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Review

Chronic tendinopathy tissue pathology, pain mechanisms, and etiology with a special focus on inflammation

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Continuing progress in research in molecular biology and biomechanics has provided considerable new information and has given rise to new hypotheses in chronic tendinopathy. Overloading is still, however, crucial in the development of tendinopathy. Most of the histologic findings in tendinopathy represent chronic degeneration, regeneration, and microtears of the tendinous tissue. The prevailing opinion is that no histological evidence of acute inflammation has been documented, but in newer studies using immunohistochemistry and flow cytometry inflammatory cells have been detected. The existing data indicate that the initiators of the tendinopathic pathway include many proinflammatory agents (e.g. cytokines, prostaglandins, different growth factors, and neuropetides). Because of the complex interaction between the classic proinflammatory agents and the neuropeptides, it seems impossible and somewhat irrelevant to distinguish sharply between chemical and neurogenic inflammation. Furthermore, glucocorticoids are, at the moment, the most effective treatment in tendinopathy with regard to reduction of pain, tendon thickness, and neovascularization. This review indicates – despite a great deal of uncertainty regarding the concepts – that an inflammatory process may be related not only to the development of tendinopathy but also chronic tendinopathy. More attention should be directed towards the "tendinitis myth" in the future.

Chronic tendon pain in Achilles and patella tendons is very common. In the general population, the lifetime cumulative incidence of Achilles tendinopathy is 5.9% among sedentary people and 50% among elite endurance athletes (Kujala et al., 2005), and the overall prevalence of patellar tendinopathy in an athletic population has been reported to be in the range of 7–40% (Kujala et al., 1986; Lian et al., 2005). Despite the frequency, there are still many unsolved questions and differences of opinion concerning pathology, pain mechanisms, etiology, and even terminology.

A few years ago, the pain in chronic tendon overuse was believed to be due to a chronic inflammatory process, but because no inflammatory cells could be demonstrated in ruptured tendons, the opinion changed from inflammation ("tendinitis") to degeneration ("tendinosis"). A large amount of scientific data have so far not shown any direct evidence of inflammation in chronic tendinopathy (Jozsa et al., 1990; Kannus & Józsa, 1991; Astrom & Rausing, 1995; Movin et al., 1997b; Alfredson et al., 1999, 2003a; Khan et al., 1999; Alfredson & Lorentzon, 2002). Today, most authors have even abandoned the "tendinitis myth" (Khan et al., 1999, 2002; Alfredson, 2004). In a recent study (Fredberg et al., 2004), however, a significant reduction in pain and tendon thickening measured by ultrasonography (US) and an increased pain detection threshold measured by pressure algometry were found only 1 week after administration of ultrasound-guided peritendinous corticosteroid injections in chronic Achilles and patella tendinopathy. These changes induced by corticosteroids are difficult to explain if the process is degenerative. The time frame is too short to expect that the corticosteroids could have influenced processes normally connected with degeneration of connective tissue, such as collagen synthesis, fibroblast migration, etc., which are processes that normally change slowly. Although the effect of the injected corticosteroid might be chemical or mediated through vasoconstriction and thereby hypoxia of the accompanying nerves, the dramatic effect could obviously be explained by the anti-inflammatory effect of the corticosteroid.

Terminology

The "*peritendon*" is the loose tissue surrounding the tendon, and it consists of the "*epitenon*" and the "*paratenon*" (Kirkendall & Garret, 1997) (see Fig. 1).

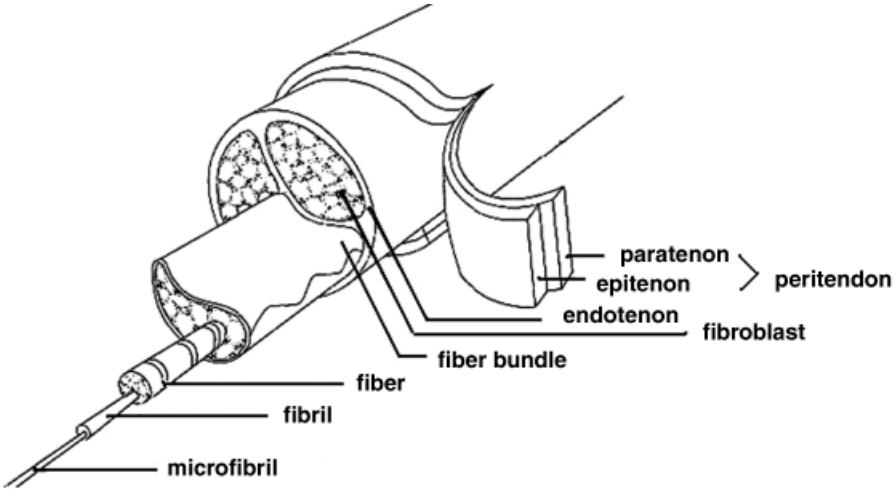

Fig. 1. Structure and model of a tendon (after Kirkendall & Garret, 1997).

