

Ultrasonography and pressure algometry in chronic Achilles and patellar tendinopathy

Ph.D. Thesis

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ORIGINAL STUDIES

Study I. Ultrasonography in evaluation of Achilles and patellar tendon thickness. U.

Fredberg, L. Bolvig, N. T. Andersen, K. Stengaard-Pedersen. **European Journal of Ultrasound 2008, 29(1):60-5.**

Study II. Ultrasonography and pressure algometry in evaluation of Achilles and patellar

tendons. Intra and inter observer variability. U. Fredberg, L. Bolvig, M Pfeiffer Jensen, N. T. Andersen, L. Hyldgaard, K. Stengaard-Pedersen.

Study III. Influence of acute physical activity immediately before ultrasonographic

measurement of Achilles tendon thickness. U. Fredberg, L. Bolvig, A. Lauridsen, K. Stengaard-Pedersen. **Scand J Rheumatology 2007, 36(6):488-9 (Letter to editor).**

Study IV. Significance of ultrasonographically detected asymptomatic tendinosis in the

patellar and Achilles tendons of elite soccer players: A longitudinal study. U. Fredberg, L. Bolvig, **Am J Sports Med 2002, 30(4): 488-91.**

Study V. Ultrasonography as a tool for diagnosis, guidance of local steroid injection and

together with pressure algometry monitoring of the treatment of athletes with chronic jumper's knee and Achilles tendinitis: a randomised, double-blind, placebo-controlled study. U. Fredberg, L. Bolvig, M. Pfeiffer-Jensen, D. Clemmensen, B.W. Jakobsen, K. Stengaard-Pedersen. **Scand J Rheumatology 2004; 33: 1-8**

OVERVIEW

Study	Title	Volunteers/ patients	Tendons
I	<p>Ultrasonography in evaluation of Achilles and patella tendon thickness</p> <p>Sub-study 1: Tendon thickness in relation to distance from the attachment at patella or calcaneus</p> <p>Sub-study 2: Longitudinal versus transversal US scan</p> <p>Sub-study 3: Method I (longitudinal and transversal scan) versus method II (longitudinal scan)</p>	87	209
II	<p>Ultrasonography and pressure algometry in evaluation of Achilles and patellar tendons. Intra- and inter-observer variability</p>	40	57
III	<p>Influence of acute physical activity immediately before ultrasonographic measurement of Achilles tendon thickness.</p>	10	20
IV	<p>Significance of ultrasonographically detected asymptomatic tendinosis in the patellar and Achilles tendons of elite soccer players: a longitudinal study</p>	54	194
V	<p>Ultrasonography as a tool for diagnosis, guidance of local steroid injection and, together with pressure algometry, monitoring of the treatment of athletes with chronic jumper's knee and Achilles tendinitis: a randomised, double-blind, placebo-controlled study.</p>	48	96
Total		239	576

PREFACE

These studies were carried out during my employment at Department of Medicine, Region Hospital Silkeborg. The clinical examinations were carried out at the Department of Radiology, Aarhus University Hospital, Department of Medicine, Region Hospital Silkeborg and at the Stadium Clinic, Atletion, House of Sport West, Aarhus, Denmark.

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ABBREVIATIONS

ACH-P	Achilles tendon group treated primarily with placebo
ACH-PS	Achilles tendon group treated primarily with placebo and secondarily with steroid
ACH-S	Achilles tendon group treated primarily with steroid
CGRP	Calcitonin gene-related peptide
COX	Cyclooxygenase
CV	Coefficient of variation
GAGs	Glycosaminoglycans
IL	Interleukine
LB ₄	Leukotrine B ₄
NSAID(s)	Non steroidal anti-inflammatory drug(s)
MMP	Matrix metalloproteinases
MRI	Magnetic resonance imaging
NRS	Numeric rating scale
PAT-P	Patellar tendon group treated primarily with placebo
PAT-PS	Patellar tendon group treated primarily with placebo and secondarily with steroid
PAT-S	Patellar tendon group treated primarily with steroid
PDGF	Platelet-derived growth factor
PDT	Pain detecting threshold
PGs	Proteoglycans
PGE	Prostaglandin E
SD	Standard deviation
SP	Substance P
TIMP	Tissue inhibitors of metalloproteinases
TNF	Tumor necrosis factor
US	Ultrasonography/ultrasound
VAS	Visual analogue scale

INTRODUCTION

1. History

Tendons are load-bearing structures that transmit the forces generated by muscle to their bony insertion, thereby making joint movement possible. Chronic tendon pain in Achilles and patellar tendons (called “jumper’s knee”) is very common, and during the past three decades the incidence has risen enormously (1). In the general population, the lifetime cumulative incidence of Achilles tendinopathy is 5.9% among sedentary people and 50% among elite endurance athletes (2), and the overall prevalence of patellar tendinopathy among high-level athletes is 12-32% in basketball and 40-45% in volleyball players (3). Furthermore, 41% of patients with Achilles tendinopathy developed a tendinopathy of the contralateral side (4). These tendinopathies are characterised by a history of gradually onset pain at the beginning and end of exercise, with a period of diminished discomfort in between (1), morning stiffness in the tendon (5-8) and sometimes also a localised swelling. Fibrin precipitated from the fibrinogen-rich fluid around the tendon can result in palpable crepitation (9). Most therapists agree that tendon injuries should be treated as soon as possible before the injury gets chronic (1;9;10). Despite the fact that the treatment includes active rest, eccentric training of the calf muscle (11-18) or the quadriceps femoris muscle (19-24), NSAID use (25-27), local glucocorticosteroid injections (28-31), sclerosing injections (32-34), shockwave application (35-37), surgery (38-43), nitric oxide administration (44;45), cryotherapy (46), ultrasound (47), deep friction massage, augmented soft tissue mobilization (48), gentle stretching (49), orthoses (46), low-dose heparin, hyaluronidase and aprotinin (50;51) and several others, these tendon injuries have a poor prognosis with a high incidence of chronicity and recurrence and will often bring the athlete’s sports activity to a premature end (52-54). Despite this, large, prospective observational studies on the natural course of this complaint are missing, and randomised medical or surgical treatment interventions with long-term follow-up are sparse. There is insufficient evidence from randomised controlled trials to determine which method of treatment is the most appropriate for the treatment of acute or chronic Achilles (55) and patellar tendon pain.

Many Achilles tendon ruptures occur without warning symptoms, but in nearly all the ruptured tendons, degenerative changes can be demonstrated (56), and several studies show ultrasonographic abnormalities in patellar tendons of asymptomatic athletes playing

volleyball, basketball, soccer and track and field athletes (57-65). The above indicates that even a seriously injured tendon in a shorter or longer period can be asymptomatic, and that it may be possible to diagnose the injury before it becomes symptomatic - which is one of the purposes for this thesis – and hereby start prophylactic training which might conceivably reduce the frequency of chronic tendon injury – hereafter called tendinopathy.

In earlier publications, tendinopathy is diagnosed and the results of treatment evaluated by interview and clinical examination, mainly based on palpation of the tendon, its surrounding tissue and its insertion, even though the clinical diagnosis of Achilles (62) and patellar tendinopathy (66), even in experienced hands, is not straightforward, and experienced examiners may have problems in reproducing the results of clinical examination based on simple tests (62). Many of the cases were incorrectly diagnosed using only clinical examination, and in some cases even total ruptures were misdiagnosed (67-72).

The results of both operative and non-operative treatment of tendinopathy of the Achilles and patellar tendons are in many studies found to be an effective treatment with “excellent” and “good” results in up to 100 % of the cases (32;41;54;73-83). The successful results after treatment of chronic tendinopathy are seldom seen in clinical practise, and reviews of the outcome after surgery in both Achilles and patellar tendinopathy have shown that poor methodology was significantly associated with higher reported success rates for surgical studies of tendinopathy (39;84).

If tendinopathy could be diagnosed more precisely and the effect of treatment could be evaluated more objectively, the results would be more realistic, and it would increase the value of future studies.

Ultrasonography and pressure algometry could be the modalities that make this possible.

Although glucocorticosteroid injections are one of the most commonly used treatments for chronic tendon disorders, there is an obvious lack of good trials defining the indications for and security and efficacy of such injections, and subsequently, many of the recommendations for the use of local injections do not rely on a sound scientific basis.

No legal treatment in sport has been so controversial as locally injected glucocorticosteroids, and many authors still believe that tendon rupture is among the side effects (85;86). Today, most authors have even abandon the “tendinitis myth” (5;87-89), and thus most authors did not recommended treatment with glucocorticosteroids.

2. Nomenclature

The “*peritendon*” is the loose tissue surrounding the tendon, and it consists of the “*epitenon*” and the “*paratenon*” (90), see figure 1 below.

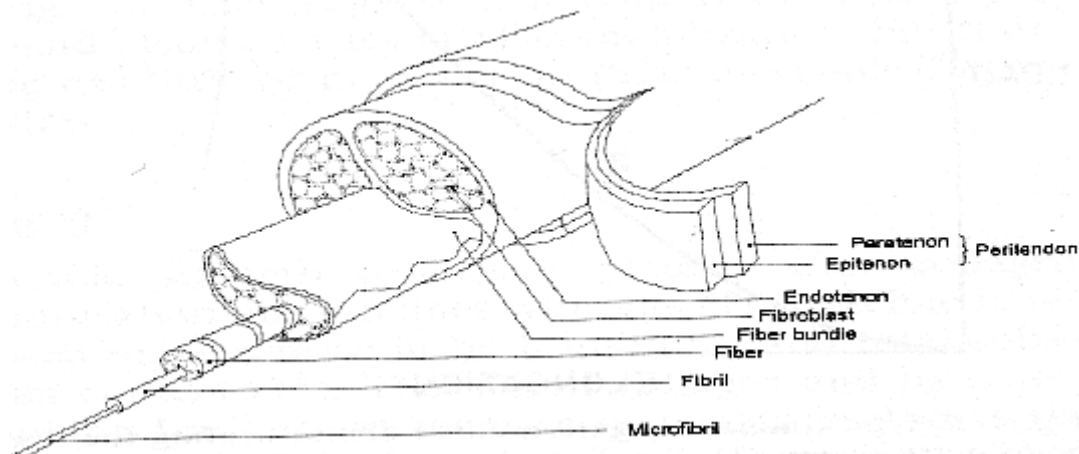


Figure 1. Tendon structure (from DT Kirkendall et al, 1997, SJMSS)

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 (91;92). The condition is often associated with reactive “*paratenonitis*” or “*peritendinitis*”, which is an inflammation of the paratenon (91). “*Tendinosis*” is not correlated with clinical symptoms (89), but the term has been widely used for patients with chronic tendon pain, and with biopsy, radiographic, ultrasonographic, or magnetic resonance imaging (MRI) showing tendon abnormalities (5;93). “*Tendinosis*” is today primarily used to describe a histopathologic finding with intratendinous degeneration and no sign of inflammation (91;92). “*Tendinopathy*” is used to signify the combination of tendon pain and impaired performance often associated with swelling of the tendon and intratendinous changes (93;94) evaluated by US or MRI. The diagnosis 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 less than 2 weeks should be described as “acute”, for 2 to 6 weeks as “subacute”, and for more than 6 weeks as “chronic” (95). These somewhat arbitrary distinctions are not based on histopathologic or clinical criteria.

Some authors state that the term patellar tendinitis or tendinopathy is a misnomer as the patellar "tendon" is in fact, a ligament connecting the inferior pole of the patella to the tibial tubercle (bone to bone) (96;97). However, the quadriceps muscle has one strong tendon, which is inserted into the tibial tubercle and contains within itself the biggest sesamoid bone in the human body, the patella. So, the quadriceps tendon and the patellar tendon are, to be precise, the same anatomic entity, and its function is controlled directly by a muscle which never occurs in a true ligament (a passive element from bone to bone). Thus, the term "patellar tendon" is as correct a name as any other for this structure.

In summary, 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 categorised as "chronic", for symptoms present between 6-12 weeks as "subacute", and for symptoms present between 0-6 weeks as "acute".

3. The normal and abnormal tendons

3.1 Anatomy.

The two strongest tendons in the body are the Achilles and the patellar tendons. The Achilles tendon is a conjoined tendon from m. gastrocnemius and soleus and together these muscles form the triceps surae muscle. The fibres rotate towards the insertion posterior on the calcaneus bone where it inserts. The anatomy of the long Achilles tendon allows it to act as a spring that can store and recover elastic energy, and the anatomy of the short and thick patellar tendon is such that it decreases the average force per tendon area, and thereby the potential for injury when transferring force for joint movement. The two tendons have many things in common (98;99). They are often injured in sport by running and jumping, and the treatment is often disappointing. They have no synovial tendon sheaths. Instead they are surrounded by an outer paratenon, a loose, fibrous, fatty tissue with an inner synovial lining (100) and an inner connective tissue sheath called epitenon, which is adherent to the tendon and allows it to glide freely over adjacent tissue (101). The epitenon consists of a loose, fibrous sheath containing the vascular, lymphatic and nerve supply. There is a thin layer of fluid between the paratenon and epitenon. Together the paratenon and epitenon are called the peritendon (see figure 1 page 13). The endotenon encloses the collagen fibres and fibre bundles and carries blood vessels, lymphatics and nerves.

Tendons consist of a systematic and densely packed organisation of connective tissue dominated by collagen organised into fibrils, fibres, fibre bundles and fascicles.

Tendon consists of 55-70% water, and 60-85% of the tendon dry weight is collagen.

The insertion of a tendon into bone – the osteotendinous junction - involves a gradual transition within 1 mm from tendon to fibrocartilage to lamellar bone. The attachment area of tendons consists of four zones: pure fibrous tissue, unmineralised fibrocartilage, mineralised fibrocartilage and bone.

The basic elements of tendon are cells, collagen bundles and ground substance. Together, the collagen and ground substances comprise the extracellular matrix (102).

3.2 Blood supply

Normal tendons have low vascularity compared to muscle. The patellar tendon receives its blood and lymphatic supply from the bone-tendon junctions and from the paratenon. The blood supply of the patellar tendon originates from the descending and the inferior medial genicular arteries, the lateral genicular arteries and the recurrent tibial anterior artery (103). The Achilles tendon receives its blood supply from three regions (101;104): at the musculotendinous junction from vessels in the muscles, along its length from vessels in the richly vascularised tissue anteriorly via the paratenon (which appears to be the main contributor (105)) and at the osteotendinous junction. The endotenon network carries the vessels to the deeper portion of the tendon (9). Poor blood flow has been implicated as a principal contributing factor to tendon injuries, particular those that occur 2-7 cm proximal to the insertion of the Achilles tendon (106), which is also the part of the tendon most prone to rupture (107). However, recent studies have lead to contradictory results. Åström (108;109) found by use of a Laser Doppler flowmeter an even distribution of blood flow in the tendon, and Langberg (110-112) and Boushel (113;114) found an up to sevenfold increased peritendinous blood flow during exercise. During exercise oxygen extraction and total haemoglobin volume increase in the peritendinous region (113). The exercise-induced peritendinous vasodilatation, increased blood flow and reduced tissue O₂ saturation indicate that blood flow around the tendon increases in relation to regional metabolic activity during dynamic exercise (115). Furthermore, it appears that tendinopathy itself is associated with an elevated blood flow (116-120).

How the blood flow is regulated is still unknown. However, bradykinin has simultaneous vasodilatory and nociceptive properties, and it is known to activate prostaglandin and nitric

oxide-dependent pathways. The interstitial concentration of bradykinin (and adenosine) increase with exercise (121). The exercise-induced increase in tendon flow was inhibited 40% by blocking prostaglandin secretion with cyclooxygenase blockers, indicating that prostanoids play a role in vasodilation in tendon during exercise (122;123). In endothelial cells, glucocorticoids suppress the production of vasodilators, such as prostacyclin and nitric oxide (124;125), therefore glucocorticoids are to some extent vasoconstrictors. Also nitric oxide, potassium, adenosine, endothelium-derived hyperpolarising factor and phospholipase-A₂ have been proposed as candidates for regulating the blood flow to the tendon, and a synergic action of nitric oxide and prostaglandins in the regulation of muscle blood flow during exercise has been demonstrated.

In summary, blood flow to tendons can increase several times during exercise, but that may not necessarily guarantee that the increased blood flow is sufficient to the demand. The regulation mechanism is unknown. There is increased vascularisation in tendinopathy, but it is unknown whether the neovascularisation is one of the causes of tendinopathy or a part of the healing process.

3.3 Nerve supply

The tendon itself is practically devoid of nerve fibres, whereas the myotendinous and osseotendinous junctions and the peritendon are well innervated.

The nerves of tendons are composed of myelinated, fast transmitting A α - and A β -fibres (mechanoreceptors) and unmyelinated, slow transmitting A γ -, A δ -, B- and C-fibres (nociceptors mediating hypalgesia and deep tissue pain, which are characteristic for tendon pain) (126;127).

Tendon innervation originates from three main sources: from cutaneous, muscular and peritendinous nerve trunks. At the musculotendinous junction, nerve fibres cross and enter the endotenon septa. Nerve fibres from rich plexuses in the paratenon penetrate the epitenon. Most nerve fibres do not actually enter the main body of the tendon but terminate as nerve endings on its surface or in the paratenon (128). In this way, the number of nerves is relatively low in the large tendons such as the Achilles and the patellar tendon. The nerves follow the vascular channels (128) that run longitudinal along the tendon. In this way the nerve fibres in the tendon are associated with the vascular, lymphatic and connective tissue channels, and some of these fibres have been reported to have direct contact with tendon collagen (129).

Both sympathetic and parasympathetic fibres have been identified (127). There are at least four types of nerve receptors: mechanoreceptors (convert physical energy, expressed as pressure or tension, into afferent nerve signals), pressure receptors (sensitive to stretch), receptors that are activated by any movement, and free nerve endings that function as pain receptors (130).

The mediators of the nervous system act through 1) fast transmitters (i.e. the classic neurotransmitters: monoamines, acetylcholine and amino acid), which directly effectuate muscle contractions or afferently relay information on painful stimuli and 2) slow transmitters (i.e. neuropeptides which act as chemical transmitters in the central as well as the peripheral nervous system). Neuropeptides are important for nociception and tissue homeostasis and can be classified in three groups:

1. Autonomic, e.g. the sympathetic neuropeptide Y (NPY) (which has an angiogenic effect (131) and is a potent vasoconstrictor often coexisting with noradrenalin (NA), which potentiates the vasoconstrictive action (132)), and the para-sympathetic vasoactive intestinal polypeptide (VIP) (which is a potent vasodilator and has a strong anti-inflammatory effect (133) by regulating immune cells and expression pro- and anti-inflammatory cytokines and growth factors (134;135)).
2. Sensory, e.g. Substance P (SP) and calcitonin gene-related peptide (CGRP), (which coexist with and potentiate the effect of SP). Both SP and CGRP have been shown to participate in the regulation of proliferation of fibroblasts, synoviocytes and endothelial cells (136-138), exert vasodilatation and enhance vasopermeability (139) with protein extravasation (136;140). Sensory nerve fibres respond to noxious thermal, mechanical and chemical stimuli in the periphery by SP release. In the spinal cord SP acts as a transmitter of pain (140), and in the periphery SP (and CGRP) have pro-inflammatory effect by enhancing cellular release of prostaglandins, histamines and cytokines (141;142) and protein extravasation and leukocytes chemotaxis. SP upregulates COX-2 protein expression and induces prostaglandin production in various cell types (143). Dexamethasone inhibites SP-mediated COX-2 expression. There is evidence of a direct effect of SP on the adrenal gland (144). However, sensory nerve fibres also contain peptides with anti-noceptive and anti-inflammatory effects (galanin, somatostatin) (145;146). In this way neurotransmitters and neuropeptides may modulate immune cell and cytokine responses and also local blood flow (147).

SP has been reported to stimulate the proliferation of fibroblasts (137) and the production of transforming growth factor β in fibroblasts (148). Administration of SP and CGRP in animals studies has been shown to accelerate wound healing (149), stimulate proliferation of endothelial cells (138) and increase tensile strength more than 100% in healing Achilles tendons (150;151), and it seems to be the most potent tissue growth stimulator in tendon healing.

3. Opioid, i.e. enkephalins, and endorphines. The effect of the endogenous opioids seem to provide a peripheral anti-noceptive system, and enkephalins also have an anti-inflammatory effect (152), a vasodilatory effect (153) and an immunosuppressive effect (154). Enkephalin-analogue injections can inhibit release of SP (155), and treatment with opioid agonists in the periphery elicits both anti-inflammatory and anti-nociceptive effects (156). There are two principal sources of opioid peptides in the periphery: immune cells (which release opioids and mitigate inflammatory pain (157)) and the peripheral nervous system.

Nerve ingrowth is known to occur as a response to tendon injury (158). In tendinopathy, including Achilles and patellar tendinopathy, a nerve ingrowth takes place into the painful tendon proper (159;160), where the nerves are seen along the neovessels (161) with increased levels of the neurotransmitters, e.g. SP, CGRP (94) and glutamate (162).

The level of SP is also high in synovial fluid in a typical inflammatory disease like rheumatoid arthritis (RA) (163;164). The synovial fibroblast in RA can produce SP (165), and neuropeptides have been shown to directly modulate immune function in RA (166). Finally, it is known that the neuroendocrine, immunologic and microvascular systems interact in RA (166-171), so it is an obvious conclusion that the same may be seen in tendinopathy. Despite tendinopathy and inflammatory arthritis being different diseases, they share some regulatory reactions.

In summary, the peripheral nervous system, in addition to classic functions such as nociception and vasoactivity, also participates in the regulation of a wide variety of efferent actions on cell proliferation, cytokine expression, inflammation, immune responses and hormone release (172-176). Because of the complex interaction between the inflammatory effects of the neuropeptides and the classic inflammatory mediators (e.g. prostaglandins,

cytokines), it seems impossible and partly irrelevant to sharply distinguish between chemical and neurogenic inflammation.

3.4 Tenocyte

The basic elements of tendon are cells, collagen bundles and ground substance. Of the cells in tendons, 90-95% are fibroblasts/tenoblasts (immature tendon cells) and tenocytes (177). The remaining 5-10% are chondrocytes located at the tendon insertions, synovial cells at the tendon surface and nerve and vascular cells, including capillary endothelial cells, smooth muscle cells of arterioles and mast cells. Adipocytes and granule containing mast cells are normally encountered only in the peritendon and endotenon. The cell mass in tendons is only 1-3% of the total dry mass of the tendon, compared to 95% in muscle or liver (128). The tenocytes with spindle-shaped nuclei and sparse cytoplasm are placed between the collagen bundles. Cells in peritendon and tendon are physically connected to each other through junctions (178;179). The signals can be transformed from cell to cell by mediator secretion or through gap junctions. Ion channels (particularly calcium channels), among many others, play an role in the signal transduced from the mechanical stimulus to a chemical signal (180). The architecture of the tenocytes of the tendon and their interconnection provide a three-dimensional network that surrounds the collagen fibrils.

