, nitric oxide synthetase (iNOS isoform), growth factors (PDGF, TGF-β, b-FGF, EGF, VEGF, IGF-1), Scleraxis and other potential modulators of tendon cell activity like glutamate and substance P (1, 2, 9-12). IL-21 is a proinflammatory cytokine of the IL-1 family and is produced mainly by CD4+ lymphocytes and natural killer T cells. It is known to modulate T-cell proliferation and B-cell differentiation. Furthermore, IL-21R (receptor) is present in higher levels in synovial fibroblasts and macrophages and IL-21R is a potential inflammatory regulator and mediator in early human tendinopathy (2). Growth factors induce neovascularization and stimulate fibroblasts and tenocyte proliferation and synthesis of collagen (1). When neangiogenesis occurs, nerves “travel with” neovessels inside the tendon (13) and this support hypothesis that neovascularization associated with pain in tendinopathy. Neurotransmitters glutamate and substance P and pro-inflammatory prostaglandin E2 and CGRP (calcitonin gene related peptide) may generate pain in tendinopathy too. Scleraxis regulates the expression of the gene COL1A1 in tendon fibroblasts (14). Different isoforms of nitric oxide synthetase (NOS) have been identified: eNOS found in endothelial cells, bNOS found in brain and neuronal tissue and iNOS that can be induced by pro-inflammatory cytokines and it is important by collagen synthesis (4). Matrix metalloproteinases (MMPs) are critical for tendon integrity because they modulate remodeling of collagen and ECM. MMPs are a family of proteolytic enzymes that can degrade components of ECM, especially collagen. In tendinopathy, there are changes in the expression and activity of various matrix-degrading enzyme metalloproteinases, particularly the collagenases (MMP-1, MP-3, MMP-8, MMP-13) and gelatinases (MMP-2, MMP-9) (15). Changes in the level of tissue inhibitors of metalloproteinase (TIMPs), which are consistent with increased proteolytic activity in degenerate tendons, are also reported (8,16). Quinolones enhance interleukin-1-mediated MMP3 release, inhibit tenocyte replication, and reduced collagen and matrix synthesis. In these conditions, the mechanisms of healing and damage are simultaneously activated. The healing mechanisms include expression of some MMPs, NOS, Scleraxis , growth and differentiation factors (GDFs). The damage mechanisms are represented by increased MMP-3 expression, which degrade extracellular matrix and by overproduction of inflammatory cytokines, such as endothelial growth factor (EGF), platelet derived growth factor (PDGF) and prostaglandin E2.

**TREATMENT AND THERAPEUTIC PERSPECTIVES**

Inflammation and degeneration work together in the pathogenetic cascade of tendinopathy. This can to explain why the response to therapy may be different from one case to another (17). Thus, until now, there is no consensus as to the best treatment for tendinopathy.

Conventional treatments are to fight pain and inflammation but they do not modify the histological structure of the tendon (18).

Non-steroidal anti-inflammatory drugs (NSAIDs) is to reduce inflammation and pain through the inhibition of COX-2 and thus NSAIDs inhibition of the synthesis of the inflammatory factors such as prostaglandins, interleukins and inflammatory cells. Both oral and local NSAIDs are a reasonable option for the control of acute pain associated with tendon injury (17).

The exact mechanism by which corticosteroid injections have an effect on tendon pain is unclear but it include a reduction of inflammation, reduction of tenocyte...
proliferation and cellular activity, antiangiogenic activity and antinoceptive action. Dexamethasone treatment of human tendon fibroblasts reduces the expression of substance P (SP) through a glucocorticoid receptor – dependent pathway (19). Corticosteroids injections can be effective in chronic tendinopathy or may be beneficial for pain and function in the early phases of disease. Thus in good practice medicine, the steroid injection or NSAIDs would be made only to decrease pain in order to get through this hyperalgic phase in order to start physiotherapy or eccentric training as soon as possible (12, 20).

Iontophoresis with NSAIDs, dermoelectroporation with dexamethasone and diclofenac (21, 22, 23), physiotherapy such as ultrasound or acupuncture show positive effects in the reduction of pain. Eccentric exercise therapy promote restoration of normal tissue structure. Training induces a progressive action on the tendon structure, cell activity and matrix remodeling, which can lead to the healing of tendinopathy, prevent relapse and chronicity (12).

Platelet-rich plasma (PRP) contains growth factors, that promote matrix synthesis and tissue repair.

Sclerosant injection reduce tendon blood flow and blocks neovascularization associated nerves and pain (8).

There are a wide variety of treatments for the management of tendinopathy, such as: extra-corporeal shock waves therapy (ESWT), botulinum toxin injections, topical glyceryl trinitrate, stem-cell or gene therapy (12). Preliminary studies utilizing adipilumab (TNF-α blocker), anakinra (IL-1 antagonist), apronitin (MMP-antagonist), tropisetron (5-HT3 receptor antagonist with anti-inflammatory properties) (4).

These treatments have a therapeutic interest and a relative efficacy. This efficacy would appear to be more important in the acute phase of tendinopathy, and regularly as adjuvant treatment with other techniques.

**CONCLUSION**

There are several conservative treatment options for tendinopathy, despite its etiology is unclear. Inflammation and degeneration work together in the pathogenetic cascade of tendinopathy. The role of inflammation is still debated. Inflammatory mediators and modulators of tendon cell activity, such as cytokines, IL-21R, metalloproteinases, growth factors, prostaglandin E2, nitric oxide synthetase, glutamate, substance P are involved in tendinopathy. These mediators and neovascularization are associated with the clinical symptomatology, and particular, with pain. Conservative treatment such as corticosteroid injection and NSAIDs reduces inflammation and pain. Eccentric exercise therapy lengthens muscle-tendon unit, promote restoration of normal tissue structure, cell activity and matrix remodeling. ESWT or PRP stimulates neovascularization, while sclerosant injection blocks neovascularization, associated nerve in growth and tendon blood flow. Tendinopathy often becomes chronic because the pathogenesis remains largely unknown and treatments are not completely satisfactory and the recurrence of symptoms is common.

**ABBREVIATIONS**

EEC-extracellular matrix; IL-interleukin; NOS – nitric oxide synthetase; FGF – fibroblast growth factor; MMP-matrix-metalloproteinase; TIMPs - tissue inhibitors of metalloproteinase; VEGF – vascular endothelial growth factor; PDGF - platelet derived growth factor; GDF- growth and differentiation factor; TNF –tumor necrosis factor; PRP - platelet-rich plasma; NSAIDs - non-steroidal anti-inflammatory drugs; ESWT - extra-corporeal shock waves therapy ; SP – substance P

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