In tendons without a synovial sheath, the epitenon is tightly bound to the tendon. Generally, ''*tendinitis*'' (or ''tendonitis'') is primarily used as a histopathologic term describing a condition in which the primary site of involvement is the tendon and with an inflammatory response being seen within the tendon (Järvinen et al., 1997; Sharma & Maffulli, 2006). The condition is often associated with reactive ''*paratenonitis*'' or ''*peritendinitis*,'' which is an inflammation of the paratenon (Järvinen et al., 1997). ''*Tendinosis*'' is not correlated with clinical symptoms (Peers & Lysens, 2005), but it has been widely used for patients with chronic tendon pain, and with biopsy, radiographic, ultrasonographic, or magnetic resonance imaging (MRI) showing tendon abnormalities (Khan et al., 1999; Alfredson, 2003). Today, ''*tendinosis*'' is primarily used to describe a histopathologic finding with intratendinous degeneration and no sign of inflammation (Järvinen et al., 1997; Sharma & Maffulli, 2006). ''*Tendinopathy*'' is used to signify the combination of tendon pain and impaired performance often associated with swelling of the tendon and intratendinous changes (Alfredson, 2003, 2005) evaluated by US or MRI. The diagnosis of tendinopathy can, in contrast to tendinitis and tendinosis, be made clinically without histopathologic examination.

No specific time criteria are used to classify tendinopathy as acute or chronic. It has been suggested that tendon symptoms present for <2 weeks be described as ''acute,'' for 2–6 weeks as ''subacute,'' and for more than 6 weeks as ''chronic'' (el Hawary et al., 1997). These somewhat arbitrary distinctions are not based on histopathologic or clinical criteria.

It is recommended that the term tendinopathy be used as a clinical diagnosis for patients with pain in the tendons. Tendinosis and tendinitis require a biopsy showing degeneration or inflammation. If symptoms are present for more than 3 months, the tendinopathy is categorized as ''chronic,'' for symptoms present between 6 and 12 weeks as ''subacute,'' and for symptoms present between 0 and 6 weeks as ''acute.''

Diagnosis

Tendinopathy is characterized by the gradual onset of morning stiffness in the tendon, decreased function, localized swelling, and sometimes neovascularization (Khan et al., 1999; Boesen et al., 2006). Fibrin precipitated from the fibrinogen-rich fluid around the tendon can result in palpable crepitation (Jòzsa & Kannus, 1997).

The diagnosis can be made clinically and is verifiable by US or MRI. The diagnosis tendinopathy is mainly based on patient complaints (sensation of pain) and palpation of the tendon, its surrounding tissue, and its insertion, even though the clinical diagnosis of Achilles (Maffulli et al., 2003) and patellar tendinopathy (Cook et al., 2001), even in experienced hands, is not straightforward, and experienced examiners may have problems in reproducing the results of clinical examination based on simple tests (Maffulli et al., 2003). Many of the cases were incorrectly diagnosed using only clinical examination (Fredberg et al., 2004), and in some cases even total ruptures were misdiagnosed (Ljungqvist, 1967; Resnick et al., 1977; Shields, 1978; Siwek & Rao, 1981; O'Brian, 1984; Ballas et al., 1998). Based on these facts, US (or MRI) is recommended in all cases of tendinopathy if shooting pain is present or if there is no positive progress during treatment.

US is more accurate than MRI in confirming clinically diagnosed patellar tendinopathy (Warden et al., 2007). US has several significant advantages over MRI: tissue with few mobile protons emits little or no signal, and, therefore, the internal architecture of the tendon is not well demonstrated with MRI. In contrast, US shows the fine internal structure of tendons, and US therefore pictures the anatomic border of the tendon more precisely than does MRI (Kamel et al., 2004). In agreement with this, the ''standard deviation'' and ''range of the mean difference'' from repeated measurement are less with US than with MRI (Koivunen-Niemela & Parkkola, 1995). The US examination is interactive. The examiner is with the patient, and any site of reported pain or tenderness can be directly correlated with its real-time scan appearance. The ultrasonographer can make use of the dynamic real-time character of US, so that tendons can be studied throughout their range of motion. Side-to-side comparison is always available during the US examination. The spatial resolution of US is much better than that of MRI (Erickson, 1997). Furthermore, US can demonstrate the neovascularization in tendinopathy. Today, US is a well-established first-choice modality and is regarded as the examiner's extended hand in daily practice, which will never be the case for MRI, and MRI has only a limited place in tendinopathy (Richards et al., 2001; Shalabi et al., 2007).

