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IS INFLAMMATION PRESENT IN EARLY HUMAN TENDINOPATHY?

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ABSTRACT

Tendinopathy is a general term, describes any painful condition, that occurs in or around tendon.The role of inflammatory cells and their products in tendinopathy is not completely understood. Tendinopathy is clinical syndrome, often implying overuse tendon injuries. Characterized by pain, sometimes localized swelling and impaired performance. 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. These data suggest that early human tendon injury has an inflammatory, which may provide novel targets in the treatment of tendinopathyes.

Key words: tendinopathy, inflammation, degeneration, treatment

INTRODUCTION

Tendon disorders – tendinopathies are frequent for much morbidity both in sport and the workplace and they are often reason for musculoskeletal pain consultation. The term tendinopathy description the clinical condition in and around tendons arising from overuse. The terms "tendinosis", "tendinitis", "tendonitis" should only be used after histopathological examination (1). The incidence of tendinopathy is rising in developed word 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. Inflammatory and degenerative changes are very often present coexist in tendon injury.

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TENDON ANATOMY

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 (EEC), between the collagen fibres, along the long axis of the tendon. Tenocytes synthesize collagen and all components of the extracellular matrix. The EEC of tendon is made up of collagen, mostly type I, elastin, which insures flexibility and elastic properties and ground substance, which consists of water, proteoglycans, glycosaminoglicans, glycoproteins, tenascin - C and several other small molecules (2). Tendons is made up of collagen, which is arranged in hierarchical levels complexity, beginning with polypeptide chain tropocollagen, which unites into fibrils and primary, secondary and tertiary fibers bundles. A collagen fibre is the smallest tendon unit. Fibres are mainly oriented longitudinally, transversely and horizontally, forming spirals and plaints and they wrapped in endotenon, which in turn is enveloped by an epitenon, forming the tendon (3). Tendons are metabolically active tissues requiring vascular

supply and they receive their blood supply from the intrinsic systems at the musculotendinous (area between muscle and tendon) and osteotendinous (insertion of a tendon into bone) and from extrinsic system via the paratenon or the synovial sheath (4). Tendon vascularity is compromised at junction zones and sites of torsion, friction or compression (1). In these hypovascular areas endostatin, an endogenous angiogenesic inhibiting factor, is overexpressed (5). Innervation of tendon is provided by nerves from the surrounding muscles and by small fasciculi from cutaneous nerves (6). The nerve endings can be classified into four categories – type I, Ruffini corpuscles, type II, Vater –Pacini corpuscles, type III, Golgi tendon organs and type IV, free nerve endings (7).

HISTOPATHOLOGY AND PATHOPHYSOLOGY

Inflammatory and degenerative changes are found very often coexist in adjacent areas of pathological samples (7). Macroscopically, affected portion of the tendon lose their normal glistening white appearance and become grey-brown and amorphous. Histolologically 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 (8, 9). 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 tropocollacen units (10). The role of inflammation is still debated, and studies support, that inflammation may play a role in the acute tendinopathy (11, 12). It has been that an inflammatory process may be related to the development of chronic tendinopathy (13). The absence of inflammatory cells in or around the lesion does not mean that inflammatory mediators are not implicated in tendinopathies (11, 12.). 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, 12-16). 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 (16). Growth factors induce neovascularization and stimulate fibroblasts and tenocyte proliferation and synthesis of collagen (1). When neo-angiogenesis occurs, nerves "travel with" neovessels inside the tendon (17) and this support hypothesis that neovascularization associated with pain in tendinopathy. Neurotransmitters glutamate and substance P and pro-inflammatory prostaglandin E_2 and CGRP (calcitonin gene related peptide) may generate pain in tendinipathy too. Scleraxis regulates the expression of the gene COL1A1 in tendon fibroblasts (18). 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 (7). Matrix metalloproteinases (MMPs) are critical for tendon integrity because they modulate remodeling of collagen and ECM. MMPs are a family of proteolitic 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) (19). Changes in the level of tissue inhibitors of metalloproteinase (TIMPs), which are consistent with increased proteolytic activity in degenerate tendons, are also reported (11,20). 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 E_2.

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 (21).Conventional treatments are to fight pain and inflammation but they do not modify the histological structure of the tendon (22). Non-steroidal anti-inflammatory drugs (NSAIDs) is to reduce inflammation and pain through the inhibition of COX-2. Both oral and local NSAIDs are a reasonable option for the control of acute pain associated with tendon injury (21).Physiotherapy such as ultrasound, iontophoresis with NSAIDs, deep transverse friction massage, or acupuncture show sometimes positive effects in the reduction of pain. Corticosteroid injections may be beneficial for pain and function in the early phases of disease, but are usually ineffective later. Thus in good practice medicine, the steroid injection 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 (23).There are a wide variety of treatments for the management of tendinopathy, such as: eccentric training, extra-corporeal shock waves therapy (ESWT), sclerosant injections, botulinum toxin injections, injections of autologous whole blood or the blood product platelet-rich plasma (PRP) , *topical glyceryl trinitrate, stem-cell or gene therapy (15).* Preliminary studies utilizing adalimumab (TNF-α blocker), anakinra (IL-1 antagonist), apronitin (MMP-antagonist), tropisetron (5-HT3 receptor antagonist with anti-inflammatory properties) (7).

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

The aetiology of tendinopathy is unclear. It seems to be multi-factorial, involving multiple intrinsic and extrinsic factors. 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, substanceP are involved in tendinopathy. These mediators and neovascularization are associated with the clinical symptomatology, and particular, with pain. 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

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