The tenocytes are active in energy generation and allow for transmission of high tensile forces, elastic recoil and longitudinal movement. Furthermore, the cellular elements synthesise the collagen and the ground substance (130;181;182) and produce the enzymes that degrade proteins.

Traditional tendons have been considered to be relatively inactive metabolically, but newer studies have shown that the tendon and the peritendinous tissues are more metabolically active in response to exercise than previously thought (183) and are influenced by heredity, diet, nerve supply, regulating hormones, prostaglandins, cytokines, and neuropeptides etc (130;184). The oxygen consumption of tendon and ligament is more than seven times lower than that of skeletal muscles (185). With increasing age, metabolic pathways shift from aerobic to more anaerobic energy production (56;182).

Normal tendon cells subjected to cyclic strain increase production or expression and activity level of :

- COX-1 and COX-2 (186;187), which is not expressed in resting connective tissue, but is induced by IL1 (188), TNF and Substance P (143).

- Prostaglandin E₂ (PGE₂) (186;187;189-195), which can be blocked by indometacin (186;190;193). Langberg showed that the level of PGE₂ was increased by 100% in the peritendinous space after exercise (192). PGE₂ modulates various cellular functions, including decrease fibroblast proliferation (196-198), inflammatory and immune responses (199;200), collagen production by the fibroblasts (196;201) and suppression of transforming growth factor- β stimulated expression of total protein, collagen and fibronectin (196;202).
- Leukotrienes (186;187;190;191;193;203). LB₄ is important in the inflammatory response (204;205). It activates neutrophils, leads to production of several cytokines (205), and in this way, causes tissue damage as a result of release of proteases and reactive oxygen species (204). Thus high levels of LB₄ production by tendon fibroblasts in response to excessive mechanical loading will result in inflammation, which can lead to development of tendinopathy (206). The production of LB₄ is inversely related to the production of PGE₂ (193). LB₄ is also elevated in rheumatoid arthritis (204).
- Cytosolic phospholipase-A₂ and secretory phospholipase-A₂ (PLA₂), which are involved in the production of the inflammatory mediators PGE₂ and leukotrienes, because PLA₂ catalyses the hydrolysis of fatty acid and, as a result, yields arachidonic acid (207), which is converted to prostaglandins and leukotrienes (187;208). Moreover PLA₂ itself has an important role in initiating tissue inflammation (209) and is implicated in the regulation of regional blood flow to inflamed sites (210).
- Matrix metalloproteinases (MMP) (211;212), which are major regulators of collagen degradation in relation to mechanical loading. Some of the activated MMPs degrades collagen and proteoglycans simultaneously (188). The activity of MMP is regulated directly or indirectly by inflammatory mediators like prostaglandins, interleukines and leukotrienes (188;193;213).
- Interleukins, e.g. interleukin-6 (IL-6) (214-216), which has been suggested to be involved in collagen metabolism and IL-1 β , which result in increased production of COX-2 and PGE₂, matrix metalloproteinase-1 (MMP-1) and MMP-3 (188;213) and down-regulate an apoptosis-inhibitor gene. Therefore IL-1 β and MMPs induced by repetitive mechanical loading can cause extracellular matrix degeneration (217).
- Thromboxane B₂ (192), which is an inflammatory mediator synthesized from arachidonic acid through the cyclooxygenase pathway.

-
- Vascular endothelial growth factor (VEGF) (218-221), which is upregulated by inflammatory cytokines and highly expressed in Achilles tendinopathy (218;222-224).
 - Insulin-like growth factor 1 (IGF-1) and its binding protein (215). IGF-1 stimulates collagen production (225).
 - Transforming growth factor β (TGF- β) (226). TGF- β 1 seems to have a role in the mechanical regulation of local collagen type I in human tendons (226).
 - Hypoxia inducible factor 1 (HIF-1) (227), which is the link between cyclic strain and VEGF (218).
 - Stress-activated protein kinase (SAPKs), which is important upstream regulators of a variety of cell processes, including apoptosis (228) and is activated from pro-inflammatory cytokines, indicating that this signal pathway may contribute to the inflammatory responses (229).
 - Neuroactive mediators, which express adrenergic receptors that respond to norepinephrine with increased intracellular calcium (230) and respond to ATP by increasing intracellular calcium (231).
 - Neuronal growth factor (NGF) (secreted from fibroblasts, and endothelial cells) can express and respond to a network of inflammatory mediators (85) and release TNF- α (232).

In tendinopathic tendons there is found:

- Increased production of PGE₂ (233) and LB₄, which are synthesised from arachidonic acid (for PGE₂ via the action of cyclooxygenase (COX) (213) and LB₄ via the action of lipoxygenase (208)). In tendons harvested from patients with patellar tendinopathy, both the tendon tissue itself and harvested cells expressed higher levels of PGE₂ than did healthy control patellar tendons (233), and a microdialysis study by Alfredson (162) has shown a 50% increase in PGE₂ in the peritendium of Achilles tendinopathy in relation to normal tendons. Alfredson pointed out that the 50% increase of PGE₂ was not significant, but the very small study only included four patients with tendinopathy (162;234). In a study using cDNA arrays and real-time PCR (224), Alfredson found that the mRNA for several cytokines and cytokine receptors was not upregulated in Achilles tendinopathy. However, all cell types in the biopsies were mixed together, consequently a theoretical isolated upregulation in fibroblast or endothelial cells could be missed.

- Increased COX-2 in fibroblast culture harvested from patients with patellar tendinopathy (233).
- Increased transforming growth factor β in fibroblast culture harvested from patients with patellar tendinopathy (233).
- Cells from tendon lesions in patellar tendinopathy were associated with expression of platelet-derived growth factor (PDGF) receptors, and cells from the lesion showed a greater response to PDGF compared with normal tendon cells (235).
- Increased matrix metalloproteinase (MMP) enzymes (including MMPs that can degrade collagen and proteoglycans (188)) in human tendinopathy (236;237). Broad-spectrum inhibitor of matrix metalloproteinases was found to induce painful tendinopathy in patients (238). MMP-3 (a broad-spectrum degradative enzyme which can cleave collagen and proteoglycans) is downregulated in tendinopathy (224;239). MMP-3 is thought to be a key regulatory enzyme in the control of matrix turnover (239), and a decline in this enzyme may represent a failure in the normal remodelling process.
- Nerve ingrowth is known to occur as a response to tendon injury (158), and new nerve ingrowth in the tendon proper with increased levels of the neurotransmitters, e.g. SP, CGRP (94) and glutamate (162), has been reported in tendinopathy. SP stimulates COX-2 and together with CGRP acts pro-inflammatory in peripheral tissues by enhancing cellular release of prostaglandins, histamines, cytokines and growth factors (141;240-242).

In summary, tenocytes and the other cells in and around the tendon can respond to mechanical load by proliferation, cell migration, cytoskeletal changes, matrix remodelling including collagen degradation and synthesis, change in biomechanical strength, production of several growth factors, neurotransmitters, cytokines, prostaglands, other pro-inflammatory mediators and tenocyte death.

3.5 Extracellular matrix (ECM)

The extracellular matrix (ECM) plays a key role in force transmission and tissue structure maintenance in tendons. Together, the collagen and ground substances comprise the extracellular matrix (102).

3.5.1 Collagen

Healthy tendons appear glistening white to the naked eye, and microscopy reveals a hierarchical arrangement of densely packed, parallel bundles of collagen fibres that have a characteristic reflectivity under polarised light.

The collagen is produced principally by fibroblasts on the membrane-bound ribosomes of the rough endoplasmic reticulum and secreted within the extracellular matrix (243).

The collagen fibril may be considered the basic force-transmitting unit of the tendon and is responsible for the structural integrity and for resisting the tensile force applied to the tendon (9;244). Normal tendons and ligaments consist of 30% collagen and 2% elastin (9). In tendons and ligaments in which tensions are only in one direction, the collagen fibres have an orderly parallel arrangement, i.e. they are regularly arranged. Collagen is arranged in hierarchical levels of increasing complexity, beginning with tropocollagen, a triple helix polypeptide chain. The collagen molecules link to form microfibrils. The microfibrils are held together with cross-links (245;246), which are important for the tensile strength of collagen by allowing increased energy absorption, and aggregate in units to form collagen fibrils (primary bundles). Groups of fibres are arranged in a bundle or a fascicle (secondary and tertiary bundles), and each tendon is then made up of multiple fascicles (see figure 1 page 13). The longitudinal fibrils run parallel but cross each other to form spirals, which may uncoil and recoil during loading and unloading and act as a buffer to resist longitudinal, rotational, transverse and horizontal force during movement (247).

There are more than 25 different collagens (248;249); however, tendons are to a large extent made up of fibrillar collagen type I, which is the most abundant collagen in the human body. It is generally estimated to represent 95% of the total collagen (250). In addition, collagen types III and II (where tendons wrap around bony or fibrous pulleys and bony attachments (251)) and others types and a small amount of elastin fibres are present (128). Ligaments have 9-12% of type III collagen and have more cells per mass than tendons (252). In the intact tendon very little type III collagen is found (1-1.5%), in contrast to the degenerative tendon where the collagen found reveals histochemical and ultrastructural characteristics typically associated with type III collagen (253). This indicates that the formation of type III collagen must be an integral part of the disease process in tendinopathy.

Tendons function like all other collagen-based structures in that they respond to external stimuli. Physical training increases collagen synthesis, the number and size of the fibrils, the concentration of metabolic enzymes, the stiffness and the tensile and maximum static strength

of tendons (130;254;255). Reduced physical activity leads to diminished biosynthesis of connective tissue components, atrophies the tendon, increases glycosaminoglycan content, decreases collagen reducible cross-links, increases alignment of collagen fibres, and the tensile strength, elastic stiffness, and the total weight of the tendon decreases (254;256).

Animal studies especially have demonstrated that prolonged training results in enlargement of tendon diameter (254;257;258), but a few studies have also demonstrated enlarged Achilles tendon cross-sectional areas in trained versus sedentary humans (259;260). Human studies did not show consistent resultants (261), and in addition, the influence of exercise on the mechanical properties of tendons is also controversial (257;262-264). Both acute and several weeks' intense physical training stimulated synthesis of type I collagen during the recovery process (255;265). Early in the process, both synthesis and degradation are elevated; whereas later, the anabolic processes dominate, causing a net synthesis of collagen (183;265;266), which may reflect both physiologic adaptation and repair of damage of extracellular matrix structures (255;265;267).

Even in patients with tendinopathy, eccentric rehabilitation increases the collagen synthesis (268).

The aging tendons undergo morphological and biochemical changes where the mean diameter of collagen fibrils increases along with a decrease in concentration of glycoprotein and in the ratio of proteoglycan to collagen (269-271). Aging is associated with a relative drop in cell density and a reduction in the intracytoplasmic organelles responsible for protein synthesis (272). This results in reduced stiffness and strength of the tendon (273). The increased amount of tendon tissue in elderly (274;275) could be a response to many years' loading or a compensation for the reduced tendon quality and strength.

Microdialysis studies indicate that mechanical loading of human tendon tissue during exercise enhanced the amounts of MMPs and TIMPs (tissue inhibitors of metalloproteinases) in the human peritendinous tissue in vivo, and that MMPs and TIMPs are playing a role in collagen adaptation to exercise in tendon tissue (211).

Several growth factors e.g. platelet-derived growth factor (PDGF) (276), transforming growth factor- β 1 (TGF- β 1) (226), insulin-like growth factor-1 and 2 (IGF-1, IGF-2) (225), fibroblast growth factor-2 (FGF-2) (277), epidermal growth factor (EGF) (278) as well as several interleukins (216) have been shown to regulate the synthesis of collagen.

In summary, cross-linked collagen provides tensile strength and stiffness. Human tendons

increase their metabolism and oxygen uptake with loading (279), and their glucose uptake with muscle contraction (280). Despite the fact that the literature on the effect of exercise training on tendon function is indecisive (281), experiments give reason to believe that physical training may modulate the properties of tendons making them larger, stronger and more resistant to injury (259).

3.5.2. Ground substance

The collagen is embedded in a hydrophilic ground substance consisting of proteoglycans (PGs), glycoproteins and glycosaminoglycans (GAGS), many of which are relatively poorly characterised, and several other small molecules (177).

PGs are macromolecules composed of a protein core, with at least one GAG-chain covalent attached and are strongly hydrophilic, enabling rapid diffusion of water-soluble molecules and the migration of cells. PGs are making up less than 1% of the dry mass of tendons (130). In tendons, PGs play a major role in structural and biochemical adaptation to changes in loading, and they are responsible for maintaining proper biomechanical function (282). For example, some PGs are upregulated with tensional load whereas other PGs are upregulated with compression load (283) and there are site-specific variations in proteoglycan content related to the mechanical history and function of the tendons. This illustrates the differentiated response to tensile and compressive loading not only on collagen but also on PGs in the ground substance and indicates specific functions for individual PGs in collagen fibrillogenesis and during load. PGs have been classified into two subfamilies: the small leucine-rich PGs (SLRPs) and the large PGs, which are further divided into two subgroups: those that do not bind hyaluronan; and the “hyalectans”, which bind both hyaluronan and lectin. The SLRP and hyalectans are the most abundant PGs in the tendon ground substances. Compressive loads applied to the tendon (at the most distal portion of the Achilles tendon and the most proximal portion of the patellar tendon) result in the synthesis of PGs that lead to fibrocartilage formation (283).

Adhesive glycoproteins participate in repair and regeneration processes in tendons (284).

GAGs are usually classified into four classes: 1) hyaluronan, 2) chondroitin sulphate and dermatan sulphate, 3) keratin sulphate and 4) heparin sulphate and heparin. Some GAGs are, as mentioned, incorporated into collagen fibrils, whereas other GAGs are interfibrillar, maintaining a hydrated viscoelastic structure and allowing sliding of fibres and fascicles relative to one another. GAGs can bind signal transducers, such as fibroblast growth factor

and vascular endothelial growth factor, and potentially serve as a reservoir, scavenger or co-factor for cell signalling (285). GAGs are increased in chronic tendon pain (286).

In summary, the ground substance contributes to the viscoelastic properties of tendons and the lubrication for interfibrillar gliding. The ground substance maintains water within the tissue, and it provides a medium for diffusion of dissolved nutrients, gasses and other agents.

3.6. Tendinopathy - pathology

Achilles and patellar tendons from patients with chronic tendon pain exhibit similar histopathological changes (99). Whether a specimen has been harvested from an Achilles or a patellar tendon is impossible to determine on the basis of histological examination, despite the fact that in the patellar tendon, chronic tendon pain occurs mainly at the attachment in the young age group between 18-30 years (5;53;287), whereas in the Achilles tendon it is more common in the midportion of the tendon in the age group between 30-60 years (5-8;244).

In stark contrast to the glistening white normal tendon, symptomatic tendons appear grey or yellow-brown and amorphous to the naked eye, and microscopy reveals discontinuous and disorganised collagen fibres that lack reflectivity under polarised light (5;288-291).

Compared with normal tendons, the characteristic features of tendinopathy under light microscopy are A) disrupted collagen and thinner than normal collagen fibres and the characteristic hierarchical structure is lost (292), B) increased ground substance, in which Movin et al (286) found a high concentration of GAGS, C) more prominent and numerous tenocytes without their normal fine spindle shape and with more rounded nuclei and atypical endothelial cellular proliferation (233;293-296) and D) extensive neovascularisation, as seen for example after introduction of the colour and power Doppler US (5;118;161;286;297;298). It is not known in what order these features develop, as all four are usually present in patients with chronic tendon pain who undergo surgery.

The histology studies of specimens removed during surgery from Achilles and patellar tendons are similar (5) and reveal hypoxic degeneration (56) mucoid or myxoid degeneration and fibrinoid necrosis (54;56;291;294-296;299-303), fatty degeneration or tendolipomatosis (56), collagen degeneration (304), pseudocyst change (296), randomised collagen with irregular fibre structure and poor fibre orientation and neovascularisation and tenocyte infiltration (5;50;54;286;290;291;305-308), microtears of the tendinous tissue (53;54;290), chronic inflammatory cell infiltration (309), acute inflammation (304), granulation tissue

(305), small foci with iron positive haemosiderophages (160), focal degeneration near the bone-tendon insertion (54;290;305;310;311), hyalin degeneration and fibrocartilaginous and bony metaplasia (296;310), calcifying tendinopathy (56), angiofibroblastic tendinosis (312), tendon oedema and different combinations of these entities (56;128;313;314). 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. The nomenclature is not systematised, and there may be some overlap between the different pathologies, but most of the histologic findings mentioned 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 (neovascularisation or angiofibroblastic tendinosis, tenocyte infiltration, chronic and acute inflammation), and
3. microtears of the tendinous tissue (the positive haemosiderophages).

Apoptotic (“programmed” cell death unleashed by enzymes, caspases) and necrotic (the integrity of the cell membrane is lost) tenocytes are both observed in tendinosis (102;315;316) and after mechanical loading (317), but it is unknown whether apoptosis is the reason or the consequence of tendinopathy. Apoptosis was increased two and one half times in tendinopathic tendons in relation to control tendons (318).

The prevailing opinion is that no histological evidence of acute inflammation has been documented in ruptured tendons (87;319) or tendinopathic tendons undergoing surgery (43;53) or biopsies (320).

In a recent study (304), however, immunohistochemical staining confirmed acute inflammation in all of 60 ruptured Achilles tendons. The neutrophils had a morphologic reminiscent of necrotic tenocytes, and their presence was confirmed on immunohistochemical staining. By using monoclonal antibodies (CD3 for detection T lymphocytes, CD 20 for detection B lymphocytes and CD 68 for detection macrophages), Schubert et al (160) demonstrated that B and T lymphocytes and macrophages were increased in Achilles tendinopathy samples. These two studies need more confirmation.

Areas of altered collagen fibre structure and increased interfibrillar ground substance, which has been shown to consist of hydrophilic GAGS, in Achilles tendinopathy correspond to the increased signal on MRI (321) and the hypoechogenic regions on US (322;323). Areas with increased signals on MRI (291;312) and granulomas and hypoechogenic regions on US

(310;324) in patellar tendinopathy appear to correspond to mucoid degeneration (291).

In summary, tendinopathy reveals abnormalities in collagen, in ground substance and cells. The collagen is disrupted, disarrayed, disorientated and separated, giving the impression of loss of the normally parallel orientation. Fibre diameter and the overall density of collagen are decreased, and collagen microtears are often seen. The ground substance is increased. Neovascularisation and tenocyte infiltration are often described. There is no histological evidence of acute inflammation in the tendon proper; however newer studies with immunohistochemical staining and flow cytometry have demonstrated inflammatory cells.

3.7 Tendinopathy - aetiology

The exact pathogenesis of chronic tendinopathy remains largely unknown but seems to be a multifactorial process. There is a wide range of suggested aetiological factors, but the scientific background for most of these suggestions is lacking. They must be characterised as non-proven theories, and, above all, their clinical importance is not well known (325). At the moment, many risk factors, both intrinsic (those from within the body) and extrinsic factors (those outside the body) have been suggested as mechanisms of overuse tendon injury (50;326):

Intrinsic factors:

Age with decreased arterial blood flow with local hypoxia, less nutrition, impaired metabolism, and free radicals (110;327;328). Tendinopathies are significantly more common in elderly athletes compared with young athletes (329;330). There is some evidence of accumulated physical damage in ageing tendons, with increases in the amount of denatured collagen and increased proteolytic cleavage of matrix component (236), changes that all are associated with deterioration in the physical properties of the tendon (217), although some authors find normal ageing of connective tissue is morphological different from degeneration (331).

Vascular perfusion. Cells in ruptured tendons showed evidence of hypoxic changes (56), and microdialysis studies have demonstrated high intra-tendinous concentrations of lactate in chronic, painful Achilles tendons (332). On relaxation, reperfusion occurs, generating oxygen free radicals (333;334).

Exercise-induced hyperthermia (335;336). During exercise, tendons may develop temperature levels above the 42.5-degree threshold for fibroblast viability (337).

Deposits of amyloid, calcification, cholesterol (338) and breakdown products of protein such as tenascin-C (339-341).

Anatomic variants, e.g. various alignment such as Q-angle and foot hyperpronation (331;342), varus and valgus deformity of the forefoot and hindfoot (49;331), pes cavus (343) and planus (344), genu valgum or varum, leg-length discrepancy (325;345), patellofemoral

malalignment and femoral neck anteversion (89;325). Åström demonstrated that biomechanical “abnormalities” were unimportant in chronic Achilles tendinopathy (6). Impingement (346;347) (despite there being no relationship between the patella and the patellar tendon evaluated with MRI (348;349)). Limited range of motion of the ankle joint (49). Joint laxity (325), e.g. excessive motion of the hindfoot in the frontal plane (350), especially a lateral heel strike with compensatory pronation, and lateral ankle instability. Muscle weakness/imbalance (351;352) and lack of flexibility (350;353;354). Gender (325). Genetic (355-361). Systemic disorders (362), e.g. inherited disorders (363), endocrine (364-366) and metabolic diseases (367;368) and rheumatologic disease (369) (e.g. rheumatoid arthritis (370;371), psoriasis (372), systemic lupus erythematosus (373;374)), infectious disease, increased serum lipids (375), hyperuricaemia (376), hypertension (365), chronic renal failure (377) and neurologic conditions (362). Sciatic pain (378). Body mass (325;365).

Extrinsic factors:

Physical load in sport/occupation, e.g. excessive force, repetitive loading, abnormal/unusual movement (379). Training errors (331;343;380), e.g. poor technique (381;382), fast progression, high intensity, fatigue. Equipment (383;384), e.g. new or worn out shoes. Environmental conditions, e.g. temperature and running surface (49;380). Medication, e.g. glucocorticosteroid injections (29;30), systemic glucocorticosteroids (385;386), oral contraceptives (365), flouoroquinolones (387;388).

While isolated introduction of these risk factors typically does not independently cause tendinopathy, their presence may potentiate the development of tendinopathy when they co-exist with other risk factors, e.g. mechanical overload. Exactly how extrinsic and intrinsic risk factors combine to generate the initial tissue damage at the onset of tendinopathy cannot be explained entirely at the moment (389).

There are several hypotheses for developing tendinopathy.