In patients with chronic tendinopathy, US shows thickening of the tendon, discontinuity of the fibers, focal hypoechoic intratendinous areas, loss of fascicle organization, intratendinous focal calcification, partial or complete ruptures, and thickening of the hypoechoic paratenon with poorly defined borders, bursitis, and adherences between the epitenon and paratenon (Gibbon et al., 2000; Blankstein et al., 2001; Fornage, 2003), and the contours of the tendon may be deformed with a bumpy appearance (Fornage, 1993).

Histologically

In stark contrast to the glistening white normal tendon, in symptomatic tendinopathy tendons appear gray or yellow-brown and amorphous to the naked eye, and microscopy reveals discontinuous and disorganized collagen fibers that lack reflectivity under polarized light (Karlsson et al., 1992; Raatikainen et al., 1994; Khan et al., 1999).

Compared with normal tendons, the characteristic features of tendinopathy under light microscopy are (A) disrupted collagen, and the collagen fibers are thinner than normal and the characteristic hierarchical structure is lost (Åstrøm & Rausing, 1995), (B) increased ground substance with a high concentration of glycosaminoglycans (Movin et al., 1997a), (C) more prominent and numerous tenocytes without their normal, fine spindle shape, and with more rounded nuclei (Colosimo & Bassett, 1990; Fritschy & Wallensten, 1993), and (D) neovascularization as seen on color and power Doppler US (Alfredson et al., 2003b).

Histologic examination of specimens removed during surgery for tendinopathy shows hypoxic degeneration (Kannus & Józsa, 1991), mucoid or myxoid degeneration (Jòzsa & Kannus, 1997) and fibrinoid necrosis (Jozsa et al., 1990; Khan et al., 1996), fatty degeneration or tendolipomatosis (Kannus & Józsa, 1991), collagen degeneration (Cetti et al., 2003), pseudocyst change (Ferretti et al., 1983), randomized collagen with an irregular fiber structure and poor fiber orientation and neovascularization and tenocyte infiltration (Kälebo et al., 1991; Astrom & Rausing, 1995; Khan et al., 1999; Ohberg & Alfredson, 2002), tenocyte necrosis (Cetti et al., 2003), microtears of the tendinous tissue (Cook et al., 1997), chronic inflammatory cell infiltration (Mourad et al., 1988; Raatikainen et al., 1994), acute inflammation (Cetti et al., 2003), granulation tissue (Kälebo et al., 1991), small foci with iron-positive hemosiderophages (Schubert et al., 2005), focal degeneration near the bone–tendon insertion (Raatikainen et al., 1994), hyalin degeneration and fibrocartilagionous and bony metaplasia (Myllymaki et al., 1990), calcifying tendinopathy (Kannus & Józsa, 1991), angiofibroblastic tendinosis (Yu et al., 1995), grayish discoloration of ground substance, tendon edema, and different combinations of these entities (Kannus & Józsa, 1991; Jòzsa & Kannus, 1997; Paavola et al., 2002).

Virtually every study of the pathology of Achilles and patellar tendinopathy has reported that there were more conspicuous and more numerous cells than in healthy tendons and inflammatory cells were absent. Most of these histologic findings above represent

1. chronic degeneration (hypoxic degeneration, mucoid or myxoid degeneration, fatty degeneration, collagen degeneration, fibrinoid necrosis, tenocyte necrosis, pseudocyst change, focal degeneration, hyalin degeneration),
2. regeneration (neovascularization or angiofibroblastic tendinosis, tenocyte infiltration, chronic and acute inflammation), and
3. microtears of the tendinous tissue (the positive hemosiderophages).

The prevailing opinion is that no histological evidence of acute inflammation has been documented in ruptured tendons (Alfredson & Lorentzon, 2002; Khan et al., 2002) or tendinopathic tendons under-

going surgery (Benazzo et al., 1996; Cook et al., 1997) or biopsies (Martinoli et al., 1993).

In a recent study (Cetti et al., 2003), however, immunohistochemical staining confirmed acute inflammation in all of 60 ruptured Achilles tendons. The neutrophils had a morphology reminiscent of necrotic tenocytes, and their presence was confirmed on immunohistochemical staining. Using monoclonal antibodies (CD3 for detection of T lymphocytes, CD 20 for detection pf B lymphocytes, and CD 68 for detection of macrophages), Schubert et al. (2005) demonstrated that B and T lymphocytes and macrophages were increased in Achilles tendinopathy samples. These two studies need more confirmation.

Areas of altered collagen fiber structure and increased interfibrillar ground substance, which has been shown to consist of hydrophilic glucosaminoglycans, in Achilles tendinopathy correspond to the increased signal on MRI (Movin et al., 1998a) and the hypoechogenic regions on US (Maffulli et al., 1987; Movin et al., 1998b). Areas with increased signals on MRI (Yu et al., 1995; Khan et al., 1996) and granulomas and hypoechogenic regions on US (Myllymaki et al., 1990; Maffulli et al., 1992) in patellar tendinopathy appear to correspond to mucoid degeneration (Khan et al., 1996).