- The over-use theory. Despite one third of patient with Achilles tendinopathy did not participate in vigorous physical activity (306;390) the traditional view of tendinopathy is a tendon injury associated with over-use (10;128;327) from repetitive mechanical load, microtears and acute and then chronic phases of inflammatory "tendinitis", which lead to tendon degeneration, despite these conditions as just mentioned also being seen in not physically active individuals (7;8). It has been found 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 (2;328). Most authors have as mentioned earlier rejected the inflammatory part of the theory, but in chronic Achilles tendinopathy low level laser therapy significantly reduces peritendinous PGE₂ concentrations and neovascularisation and increases pressure pain threshold and single jump hop test suggesting an inflammatory component to chronic tendinopathy (391). In the “neurogen over-use hypothesis” the nerve endings in the mast cells in the matrix release neuropeptides (SP and CGRP) and the mast cells degranulate, releasing a panoply of agents, which modulate cell activity in the matrix. In this way excessive stimulation leads to tissue breakdown and degeneration (392) via neurogenic inflammation.

- The under-use theory. Newer studies have put a question mark over the over-use theory. Recently, it has been shown that the lowest tensile strain in Achilles and patellar tendons is measured at exactly the site where the changes of classic patellar tendinopathy and Achilles entesopathy are found (393-395). The strain patterns in tendons may not be uniform, as tendons show stress-shielded areas and areas subjected to compressive loading at the enthesis. This indicates that some tendinopathies may paradoxically be considered as “under-use” lesions (396).
- The ageing and vascular theories are mentioned above. Despite exercise resulting in peritendinous blood flow increases up to sevenfold (113;114) and oxygen extraction and total haemoglobin volume increases in the peritendinous region (113), this does not guarantee that the increase in blood flow (especially in the elderly) is sufficient to meet the oxidative needs of the tendons during exercise. Theoretically, ischaemia can trigger neovascularisation and initiate apoptosis, which is increased in tendinopathy (318), perhaps by ischaemia-induced increased intracellular calcium or high NO concentrations (334), which also have been associated with activating the apoptotic pathway (397;398).

To evaluate the different hypotheses, experimental models of tendinopathy have been constructed. Tendinopathies in animal studies have been produced by repetitive mechanical loads, injection of collagenase, cytokines and inflammatory prostaglandins:

- Backman (399) demonstrated an experimental model of Achilles tendinopathy in rabbits. The rabbits were exercised in a kicking machine that produced passive

flexions and extensions of the ankle joint, and active contractions of the triceps surae muscles were induced by electrical stimulation via surface electrodes. The animals were exercised for 5 to 6 weeks, with a rate of 150 flexions and extensions per minute for 2 hours, three times a week. Light microscopic examination showed degenerative changes of the tendon, and increased number of capillaries, infiltrates of inflammatory cells, oedema and fibrosis in the paratenon.

- The tendons injected with collagenase (400-403) caused tendon degeneration and later on healing with increased angiogenesis of the matrix, focal fibrosis, myxoid changes, and collagen-bundle disarray with persistent increase in cellularity. There was a significant increase in cross-sectional area and a significant increase in crosslinking.
- The tendons injected with cytokines (401) demonstrated increased cellularity, but the matrix appeared unchanged. Biomechanically, a significant decrease in ultimate load was seen in the tendons injected with cytokines, but no change was seen in cross-sectional area.
- PGE₁ peritendinous injection in patellar tendons (404) leads to degeneration as well as inflammation around and within the tendon and results in significantly higher values for average water content of the tendons and a histological picture of acute inflammation. After 5 weeks, tendons showed fibrosis of the paratenon, with adhesions and intra-tendinous degeneration.
- PGE₂ intratendinous injections in patellar tendons (405) caused focal areas of hypercellularity, tendon disorganisation and degeneration and loss of normal tissue architecture. Tendons injected exhibited loosely organised collagen fibrils and had thinner collagen fibril diameter compared with control tendons.
- Fluoroquinolone antibiotics have been shown to induce tendinopathy (406), modulate MMP activity (407;408) and stimulate inflammatory pathways in or around tendons (409). In this way, treatment of rodents with fluoroquinolone antibiotics can induce tendinopathy, with inflammation of the paratenon preceding degenerative changes in the tendon matrix (410). Animal models are being tested, but it is too early to know whether they can be used to test new treatment methods (411).
- Human patellar tendon fibroblasts treated with PGE₂ showed that fibroblast proliferation was significantly decreased, and the proliferation of and collagen production by human patellar tendon fibroblasts was affected by PGE₂ in a dosage-dependent manner (196). Thus high PGE₂ produced by fibroblasts in response to

repetitive mechanical loading can be involved in the development of tendinopathy by the tendon inflammation induced. Taken together, these results show that high levels of PGE₂ present in the tendon matrix in vivo not only participate in the tendon inflammation but also decrease fibroblast proliferation and collagen production, which may lead to tendon matrix degeneration.

Arnoczku (228) has shown a direct relationship between the amount of stress that tendon cells are exposed to and the induction of a stress-activated protein kinase SAPK, such as c-Jun N-terminal kinase (JNK). SAPK is a signal transduction protein that is activated through a diverse set of environmental conditions, such as heat, shock and pro-inflammatory cytokines (229), indicating that this signal pathway can be a part of the inflammatory response. Although transient activation of JNK is associated with normal cell processes, persistent JNK activation has been linked to the initiation of apoptosis, which has been shown to be increased in tendinopathy (318).

Repeated heavy loading, with or without the presence of one or more intrinsic risk factors, may produce initial pathological changes in either the extracellular matrix or 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 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 in nature). Collagen fibres begin to slide past one another (causing breakage of their cross-linked structure) and denature (with inflammation oedema and pain) causing a focal area of intratendinous degeneration, partial tears and complete ruptures (9;412). The cumulative trauma is thought to weaken collagen cross-linking and the non-collagenous matrix and vascular elements of the tendon, finally leading to "tendinopathy". Hitherto the prevailing opinion has therefore been that tendinopathy may begin with disrupted collagen due to mechanical overload (325). However, studies of rats sacrificed 2 weeks after tendon overload showed tenocyte activation but no other features of tendinosis – ground substance, collagen and vascularisation remained normal (413), whereas all specimens exhibited all four features of tendinosis after 5 weeks of Achilles tendon overload (399). In a study (297) investigating the prevalence of the same four light microscopic features of patellar tendinosis in asymptomatic athletic subjects undergoing patellar tendon anterior cruciate ligament reconstruction, 36% of the patellar ligaments were

abnormal on light microscopy. In nearly all of the abnormal tendons, including tendons with increased ground substance and collagen separation, tenocyte changes were found, while no tendons demonstrated neovascularisation. These data indicate that tendinopathy begins with cellular activation and proceeds through phases of increased ground substance, then collagen separation and eventually neovascularisation.

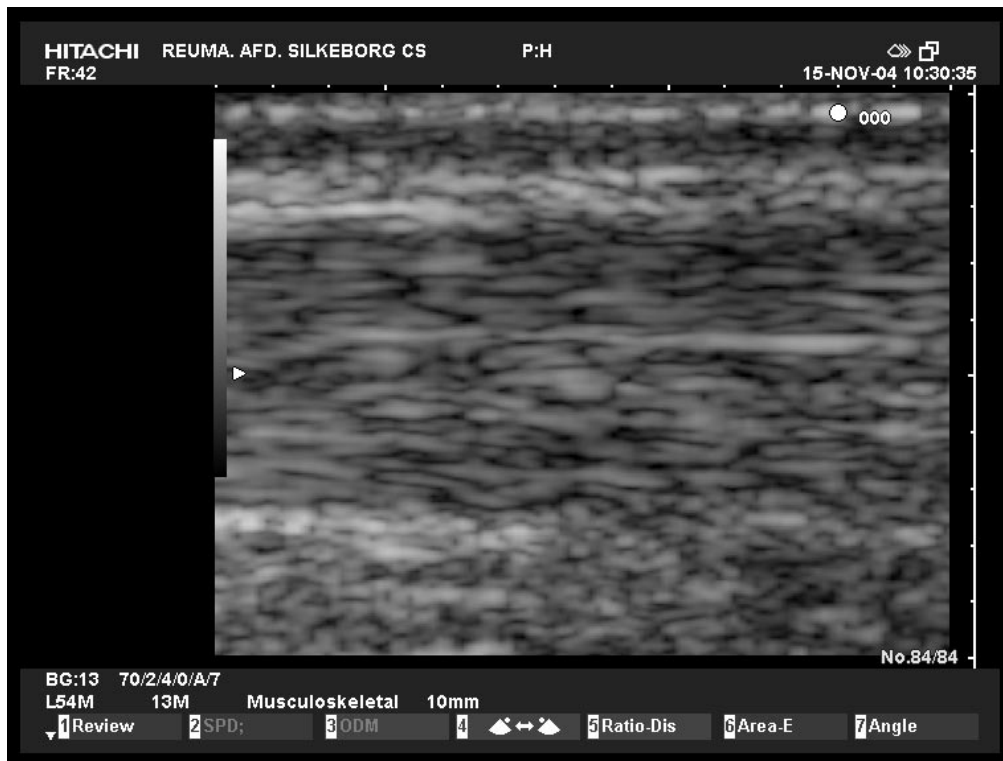
In summary, there remains a substantial lack of understanding about the chain of events leading to tendinopathy. The literature is dominated by several hypotheses on the reason for tendon rupture, e.g. overload, underload, ageing, and vascular. However, the different theories are not mutually exclusive. All the different theories could be explained by a misbalance between load and training level, most probably because of a too rapid increase in training intensity. Overloading is crucial in the development of tendinopathy in individuals who, perhaps because of genetic factors, are predisposed. Repetitive mechanical stretching of human tendon fibroblasts will increase the expression and activity levels of phospholipase-A₂, COX-2 expression, PGE₂ and LB₄ production and production of many other pro-inflammatory mediators, including cytokines and neuropeptides, all of which are interconnected. Human microdialysis studies have shown increased PGE₂ peritendinous after exercise, and some studies had shown increased PGE₂ and neuropeptides in chronic tendinopathy. Finally, in vivo animal studies using patellar tendons revealed that repeated exposure to PGE₂ and cytokines causes degenerative changes in the tendon. Therefore, most probably – despite a great deal of uncertainty still being included in these concepts - an inflammatory process may be related to the development of tendinopathy, and the inflammation may also play a role in chronic tendinopathy.

However, there are still no good answers for many questions, e.g. why patellar tendinopathy is seen in younger persons than is Achilles tendinopathy and why does the damage appear to be permanent in as much as the injuries are not healed after months of rest and avoidance of the trigger factors that are supposed to cause the injury?

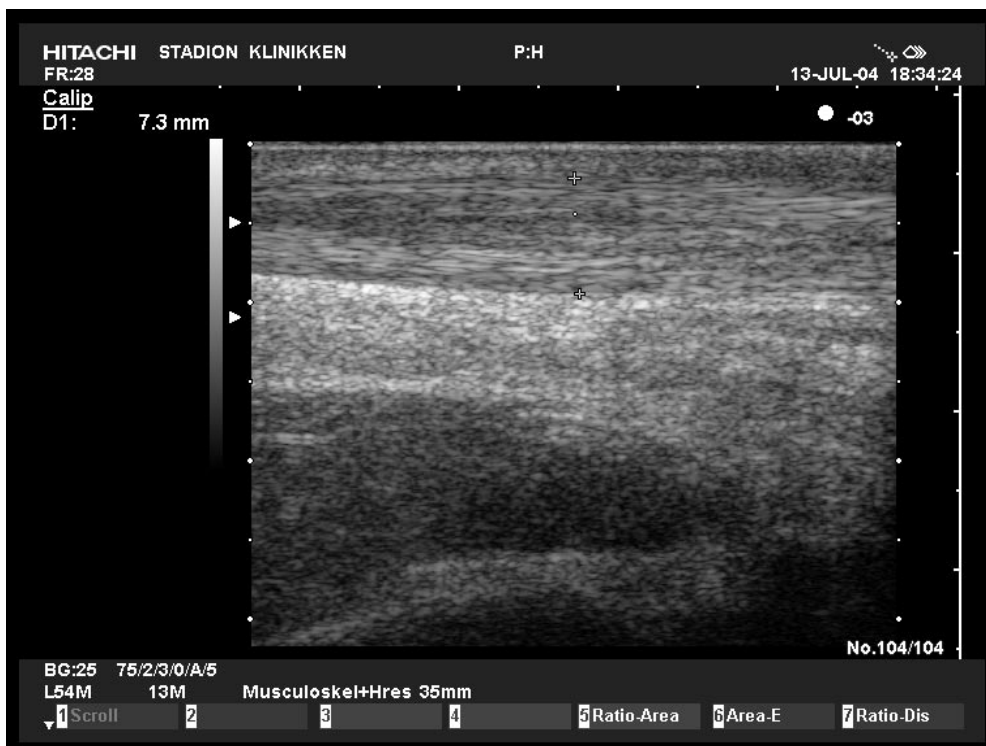
4. Ultrasonography

Ultrasonography (US) has, during the last 20 years, been increasingly employed in diagnosing pathologies of the Achilles and patellar tendons (286;305;414-421) because it provides a readily-available, quick, safe and inexpensive method to image tendon tissue structure. Tendons are composed largely of parallel running fascicles of collagen fibres that interweave

and interconnect. These fascicles are large enough to be visible to the naked eye as well as US (320;422;423):



Very subtle changes in the architecture can be seen in intrasubstance tendon degeneration and partial-thickness tears:



Reflectivity, attenuation and backscatter of the US signal are highly anisotropic characteristics

in tendons. These parameters depend on the orientation of the US beam relative to the tendon structure (424).

It is important to alternate frequently between longitudinal and transversal scans to gain a three-dimensional impression of the structure under evaluation (415;416). On longitudinal scan, the tendon appears as a band-like structure containing hyperechoic lines. This bright fibrillar structure is best visualised when the transducer is perfectly perpendicular to the tendon (see photos above). Longitudinal images allow the examiner to distinguish separate tendon fibres more clearly (425). The cross-sectional profile of the Achilles tendon is bright oval-shaped and rectangular in the patellar tendon (417).

In most other studies, the measurement of the tendons is not clearly described (66;118;426-429), and when the method is described, the anteroposterior (AP) diameter (method I, see figure 2 below) was often measured in either transversal (418;430-433) or longitudinal (434) scans. Fornage (422) emphasised that since the orientation of the (Achilles) tendon is generally oblique, true sagittal (AP diameter) ultrasonograms (method I) may overestimate the tendon thickness. Fornage recommended method II (diameter measured perpendicular to the greatest width, see figure 2 below), which allows measurement with both longitudinal and transversal scans after the three-dimensional impression of the tendons is gained.

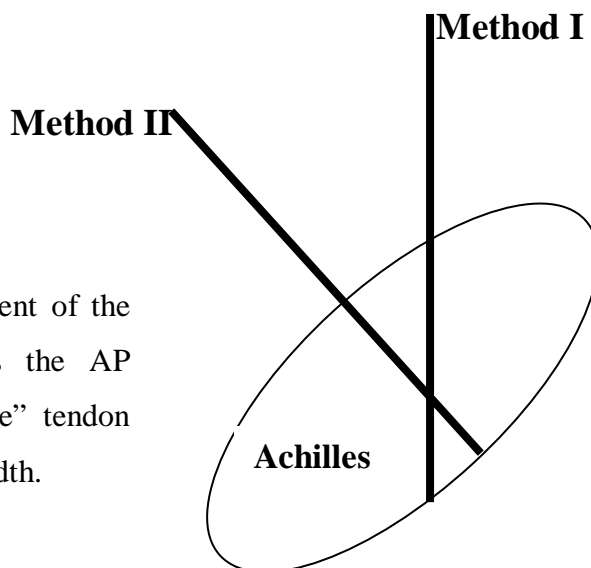


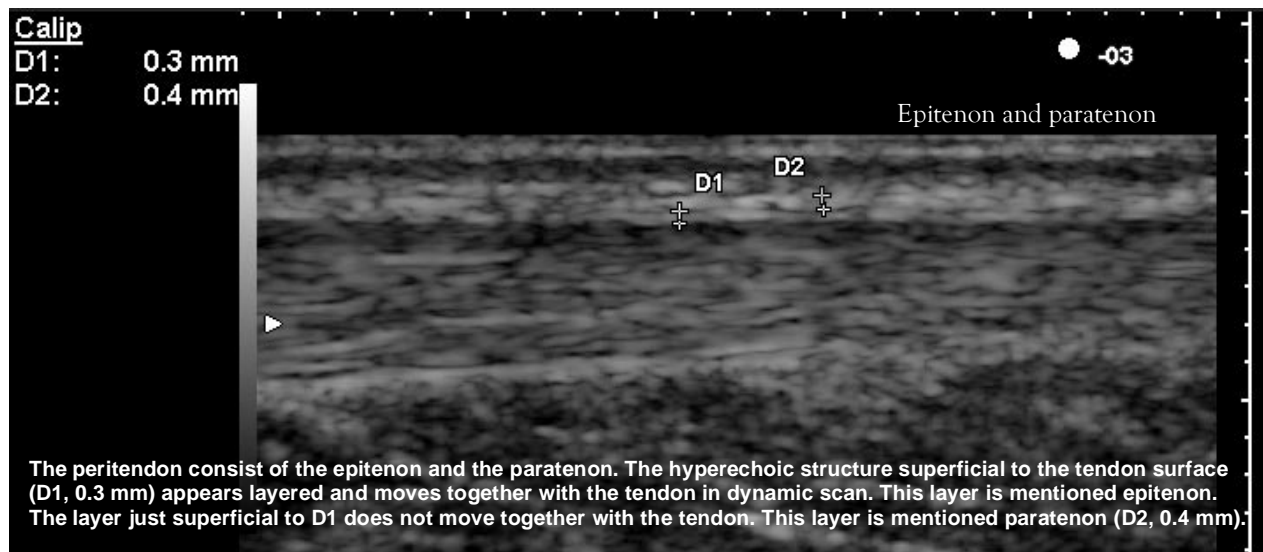
Figure 2. US scan planes for measurement of the tendon thickness. Method I measures the AP thickness. Method II measures the “true” tendon thickness perpendicular to the greatest width.

Kallinen (435) found difficulties in reproducing the exact location of the ultrasonographic imaging plane in repeated measurements of tendon thickness, and he suggested improving the

method by marking the site with a metal wire to cast an acoustic shadowing line which would be easy to see during imaging. However, as in this thesis, the ultrasonographic longitudinal scan of the tendon allows the examiner to record the distance from the measuring point to the insertion with 0.1-0.2 mm precision, and thereby measure the tendon thickness at exactly the same point during subsequent controls. This is particularly important when measuring the tendon thickness of the patellar tendon, which is cone-shaped with a significantly greater diameter at the proximal end.

While tendon thickness can be measured in both the longitudinal and transversal scan (436), the tendon width and length (which is not used in this thesis) can of course only be measured in the transversal and longitudinal scan, respectively.

Tendons without a synovial sheath are slightly more difficult to examine using US than tendons with a synovial sheath. In tendons without a synovial sheath, the epitenon is tightly bound to the tendon, and during dynamic scanning the tendon can be seen to move in relation to the paratenon. Ultrasonographically, the epitenon is seen as a reflective line surrounding the tendon (422).



In patients with chronic Achilles tendon disease, US shows spindle shaped thickening of the tendon (either the superficial gastrocnemius, the profound soleus or both), discontinuity of the fibres, focal hypoechoic intratendinous areas, intratendinous focal calcification, partial ruptures and thickening of the paratenon with poorly defined borders (especially the profound border at the attachment at the calcaneus), bursitis (retrocalcaneal and superficial) (414;437;438) and the contours of the Achilles tendon may be deformed with a bumpy

appearance (415).

In patients with chronic patellar tendon disease, US shows a cone-shaped, hypoechoic area in the patellar tendon often located in the upper insertion at the lower pole of the patella, intratendinous focal calcification, discontinuity of the fibres, partial ruptures, irregular hypoechoic paratenon with poorly defined borders (especially the proximal profound border) and bursitis (profound and superficial). The thickening of the tendon can be localised or diffuse including the whole tendon (300;439).

In earlier studies, these ultrasonographic abnormalities have been found to correspond to the areas of altered collagen fibre structure and increased interfibrillar ground substance (hydrophilic glycosaminoglycans) in Achilles tendinopathy (7;322;323) and mucoid degeneration (291) in patellar tendinopathy (310;324).

Some studies have compared US with operative findings (426;427;440) and US with MRI and operative findings (291;418;436;441) and found that US is a suitable imaging modality in chronic disorders in the Achilles and patellar tendons. Several authors (57;59;117;418;421;430;442-444) showed that US can be used to predict the outcome of tendinopathy, whereas other studies found no such correlation (433). In a review, Warden (445) found that 85% of athletes with symptoms of jumper's knee have ultrasonographically abnormal patellar tendons (94%, if the oldest study from 1990 (310) was excluded) whereas this is the case in 23% of asymptomatic athletes.

Cook et al (57) found the relative risk for developing symptoms of jumper's knee is 4.2 times greater in elite junior basketball players with ultrasonographic hypoechoic areas in the patellar tendon than in controls with ultrasonographic normal patellar tendons, whereas Warden in the above review (445) found the risk for developing symptoms of jumper's knee increased from 4% to 26% if ultrasonographic abnormalities were found in the patellar tendon. In some studies of late stage tendinopathy, a close relationship has been described between clinical symptoms and signs and ultrasonographic changes (53;305;306;446). As mentioned above, these findings have been in accordance with subsequent histological examination after operation and Öhberg et al (13) and Gisslen et al (421) showed that structural abnormalities seen by US seem to be associated with pain in the tendons.

In contrast, Lian et al (58) found that in earlier stages of the disease, the results may be more dissociated, and in a study from 1990 Myllymaki (310) found only that 50% of athletes with

jumper's knee have ultrasonographically abnormal patellar tendons. Khan et al (433) found that US showed only moderate correlation with clinical assessment of acute and chronic Achilles tendon disorders.

MRI has also been used for musculoskeletal imaging during the last 20 years, and both MRI and US are competing modalities in the diagnosis of tendon pathology. US has several significant advantages over MRI. The greatest strength of the US is that it is interactive and the examiner is in contact with the patient, and any site of reported pain or tenderness can be directly correlated with its real-time scan appearance on the screen. The ultrasonographer can make use of the dynamic real-time character of US, so that tendons can be studied throughout their range of motion and side-to-side comparison is always available during the US examination. This unique advantage over other cross-sectional imaging modalities like CT and MRI is of course especially applicable in the evaluation of mobile structures such as tendons (447;448). Tissue with few mobile protons emits little or no signal and, therefore, the internal architecture of the tendon is not well demonstrated in MRI (449-451). In contrast, US shows the fine internal structure of tendons, and US therefore pictures the anatomic border of the tendon more precisely than MRI (428), and in agreement with this the "standard deviation" (SD) and "range of the mean difference" from repeated measurement are less in US than in MRI (432). In agreement with this, Warden has shown that US is more accurate than MRI in confirming clinically diagnosed patellar tendinopathy (452). MRI requires complex surface coils to attain maximal spatial resolution. It is much easier to change to a higher-frequency US transducer to obtain greater spatial resolution. In fact, the spatial resolution of US is much better than that of MRI if both examinations are performed with the most modern equipment (449;453). Furthermore, US can demonstrate the neovascularisation in tendinopathy; however, this was not a part of this study.

Despite the fact that US is increasingly used in sports medicine, only modest methodological studies exist concerning US of tendons with measurement of the inter- and intra-observer variation (449;454;455), and there is no documented consensus as to where and how tendons should be measured. MRI is well established as an imaging modality in tendon research (456;457) because MRI hitherto is regarded as being more easy to perform in a standardised manner than US (321). It is also possible with US to examine the exact same fix point of the tendon during repeated measures by recording, in the longitudinal scan plane, the distance from the measuring point to the bony attachment of the tendons. This technique – as evaluated

in this thesis - will probably reduce the variation of repeated measurement. And if US has acceptable inter- and intra-observer variation, it can be turned to practical account, and the examiner will have a method easy to use and which allows the examiner to improve monitoring of treatment not only in daily clinic but also in future studies.

One of the purposes of this study was to evaluate US in preparation for improving the accuracy of measurement of tendon thickness and objectivity of the treatment control of patients in the daily clinic and in future studies. The purpose of this study is not to compare US and MRI, because US today is a well established first choice modality regarded as the examiner's extended hand in the daily clinic, which will never be the case for MRI, although new MRI techniques are being developed (450;458).

In summary, US is a readily available, quick, safe and inexpensive method to image tendon tissue structure. Today US is a well established first choice modality regarded as the examiner's extended hand in the daily clinic.

5. Pressure algometry

Pressure algometry, as a method for inducing experimental pain, has been used for decades (459). The essence of pressure algometry is that increasing pressure is applied to the part of the body that is being investigated, and the outcome is the patients' reaction to the pressure. The outcome measurement in pressure algometry is the pain detection threshold (PDT), i.e.: the point at which pressure pain is first experienced by the patient. Numerous studies involving measurement of pressure pain in deep tissues, myofascial pain syndromes, headaches, wounds and joints have been performed (460-468). Short-term reliability has been documented, long-term reliability has been evaluated but is more questionable, and diurnal variation in PDT has been shown to be small (464). Hitherto only a few studies have used pressure algometry to examine tendon PDT in athletes with chronic tendinopathy (391;468). If pressure algometry can be proved to be valuable in monitoring the effect of treatment in chronic tendinopathy, then the technique can be beneficial in future studies.

In summary, pressure algometry is an objective method for measuring the pain detecting level. Hitherto only a few studies have used pressure algometry in examining chronic tendinopathy.

6. Glucocorticosteroids

The mechanisms of action of the anti-inflammatory action of glucocorticosteroids are not completely understood, but glucocorticosteroids modulate inflammation through an effect on, not only prostaglandin production, but also by modulating the cytokine activity with suppression of cytokines as IL-6 and IL-1- β (235) in the parenchymal tissue as well as the cellular component. The classic inflammation and the neurogenic inflammation are overlapping, and glucocorticosteroids can inhibit the Substance P-mediated COX2 expression. Glucocorticosteroids regulate vascular reactivity by acting on both endothelial and vascular smooth muscle cells and glucocorticosteroid receptor protein has been identified in endothelial and vascular smooth muscle cells and in the cytoplasm (469). In endothelial cells, glucocorticosteroids suppress the production of vasodilators, such as prostacyclin and nitric oxide (124;125). Therefore glucocorticosteroids are to some extent vasoconstrictors. The effects of glucocorticosteroids differ significantly with cell type, and effects may vary with the growth state and other associated factors. For example, glucocorticosteroids block the growth of hepatocytes (470) but induce cell growth and proliferation in fibroblasts (471). The direct effects of local injected glucocorticosteroids on the material properties of the tendon are unknown, and documentation of the effect and side effects is inadequate (55;472). Local injections of glucocorticosteroids have a few well-known side effects (473): iatrogenic infection (the most serious but less common complication), local irritation (postinjection “flare”), erythema of the face and torso, skin atrophy and a minor systemic effect. Local injection with glucocorticosteroids is a common treatment for tendinopathies, although several case reports of tendon rupture have been published (86;474;474-478), but the question remains unanswered: Was the rupture of the tendon a result of the disease within the tendon that predated the injection, or was it the result of the effects of the injection of glucocorticosteroids? In two studies including more than 400 patients (479;480) all with Achilles tendinopathy, the rupture rate were not higher in the group treated with local glucocorticosteroid injections (3.7 - 6%) than in the non-treated group (3.5 - 8%). Read (481) found a 3% rupture rate in patients receiving glucocorticosteroid injections, while Nehrer (430) in a small study showed that in the patients with US-verified thickening of the Achilles tendons and chronic pain, a spontaneous rupture in non-glucocorticosteroid-treated occurred in 28% of the cases after a follow-up of 48 months.

A number of animal and laboratory studies have addressed the topic of glucocorticosteroid injections into or around tendons, with mixed results. Several studies have shown that local

and systemic glucocorticosteroids decrease cell proliferation, human tenocytes activity, metabolism, and collagen synthesis (causing a reduction of tensile strength of tendons and isolated collagen fascicles (482-492)), and suppress proteoglycan production in human tenocytes (493;494); although other studies have failed to demonstrate any deleterious effect of glucocorticosteroid injections (495-498). In cultured human tenocytes the suppression of glucocorticosteroids was reversed by simultaneous addition of platelet-derived growth factor (PDGF) (493;494).

Intratendinous injection of glucocorticosteroids is usually condemned, although obviously not all studies, as mentioned above, agree, and even in human pilot studies (499;500), intratendinous glucocorticosteroid injection has no side effects. But, no evidence of any serious side effects (except infection) of peritendinous glucocorticosteroids injections in human *in vivo* exists in the literature (28;30;480;501). There are only few randomised, placebo controlled studies concerning the effect of local glucocorticosteroids and chronic tendon injuries especially in the Achilles and patellar tendons (29;30;55;501;502). An effect has been shown in treatment of trigger finger (503-505) and (sub)acute Achilles tendinitis (31), whereas only a short-term effect has been shown in tennis elbow (506;507) and rotator cuff tendinitis (508-512). With these conditions, studies with a higher methodological score produced more favourable results. However, a double blind randomised controlled trial examining the effectiveness of glucocorticosteroid injections in Achilles paratenonitis showed no benefit (pain, tenderness and return to normal activity) of peritendinous methylprednisolone and marcaïne over marcaïne injections alone (501).

It is well known that most blindly injections are not correctly placed. Among others, Eustance found that even in the hands of musculoskeletal specialists, only a minority of injections are performed accurately (29% of subacromial and 42% of intra-articular shoulder injections) and that outcome correlates significantly with accuracy of injection (513;514). Zhingis et al found similar results in subjects with tenosynovitis stenosans (De Quervain's) (515). US-guided injection – as used in this thesis - will increase the accuracy of injections, and that will most likely reduce side effects and increase effect.

In summary, the use of glucocorticosteroids injections is widespread in the treatment of chronic tendon overload syndromes, despite there being little reproducible evidence in the literature to support the efficacy of glucocorticosteroid injection in managing tendinopathies.

No randomised, placebo-controlled human studies exist concerning glucocorticosteroid injection in the treatment of chronic Achilles or patellar tendinopathy. Many experimental studies had shown a decreased collagen synthesis, and many human case reports of tendon ruptures in chronic tendinopathy have been published. However, it is not possible to decide, based on the published evidence, whether the ruptures are due to the injection or the disease for which the injections were given. The rate of rupture in patients with Achilles tendinopathy seems to be 3-8% irrespective of treatment. Whether the blockade of the arachidonic pathways to limit inflammation has a stimulating or detrimental effect on regeneration or healing processes in tendinopathies *in vivo* is unknown.

AIMS OF THE THESIS

The overall aim of this study was to gain new knowledge about the treatment of Achilles and patellar tendinopathy with peritendinous injected glucocorticosteroids and to evaluate the usefulness of US and pressure algometry in managing tendinopathy.

Specific aims were:

- * Study the effect of ultrasonographically guided peritendinous glucocorticosteroid injections in chronic Achilles and patellar tendinopathy.
- * Examine whether it is possible by US of the Achilles and patellar tendons to identify a group of asymptomatic athletes with an increased risk of developing symptomatic injuries in the Achilles and patellar tendons.
- * Evaluate the intra- and inter-observer variations of US and pressure algometry with special emphasis on using the modalities as objective measurements of the effect of treatment.

MATERIALS

Study I

Ultrasonography in evaluation of Achilles and patellar tendon thickness.

Sub-study 1:

Among 30 voluntary elite football players, we studied the following tendons

38 Achilles tendons (mean age 26.3 years, height 180 cm, weight 77.5 kg)

27 patellar tendons (mean age 26.4 years, height 179 cm, weight 77.1 kg)

Sub-study 2:

Among 30 voluntary elite football players, we studied the following tendons:

33 normal Achilles tendons (mean age 26.6 years, height 180 cm, weight 78.1 kg),

14 abnormal Achilles tendons (mean age 28.8 years, height 183 cm, weight 83.7 kg),

35 normal patellar tendons (mean age 26.2 years, height 180 cm, weight 77.9 kg),

10 abnormal patellar tendons (mean age 26.3 years, height 182 cm, weight 80.3 kg).

Sub-study 3:

Among 27 voluntary males and females, we studied the following tendons:

52 Achilles tendons (mean age 24.0, height 183 cm, weight 77.7 kg).

Study 2

In this study (**Ultrasonography and pressure algometry in evaluation of Achilles and patellar tendons. Intra and inter observer variability**) the following volunteers were included:

Among 40 voluntary patients, we studied the following:

57 tendons with US and

47 tendons by pressure algometry.

12 algometry measurements were made at the temporal region as a reference point.

None of the above 40 voluntary patients were included in other studies.

Study 3**Influence of acute physical activity immediately before ultrasonographic measurement of Achilles tendon thickness.**

Among 10 asymptomatic female elite handball players (mean age 26 years, height 175 cm, weight 69 kg), we studied 20 Achilles tendons by US.

None of the above 20 voluntary female elite handball players were included in other studies.

Study 4**Significance of ultrasonographically detected asymptomatic tendinosis in the patellar and Achilles tendons of elite soccer players: A longitudinal study.**

Among 54 volunteer professional male soccer players (18-35 years of age) from two clubs in the best Danish league (SAS League), we examined the following tendons:

98 asymptomatic patellar tendons and

96 asymptomatic Achilles tendons were included.

None of the above 54 soccer players were included in other studies.

Study 5

In this study (**Ultrasonography as a tool for diagnosis, guidance of local steroid injection and together with pressure algometry monitoring of the treatment of athletes with chronic jumper's knee and Achilles tendinitis**) the following were included:

24 athletes (mean age 43.7 years, height 180 cm, weight 84,8 kg) with unilateral chronic Achilles tendinitis for more than 6 months and

24 athletes (mean age 28.4 years, height 180 cm, weight 78,7 kg) with unilateral chronic jumper's knee for more than 6 months.

None of the above 48 athletes were included in other studies.

ETHICS

All studies were carried out according to the Helsinki declaration and were approved by the local ethics committees. All patients and volunteers entered the study after oral and written information and gave consent to participate.

METHODS

Ultrasonography (US)

In study I, a SonoSite TITAN portable ultrasonograph with an electronic 10 MHz linear transducer was used for the ultrasonographic examination in sub-studies 1 and 2. A high resolution Hitachi 8500 ultrasonograph with a 12 MHz linear transducer was used in sub-study 3. In studies II, III, IV and V a high resolution Toshiba ECCOCEE ultrasonograph with a mechanical 7.5 MHz linear and phased array transducer with waterpad was used for the ultrasonographic examinations.

All tendons were scanned longitudinally and transversally, and the tendons were measured in accordance with earlier studies: The Achilles tendons were measured with patients in a prone position and their heels overhanging the examination couch to enable movement of the feet (59;118;418;426;429-434), and the patellar tendons were measured with patients in supine position (65). Both the ankles and the knees were flexed 90 degrees which ensures standardised tension on the tendon and provides the best imaging during contraction of the quadriceps and gastrocnemius muscles. This position straightens the extensor tendons to avoid the waving appearance of the tendons, clear the artefact and show the normal fibrillar texture of the tendons, which is best seen in the longitudinal scan (415). Ninety degrees flexion was chosen because it is easy to assess without a goniometer. Other studies have chosen 30 degrees (449) and 45 (455) degrees knee flexion. The tendons were examined at rest and during active and passive flexion/extension manoeuvres (415) so the dynamic nature of the real-time examination was exploited to the fullest.

When three-dimensional impressions of the tendon were gained by moving the transducer side to side in the longitudinal scan and proximal to distal in the transversal scan, the tendon thickness could be measured at the thickest point in both longitudinal and transversal scans.

In the longitudinal scan, the thickness of the normal Achilles tendons was measured 20 mm

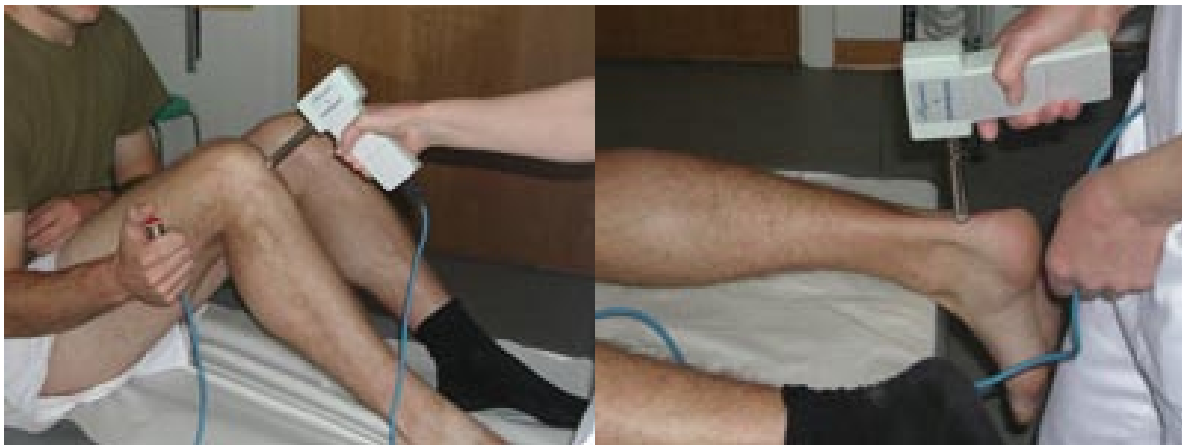
from the attachment of the calcaneus, and the thickness of the normal patellar tendons was measured 6 mm from the attachment of the patella. In the longitudinal scan, the thickness of the abnormal Achilles and patellar tendons was measured at the thickest point, and the distance from the point of measuring to the attachment of the calcaneus or patella was recorded.

In studies III, IV and V, the maximum anteroposterior (AP) diameter (method I, figure 2) was measured in the longitudinal scan. In all other measurements, the transducer in the longitudinal scan was moved and angled medially and laterally until the diameter perpendicular to the greatest width of the tendon was measured (method II, figure 2), corresponding to the shortest diameter at the thickest point in the tendon.

Pressure algometry

For pressure algometry, a Somedic Algometer was used. Pressure diameter was 1.0 cm² and pressure rate was 40 kPa/sec. In the Somedic Algometer it is possible to control pressure rate by visual feedback. Such control, however, relies to some degree on the ability of the investigators to perform standardised pressure applications (464).

The ankle and knee joints were held in a standardised angle (90°), allowing the algometric investigations of the tendons to be performed under exactly the same circumstances throughout the entire study (see photos below).



After the distance from the tendon insertion on calcaneus or patella to the thickest point of the tendon was recorded by US in the longitudinal scan, the thickest point of the tendon was marked with a pen on the skin so the pressure algometry could be made at exactly that same point during all measurements.

When the patients experienced pressure pain, he/she activated the hand-held stop-button and the corresponding pressure (kPa) could be read on the display as PDT.

Questionnaire.

On the first day, the athletes were introduced to a questionnaire with a numeric pain rating scale (NRS) for “pain at rest” and “pain during walking”. The athletes completed the questionnaire at all the follow-ups without assistance from the investigators. After filling in the questionnaire, the athletes were interviewed by the same examiner. The VAS and NRS represent a quantitative assessment of subjective factors (516), and the reliability of VAS (and NRS) has earlier been documented (516;517), and their application is today widespread (518).

Clinical examination.

The diagnosis was made by US, interview and clinical examination, mainly based on palpation of the tendon, its surrounding tissue and its insertion. The tendons were palpated with the knees stretched and the ankles slightly plantar flexed because the tenderness significantly decreases or the tendon becomes totally painless when they are stretched. The palpation of the Achilles tendon was performed by gently palpating the whole length of the Achilles tendon, by gently squeezing the tendon between the thumb and the index finger. The palpation of the patellar tendon was performed by pressure from the thumb against the tendon at the insertion at the lower pole of patella. The athletes were asked to state whether palpation tenderness was present or absent. The examiner graduated the pain reaction as none, light, modest and severe (with avoiding reaction).

Blinding procedure

The glucocorticosteroid and placebo injections were blinded for both the athletes and the examiners. One person who did not participate in patient contact or measurements had the responsibility for the treatment code and for mixing the injections. The syringe was carefully shaken to prevent the precipitation of the glucocorticosteroids (see the section “Medicine and placebo” below).

In study I (sub-studies 2 and 3) and in study II, the US measurements were blinded for the examiners. That part of the screen of the ultrasonograph where the result of the measurement could be seen was covered for the examiner. Either the blinded records were measured by an independent observer or the ultrasonographic images, including the blinded measurement,

were printed out for later recording.

In study II, the pressure algometry measurements were blinded for the examiners. The examiner could not see the results of the PDT measurement, and another person recorded the results. Moreover, it is impossible to produce specific values in PDT measurements by changing the pressure or the pressure rate.

In study V, the US and PDT measurements were done with intervals of several days, weeks and months. The examiners had no possibility of remembering the details of the US or PDT of the previous measurements.

Medicine and placebo.

The active (glucocorticosteroid) injection contained 3.5 ml of 10 mg/ml lidocain and 0.5 ml Kenalog® (containing 20 mg triamcinolone) in a 5 ml syringe. The placebo injection contained 3.5 ml of 10 mg/ml lidocain and 0.5 ml 20% Intralipid® in a 5 ml syringe. Intralipid® was added in order to make the placebo look like the milky Kenalog® solution. It was not possible to tell the difference between placebo and active treatment by colour or viscosity.



Rehabilitation

All athletes were given the same explanation and instruction by the same examiner. They were allowed to start rehabilitation 4 days after the first injection by running within the limit of pain. They were instructed in stretching and graduated strength training for the calf or thigh muscles. They were allowed to train all other parts of the body without limitations.

Statistic

In all studies I-IV the level of significance was set at 5 % ($p < 0.05$).

Study I. (*Ultrasonography in evaluation of Achilles and patella tendon thickness*).

In sub-study 1, a test for interaction was used for testing the difference in thickness at

different points of the tendons.

The repeated measurements were tested by paired t-test in sub-studies 2 and 3.

The variation in the measurements of the same tendon consists of a systematic variation and a random variation. The systematic variation can be corrected if known, whereas this is not possible for the random variation. SD_{intra} expresses the random variation (standard deviation) within an observer's repeated measurements using the same method and was calculated as $SD_{intra}^2 = SD_{dif-intra}^2/2$, where $SD_{dif-intra}$ is the standard deviation of the difference between two measurements performed by the same method. The average of the two SD_{intra}^2 was subsequently calculated. SD_{inter} was defined as the additional variation the two different methods' measurements would add to the random variation within the observer's repeated measurements (using the same method). If SD_{inter} was calculated as negative, it was counted as 0. SD_{total} expressed the total random variation between the repeated measurements of different methods. This variation included both the variation between the observer's first and second measurements (SD_{intra}) and the additional variation due to measurements using different methods (SD_{inter}). Therefore the total variation $SD_{total}^2 = SD_{inter}^2 + SD_{intra}^2$, considering that $SD_{inter}^2 = (SD_{dif-inter}^2 - SD_{intra}^2)/2$, and $SD_{dif-inter}$ was the standard deviation of the difference between the two methods' means.

The variation was described absolutely calculated from differences (mm). Because the variations seem to be directly proportional to the thickness of the tendons, the relative variations measured as the SD on the logarithmically transformed data on a single measurement within each method were calculated. The standard deviations (SD) calculated from the relative differences were estimates of the coefficient of variation ($CV = SD/Mean \cdot 100$).

In sub-study 2, the systematic variation was described by mean differences and compared by paired t-test.

The standard deviations within methods in sub-study 3 were compared pair-wise by the Pitman test and the means of the three methods by ANOVA.

Study II. (*Ultrasonography and pressure algometry in evaluation of Achilles and patellar tendons. Intra- and inter-observer variability*).

SD_{intra} expresses the random variation (standard deviation) within an observer's repeated measurements and was calculated for both observers as $SD_{intra}^2 = SD_{dif-intra}^2/2$, where $SD_{dif-intra}$ is the standard deviation of the difference between two measurements performed by the same

observer. Finally, the average of the two SD_{intra}^2 was calculated. SD_{inter} was defined as that additional variation the two different observers' measurements would add to the random variation within the observer's repeated measurements. If SD_{inter} was estimated as negative, it was counted as 0. SD_{total} expressed the total random variation between the repeated measurements of different observers. This variation included both the variation between the observer's first and second measurements (SD_{intra}), and the additional variation due to measurements of different observers (SD_{inter}). Therefore the total variation $SD_{total}^2 = SD_{inter}^2 + SD_{intra}^2$ considering that $SD_{inter}^2 = (SD_{dif-inter}^2 - SD_{intra}^2)/2$, where $SD_{dif-inter}$ was the standard deviation of the difference between the means of the two observers.

The variation was described both absolutely, calculated from differences (mm or kPa), and relatively, calculated from relative differences (%). The standard deviations (SD) calculated from the relative differences were estimates of the coefficient of variation ($CV = SD/Mean \cdot 100$).

Changes/differences within persons were compared by paired t-test.

Study III. (*Influence of acute physical activity immediately before ultrasonographic measurement of Achilles tendon thickness*).

One sample t-test on differences was used.

Study IV. (*Significance of asymptomatic ultrasonographic tendinosis in the patellar and Achilles tendons among elite soccer players: A longitudinal study*).

The risk of developing symptoms during the season (+/-) related to the ultrasonography of the tendons (sick/normal) was tested with Fisher exact test.