Biochemically

Several cell types in and around the tendon respond to physical activity and can produce and respond to many inflammatory mediators.

Endothelial cells can express and respond to a network of inflammatory mediators, such as interleukins, prostaglandins (PGE_1, PGE_2), and nitric oxide (NO) (Scott et al., 2004).

Tendon cells subjected to cyclic strain increase the production of:

- COX-2 (Wang et al., 2003) [which is not expressed in resting connective tissue, but is induced by interleukin-1 (IL-1) and tumor necrosis factor (TNF)],
- PGE_2 (Almekinders et al., 1993, 1995; Wang et al., 2003, 2004; Li et al., 2004),
- IL-6 (Skutek et al., 2003),
- IL-1 β [which results in increased production of COX-2, matrix metalloproteinases (MMP-1, MMP-3, MMP-13, which cause matrix destruction and a loss of tendon biomechanical properties), PGE_2, intracellular calcium [which can lead to apoptosis (Arnoczku et al., 2002)] and strongly downregulates an apoptose-inhibitor gene, which could contribute to increased cell death] (Archambault et al., 2002; Tsuzaki et al., 2003; Banes et al., 2007),
- vascular endothelial growth factor (Senger et al., 1983; Ferrara, 1999; Neufeld et al., 1999; Pufe et al., 2005) [which are upregulated by inflammatory cytokines and highly expressed in Achilles tendinopathy] (Pufe et al., 2001, 2005; Petersen et al., 2002),
- increase the expression level of cytosolic phospholipase-A2 and activity level of secretory phospholipase-A2 [which are involved in the production of PGE_2 and other inflammatory mediators] (Wang et al., 2004), and
- increase activation of stress-activated protein kinase (Arnoczku et al., 2002) [which is activated from pro-inflammatory cytokines, indicating that this signal pathway may contribute to the inflammatory responses] (Ip & Davis, 1998).

However, many of these investigations have used non-physiologic strain patterns or the addition of external factors to elicit these cell responses. Thus, the clinical relevance of many of the studies must be called into question.

COX-2 expression is usually low but can be induced by numerous factors, including neurotransmitters, growth factors, pro-inflammatory cytokines, lipopolysaccharides, calcium, phorbol esters, and small peptide hormones (O'Banion, 1999) and can be reduced by glucocorticoids.

Tissue injury is associated with inflammation and increased prostanoid synthesis and pain hypersensitivity. Prostanoids influence inflammation and immune responses, and their administration reproduces the major signs of inflammation, including augmented pain sensitivity (Tilley et al., 2001). Peripheral inflammation increases prostanoid levels at the site of inflammation, and this local release contributes directly to inflammation and pain. More recently, peripheral inflammation has also been shown to increase central prostanoid levels (Dirig & Yaksh, 1999; Vanegas & Schaible, 2001). Constitutive production of prostanoids is normally low, but can be increased within minutes by inflammatory stimuli acting on constitutively expressed prostanoid synthetic enzymes (Funk, 2001). Pro-inflammatory signals trigger multiple transcriptional and post-translational changes that alter the synthetic enzyme levels and activity, and this leads to early, massive, and sustained increases in prostanoid levels (Samad et al., 2003).

In tendons from patients with patellar tendinopathy, both the tendon tissue itself and harvested cells express higher levels of COX-2 and PGE_2 than do healthy control patellar tendons (Fu et al., 2002).

Human microdialysis studies have shown that peritendinous pro-inflammatory agents like PGE_2 (Langberg et al., 1999a, b), IL-6 (Langberg et al., 2002), and thromboxane B_2 (Langberg et al., 1999a) are increased after exercise, indicating that the production is local (Langberg et al., 1999a, b), and that peritendinous pro-inflammatory agents like

PGE_2 are increased 50% in patients with chronic tendinopathy compared with normal tendons (Alfredson et al., 1999, 2001b), although the differences were not significant in this very small study of only four patients.

The nociceptive substance P (SP) and calcitonin gene-related peptide (CGRP) positive nerve fibers are significantly increased in chronic tendinopathy (Forsgren et al., 2005; Schubert et al., 2005).

Using microdialysis techniques, Alfredson et al. (1999) found a high level of the excitatory neurotransmitter glutamate in tendons from patients with Achilles tendinopathy [and the occurrence of glutamate *N*-methyl-D-aspartate receptors (Alfredson et al., 2001a)].

Neuropeptides have been found to exert trophic effects in different tissues in addition to their nociceptive and pro-inflammatory actions (Strand et al., 1991; Schwartz, 1992; Hökfelt et al., 2000). SP and CGRP, representing the sensory system, participate in the regulation of fibroblast and synoviocyte proliferation and of angiogenesis (Brain et al., 1985; Haegerstrand et al., 1990). They have also been implicated in the synthesis and release of cytokines and growth factors (Broome & Miyan, 2000; Monneret et al., 2000). SP upregulates COX 2 and IL-β in the peritendon (Hart et al., 1998). Neurogenic inflammation could initiate peritendinitis, with both SP and GCRP implicated in this pathway (Hart et al., 1998), and long-term peritendinitis can lead to degenerative changes in the tendon (Sullo et al., 2001).

In nociception, CGRP potentiates the effects of SP (Wiesenfeld-Hallina et al., 1984). Galanin, also occurring in primary afferents, has been shown to mitigate nociception and inflammation (Heppelmann et al., 2000).

SP and CGRP have a stimulatory role in the proliferation of cultured fibroblasts (Nilsson et al., 1985). SP and CGRP are also known to stimulate the proliferation of endothelial cells (Nilsson et al., 1985; Haegerstrand et al., 1990; Ziche et al., 1990).

Not only is the level of SP increased significantly in chronic tendinopathy, but SP is also increased in the synovial fluid in a typical inflammatory disease like rheumatoid arthritis (RA) (Westermark et al., 2001). The synovial fibroblast in RA can produce SP (Inoue et al., 2001), and neuropeptides have been shown to modulate immune function directly through expressed receptors and undergo distinct alteration in RA (Sedo et al., 2005).

It is known that the neuroendocrine, immunologic, and microvascular systems interact in RA (Masi et al., 1999; Hernanz et al., 2003; Sedo et al., 2005) thus, it is an obvious conclusion that the same could be seen in tendinopathy. Some of the mechanisms in tendinopathy and inflammatory RA seem to be the same.

In a recent study (Danielson et al., 2006b), an upregulation of the cholinergic system was found concerning levels of expression of the muscarin receptors M2 and choline acetyltransferrase in tendinopathy, and the tenocytes were suggested to be a source of acetylcholinesterase production. It is known that cytokines can induce upregulation of the M2 receptors (Ebriques de Salamanca et al., 2005). Thus, non-neural acetylcholinesterase production may have effects on immune function, cell proliferation and differentiation, and several other basic cell functions (Wessler et al., 2001).

In contrast, in a study using cDNA arrays and real-time PCR (Alfredson et al., 2003a) on biopsies from tendons with tendinopathy, Alfredson found that the mRNA for several cytokines and cytokines receptors was not upregulated in Achilles tendinopathy. Based on the findings in these tendon biopsies, Alfredson concluded that there is no chemical inflammation involved in the chronic stage of tendinopathy, but there could be a neurogenic inflammation involving neuropeptides like SP and CGRP. However, there was a mixture of all cell types in the biopsies, and consequently, a theoretically possible, isolated upregulation of fibroblast or endothelial cells could have been missed.

Pain mechanism

The pain mechanism is partly unknown. Traditional theories state that pain arises through inflammation or due to separation of collagen fibers in more severe forms of tendinopathy. Other theories include biochemical stimulation of the nociceptors due to extravasation of glucosaminoglycans, especially chondroitin sulfates (Benazzo et al., 1996; Khan et al., 1996; Jòzsa & Kannus, 1997) and other biochemical irritants. In biopsies from athletes with patellar tendinopathy, Danielson et al. (2006b) recently found that tenocytes produce acetylcholine and that nerve fibers showing immunoreactions for the acetylcholine-receptor M2 were observed in association with the small blood vessels in tendinopathy.

Prostaglandins, prostacyclins, and thromboxanes (prostanoids) contribute to the development of pain by acting both peripherally and centrally. Peripherally, they play a major role in generating peripheral sensitization by increasing the sensitivity of the peripheral terminals of high-threshold pain fibers (nociceptors). They increase excitability, reduce the pain threshold, and potentiate the action of pain-producing stimuli, such as heat or irritant molecules like bradykinin (Khasar et al., 1998; Gold, 1999).

Currently, investigations are increasingly focused on the nerve supply to the tendons. Neuropeptide-containing nerve fibers have both afferent and effer-

ent roles with respect to bone cell regulation, and they may be involved in the healing of tendons and fractures. The nerve fibers are mainly located in the periosteum, synovium, the fat pad (Witonski & Wagrowska-Danielewicz, 1997), and the loose peritendinous connective tissue. However, nerve ingrowth is known to occur as a response to tendon injury (Ackermann et al., 2002), and a number of studies have demonstrated new nerve ingrowth in the tendon proper in tendinopathy (Schubert et al., 2005; Lian et al., 2006). In tendinopathy, nerve fibers accompany the blood vessels into the tendon (Danielson et al., 2006a). It has been suggested that these nerves are a potential origin of the pain in tendinopathy (Alfredson et al., 2003b).