Study V. (*Ultrasonography as a tool for diagnosis, guidance of local steroid injection and together with pressure algometry, monitoring of the treatment of athletes with chronic jumper's knee and Achilles tendinitis: a randomised, double-blind, placebo-controlled study*).

Since the difference between the two measurements in tendon thickness before and after treatment seemed to depend on the magnitudes of the changes, natural logarithmic transformation was used. Instead of looking at absolute differences, we used relative changes. Unpaired t-tests were used to compare changes in the treatment groups. The correlation between the changes in diameter of an affected tendon, as measured by ultrasonography, and

age of athletes was tested by Spearman's rank correlation test. The difference between the results of the questionnaire (NRS value) in the glucocorticosteroid and the placebo groups was tested by Fisher exact test, 2-tailed. Breslow-Day test for homogeneity of the odds ratio for improvement was $p = 0.778$, which allowed the uniting of the two groups (ACH and PAT) when the odds ratio was calculated.

RESULTS

In this section, the main results from the four studies are summarised. Details are given in the original papers at the end of this book.

Study I

Ultrasonography in evaluation of Achilles and patella tendon thickness

Sub-study 1. Tendon thickness in relation to distance from the attachment at patella or calcaneus.

The changes of the thickness of the left and right tendons measured by ultrasonography at different distances were not significantly different, either for the Achilles tendons ($p = 0.12$) or for the patellar tendons ($p = 0.27$). The difference in the thickness of the right and left Achilles tendons was calculated to 0.1 mm (se = 0.10, $p = 0.39$) and to -0.3 mm (se = 0.13, $p = 0.02$) for the patellar tendons.

The thickness of the Achilles tendon 10, 20, 30, 40 and 50 mm from the attachment at the calcaneus was not significantly different, $p = 0.45$. However, the thickness of the patellar tendon was significantly higher proximal than distal. From 5 mm to 30 mm from attachment the patellar tendon decrease 0.74 mm in thickness (se = 0.07, $p < 0.001$).

Sub-study 2. Transversal contra longitudinal scan.

In general, in repeated ultrasonographic measurements, all the second measurements in both transversal and longitudinal scans (except longitudinal scan of the normal patellar tendon) were higher on average than the first measurements. However, these differences were only significant in the transversal scan for both the normal left ($p = 0.04$) and right ($p = 0.02$) patellar tendon, and for the left and right tendons analysed together ($p = 0.001$).

In general in the measurements of tendon thickness by ultrasonography, SD and CV were increased in all the transversal scans in relation to the longitudinal scan (except the normal left Achilles tendons). However, these differences were only significant for the right normal Achilles ($p = 0.003$) and the abnormal patellar tendons ($p = 0.008$). When the normal left and right Achilles tendons were analysed together, there were no significant difference between longitudinal and transversal scans ($p = 0.51$), and when the normal left and right patellar tendons were similarly analysed, there were still no significant differences between longitudinal and transversal scans ($p = 0.07$).

In the total variation (SD_{total}), the contribution caused by the different methods of

measurement (longitudinal and transversal), SD_{inter} , was negligible in normal tendons but not in abnormal tendons.

Sub-study 3. Method I contra method I

The thickness of the Achilles tendons measured with methods A (AP thickness, transversal scan), B (AP thickness, longitudinal scan) and C (the “true” thickness, longitudinal scan) were significantly different (on average 5.58 mm, 5.17 mm and 4.78 mm, respectively) with $p < 0.001$. The SD on repeated measurement within each method was calculated to 0.344 mm, 0.308 mm and 0.209 mm, respectively. There was no significant difference between methods A and B ($p = 0.36$), but the average of method C was significantly less than method A ($p < 0.001$) and method B ($p = 0.008$).

The relative variations measured as the SD on the logarithmically transformed data on a single measurement within each method (CV) were calculated to be 6.1%, 5.2% and 4.4%, respectively. There was no significant difference between methods A and B, or between methods B and C, whereas the SD of method C was significantly less than that of method A ($p = 0.02$).

Study II

Ultrasonography and pressure algometry in evaluation of Achilles and patellar tendons. Intra- and inter-observer variability.

The random total variation (SD_{total}) between the two observers' measurements in normal and abnormal Achilles and patellar tendons was 0.25 – 0.33 mm (3.8 – 8.7 %), and the contribution caused by the different observers' measurement was less than the variance due to one observer's repeated measurement.

There were no systematic statistically significant differences between the two observers' ultrasonographic measurements of the Achilles and patellar tendon thickness (although observer1 on average had higher values than did observer2).

There was no statistical difference between one observer's repeated ultrasonographic measurements (intraobserver variation).

The random total variation (SD_{total}) between the two observers' PDT measurements in normal and abnormal Achilles and patellar tendons and the temporal regions was 12.8 – 21.1 %.

There was a systematic statistically significant difference in the means of the two observers' PDT measurements of the normal tendons and in the temporal region. In contrast there were no significant differences in the measurements of the abnormal tendons.

In all PDT measurements, the means for the observer's first measurements were higher than the means for the second measurements, and in several cases these differences were statistically significant.

There was no statistical difference between one observer's repeated measurements of PDT (intra-observer variation).

Study III

Influence of acute physical activity immediately before ultrasonographic measurement of Achilles tendon thickness.

Before acute intensive exercise the mean thickness of the 10 right Achilles tendons was 5.0 mm (SD 0.5 mm), and for the 10 left Achilles tendons 5.0 mm (SD 0.84 mm).

The mean thickness of the 10 right Achilles tendons was increased by 0.04 mm and the 95% confidence intervals was from -0.19 to 0.26 mm (95%CI -0.19;0.26) and for the 10 left Achilles tendons the mean thickness was increased 0.22 mm (95%CI -0.05;0.49 mm). The difference (before/after exercise) in the mean value of the right and the left Achilles tendons was not statistically different from 0 ($p = 0.13$). The mean thickness of all the 20 Achilles tendons was on average increased by 0.13 mm (95%CI -0.09;0.35 mm) after the acute exercise, but the difference was not statistically significantly different from 0 ($p=0.25$).

Study IV

Significance of ultrasonographically detected asymptomatic tendinosis in the patellar and Achilles tendons of elite soccer players: a longitudinal study.

At the start of the season in January, the average anteroposterior diameter of the Achilles tendons was 4.7 mm (SD, 0.54) in players *without* spindle-shaped thickening, and 6.5 (SD, 1.27) mm in players *with* spindle-shaped thickening. Ultrasonographically detected spindle-shaped thickening was found in 11 of the 96 asymptomatic Achilles tendons.

At the end of the season in December, 36% of the asymptomatic ultrasonographic abnormal Achilles tendons were still asymptomatic, but the tendons appeared, ultrasonographically, to have normalised, while 45% of the tendons had become symptomatic during the season.

In relation to the group with normal Achilles tendons, the risk of developing symptoms related to the Achilles tendons during the season was significantly higher in the group that had spindle-shaped thickening of the Achilles tendon at the start of the season in January ($p < 0.05$).

At the start of the season in January, the average anteroposterior diameter of the patellar tendons was 4.2 mm (SD, 0.76) in the players without ultrasonographically defined hypoechoic regions. In players with hypoechoic regions, it was 6.4 mm (SD, 1.15). Hypoechoic regions were detected ultrasonographically in 18 of the 98 asymptomatic patellar tendons at the start of the season in January.

At the end of the season in December, 33% of the asymptomatic ultrasonographic abnormal patellar tendons were still asymptomatic, but the tendons appeared, ultrasonographically, to have normalised, while 17% of the tendons had become symptomatic during the season.

The risk of developing symptomatic jumper's knee during the season was significantly greater for the asymptomatic group that had hypoechoic regions in the patellar tendon at the start of the season in January than for the group with normal patellar tendon ($p < 0.05$).

Study V

Ultrasonography as a tool for diagnosis, guidance of local steroid injection and, together with pressure algometry monitoring, of the treatment of athletes with chronic jumper's knee and Achilles tendinitis: a randomised, double-blind, placebo-controlled study.

Even though the athletes were referred from orthopaedic departments, only one-third of them fulfilled the inclusion criteria. Two of the referred athletes had a neglected total rupture of an Achilles tendon. The patella group (PAT) was on average 15 years younger than the Achilles group (ACH).

Tendon diameter as measured by ultrasonography was significantly reduced after glucocorticosteroid injections in both the ACH-S, and PAT-S groups. As early as 1 week after the first glucocorticosteroid injection, the average diameter of the affected tendons was significantly reduced in the ACH-S group from 9.8 mm to 9.0 mm ($p = 0.002$), and in the PAT-S group from 7.8 mm to 6.9 mm ($p < 0.0001$). After 3 weeks, average diameter was reduced further to 8.0 mm ($p = 0.0003$) in the ACH-S group and to 6.1 mm ($p < 0.0001$) in the PAT-S group. After 6 months, tendon diameter in the ACH-S group was increased to 8.6 mm and in the PAT-S group to 6.4 mm, which was still significantly less than the first measurement ($p = 0.002$ for both groups). There was no change in diameter at any time in the placebo-treated groups (ACH-P and PAT-P). In all tendons, there was reduction in pathological change (tendon thickening and inflammation/oedema of the tendon), but only in seven of the asymptomatic athletes, who believed they were well, were the tendons ultrasonographically completely normalised, compared with the contralateral side.

There was a significant difference in pressure pain detection threshold between the affected tendons and the controls. One week after first injection, the pressure pain detection threshold was higher both in the ACH-S group, having increased from 339 kPa to 436 kPa ($p = 0.01$), and in the PAT-S group, having increased from 430 kPa to 535 kPa ($p = 0.07$). After 3 weeks, the pressure pain detection threshold had further increased in the ACH-S group to 599 kPa ($p = 0.0006$), and in the PAT-S group to 639 kPa ($p = 0.003$). After 6 months, the pressure pain detection threshold in the ACH-S group was decreased to 487 kPa ($p = 0.02$) and 542 kPa ($p = 0.07$) in the PAT-S group. There was no change in the pressure pain detection threshold in the placebo-treated groups (ACH-P and PAT-P).

As early as 1 week after the first glucocorticosteroid injection, walking pain measured on a numeric rating scale (NRS) of 0 – 10 was reduced from 3.6 to 2.1 in the ACH-S group and from 2.9 to 1.7 in the PAT-S group. After 4 weeks, the pain was further reduced to 0.7 in the ACH-S group and to 1.3 in the PAT-S group. After 6 months, walking pain in the ACH-S group was increased to 1.9 and to 2.4 in the PAT-S group. Of the 24 athletes primarily treated with glucocorticosteroids (ACH-S and PAT-S), 15 patients had reduced walking pain after the first injection. Of the 24 placebo-treated athletes (ACH-P and PAT-P), only six had reduced walking pain. The difference between the glucocorticosteroid and the placebo groups is significant ($p = 0.02$), and the estimated odds ratio for improvement was 5.00 (95% confidence interval 1.46 – 17.10).

Atrophy was seen in 11 of the 24 glucocorticosteroid-treated in the ACH groups, and in nine of the 24 glucocorticosteroid-treated in the PAT groups. In nearly half of the athletes, the changes disappeared before the 6-month control. In none of the athletes did the atrophy give any problems. One of the athletes in the ACH-S-group developed a total rupture of the Achilles tendon.

DISCUSSION

Despite the fact that chronic injuries in the Achilles and patellar tendons are common injuries with increasing incidence, there are still many unanswered questions.

Primarily, there are problems with both the accuracy of the diagnosis and the evaluation of the treatment, and there is little scientific evidence for the majority of treatments proposed and used for chronic tendon problems. Furthermore, the pathology and aetiology are still debated. In agreement with earlier studies (62;66;433), this thesis showed that it can be very difficult to decide by clinical examination alone whether a tendon is thicker than normal, and only 1/3 of the referred patients in this study fulfilled the inclusion criteria, despite most patients being referred from sports clinics established in orthopaedic departments. In Cook's studies (64;66), only 22-41 % of the athletes with clinical jumper's knee and tenderness to palpation of the proximal third of the patellar tendon have US lesions in the tendon, and in the studies of Maffulli (62) and Cook (66), the sensitivity to predict US tendon changes in symptomatic Achilles and patellar tendinopathy by palpation of the tendon was 58% and 68%, respectively. Many of patients referred with clinical suspicion of chronic tendinopathy had ultrasonographically normal tendons or only minimal intratendinous changes, or in rather few cases peritendinitis, bursitis, partial or even total ruptures of the (Achilles) tendons. Intra-articular lesions (menisc lesions, osteoarthritis, chondromalacia, osteochondritis, (osteo)chondral lesions, hypertrophic plica, synovitis and subluxation of the patella) were also seen as a part of the well-known differential diagnosis (305;519). In the light of these facts, it seems likely that most of the earlier studies concerning chronic tendinopathy have included (many) patients who did not have thickening of the tendons, and who therefore would be expected to have a better prognosis (442;520). Using US, the homogeneity of a study group of patients with tendinopathy can be increased. US should therefore be used as the diagnostic modality in future studies of Achilles and patellar tendinopathy.

In conformity with earlier findings (432;449), US of Achilles and patellar tendon thickness has, in this thesis, an acceptable inter- and intra-observer variation. The US measurements of the Achilles and patella tendons had a total coefficient of variation (CV) less than 9 %, and in the study by O'Conner (449), the CV was less than 10% for both normal Achilles and patellar tendons. In an earlier study, even interobserver reliability in assessment of the hypoechoic areas in the patellar tendons has been found to be high (455).

If the same observer makes all US measurements, the total variance (SD_{total}) will generally be reduced, but because the contribution from the inter-observer variation (SD_{inter}) is negligible, the total variation will only increase slightly. Therefore, two different observers can make the repeated measurements in future studies. This opens the possibility that totally blinded control measurements can be made by an observer at a department not involved in a particular study. This could increase the objectivity of a study. The result also indicates that ultrasonography of Achilles and patella tendons are excellent for evaluation of changes in tendon thickness in tendinopathy, not only between groups of patients with Achilles or patella tendinopathy, but also for monitoring individuals over time.

If the distance from the point of measurement to the bone attachment of the tendon is recorded, then the following observers can measure the tendon thickness at exactly the same point.

Pressure algometry was used as objective evaluation of the effect of treatment in Achilles and patellar tendinopathy for the first time. The inter- and intra-observer variability was in agreement with earlier joint, muscles and myofascial triggerpoints studies (454;464;466;467) and tendon studies (391;468). The variation in PDT was more marked in normal tendons than in abnormal tendons, and the differences between the two observers' PDT measurements were statistically significant in normal but not in abnormal tendons. Normal tendons needed a higher pressure to reach the PDT, and when the pressure increased, it was more difficult to produce a constantly increasing pressure. This could explain the increased variation in PDT in normal tendons compared with abnormal tendons.

The technique of pressure algometry is easily learned, and in this study, where one observer was very experienced in pressure algometry while the other observer was relatively inexperienced, the variation in PDT measurements of the inexperienced observer were not higher than those of the experienced observer. PDT measurement is recommended as an objective effect parameter in future studies. However, because of a relative high variation of repeated measurements (CV 12.8-21.1%), as also found in earlier studies (454), pressure algometry should only be used for examination of groups of athletes. This is in agreement with previous studies (521-523).

The intra- and inter-observer variability of repeated measurements of Achilles and patellar tendon thickness with US were slightly smaller in longitudinal scan than in transversal scan. This is in agreement with Richard et al (436), who found a higher kappa value when tendon

thickness was measured in longitudinal scan than in transversal scan, whereas Kallinen and Suominen (435) found equal SD in longitudinal and transversal scan, and O'Connor (449) reported that longitudinal and transversal measurement performs equally well at the anatomical site assessed. When moving the tendons in longitudinal scan, the tendon, epitendon and paratenon can usually be distinguished from each other, which can be difficult in transversal scan. There is therefore a risk in transversal scan to include epitendon and part of the paratenon in the measurement of tendon thickness (432). In this study, there were, however, no significant differences in tendon thickness measured by transversal and longitudinal scan (except the abnormal patellar tendons), but in the study by Kallinen (435), he found a 10% increase in tendon thickness in transversal scan in relation to longitudinal scan. Both the results of the study by Kallinen and our data are in discrepancy with Fornage (422), who stated that transversal scan is crucial for measuring the true thickness of the Achilles tendon because longitudinal scan overestimates tendon thickness. Fornage's statement, however, was only based on reflections and not supported by scientific studies. In longitudinal scan, the transducer can be tilted medially and laterally, but in transversal scan the transducer can, in addition, also be tilted proximally and distally, which of course increases the possibility for errors in measurements. In the longitudinal scan, tendon thickness and the distance from the point of measurement to the bony attachment can be made easily and rapidly be measured. This allows the examiner to measure exactly the same part of the tendon in future measurements. This is especially important in US of the patellar tendon, where the upper attachment of the patellar tendon is cone-shaped. In study I (substudy 2), an increased SD of the differences in repeated measurement of the thickness of the patellar tendon was found when the thickness was measured in transversal scan plane in relation to longitudinal scan plane. Only a few millimetres proximal-distal displacement of the transducer in transversal scan will change the measured thickness of the cone-shaped upper part of the patellar tendon significantly, especially in the abnormal tendons. In future, US measurement of patellar tendon thickness should be done in longitudinal scan, whereas Achilles tendon thickness can be measured in both longitudinal and transversal scan.

We found that acute intensive exercise (150 tiptoe in 1½ minute) has no significant effect on Achilles tendon thickness in patients with normal tendons. The mean thickness of all the Achilles tendons was on average increased by 0.13 mm (3%) 20 minutes after the exercise. In another study, the effect of acute exercise of the calf muscles (45 heavy-load eccentric

repetitions with the knee straight and 45 repetitions with the knee bend) on the tendon volume (and intratendinous signals) in patient with Achilles tendinopathy and normal Achilles tendons was evaluated by MRI before and “immediately after” the exercise (456). In this study, tendon volume was significantly increased in both patients with tendinopathy (12%) and with normal tendons (20%), corresponding to a 6% increase in tendon thickness (assuming the Achilles tendons to be cylindrical). The intratendinous signals were increased approximately 30%. Boesen et al (298) found that acute exercise increased the Doppler signals in both normal (5 km fast running) and tendinopathic (45 heavy-load eccentric repetitions) Achilles tendons. No one has examined how long changes persist after acute exercise. Based on the above findings, it seems sufficient to recommend that intensive acute training is not carried out immediately before ultrasonographic examination.

In this study, the prevalence of asymptomatic thickening and hypoechoic regions was 18% in the patellar and 11% in the Achilles tendon. In earlier studies of thickening and hypoechoic regions in the patellar tendon, both a lower (14 %) (57) and a higher prevalence (20 %-70 %) were found (57;58;61;62;64;65;433;443;519;524). MRI studies in asymptomatic subjects have shown that 7 % have “tendon tears” (63) and 6 % have “abnormal morphology” of the Achilles tendons (433) whereas 24% have unequivocal intratendinous lesion and 47% have equivocal changes of the patellar tendons (524). The lower prevalence of ultrasonographic intratendinous changes in this thesis is most likely due to the definition of “abnormal”. In this study only tendons with at least 1 mm thickening were defined as “abnormal”. In most other studies “hypoechoic regions” (without tendon thickening) were included (62;64;433;443;518) in the definition. It seems reasonable to have a lower limit for registration of “lesions” by US because the improvement in imaging devices will detect smaller and smaller changes in the tendons, and the limit between normal and abnormal will diminish. Thus, in a recent study (65), prevalence of hypoechoic lesion in the patellar tendons in asymptomatic elite basketball players was as high as 70%. It is important to define clearly the ultrasonographic inclusion criteria for comparability with others studies. One definition of “increased thickening” could be that Achilles tendons with mid-portion spindle-shaped ultrasonographic thickening of more than 1 mm in relation to the normal distal part of the tendon and patellar tendons with thickening and a hypoechoic region more than 2 mm (AP diameter) in the transverse scan plane be classified as “severely abnormal”. Hypoechoic Achilles tendons with ultrasonographically detected mid-portion tendon thickening between 0.5-1 mm and patellar

tendons with hypoechoic regions between 1 and 2 mm (AP diameter) in the transverse scan plane could be classified as “slightly abnormal”

Studies of post-mortem material (56) have indicated that tendon degeneration is present in up to 30% of asymptomatic individuals. Combined with the results of this study, where asymptomatic players with ultrasonographic intratendinous abnormalities are in an increased risk group for developing symptoms during the next 12 months, it seems plausible that tendons run through an asymptomatic period before they become symptomatic. It is possible that tendons have a baseline mechanical strength that depends on the loading history of the tendon (training level). Once rapid increase in training load, frequency or duration occurs, the tendon may not be able to adapt fast enough to this change. Under normal circumstances, small overload “injuries” will heal as a normal part of tendon remodelling, but if the overload continues, the degradation of collagen will exceed the synthesis of collagen and the tendon will be weaker, resulting in progressive pathologic and ultrasonographic tendon changes that, after an asymptomatic period of several months, slowly aggravate and finally reach the pain limit and become symptomatic.

This subclinical period could explain why “US appearance does not correspond precisely with clinical features” and the many “false positives” as some authors have noted (433;443), and also explain why tendinopathy is found in nearly all spontaneous tendon ruptures in asymptomatic athletes (56;525). Studies using post-mortem biopsy material (56) indicate that tendon degeneration is present in up to 30 % of asymptomatic individuals, or nearly the same frequency of abnormalities found on ultrasonography in asymptomatic athletes in this and other studies.