Free-sprouting SP and CGRP fibers are found around newly formed blood vessels in ruptured Achilles tendons, and Ackermann et al. (2003) demonstrated that the healing process in tendon in the inflammatory and early proliferation phase of healing (weeks 1–2) is associated with new nerve ingrowth and a specific temporal pattern of neuropeptide occurrence. The rate of change in peripheral neuropeptides occurrence is related to nociceptive thresholds, which presumably reflect a regulatory role in both nociception and tissue repair. This was followed by nerve fiber withdrawal (weeks 6–12) from the tendon tissue. It is however, well known that the pain continues even during weeks 6–12, as well as afterwards. The level of the excitatory neurotransmitter glutamate and the number of nociceptive SP and CGRP positive nerve fibers are also known to be significantly increased in chronic tendinopathy (Alfredson et al., 2001a; Forsgren et al., 2005; Schubert et al., 2005) in both vessels and nerve fascicles, indicating that the peptides not only have an effect in relation to blood flow regulation but could also have effects within the nerve fascicles.

Acetylcholinesterase may have an effect on sensory nerve fibers, and in this way, the acetylcholinesterase in non-neural cells may play a role in modulating peripheral nociception (Weiss et al., 2003).

Why glucocorticoids have the same dramatic clinical effect on pain and hyperemia in tendinopathy as they do in RA (Terslev et al., 2003; Koenig et al., 2004) is still partly unknown, but many of the same pro-inflammatory agents are found in both diseases. It has been postulated that the dramatic reduction in tendon thickness (and maybe the pain) after steroid treatment is due to glucocorticoid reducing the water content in the tendons. However, in an experimental animal study (Sullo et al., 2001), the intratendinous water in PGE_1-induced tendinopathy was close to the water content of the normal control tendons. This animal study does not indicate that the considerable reduction in the tendon thickness and pain 1 week after steroid injection (Fredberg et al., 2004) is due to a reduction in water content. In biopsies from Achilles tendinopathy tendons and normal tendons, water content was the highest in the tendinopathy tendons (de Mos et al., 2007). The effect of glucocorticoids could theoretically be due to an analgesic effect on the neuropeptides (CGRP and SP), which, as mentioned above, are increased in tendinopathy, but it seems unlikely that this could explain the dramatic reduction in tendon thickness.

Glucocorticoids regulate vascular reactivity by acting on both endothelial and vascular smooth muscle cells. Glucocorticoid receptor protein and mRNA have been identified in endothelial and vascular smooth muscle cells. In endothelial cells, glucocorticoids suppress the production of vasodilators, such as prostacyclin and NO (Suzuki et al., 2003; Yang & Zhans, 2004). Glucocorticoids are to some extent vasoconstrictors, which may explain the change in vascularity, and secondly, the reduction in thickness and pain, due to a reduction in the supply of different noxious stimuli and pro-inflammatory agents like PGE, cytokines, and neuropeptides, whose effects will further be reduced by steroids.

Glucocorticoids are the most effective treatment in tendinopathy with regard to reduction of pain, tendon thickness (Fredberg et al., 2004), and neovascularization. The effects when glucocorticoids are injected around chronic tendinopathies and into inflammatory joints of patients with RA, which is a well-established inflammatory chronic disease, are nearly the same. Because glucocorticoids do not cure either tendinopathy or RA, the symptoms often relapse in both diseases. The two diseases have many symptoms in common (rubor, dolor, tumor, calor, functio laesae), and because the clinical responses to glucocorticoids in chronic tendinopathy and inflammatory RA are comparable, a conclusion that immediately suggests itself is that the effect of glucocorticoids in chronic tendinopathy is due to their anti-inflammatory properties as in inflammatory arthritis.

Etiology

The exact pathogenesis of chronic tendinopathy remains largely unknown but seems to be a multifactorial process. The following are a wide range of suggested intrinsic and extrinsic etiological factors that are assumed to be the mechanisms of tendinopathy (Williams, 1986; Murphy et al., 2003): age [with decreased arterial blood flow with local hypoxia, less nutrition, impaired metabolism, and free radicals (Archambault et al., 1995; Langberg et al., 2001; Kettunen et al., 2006)]; vascular perfusion [ischemia occurs when a tendon is under maximal

tensile load and microdialysis studies have demonstrated high intratendinous concentrations of lactate in chronic, painful Achilles tendons (Alfredson et al., 2002) and on relaxion, reperfusion occurs, generating oxygen free radicals (Goodship et al., 1994; Bestwick & Maffulli, 2004)]; nutrition; exercise-induced hyperthermia (Arancia et al., 1989; Brich et al., 1997); anatomic variants: various alignments such as Q-angle, hyperpronation (Clement et al., 1984; Nigg, 2001), limited range of motion of the ankle joint (Kvist, 1991), excessive motion of the hindfoot in the frontal plane (Kaufman et al., 1999), especially a lateral heel strike with compensatory pronation, varus deformity of the forefoot (Clement et al., 1984; Kvist, 1991), pes cavus, pes planus (Williams et al., 2001), lateral ankle instability, leg-length discrepancy (Kannus, 1997), impingement (Johnson et al., 1996; Schmidt et al., 2002), and other biomechanical factors (Kvist, 1994); muscle weakness/imbalance (Wityrouw et al., 2001; Mahieu et al., 2006); increased tightness of the gastrocnemius (Kaufman et al., 1999): physical load (sport/occupation); excessive force; repetitive loading; abnormal/unusual movement; poor technique; training errors: fast progression and high intensity; fatigue; shoes and equipment; environmental conditions; temperature and running surface (Kvist, 1991); gender (Kannus, 1997); genetic (Józsa et al., 1989; Kannus & Natri, 1997; Mokone et al., 2005, 2006) and genetically determined collagen abnormalities; infectious disease; neurological conditions; hyperparathyroidism (Preston, 1972); hypertension (Holmes & Lin, 2006); body weight (Holmes & Lin, 2006); increased serum lipid (Qzgurtas et al., 2003); glycogen storage disease (Carvès et al., 2003); systemic disease/treatment [direct injection of corticosteroids (Shrier et al., 1996; Fredberg, 1997)]; systemic corticosteroid (Newham et al., 1991; Khurana et al., 2002); oral contraceptives (Holmes & Lin, 2006); fluoroquinolones (Malaguti et al., 2001; Chhajed et al., 2002); RA (Peiro et al., 1975); psoriasis (Aydingöz & Aydingöz, 2002); systemic lupus erythematosus (Pritchard & Berney, 1989; Jakobsen et al., 2000); chronic renal failure (Kricun & Kricun, 1980); hyperuricemia (Hofmann et al., 1990); hyperthyroidism; arteriosclerosis; and diabetes mellitus (Webb & Bannister, 1999; Holmes & Lin, 2006).

The scientific background for most of these suggestions is lacking, and they must to be characterized as non-proven theories, and, above all, their clinical importance is not well known.

The traditional view of tendinopathy is a tendon injury associated with overuse (Curwin, 1994; Archambault et al., 1995; Jòzsa & Kannus, 1997) from repetitive mechanical load, microtears, and acute and then chronic phases of inflammatory "tendinitis" that lead to tendon degeneration, despite these conditions also being seen in physically inactive individuals (Movin, 1998; Alfredson & Lorentzon, 2000). At the moment, the mechanical strain theory is the most accepted theory to explain the injury mechanisms of tendon overload injuries (Stanish et al., 1985; Archambault et al., 1995; Khan et al., 1999): repeated heavy loading may produce initial pathological changes in either the extracellular matrix or the cellular components of a tendon. When the load exceeds the tendon's strength (resistance), the progressive damage (the basal ability of the tissue to repair itself after being overwhelmed by the repetitive microtraumatic process) may lead to the structure of the tendon being disrupted micro- and macroscopically by this repetitive strain (often eccentric by nature), and collagen fibers begin to slide past one another (causing breakage of their cross-linked structure) and denature (with inflammation edema and pain), causing a focal area of intratendinous degeneration, partial tears, and complete ruptures (Jòzsa & Kannus, 1997; Kannus, 1997). The cumulative trauma is thought to weaken collagen cross-linking and the non-collagenous matrix and vascular elements of the tendon, and finally leads to tendinopathy.

It is highly probable that overload exercise plays a decisive role in tendinopathy because the lifetime cumulative incidence of Achilles tendinopathy is nearly 10 times higher among elite endurance athletes than among sedentary people (Kujala et al., 2005). Moreover, exercise has important modulatory effects on immunocyte dynamics and possibly on the immune function. These effects are mediated by diverse factors, including, among others, exercise-induced release of classical stress hormones, hemodynamic effects involving cell distribution (Pedersen & Hoffmann-Goetz, 2000), and release of a soup of pro-inflammatory mediators, as for example, cytokines (which can be detected in plasma and urine during and after exercise) (Ostrowski et al., 1999), prostaglandins, and neuropeptides (Lind et al., 1996; Hasbak et al., 2002; Karahan et al., 2002). The tendon and endothelial cells seem to be able to produce most of these mediators.

Animal studies support both the overload theory and the notion that cytokines and prostaglandins play a role in the etiology of tendinopathy. Backman et al. (1990) demonstrated that exercised rabbits showed light microscopic degenerative changes in tendons and increased numbers of capillaries, infiltrates of inflammatory cells, edema, and fibrosis in the paratenon.

In animal studies, injections of collagenase, cytokines, and inflammatory prostaglandins (PGE_2), which, as mentioned above, are increased in exercise, have been shown to cause tendinitis and tendinosis (Stone et al., 1999; Sullo et al., 2001; Cilli et al., 2004; Khan et al., 2005).