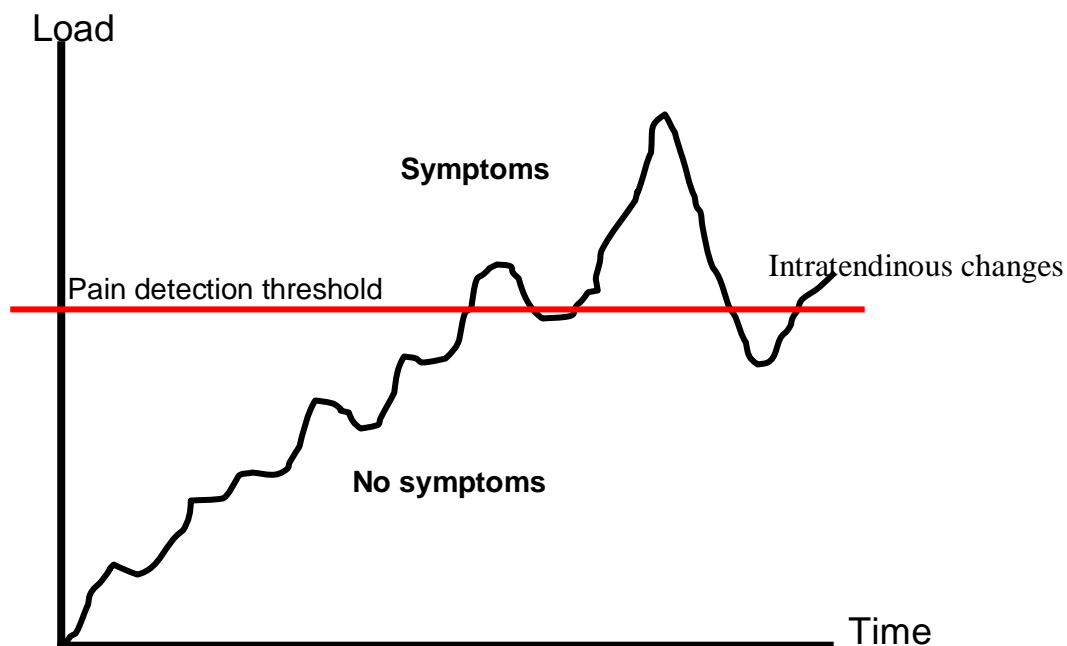


Figure 3. The tendinopathic “iceberg”

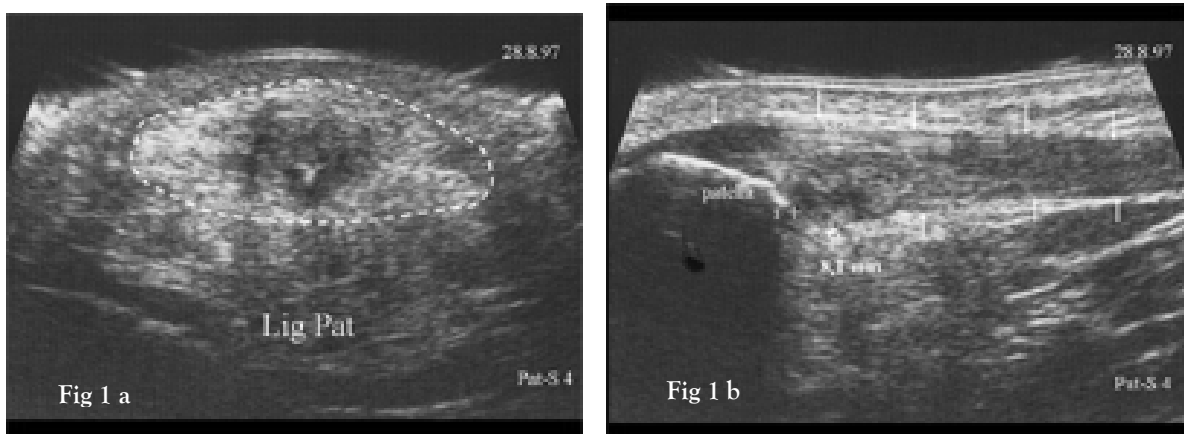
Chronic tendinopathy can be compared to an iceberg, with pain being the tip of the iceberg. This “iceberg theory” can also explain the frequent relapse of symptoms when the athletes resume sports activity with insufficiently strengthened tendons after too short a rehabilitation period (or too shortly after medical treatment, as in this thesis), because the player only just comes under the PDT, while most of the intratendinous abnormalities in the tendon still exist. The ultrasonographic intratendinous abnormalities in the asymptomatic Achilles and patellar tendons might represent old changes from earlier lesions. More probable, the ultrasonographic abnormalities represented subclinical tendon changes (injuries, adaptation) with the potential to either resolve spontaneously (27% in this study of jumper’s knee resolved spontaneously consistent with 28-40% in earlier studies (443;518;519)), or to remain unchanged asymptomatic (55% in this study remain unchanged asymptomatic consistent with 50-69% in earlier studies (443;518;519)), or progress to clinical tendinopathy (57), which was also seen in this study. Although other studies have found that asymptomatic hypoechoic areas in patellar tendons increase the frequency for developing symptomatic jumper’s knee (57), this study also demonstrated a significant correlation between athletes with asymptomatic ultrasonographic intratendinous abnormalities in Achilles tendons and the risk for developing symptoms during the next 12 months. The asymptomatic ultrasonographic abnormalities in Achilles tendons result in a higher risk of developing symptoms than the analogous

abnormalities in the patellar tendons. Future studies will show whether it is possible to take advantage of this subclinical period to start prophylactic treatment or rehabilitation of this asymptomatic high risk group of athletes to prevent the intra-tendinous lesions aggravating to a symptomatic stage, and to what extent it is necessary to wait for the ultrasonographic normalisation of the tendons before allowing the athletes to return to maximal sport.

Ultrasonographically guided peritendinous injection of glucocorticosteroids was very effective in reducing the pain and thickness of Achilles and patellar tendons in athletes with chronic tendinitis. As early as 1 week after the first glucocorticosteroid injection, walking pain was reduced from 3.6 to 2.1 in the group with Achilles tendinopathy and from 2.9 to 1.7 in the group with patellar tendinopathy (after 4 weeks, walking pain was further reduced to 0.7 and 1.3, respectively, and after 6 months increased to 1.9 and 2.4, respectively). Read (480) found that the pain measured by the VAS was significantly reduced from 5.5 to 0.2 in 7-14 days after peritendinous glucocorticosteroid injection in Achilles tendinopathy. In two other studies evaluating eccentric exercise in patellar tendinopathy (21;526), the pain was reduced after 12 weeks from 7.4 to 2.9 and from 7.3 to 2.3 (pain during “activity” and pain during “sports activity,” respectively).

US before and after treatment showed that the intratendinous changes are reversible (see figure 1 a-d) and intratendinous lesions should therefore not uncritically be removed by surgery as suggest by some authors.

Figure 1 a, b, c, d



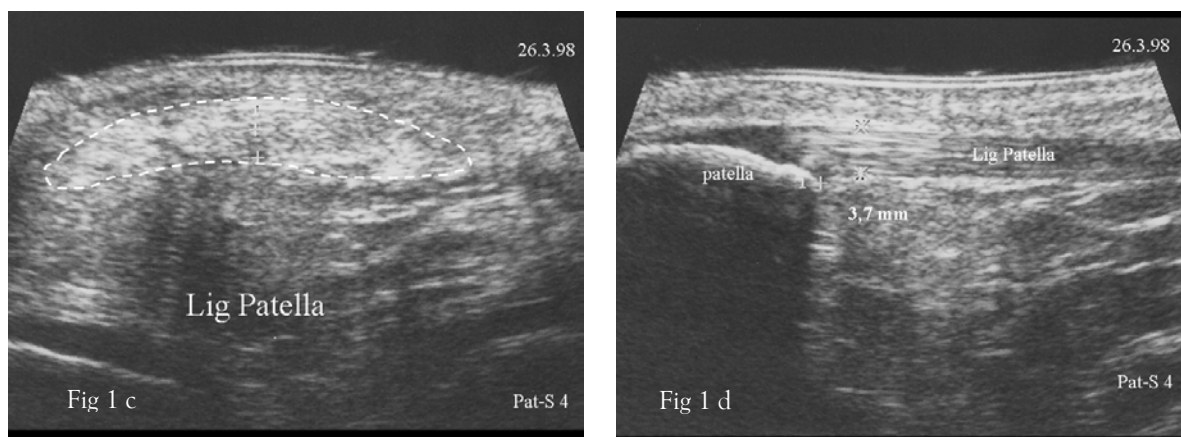


Figure 1 a and b: US of the patellar tendon (transversal and longitudinal scan) before treatment.

Figure 1 c and d: US of the same patellar tendon (transversal and longitudinal scan) a half year after treatment with peritendinous glucocorticosteroid injections. The tendon diameter is reduced from 8.1 mm to 3.7 mm, and the intra tendinous hypoechoic granuloma has disappeared.

No treatment mentioned in the literature has demonstrated such a dramatic and rapid effect on tendinopathy with regard to reduction of pain and tendon thickness as the peritendinous glucocorticosteroid injections. Despite the dramatic effect, most of the athletes in this thesis had a relapse of symptoms after 6 months, which may have occurred because the tendons were still not healed or because of too aggressive rehabilitation that allowed running as early as 4 days after the injections. If the athletes resumed the sports activity after a too short and insufficient period of rehabilitation during which the player only just came under the PDT, a relapse of symptoms could be expected. The overload injury arises when the load exceeds the strength of the tissue. The glucocorticosteroids can naturally not change this disproportion between load and strength, and if this disproportion continues, the tendinopathy will of course recur. Glucocorticosteroids can reduce the pain and the period of deleterious immobilisation and allow the athlete to start rehabilitation faster, but (very) slowly increasing rehabilitation levels and adjusting (eccentric) training intensity seems to be the main treatment, glucocorticosteroids being only a supplement. The effect of the glucocorticosteroid used (triamcinolone) is 6 weeks. The results 6 months after treatment tell us therefore more about the rehabilitation than the effect of glucocorticosteroids.

Of course, glucocorticosteroid injections should never be misused to reduce the pain to just under the PDT and allow the athletes to continue the deleterious over loading, which most

likely increases the risk for rupture of the tendons. If rehabilitation does not cure the chronic tendinopathy, US-guided peritendinous injection with long-acting glucocorticosteroids can be used as a part of a long-term rehabilitation period, which, based on the findings in this thesis, must necessarily be spread over several months (may be a half year) before maximum exercise is allowed. Because the effect of the injected glucocorticosteroids increased the first 4 weeks, it seems reasonable to repeat the injection earliest after 4-6 weeks if the first injection has clearly reduced but not totally removed the symptoms and the progress in improvement has stopped. Because the US-guided injection is correctly placed, further injections are not recommended if the first injection had no effect at all.

In contrast to peritendinous injected glucocorticosteroids, operation increases the thickness of the tendons significantly, and the new sclerosing therapy of the neovessels in chronic Achilles tendinopathy (11;32;308;527) does not reduce the thickness after 1 week and only slightly after 6 months. An explanation for the effect of operation (and sclerosing therapy) could, among others, be that the treatment results in a denervation of the small nerves that accompany the neovessels. The increased thickness after operation and shock wave indicate different paths of action in relation to peritendinous glucocorticosteroid injections.

In contrast to peritendinous glucocorticosteroid injection, intratendinous glucocorticosteroid injections (499) do not decrease tendon thickness after 1 week, maybe because the intratendinous injection causes an acute intratendinous lesion.

Despite the aggressive treatment and rehabilitation used in the investigations making up this thesis, only one athlete (corresponding to 2 % of the players with tendinopathic tendons and 4% of those with Achilles tendinopathy) had a total rupture of the treated tendon in the 2 year follow-up. This corresponds to earlier reported rupture frequencies of 3.5 - 8% (479;480), independent of treatment. This one athlete was the only athlete with insertional Achilles tendinopathy, which is known to have a worse prognosis than mid-point Achilles tendinopathy (14). A previous study (430) showed that in the patients with US verified thickening of the Achilles tendons and chronic pain, a spontaneous rupture occurred in 28% of the cases after a follow-up of 48 months (+/- 8 months). This naturally does not allow us to argue that US-guided peritendinous injection of long-acting glucocorticosteroids in humans does not increase the risk of tendon rupture, but it does mean that the increased risk of rupture especially as seen in animal and experimental studies due to decreased collagen syntheses, is not - based on the available evidence in humans – enough to condemn the treatment if the diagnosis is US verified (499), and if the athletes are properly rehabilitated before maximal

load is allowed.

Based on these considerations, peritendinous glucocorticosteroid injection is, at present, the most effective agent to reduce the pain and the thickness of the tendons in chronic tendinopathy, and it is, together with rest and rehabilitation with eccentric exercise (13), the only treatment with a documented capability to normalise the US image of the tendons. Future human studies with US-guided peritendinous glucocorticosteroids injection in combination with growth factors (for example platelet-rich plasma (PRP) containing platelet-derived growth factor (493;494;528;529) and exogenous vascular endothelial growth factor (VEGF) (530)) will show whether this combination could increase the healing rate and reduce the rupture frequency even more.

It has been postulated that the dramatic reduction in tendon thickness (and maybe the pain) after glucocorticosteroid treatment is due to glucocorticosteroids reducing the water content in the tendons. However, in an experimental animal study of Achilles tendinopathy induced by peritendinous injections of PGE₁ (404), the thickness of the Achilles tendons 1 week after peritendinous injections of PGE₁ was 134% of the non-injected control value. At the end of the study, tendon thickness in the PGE₁ injected was 120% of the control value. In the PGE₁ injected tendons, intratendinous water content increased sharply after the first week (160% of control value). With time, the intratendinous water content decreased, and, by the end of the study, it had returned to close to the water content of the control tendons (404). This animal study does not suggest that the considerable glucocorticosteroid- induced reduction in tendon thickness found in this thesis only 1 week after glucocorticosteroid injection solely is due to reduction in water content, because the water content in the chronic tendinopathies was normal. However, in biopsies from Achilles tendinopathy tendons and normal tendons, water content was highest in the tendinopathy tendons (531).

The effect of glucocorticosteroids could theoretically be due to an analgesic effect on the neuropeptides (calcitonin gene-related peptide (CGRP) and substance P (SP)), which are increased in tendinopathy, but it seems unlikely that this could explain the dramatic reduction in tendon thickness.

To some extent glucocorticosteroids are vasoconstrictors, which may explain the change in vascularity, and, secondly, the reduction in thickness and the decreased pain, due to reduction in the supply of different noxious stimuli and pro-inflammatory agents like, e.g. PGE and cytokines, whose effect will further be reduced by the glucocorticosteroids. However, if the

effect of glucocorticoids is mainly based on the effect of vasoconstriction, a more rapid relapse could be expected, when the effect of steroid ends after 4-6 weeks.

The glucocorticoids with their anti-inflammatory effect have the same dramatic clinical effect on pain, swelling and hyperaemia in tendinopathy (499;532) as they do in rheumatoid arthritis (RA). The two diseases have many of the same pro-inflammatory agents in common. Because glucocorticosteroids do not cure either tendinopathy or RA, the symptoms often relapse in both diseases. The two diseases have also many symptoms in common (rubor, dolor, tumor, calor, functio laesae), and because the clinical responses to glucocorticosteroids in chronic tendinopathy and inflammatory RA are comparable, a conclusion which immediately suggests itself is that the effect of glucocorticosteroids in chronic tendinopathy is due to their anti-inflammatory properties as is their effect in inflammatory arthritis.

A few years ago, chronic tendon overuse was believed to be due to a chronic inflammatory process, but because no inflammatory cells were demonstrated in the ruptured tendons, the opinion changed from inflammation (“tendinitis”) to degeneration (“tendinosis”). It was not the purpose of this thesis to study the question whether or not Achilles and patellar tendinopathy is an inflammatory rather than a degenerative condition, but the significant reduction in tendon thickening and pain, and increase in PDT only 1 week after peritendinous glucocorticosteroid injections, can most likely be explained by a reduction in an inflammatory process. Furthermore, if the changes induced by glucocorticosteroids are due to changes in a degenerative process, the time frame is too short to expect that glucocorticosteroids could influence processes that are usually connected to degeneration of the connective tissue, such as collagen synthesis and fibroblast migration, processes that normally changes slowly. These results put a question mark over the pure degeneration theory.

Continuing progress in research in molecular biology and biomechanics has provided much new information and given birth to new hypotheses in chronic tendinopathy. Overloading is still, however, crucial in the development of tendinopathy in individuals who, perhaps because of genetic factors, are predisposed. Under normal circumstances, small overload injuries will heal as a normal part of tendon remodelling, but if the overload 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.

Ultrasonography can reveal this asymptomatic period.

The existing data indicate that prolonged mechanical stimuli induce the production of several different pro-inflammatory mediators (including cytokines, interleukines, prostaglandins and neuropeptides). The tendon cells can produce these agents when subjected to cyclic stress. When cytokines and prostaglandins are injected around healthy animal tendons, they result in tendinopathy.

It seems plausible that tendinopathy begins with cellular activation and inflammation, which proceeds through phases of increased ground substance, collagen separations and eventually neovascularisation, and that the glucocorticosteroid sensitive mechanisms play a crucial role in this process. The literature indicates – despite a great deal of uncertainty regarding the concepts – that the inflammatory process may be related to the development of tendinopathy and that inflammation may also play a role in chronic tendinopathy. Furthermore, glucocorticoids are, at the moment, the most effective treatment in tendinopathy with regard to reduction of pain, tendon thickness and neovascularisation

The following are one of the major questions for the future. 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 to the “tendinitis myth” in the future.

FUTURE ASPECTS

On the basis of the results in this thesis, further studies should, among other things, focus on:

- * finding out to what extent specific prophylactic training among asymptomatic athletes with ultrasonographically abnormal Achilles and patellar tendons can reduce the frequency of athletes that later develop symptoms from these tendons.
- * determining in what extent athletes who are asymptomatic after treatment for tendinopathy should wait until US of the tendon is normalised before they participate in vigorous sport.
- * investigating the effect of US-guided peritendinous glucocorticosteroids combined with (3-) 6 months' rehabilitation on tendinopathy with special focus on reducing the frequency of relapse of symptoms.
- * making clear that use of US should be mandatory for making the diagnosis of tendinopathy in future studies of Achilles and patellar tendons. Ultrasonography, pressure algometry and VAS or NRS pain should be used before and after treatment as effect parameters.
- * investigate new medical treatment eventual combined with platelet-rich plasma or other growth factors.

ENGLISH SUMMARY

Measuring of the Achilles and patellar tendon thickness by ultrasound has an acceptable inter- and intra-observer variation in this thesis.

Ultrasonography is recommended for use in the diagnosis of Achilles and patellar tendinopathy, and together with pressure algometry measurement recommended as an objective effect parameter in future studies. However, because of a high inter- and intra-observer variation of repeated measurements, pressure algometry should only be used for examination of groups of athletes, whereas ultrasonography can be used to follow a single patient over time.

Continuing progress in research in molecular biology and biomechanics has provided much new information and given birth to new hypotheses in chronic tendinopathy. Overloading is still, however, crucial in the development of tendinopathy in individuals who, perhaps because of extrinsic and intrinsic (including genetic) factors, are predisposed.

Under normal circumstances, small overload injuries will heal as a normal part of tendon remodelling, but if the overload 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. The pain is only the tip of the iceberg. The asymptomatic period can be detected by ultrasonography.

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.

Nerve ingrowth is known to occur as a response to tendon injury, and a number of studies have demonstrated new nerve ingrowth in the tendon proper in tendinopathy. The ingrown nerves express substance P (SP) and calcitonin gene-related peptide (CGRP), which can be one of the explanations for the pain in tendinopathy.

The existing data indicate that the initiators of the tendinopathic pathway include traumatic events, or a prolonged repetitive motion injury inducing production of many proinflammatory agents (e.g. cytokines, prostaglandins, different growth factors and neuropeptides). The proinflammatory mediators induce apoptosis, elaboration of pain mediators and MMP, which degrade collagen and proteoglycans. The end result is a weak tendon with an increased risk of rupture. These agents can be produced by tendon cells, are found in tendinopathy and cause

tendinopathy when injected in or around tendons in animals. Because of the complex interaction between the proinflammatory agents and the neuropeptides, it seems impossible and somewhat irrelevant to distinguish sharply between chemical and neurogenic inflammation.

Furthermore, this thesis shows ultrasound-guided peritendinous injected glucocorticoids are, at the moment, the most effective treatment in tendinopathy with regard to reduction of pain and tendon thickness.

The evidence in the literature and the dramatic effect of injected glucocorticoids (although many of the athletes have a relapse of symptoms after 6 months) in this thesis indicates – despite a great deal of uncertainty regarding the concepts – 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 following are one of the major questions for the future. 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 to the “tendinitis myth” in the future.

DANSK RESUME

Ultralydsscanning af Achilles- og knæskalssener har i dette studie en acceptabel inter- og intraobservatør variation.

Ultralydsscanning anbefales i fremtidige studier anvendt dels i diagnostikken af tendinopater i Achilles- og patelarsenerne, og dels sammen med trykalgometri som en objektiv effektparameter. På grund af en større inter- og intraobservatør variation, anbefales trykalgometri fortrinsvis til gruppeundersøgelser, mens ultralydsscanninger kan anvendes såvel til at sammenligne grupper som til at kontrollere patienter longitudielt.

Fremskridt i molekylærbiologiske og biomekaniske forskning har afstedkommet megen ny viden og affødt nye teorier omkring kronisk tendinopati. Overbelastning er imidlertid fortsat afgørende i udviklingen af tendinopati hos personer, som måske pga genetiske forhold er disponeret.

Sædvanligvis vil små overbelastningsskader hele op som en normal del af senens remodellering. Hvis overbelastningen forsætter, vil disse småskader medføre progredierende seneændringer og efter en periode over flere måneder langsomt forværres og sluttelig nå smertegrænsen og blive symptomatiske. Smerten ved tendinopati er kun toppen af isbjerget. Den asymptomatiske periode kan påvises ved ultralydsscanning.

De fleste histologiske forandringer ved tendinopati repræsenterer kronisk degeneration, regeneration og mikroskopiske bristninger i senevævet. Den almindelige holdning er, at der ikke er evidens for akut inflammation, men i nyere studier, hvor immunohistokemi og flow cytometri anvendes, er der påvist inflammationsceller.

Nerveindvækst opstår som respons på seneskader, og mange undersøgelser har vist ny nerveindvækst i sener med tendinopati. Fra nerverne frigøres neuropeptiderne substance P (SP) og calcitonin gene-related peptide (CGRP), som kan være en af forklaringen på smerten i tendinopati.

Eksisterende data indikerer, at initieringen af den "tendinopatiske kaskade" inkluderer traumer eller langvarige, gentagne belastningsskader, der inducerer produktionen af mange inflammatoriske stoffer (f.eks. cytokiner, prostaglandiner, vækstfaktorer og neuropeptider).

De proinflammatoriske stoffer inducerer apoptosis, smertemediatorer og metalloproteinaser (MMP), som nedbryder kollagen og proteoglykaner. Slutresultatet er reduceret senestyrke og øget risiko for bristninger. Disse stoffer kan produceres af celler i senen, findes i sener med tendinopati og fremkalder tendinopati, hvis de injiceres i eller rundt om senerne hos dyr.

På grund af den komplekse interaktion mellem de proinflammatoriske stoffer og neuropeptiderne, synes det umuligt og delvist irrelevant at skelne skarpt mellem kemisk og neurogen inflammation.

Resultaterne i denne undersøgelse viser, at ultralydvejledt injektion af peritendinøs glucocorticosteroid i øjeblikket er den mest effektive behandling ved tendinopati, hvad angår smerte og senetykkelse.

Evidensen i litteraturen og den dramatiske effekt af injiceret glucocorticosteroid (skønt mange af idrætsudøverne fik tilbagefald efter 6 måneder) i denne undersøgelse indikerer – trods en stor del usikkerhed omkring antagelsen – at inflammation er relateret til ikke kun udviklingen af tendinopati, men også spiller en rolle i kronisk tendinopati.