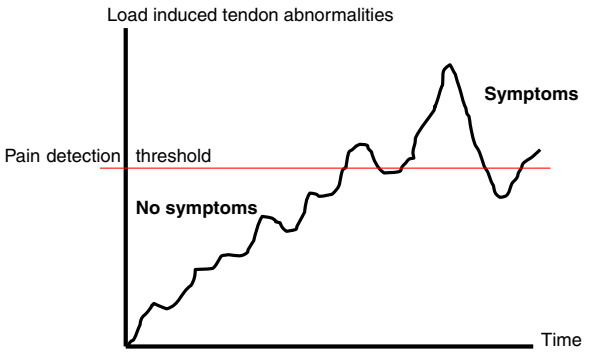

Fig. 2. The tendinopathic "iceberg."

Some people may have a genetic predisposition toward developing tendinopathies (Mokone et al., 2005, 2006), which may explain why many patients with tendinopathies do not go in for sport.

Most Achilles tendon ruptures occur without warning symptoms, but in nearly all the ruptured tendons, degenerative changes can be demonstrated (Kannus & Józsa, 1991), and several studies show ultrasonographic abnormalities in patellar tendons of asymptomatic athletes playing volleyball, basketball, soccer, and track and field athletes (Gibbon et al., 1999; Cook et al., 2000; Fredberg & Bolvig, 2002; Major & Helm, 2002; Maffulli et al., 2003). Even severe tendinopathies are asymptomatic for long periods. Thus, chronic tendinopathy can be compared with an iceberg, pain being the tip of the iceberg (see Fig. 2).

This "iceberg theory" can explain the frequent relapse of symptoms when athletes resume the sport activity after too short a rehabilitation period, during which pain recedes to just below the detection threshold while most of the intratendinous abnormalities in the tendon still exist.

A study (Fredberg & Bolvig, 2002) showed that US can identify these asymptomatic athletes who have an increased risk of developing serious tendon injuries in the future.

Conclusion

Even in experienced hands, the diagnosis of tendinopathy is not straightforward, and experienced examiners may have problems in reproducing the results of clinical examination based on simple tests. Therefore, the diagnosis should be verified by US, which is a more accurate modality than MRI in confirming clinically diagnosed tendinopathy (Warden et al., 2007).

Overuse is crucial in the development of tendinopathy in individuals who, perhaps because of extrinsic and intrinsic (including genetic) factors, are predisposed.

It seems plausible that tendons have a baseline mechanical strength, which depends on the loading history of the tendon (training level). Once a rapid increase in training load, frequency, or duration occurs, the tendon may not be able to adapt fast enough to these changes. The mechanical strength of the tendon may be exceeded, and a small injury may occur. Under normal circumstances, this small injury will heal as a normal part of tendon remodeling, but if the training and overloading continues, these small injuries result in progressive tendon changes that, after an asymptomatic period of several months, slowly aggravate and finally reach the pain limit and become symptomatic (see Fig. 2).

It seems plausible that tendinopathy begins with cellular activation and inflammation and proceeds through phases of increased ground substance, collagen separations, and eventually neovascularization, and that the corticosteroid-sensitive mechanisms play a crucial role in this process.

Virtually every study of the pathology Achilles and patellar tendinopathy has reported that there are more conspicuous and more numerous cells than in healthy tendons and inflammatory cells are absent. Two newer studies, in which immunohistochemical staining and monoclonal antibodies were used for detection of T and B lymphocytes and macrophages, confirmed the presence of inflammation in both ruptured and non-ruptured chronic Achilles tendinopathies.

The existing data indicate that the initiators of the tendinopathic pathway include traumatic events, or a prolonged repetitive motion injury induces the production of many pro-inflammatory agents (including cytokines such as IL-1-β, prostaglandins such as PGE_2, NO, different growth factors, and neuropetides). The pro-inflammatory mediators induce apoptosis, elaboration of pain mediators, and MMP, which degrade collagens and proteoglycans. The end result is a weak tendon with an increased risk of ruptures. The tendon cells can produce these agents when subjected to cyclic stress, and in animal studies these inflammatory agents can be used to produce experimental chronic tendinopathy. Furthermore, many of the pro-inflammatory mediators and neuropeptides are also found in chronic tendinopathy. Because of the complex interaction between the pro-inflammatory agents and the neuropeptides, it seems impossible and partly irrelevant to distinguish sharply between chemical and neurogenic inflammation.

This review indicates – without definitive proof – that an inflammatory process may be related to the development of tendinopathy and that the inflammation may also play a role in chronic tendinopathy.

The major questions for the future are therefore: is it advantageous to block this inflammatory cascade, and what is the most effective way to block it with the smallest possible number of side effects?

More attention should be directed toward the tendinitis myth in the future.

Key words: tendonitis, tendinosis, tendinitis, tendinopathy, Achilles tendon.

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