Det følgende er et af de væsentlige spørgsmål til fremtiden. Er det fordelagtigt at blokere denne inflammatoriske kaskade, og hvad er den mest effektive måde at blokere denne på med færrest muligt bivirkninger?

Mere opmærksomhed anbefales i fremtiden rette mod ”tendinitis myten”.

References

1. Kader D, Saxena A, Movin T, Maffulli N. Achilles tendinopathy: some aspects of basic science and clinical management. *Br J Sports Med* 2002;36(239):249.
2. Kujala UM, Sarna S, Kaprio J. Cumulative incidence of achilles tendon rupture and tendinopathy in male former elite athletes. *Clin J Sport Med* 2005;15(3):133-5.
3. Lian O, Engebretsen L, Bahr R. Prevalence of jumper's knee among elite athletes from different sports: a cross-sectional study. *Am J Sports Med* 2005;33(4):561-7.
4. Paavola M, sakari O, Leppilahti J, Kannus P, Järvinen M. Chronic Achilles tendon overuse injury: complications after surgical treatment. *Am J Sports Med* 2000;28(1):77-82.
5. Khan KM, Cook JL, Bonar F, Harcourt P, AM. Histopathology of common tendinopathies. Update and implications for clinical management. *Sports Med* 1999;27(6):393-408.
6. Åström M. On the nature and etiology of chronic Achilles tendinopathy. [dissertation]. University of Lund, Sweden.; 1997.
7. Movin T. Aspects of aetiology, pathoanatomy and diagnostic methods in chronic midportion Achillectomy. [dissertation]. Karolinska Institute, Stockholm, Sweden.; 1998.
8. Alfredson H, Lorentzon R. Chronic Achilles tendinosis: recommendations for treatment and prevention. *Sports Med* 2000;29(2):135-46.
9. Józsa L, Kannus P. Human Tendons. Anatomy, Physiology and Pathology. Canada: Human Kinetics; 1997.
10. Curwin S. The aetiology and treatment of tendinitis. In: Harris M, Williams C, Stannish WD, Michelis L, editors. *Oxford Textbook of Sports Medicine*. Oxford: Oxford University Press; 1994. p. 512-28.
11. Alfredson H, Pietilä T, Jonsson P, Lorentzon R. Heavy-load eccentric calf muscle training for the treatment of chronic Achilles tendinosis. *Am J Sports Med* 1998;26(3):360-6.
12. Mafi N, Lorentzon R, Alfredson H. Superior short-term results with eccentric calf muscle training compared to concentric training in a randomized prospective multicenter study on patients with chronic Achilles tendinosis. *Knee Surg Sports Traumatol Arthrosc* 2001;9(1):42-7.
13. Ohberg L, Lorentzon R, Alfredson H. Eccentric training in patients with chronic Achilles tendinosis: normalised tendon structure and decreased thickness at follow up. *Br J Sports Med* 2004;38(1):8-11.
14. Fahlstrom M, Jonsson P, Lorentzon R, Alfredson H. Chronic Achilles tendon pain treated with eccentric calf-muscle training. *Knee Surg Sports Traumatol Arthrosc* 2003;11(5):327-33.
15. Silbernagel KG, Thomee R, Thomee P, Karlsson J. Eccentric overload training for patients with chronic Achilles tendon pain--a randomised controlled study with reliability testing of the evaluation methods. *Scand J Med Sci Sports* 2001;11(4):197-206.
16. Stanish WD, Curwin S, Rubinovich M. Tendinitis: the analysis and treatment for running. *Clin Sports Med* 1985;4(4):593-609.
17. Ross EM, Engström M, Lagerquist A, Söderberg B. Clinical improvement after 6 weeks of eccentric exercise in patients with mid-portion Achilles tendinopathy -- a randomized trial with 1-year follow-up. *Scand J Med Sci Sports* 2005;14(5):286-95.
18. Woodley BL, Newsham-West RJ, Baxter GD. Chronic tendinopathy: effectiveness of eccentric exercise. *Br J Sports Med* 2007;41(4):188-98.

19. Jensen K, Di Fabio RP. Evaluation of eccentric exercise in treatment of patellar tendinitis. *Phys Ther* 1989;69(3):211-6.
20. Cannell LJ, Taunton JE, Clement DB, Smith C, Khan KM. A randomised clinical trial of the efficacy of drop squats or leg extension/leg curl exercises to treat clinically diagnosed jumper's knee in athletes: pilot study. *Br J Sports Med* 2001;35(1):60-4.
21. Purdam CR, Johnsson P, Alfredson H, Lorentzon R, Cook JL, Khan KM. A pilot study of the eccentric decline squat in the management of painful chronic patellar tendinopathy. *Br J Sports Med* 2004;38:395-7.
22. Bahr R, Fossan B, Loken S, Engebretsen L. Surgical Treatment Compared with Eccentric Training for Patellar Tendinopathy (Jumper's Knee) A Randomized, Controlled Trial. *J Bone Joint Surg Am* 2006;88(8):1689-98.
23. Frohm AM, Saartok T, Halvorsen K, Renström P. Eccentric treatment for patellar tendinopathy - a prospective randomised short-term pilot study of two rehabilitation protocols. *Br J Sports Med* 2007;41(7):e7.
24. Visnes H, Bahr R. The evolution of eccentric training as treatment for patellar tendinopathy (jumper's knee) - a critical review of exercise programs. *Br J Sports Med* 2007;41(4):217-23.
25. Weiler JM. Medical modifiers of sports injury. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) in sports soft-tissue injury. *Clin Sports Med* 1992;11(3):626-44.
26. Astrom M, Westlin N. No effect of piroxicam on achilles tendinopathy: a randomized study of 70 patients. *Acta Orthop Scand* 1992;63:631-4.
27. Denley BG, Moore T, Sferra J, Gozdanovic J, Smith R. The efficacy of oral nonsteroidal anti-inflammatory medication (NSAID) in the treatment of plantar fasciitis: a randomized, prospective, placebo-controlled study. *Foot Ankle Int* 2007;28(1):20-3.
28. Mahler F. Partial and complete ruptures of the Achilles tendon and local corticosteroid injections. *Br J Sports Med* 1992;26(1):7-14.
29. Shrier I, Matheson GO, Kohl HW3. Achilles tendonitis: are corticosteroid injections useful or harmful? *Clin J Sport Med* 1996;6(4):245-50.
30. Fredberg U. Local corticosteroid injection in sport: review of literature and guidelines for treatment. *Scand J Med Sci Sports* 1997;7(3):131-9.
31. Neeter C, Thomee R, Silbernagel KG, Thomee P, Karlsson J. Iontophoresis with or without dexamethazone in the treatment of acute Achilles tendon pain. *Scand J Med Sci Sports* 2003;13(6):376-82.
32. Alfredson H, Ohberg L. Sclerosing injections to areas of neo-vascularisation reduce pain in chronic Achilles tendinopathy: a double-blind randomised controlled trial. *Knee Surg Sports Traumatol Arthrosc.* 2005;13(4):338-44.
33. Alfredson H, Ohberg L. Neovascularisation in chronic painful patellar tendinosis--promising results after sclerosing neovessels outside the tendon challenge the need for surgery. *Knee Surg Sports Traumatol Arthrosc* 2005;13(2):74-80.
34. Hoksrud A, Ohberg L, Alfredson H, Bahr R. Ultrasound-Guided Sclerosis of Neovessels in Painful Chronic Patellar Tendinopathy. A Randomized Controlled Trial. *Am J Sports Med* 2006;34:1738-46.
35. Furia JP. Extracorporeal shockwave therapy in the treatment of chronic insertional Achilles tendinopathy. *Orthopade* 2005;34(6):571-8.

36. Wang CJ, Ko JY, Chan YS, Weng LH, Hsu SL. Extracorporeal Shockwave for Chronic Patellar Tendinopathy. *Am J Sports Med* 2007;35(6):972-8.
37. Chung B, Wiley JP. Extracorporeal shockwave therapy: a review. *Sports Med* 2002;32(13):851-65.
38. Leadbetter WB, Moar PA, Lane GJ, Lee SJ. The surgical treatment of tendinitis. Clinical rationale and biologic basis. *Clin Sports Med* 1992;11(4):679-712.
39. Coleman BD, Khan KM, Maffulli N, Cook JL, Wark JD. Studies of surgical outcome after patellar tendinopathy: clinical significance of methodological deficiencies and guidelines for future studies. *Scand J Med Sci Sports* 2000;10(1):2-11.
40. Paavola M, Kannus P, Orava S, Pasanen M, Jarvinen M. Surgical treatment for chronic Achilles tendinopathy: a prospective seven month follow up study. *Br J Sports Med* 2002;36(3):178-82.
41. Testa V, Capasso G, Benazzo F, Maffulli N. Management of Achilles tendinopathy by ultrasound-guided percutaneous tenotomy. *Sci Sports Exerc* 2002;34(4):573-80.
42. Saxena A. Results of chronic Achilles tendinopathy surgery on elite and nonelite track athletes. *Foot Ankle Int* 2003;24(9):712-20.
43. Benazzo F, Stennardo G, Valli M. Achilles and patellar tendinopathies in athletes: pathogenesis and surgical treatment. *Bull Hosp Jt Dis.* 1996;54(4):236-40. 1996;54(4):236-40.
44. Paoloni JA, Appleyard RC, Nelson J, Murell GA. Topical glyceryl trinitrate treatment of chronic noninsertional achilles tendinopathy. A randomized, double-blind, placebo-controlled trial. *J Bone Joint Surg Am.* 2004 May;86-A(5):916-22. 2004;86-A(5):916-22.
45. Murell GA. Using nitric oxide to treat tendinopathy. *Br J Sp Med* 2007;41(4):227-31.
46. Rivenburgh DW. Physical modalities in the treatment of tendon injuries. *Clin Sports Med* 1992;11(3):645-59.
47. Jackson BA, Schwane JA, Starcher BC. Effect of ultrasound therapy on the repair of Achilles tendon injuries in rats. *Med Sci Sports Exerc* 1991;23:171-6.
48. Cyriax J. Manipulations trials. *Br Med J* 1980;280(6270):111.
49. Kvist M. Achilles tendon injuries in athletes. *Ann Chir Gynaecol* 1991;80(2):188-201.
50. Williams JGP. Achilles tendon lesions in sport. *Sports Med* 1986;3:114-35.
51. Sundqvist H, Forsskahl B, Kvist M. A promising novel therapy for achilles peritendinitis: double-blind comparison of glycosaminoglycan polysulfate and high-dose indomethacin. *Int J Sports Med* 1987;8:298-303.
52. Kettunen JA, Kvist M, Alanen E, Kujala UM. Long-term prognosis for jumper's knee in male athletes. A prospective follow-up study. *Am J Sports Med* 2002;30(5):689-92.
53. Cook JL, Khan KM, Harcourt P, Grant M, Young DA, Bonar F. A cross sectional study of 100 athletes with jumper's knee managed conservatively and surgically. The Victorian Institute of Sport Tendon Study Group. *Br J Sports Med* 1997;31(4):332-6.
54. Roels J, Martens M, Mulier JC, Burssens A. Patellar tendinitis (jumper's knee). *Am J Sports Med* 1978;6(6):362-36.
55. McLauchlan GJ, Handoll HHG. Interventions for treating acute and chronic Achilles tendinitis. *Cochrane Database of Systematic Reviews* 2001;Issue 2. Art. No.: CD000232. DOI:

- 10.1002/14651858.CD000232.
56. Kannus P, Józsa L. Histopathological changes preceding spontaneous ruptures of a tendon. A controlled study of 891 patients. *J Bone Joint Surg Am* 1991;73(10):1507-25.
 57. Cook JL, Khan KM, Harcourt PR, Kiss ZS, Fehrmann MW, Griffiths L et al. Patellar tendon ultrasonography in asymptomatic active athletes reveals hypoechoic regions: a study of 320 tendons. *Clin J Sports Med* 1998;8:73-7.
 58. Lian O, Holen KJ, Engebretsen L, Bahr R. Relationship between symptoms of jumper's knee and the ultrasound characteristics of the patellar tendon among high level male volleyball players. *Scand J Med Sci Sports* 1996;6:291-6.
 59. Gibbon WW, Cooper JR, Radcliffe GS. Sonographic incidence of tendon microtears in athletes with chronic Achilles tendinosis. *Br J Sports Med* 1999;33(2):129-30.
 60. Soila K, Karjalainen PT, Aronen HJ, Pihlajamaki HK, Tirman PJ. High-resolution MR imaging of the asymptomatic Achilles tendon: new observations. *AJR Am J Roentgenol* 1999;173(2):323-8.
 61. Major NM, Helm CA. MR imaging of the knee: findings in asymptomatic collegiate basketball players. *AJR Am J Roentgenol* 2002;179(3):641-4.
 62. Maffulli N, Kenward MG, Testa V, Capasso G, Regine R, King JB. Clinical diagnosis of Achilles tendinopathy with tendinosis. *Clin J Sport Med* 2003;13(1):11-5.
 63. Haims AH, Schweitzer ME, Patel RS, Hecht P, Wapner K. MR imaging of the Achilles tendon: overlap of findings in symptomatic and asymptomatic individuals. *Skeletal Radiol* 2000;29(11):640-5.
 64. Cook JL, Khan KM, Kiss ZS, Griffiths L. Patellar tendinopathy in junior basketball players: a controlled clinical and ultrasonographic study of 268 patellar tendons in players aged 14-18 years. *Scand J Med Sci Sports* 2000;10(4):216-21.
 65. Terslev L, Qvistgaard E, Torp-Pedersen S, Laetgaard J, Danneskiold-Samsøe B, Bliddal H. Ultrasound and Power Doppler findings in jumper's knee - preliminary observations. *Eur J Ultrasound* 2001;13:183-9.
 66. Cook JL, Khan KM, Kiss ZS, Purdam CR, Griffiths L. Reproducibility and clinical utility of tendon palpation to detect patellar tendinopathy in young basketball players. *Victorian Institute of Sport tendon study group. Br J Sports Med* 2001;35(1):65-9.
 67. Ljungqvist R. Subcutaneous partial rupture of the Achilles tendon. *Acta Orthop Scand Suppl* 1968:113.
 68. Shields CL. The Cybex II evaluation on surgical repaired Achilles tendon ruptures. *Am J Sports Med* 1978;7:15-7.
 69. Resnick D, Feingold ML, Curd J, Niwayama G, Goergen TG. Calcaneal abnormalities in articular disorders. Rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and Reiter syndrome. *Radiology* 1977;125(2):355-66.
 70. Siwek CW, Rao JP. Ruptures of the extensor mechanism of the knee joint. *J Bone Joint Surg Am* 1981;63(6):932-7.
 71. Ballas MT, Tytko J, Mannarino F. Commonly missed orthopedic problems. *Am Fam Physician* 1998;57(2):267-74.
 72. O'Brian T. The needle test for complete rupture of the Achilles tendon. *J Bone Joint Surg Am* 1984;66(7):1099-101.

73. Ogon P, Maier D, Jaeger A, Suedekamp NP. Arthroscopic patellar release for the treatment of chronic patellar tendinopathy. *Arthroscopy* 2006;22(4):e1-5.
74. Yodlowski ML, Scheller ADJ, Minos L. Surgical treatment of Achilles tendinitis by decompression of the retrocalcaneal bursa and the superior calcaneal tuberosity. *Am J Sports Med* 2002;30(2):318-21.
75. Wilcox DK, Bohay DR, Andersson JG. Treatment of chronic achilles tendon disorders with flexor hallucis longus tendon transfer/augmentation. *Foot Ankle Int* 2000;21(12):1004-10.
76. Alfredson H, Pietilä T, Jonsson P, Lorentzon R. Heavy-load eccentric calf muscle training for the treatment of chronic Achilles tendinosis. *Am J Sports Med* 1998;26(3):360-6.
77. Maffulli N, Testa V, Capasso G, Bifulca G, Binfield PM. Results of percutaneous longitudinal tenotomy for Achilles tendinopathy in middle- and long-distance runners. *Am J Sports Med* 1997;25(6):835-40.
78. Schepsis AA, Wagner C, Leach R. Surgical management of Achilles tendon overuse injuries. A long-term follow-up study. *Am J Sports Med* 1994;22(5):611-9.
79. Ferretti A, Conteduca F, Camerucci E, Morelli F. Patellar tendinosis: a follow-up study of surgical treatment. *J Bone Joint Surg Am* 2003;84-A(12):2179-85.
80. Verheyden F, Geens M, Nelen G. Jumper's knee: results of surgical treatment. *Acta Orthop Belg* 1997;63(2):102-5.
81. Maffulli N, Binfield PM, Leach WJ, King JB. Surgical management of tendinopathy of the main body of the patellar tendon in athletes. *Clin J Sport Med* 1999;9(2):58-62.
82. Zini R, Coari GC. Arthroscopic management of patellar tendinitis. *J Sports Traumatol Rel Res* 1997;19:75-82.
83. Boesen MI, Torp-Pedersen S, Koenig MJ, Christensen R, Langberg H, Holmich P et al. Ultrasound guided electrocoagulation in patients with chronic non-insertional Achilles tendinopathy: a pilot study. *Br J Sports Med* 2006;40(9):761-6.
84. Tallon C, Coleman BD, Khan KM, Maffulli N. Outcome of surgery for chronic Achilles tendinopathy. A critical review. *Am J Sports Med* 2001;29(3):315-20.
85. Scott A, Khan KM, Roberst CR, Duronio V. What do we mean by the term "inflammation"? A contemporary basic science update for sports medicine. *Br J Sports Med* 2004;38:372-80.
86. Csizy M, Hintremann B. Rupture of the Achilles tendon after local steroid injection. Case reports and consequences for treatment. *Swiss Surg* 2001;7(4):184-9.
87. Khan KM, Cook JL, Kannus P, Maffulli N, Bondesteam S. Time to abandon the "tendinitis" myth (editorial). *BMJ* 2002;324(7338):626-7.
88. Alfredson H. Letter to Editor. *Scand J Med Sci Sports* 2004;14(4):269.
89. Peers KH, Lysens RJJ. Patellar tendinopathy in athletes: current diagnostic and therapeutic recommendations. *Sports Med* 2005;35(1):71-8.
90. Kirkendall DT, Garret WE. Function and biomechanics of tendons. *Scand J Med Sci Sports* 1997;7(2):62-6.
91. Järvinen M, Jõzsa L, Kannus P, Järvinen TJN, Kvist M, Leadbetter WB. Histopathological findings in chronic tendon disorders. *Scand J Med Sci Sports* 1997;7:85-95.

92. Sharma P, Maffulli N. Biology of tendon injury: healing, modeling and remodeling. *J Musculoskeletal Neuronal Interact* 2006;6(2):181-90.
93. Alfredson H. Chronic midportion Achilles tendinopathy: an update on research and treatment. *Clin Sports Med* 2003;22:727-41.
94. Alfredson H. The chronic painful Achilles and patellar tendon: research on basic biology and treatment. *Scand J Med Sci Sports* 2005;15(4):252-9.
95. el Hawary R, Stanish WD, Curwin S. Rehabilitation of tendon injuries in sport. *Sports Med* 1997;24:347-58.
96. Andersson JE. Grant's atlas of anatomy. 7th ed. Baltimore: Williams & Wilkins; 1980.
97. Hollinshead WH, Rosse C. In: Harper & Row, editor. Textbook of anatomy. 4th ed. Philadelphia: 1985. p. 434-5.
98. Maffulli N, Wong J. Rupture of the Achilles and patellar tendons. *Clin Sports Med* 2003;22(4):761-76.
99. Maffulli N, Testa V, Capasso G, Ewen SW, Sullo A, Benazzo F et al. Similar histopathological picture in males with Achilles and patellar tendinopathy. *Med Sci Sports Exerc* 2004;36(9):1470-5.
100. Kannus P. Structure of the tendon connective tissue. *Scand J Med Sci Sports* 2000;10:312-20.
101. Schatzker J, Branemark PI. Intravital observations on the microvascular anatomy and microcirculation of the tendon. *Acta Orthop Scand* 1969;126:1-23.
102. Scott A, Khan KM, Cook JL, Duronio V. Human tendon overuse pathology: histopathologic and biochemical findings. In: Woo SL, Renström P, Arnoczku SP, editors. *Tendinopathy in athletes*. 1 ed. Blackwell Publishing.; 2007. p. 69-84.
103. Soldado F, Reina F, Yuguere M, Rodriguez-Baeza A. Clinical anatomy of the arterial supply of the human patellar ligament. *Surg Radiol Anat* 2002;24(3-4):177-82.
104. Clark MG, Clerk LH, Newmann JM, Rattigan S. Interaction between metabolism and flow in tendon and muscle. Review. *Scand J Med Sci Sports* 2000;10(6):338-45.
105. Barfred T. Achilles tendon rupture. Aetiology and pathogenesis of subcutaneous rupture assessed on the basis of the literature and rupture experiments on rats. *Acta Orthop Scand* 1973;152:1-126.
106. Zantop Z, Tillmann B, Petersen W. quantitative assessment of blood vessels of the human Achilles tendon: an immunohistochemical cadaver study. *Arch Orthop Trauma Surg* 2003;123:501-4.
107. Carr AJ, Norris SH. The blood supply of the calcaneus tendon. *J Bone Joint Surg (Br)* 1989;71:100-1.
108. Åström M. Laser Doppler flowmetry in the assessment of tendon blood flow. *Scand J Med Sci Sports* 2000;10(6):365-7.
109. Åström M, Westlin N. Blood flow in the human Achilles tendon assessed by laser Doppler flowmetry. *J Orthop Res* 1994;12:246-52.
110. Langberg H, Olesen JL, Skovgaard D, Kjaer M. Age related blood flow around the Achilles tendon during exercise in humans. *Eur J Appl Physiol* 2001;84:246-8.
111. Langberg H, Bulow J, Kjaer M. Standardized intermittent static exercise increases peritendinous blood flow in human leg. *Clin Physiol* 1999;19(1):89-93.
112. Langberg H, Bulow J, Kjaer M. Blood flow in the peritendinous space of the human Achilles tendon

- during exercise. *Acta Physiol Scand* 1998;163(2):149-53.
113. Boushel R, Langberg H, Green S, Skovgaard D, Bulow J, Kjaer M. Blood flow and oxygenation in peritendinous tissue and calf muscle during dynamic exercise in humans. *J Physiol* 2000;1(524):305-13.
 114. Boushel R, Langberg H, Olesen J, Novak M, Simonsen L, Bulow J et al. Regional blood flow during exercise in humans measured by near-infrared spectroscopy and indocyanine green. *J Appl Physiol* 2000;89(5):1868-78.
 115. Boushel R, Langberg H, Green S, Skovgaard D, Bulow J, Kjaer M. Blood flow and oxygenation in peritendinous tissue and calf muscle during dynamic exercise in humans. *J Physiol*. 2000;524(1):305-13.
 116. Knobloch K, Kraemer R, Lichtenberg A, Jagodzinski M, Gossling T, Richter M et al. Achilles tendon and patellar tendon microcirculation in midportion and insertional tendinopathy in athletes. *Am J Sports Med* 2005;34(10):61.
 117. Zanetti M, Metzdorf A, Kundert HP, Zollinger H, Vienne P, Seifert B et al. Achilles tendons: clinical relevance of neovascularization diagnosed with power Doppler US. *Radiology* 2003;227(2):556-60.
 118. Ohberg L, Lorentzon R, Alfredson H. Neovascularisation in Achilles tendons with painful tendinosis but not in normal tendons: an ultrasonographic investigation. *Knee Surg Sports Traumatol Arthrosc* 2001;9:233-8.
 119. Åström M, Westlin N. Blood flow in the chronic Achilles tendinopathy. *Clin Orthop* 1994:166-72.
 120. Knobloch K, Kraemer R, Lichtenberg A, Jagodzinski M, Gossling T, Richter M et al. Achilles tendon and paratendon microcirculation in midportion and insertional tendinopathy in athletes. *Am J Sports Med* 2006;34(1):92-7.
 121. Langberg H, Bjorn C, Boushel R, Hellsten Y, Kjaer M. Exercise-induced increase in interstitial bradykinin and adenosine concentrations in skeletal muscle and peritendinous tissue in humans. *J Physiol* 2002;1(542):977-83.
 122. Langberg H, Boushel R, Skovgaard D, Risum N, Kjaer M. Cyclo-oxygenase-2 mediated prostaglandin release regulates blood flow in connective tissue during mechanical loading in humans. *J Physiol* 2003;1(55):683-9.
 123. Karim F, Kidd C, malpus CM, Penna PE. The effects of stimulation of the left atrial receptors on sympathetic efferent nerve activity. *J Physiol* 1972;227(1):243-60.
 124. Yang S, Zhans L. Glucocorticoids and vascular reactivity. *Curr Vasc Pharmacol* 2004;2(1):1-12.
 125. Suzuki T, Nakamura Y, Moriya T, Sasano H. Effects of steroid hormones on vascular functions. *Microsc Res Tech* 2003;60(1):76-84.
 126. Ackermann PW, Dahl J, Bring DK-I, Renström PAFH. Tendon innervatoin: understanding of pathology abd potential implications for treatment. In: Woo SL, Renström P, Arnoczku SP, editors. *Tendinopathy in athetes*. 1 ed. Blackwell Publishing; 2007. p. 123-1144.
 127. Ackermann PW, Jian L, Finn A, Ahmed M, Kreicberg A. Autonomic innervation of tendons, ligaments and joint capsules: a morphologic and qualitative study in the rat. *J Orthop Res* 2005;19(3):372-278.
 128. Jozsa L, Kannus P. *Human Tendons. Anatomy, Physiology and Pathology*. Canada: Human Kinetics; 1997.
 129. Andreas KH, von During M, Schmidt RF. Sensory innervation of the Achilles tendon by group III and IV afferent fibres. *Anat Embryol (Berl)* 1985;172(2):145-56.

130. O'Brien M. Structure and metabolism of tendons. *Scand J Med Sci Sports* 1997;7(2):55-61.
131. Grant DS, Zukowska Z. Revascularization of ischemic tissues with SIKVAV and neuropeptide Y (NPY). *Experiment Med Biol* 2000;476:139-54.
132. Lundberg JM, Hökfelt T. Multiple co-existence of peptides and classic transmitters in peripheral autonomic and sensory neurons; functional and pharmacological implications. *Progres Brain Res* 1986;68:241-62.
133. Dickinson T, Mitchell R, Robberecht P, Fleetwood-Walker SM. The role of VIP/PACAP receptor subtypes in spinal somasensory processing in rats with an experimental peripheral mononeuropathy. *Neuropharmacology* 1999;38:167-80.
134. Delgado M, Abad C, Martinez C, Leceta J, Gomariz RP. Vasoactive intestinal peptide prevents experimental arthritis by downregulating both autoimmune and inflammatory components of the disease. *Nat Med* 2001;7(5):563-8.
135. Ackermann PW, Dahl J, Bring DK-I, Renström PAFH. Tendon innervation: understanding of pathology and potential implications for treatment. In: Woo SL, Renström P, Arnoczku SP, editors. *Tendinopathy in athletes*. 1 ed. Blackwell Publishing; 2007. p. 123-1144.
136. Brain SD, Williams JR, Tippins JR, Morris HR, MacIntyre I. Calcitonin gene-related peptide is a potent vasodilator. *Nature* 1985;313(5997):54-6.
137. Nilsson J, von Euler AM, Dalsgaard CJ. Stimulation of connective tissue cell growth by substance P and substance K. *Nature* 1985;315(6014):61-3.
138. Haegerstrand A, Dalsgaard CJ, Jonzon B, Larsson O, Nilsson J. Calcitonin gene-related peptide stimulates proliferation of human endothelial cells. *Proc.Nat.Acad.Sci.USA* 1990;87(9):3299-303.
139. Saria A, Lundberg JM, Skofitsch G, Lembeck F. Vascular protein linkage in various tissue induced by substance P, capsaicin, bradykinin, serotonin, histamin and by antigen challenge. *Naunyn-Schiedeberg's Archives of Pharmacology*. 1983;324:212-8.
140. Snijdelaar DG, Dirksen R, Slappendel R, Crul BJ. Substance P. *Eur J Pain* 2000;4(2):121-35.
141. Schaible HG, Grubb D. Afferent and spinal mechanisms of joint pain. *Pain* 1993;55(1):5-54.
142. Vasko MR, Campell WB, Waite KJ. *J Neurosci* 1994;14:4987-97.
143. Gallicchio M, Rosa AC, Benetti E, Collino M, Dianzani C, Fantozzi R. Substance P-induced cyclooxygenase-2 expression in human umbilical vein endothelial cells. *Br J Pharmacol* 2006;147(6):681-9.
144. Prasad A, Naskar R, Dubey R, Raha D, Ahmed MF. Modulation of serum cortisol by substance P in albino rats: evidence of a direct effect on adrenal gland. *Indian J Exp Biol* 2006;44(2):163-4.
145. Cridlans RA, Henry JL. Effects of intrathecal administration of neuropeptides on a spinal nociceptive reflex in the rat: VIP, galanin, CGRP, TRH, somatostatin and angiotensin II. *Neuropeptides* 1988;11:23-32.
146. Szolcsanyi J, Helyes Z, Oroszi G, Nemeth J, Pinter E. Release of somatostatin and its role in mediation of the anti-inflammatory effect induced by antidromic stimulation of sensory fibres of rat sciatic nerve. *Br J Pharmacol* 1998;123:936-42.
147. Schaffer M, Beiter T, Becker HD, Hunt TK. Neuropeptides: mediators of inflammation and tissue repair? *Arch Surg* 1998;133(10):1107-16.

148. Lai XN, Wang ZG, Zhu JM, Wang LL. Effect of substance P on gene expression of transforming growth factor beta-1 and its receptors in rat's fibroblasts. *Chinese J Traumatol* 2003;6(6):350-4.
149. Khalil Z, Helme R. Sensory peptides as neuromodulators of wound healing in aged rats. *J Gerontol* 1996;51(5):354-6.
150. Burssens P, Steyaert A, Forsyth R, van Ovost EJ, Verdonk R. Exogenously administered substance P and neutral endopeptidase inhibitors stimulate fibroblast proliferation, angiogenesis and collagen organization during Achilles tendon healing. *Foot Ankle Int* 2005;26(10):832-9.
151. Steyaert AE, Burssens PJ, Vercruyse CW, Vanderstraeten GG, Verbeck RM. The effect of substance P on the biomechanic properties of ruptures ret Achilles' tendon. *Arch Phys Med Rehabil* 2006;87:254-8.
152. Hong Y, Abbott FV. Peripheral opioid modulation of pain and inflammation in the formalin test. *Eur J Pharmacol* 1995;277(1):21-8.
153. Moore RH, Dowling DA. Effects of enkephalins on perfussion pressure in isolated hindlimb preparations. *Life Sci* 2007;31:1559-66.
154. Zagon IS, McLaughlin PJ. Iditenfication of opioid peptides regfulating proleferation of neurons and glia in the developing nervous system. *Brain Res* 1991;542:318-23.
155. Yaksh TL. Substance P release from knee joint afferent terminals. *Brain Res* 1999;458:319-24.
156. Zhou L, Zhang Q, Stein C, Scahfer M. Contribution of opioiod receptors on primary afferent versus sympathetic neurons to peripheral opioid analgesia. *J Pharmacol Exper Therap* 1998;286:1000-6.
157. Cabot PJ. Immune-derived opioids and peripheral antinociception. *Clin Exp Pharmacol Physiol* 2007;28(3):230-2.
158. Ackermann PW, Ahmed M, Kreicberg A. Early nerve regeneration after Achilles tendon rupture: a preerquisite for healing? A study in the rat. *J Orthop Res* 2002;20:849-56.
159. Lian O, Dahl A, Ackermann PW, Frihagen F, Engebretsen L, Bahr R. Pronociceptive and antinociceptive neuromediators in patellar tendinopathy. *Am J Sports Med* 2006;34(11):1801-8.
160. Schubert TE, Weidler C, Lerch K, Hofstadter F, Straub RH. Achilles tendinosis is associated with sprouting of substance P positive nerve fibres. *Ann Rheum Dis* 2005;64(7):1083-6.
161. Alfredson H, Ohberg L, Forsgren S. Is vasculo-neural ingrowth the cause of pain in chronic Achilles tendinosis? An investigation using ultrasonography and colour Doppler, immunohistochemistry, and diagnostic injections. *Knee Surg Sports Traumatol Arthrosc* 2003;11(5):334-8.
162. Alfredson H, Thorsen K, Lorentzon R. In situ microdialysis in tendon tissue: high levels of glutamate, but not prostaglandin E2 in chronic Achilles tendon pain. *Knee Surg Sports Traumatol Arthrosc* 1999;7(6):378-81.
163. Westermark T, Rantapaa-Dalqvist S, Wallberg-Jonsson S, Kjorell U, Forsgren S. Increased content of bombesin/GRP in human synovial fluid in early arthritis: different pattern compared with substance P. *Clin Exp Rheumatol* 2001;19(6):715-20.
164. Menkes CJ, Renoux M, Laoussadi S, Mauborgne A, Bruxelles J, Cesselin F. Substance P level in the synovium and synovial fluid from patients with rheumatoid arthritis and osteoarthritis. *J Rheumatol* 2007;377:532-5.
165. Inoue H, Shimayama Y, Hirabayashi K, Kajigaya H, Yamamoto S, Oda H et al. Production of neuropeptide substance P by synovial fibroblasts from patients with rheumatoid arthritis and osteoarthritis. *Neurosci Lett* 2001;303(3):149-52.

166. Sedo A, Duke-Cohan JS, Balaziová E, Sedová LR. Dipeptidyl peptidase IV activity and/or structure homologs: contributing factors in the pathogenesis of rheumatoid arthritis? *Arthritis Res Ther* 2005;7(6):253-69.
167. Masi AT, Bijlma JW, Chikanza IC, Pitzalis C, Cutolo M. Neuroendocrine, immunologic, and microvascular systems interactions in rheumatoid arthritis: physiopathogenetic and therapeutic perspectives. *Semin Arthritis Rheum* 1999;29(2):65-81.
168. Lotz M, Vaughan JH, Carson DA. Effect of neuropeptides on production of inflammatory cytokines by human monocytes. *Science* 1988;241(4870):1218-21.
169. Lambert N, Lescoulié PL, Yassine-Diab B, Enault G, Mazieres B, De Preval C et al. Substance P enhances cytokine-induced vascular cell adhesion molecule-1 (VCAM-1) expression on cultured rheumatoid fibroblast-like synoviocytes. *Clin Exp Immunol* 1988;113(2):269-75.
170. Hernanz A, Medina S, de Miguel E, Martín-Mola E. Effect of calcitonin gene-related peptide, neuropeptide Y, substance P, and vasoactive intestinal peptide on interleukin-1 β , interleukin-6 and tumor necrosis factor- α production by peripheral whole blood cells from rheumatoid arthritis and osteoarthritis patients. *Regul Pept* 2003;115(1):19-24.
171. Covas MJ, Pinto LA, Pereira Da Silva JA, Victorino RM. Effects of the neuropeptide, substance P, on lymphocyte proliferation in rheumatoid arthritis. *J Int Med Res* 1995;23(6):431-8.
172. Brain SD. Sensory neuropeptides: their role in inflammation and wound healing. *Immunopharmacology* 1997;37:133-52.
173. Onuoha GN, Alpar EK. Levels of vasodilators (SP, CGRP) and vasoconstrictors (NPY) peptides in early human burns. *Eur J Endocrinol* 2001;31:253-7.
174. Schwartz JP. Neurotransmitters as neurotrophic factors: a new set of functions. *Int.Rev.Neurobiol* 1992;34:1-23.
175. Hökfelt T, Broberger C, Xu Z-QD, Sergejev V, Ubink R, Diez M. Neuropeptides--an overview. *Neuropharmacology* 2000;39(8):1337-56.
176. Strand FL, Rose LZLA, Kume J, Alves SE, Anatonawich FJ, Garrett LY. Neuropeptide hormones as neurotrophic factors. *Physiol.Rev* 1991;71(4):1017-46.
177. Kannus P, Józsa L. Basic science of tendons. In: Garret WEJ, Speer KP, Kirkendall DT, editors. *Principles and practice of orthopaedic sports medicine*. Philadelphia: Lippincott Williams and Wilkins; 2000. p. 21-37.
178. Chaplin DM, Greenlee TKJr. The development of human digital tendons. *J Anat* 1975;120(Pt2):253-74.
179. McNeilly CM, Banes AJ, Benjamin M, Ralphs JR. Tendon cells in vivo form a three dimensional network of cell processes linked by gap junctions. *J Anat* 1996;189(Pt3):593-600.
180. Wall ME, Banes AJ. Early responses to mechanical load in tendon: Role for calcium signaling, gap junctions and intercellular communication. *J Musculoskelet Neuronal Interact* 2005;5(1):70-84.
181. Martínez-Hernández A, Amenta PS. Basic concepts in inflammation. In: Leadbetter WB, Buckwalter JA, Gordon ES, editors. *Sport-Induced Inflammation*. Park Ridge: American Academy of Orthopedic Surgeons; 1990. p. 55-102.
182. Kvist M, Józsa L, Järvinen M, Kvist H. Chronic Achilles paratendonitis in athletes: A histological and histochemical study. *Pathology* 1987;19:1-11.
183. Langberg H, Skovgaard D, Petersen L, Bülow J, Kjaer M. Type I collagen synthesis and degradation in peritendinous tissue after exercise determined by microdialysis in humans. *J Physiol* 1999;521:299-306.

184. Goldring MB, Goldring SR. Skeletal tissue response to cytokines. *Clin Orthop Relat Res* 1990;258:245-78.
185. Vailais AC, Tipton CM, Laughlin HL, Tchong TK, Matthes RD. Physical activity and hypophysectomy on the aerobic capacity of ligaments and tendons. *J Appl Physiol* 1978;44(4):542-6.
186. Wang JH, Jia F, Yang G, Yang S, Cambell BH, Stone D et al. Cyclic mechanical stretching of human tendon fibroblasts increases the production of prostaglandin E2 and levels of cyclooxygenase expression: a novel in vitro model study. *Connect Tissue Res* 2003;3-4(44):128-33.
187. Wang JH, Li Z, Yang G, Khan M. Repetitively stretched tendon fibroblasts produce inflammatory mediators. *Clin Orthop Relat Res* 2004;422:243-50.
188. Tsuzaki M, Guyton G, Garret W, Archambault J.M., Herzog W, Almekinders LC et al. IL-1 beta induces COX2, MMP-1, -3 and -13, ADAMTS-4, IL-1 beta and IL-6 in human tendon cells. *J Orthop Res* 2003;21(2):256-64.
189. Li Z, Khan M, Stone D, Woo SL, Wang JH. Inflammatory response of human tendon fibroblasts to cyclic mechanical stretching. *Am J Sports Med* 2004;32(2):435-40.
190. Almekinders LC, Banes AJ, Ballenger CA. Effects of repetitive motion on human fibroblasts. *Med Sci Sports Exerc* 1993;25:603-7.
191. Almekinders LC, Banes AJ, Bracey LW. An in vitro investigation into the effect of repetitive motion and nonsteroidal antiinflammatory medication on human tendon fibroblasts. *Am J Sports Med* 1995;23:119-23.
192. Langberg H, Skovgaard D, Karamouzis M, Bulow J, Kjaer M. Metabolism and inflammatory mediators in the peritendinous space measured by microdialysis during intermittent isometric exercise in humans. *J Physiol* 1999;15(515):919-27.
193. Li Z, Yang G, Khan M, Stone D, Woo SL, Wang JHC. Inflammatory response of human tendon fibroblasts to cyclic mechanical stretching. *Am.J.Sports Med.*2004; 32; 435 2004;32(2):435-40.
194. Baracos V, Rodemann HP, Dinarello CA, Goldberg AL. Stimulation of muscle protein degradation and prostaglandin E2 release by leukocytic pyrogen (interleukin-1). A mechanism for the increased degradation of muscle proteins during fever. *New Eng J Med* 1983;308(10):441-6.
195. Effect of different tension magnitudes of tension force on prostaglandin E2 production by human periodontal ligament cells. *Arch Oral Biol* 1994;39:877-84.
196. Cilli F, Khan M, Fu F, Wang JH. Prostaglandin E2 affects proliferation and collagen synthesis by human patellar tendon fibroblasts. *Clin J Sport Med* 2004;14(4):232-6.
197. Elias JA, Rossmann MD, Zurier RB, Daniele RP. Human alveolar macrophage inhibition of lung fibroblast growth. A prostaglandin-dependent process. *Am Rev Respir Dis* 1985;131(1):94-9.
198. Elias JA, Zurier RB, Schreiber AD, Leff JA, Daniele RP. Monocyte inhibition of lung fibroblast growth: relationship to fibroblast prostaglandin production and density-defined monocyte subpopulations. *J Leukocyt Biol* 1985;37:15-28.
199. Harda Y, Tanaka K, Uchida Y. Changes in the levels of prostaglandins and tromboxane and their roles in the accumulation of exudate in rat carrageenin-induced pleurisy: a profile analysis using gas chromatography-mass spectrometry. *Prsotaglandins* 1982;23:881-95.
200. Betz M, Fox BS. Prostaglandin E2 inhibits production of Th1 lymphokines but not Th2 lymphokines. *J Immunol* 1991;146:108-13.
201. Diaz A, Munoz E, Johnston R, Korn JH, Jimenez SA. Regulation of human lung fibroblast alpha 1 (I)

- procollagen gene expression by tumor necrosis factor alpha, interleukin-1 beta, and prostaglandin E2. *J Biol Chem* 1993;268:10364-71.
202. Diaz A, Varga J, Jimenez SA. Transforming growth factor-beta stimulation of lung fibroblast prostaglandin E2 production. *J Biol Chem* 1989;264(20):11554-7.
 203. Denzlinger C, Rapp S, Hagmann W, Keppler D. Leukotrienes as mediators in tissue trauma. *Science* 1985;230:330-2.
 204. Crooks SW, Stockley RA. Leukotriene B4 in the immune system. *Int J Biochem Cell Biol* 1998;30:173-8.
 205. Ford-Hutchinson AW. Leukotrienes B4 in inflammation. *Crit Rev Immunol* 1990;10:1-12.
 206. Leukotrienes promote plasma leakage and leukocyte adhesion in postcapillary venules: in vivo effects with relevance to the acute inflammatory response. *Proc Natl Acad Sci USA* 1981;78:3887-91.
 207. Kaiser E. Phospholipase A2: its usefulness in laboratory diagnostics. *Crit Rev Clin Lab Sci* 1999;36(2):65-163.
 208. Wang JHC, Woo SL, Stone D. Mechanobiologic studies of cellular and molecular mechanisms of tendonopathy. In: Woo SL, Renström P, Arnoczku SP, editors. *Tendonopathy in athletes*. 1 ed. Blackwell Publishing.; 2007. p. 85-100.
 209. Gonzalez-Burtica H, Khamashita MA, Huges GR. Synovial fluid phospholipase A2s and inflammation. *Ann Rev Dis* 1989;48(4):267-9.
 210. Vadas P, Wasi S, Movat HZ, Hay JB. Extracellular phospholipase A2 mediates inflammatory hyperaemia. *Nature* 1981;293(5833):583-5.
 211. Koskinen SO, Heinemeier KM, Olesen JL, Langberg H, Kjaer M. Physical exercise can influence local levels of matrix metalloproteinases and their inhibitors in tendon-related connective tissue. *J Appl Physiol* 2004;96(3):861-4.
 212. Yang G, Im HJ, Wang JH. Repetitive mechanical stretching modulates IL-1beta induced COX-2, MMP-1 expression, and PGE2 production in human patellar tendon fibroblasts. *Gene* 2005;363:166-72.
 213. Archambault J.M., Tsuzaki M, Herzog W, Banes AJ. Stretch and interleukin-1beta induce matrix metalloproteinases in rabbit tendon cells in vitro. *J Orthop Res* 2002;20(1):36-9.
 214. Skutek M, van Griensven M, Zeichen J, Brauer N, Bosch U. Cyclic mechanical stretching enhances secretion of Interleukin 6 in human tendon fibroblasts. *Knee Surg Sports Traumatol Arthrosc* 2003;9(5):322-6.
 215. Langberg H, Olesen JL, Gemmer C, Kjaer M. Substantial elevation of interleukin-6 concentration in peritendinous tissue, in contrast to muscle, following prolonged exercise in humans. *J Physiol* 2002;542(3):985-90.
 216. Van Snick J. Interleukin-6: an overview. *Annu Rev Immunol*.1990;8:253-78. 1990;8:253-78.
 217. Jarvinen M, Józsa L, Kannus P, Jarvinen TLN, Kvist M, Leadbetter WB. Histopathological findings in chronic tendon disorders. *Scand J Med Sci Sports* 1997;7(2):86-95.
 218. Pufe T, Petersen WJ, Mentlein BN, Tillmann BN. The role of vasculature and angiogenesis for the pathogenesis of degenerative tendons disease. *Scand J Med Sci Sports* 2005;15(4):211-22.
 219. Senger DR, Gali SJ, Dvorak AM, Peruzzi CA, Harvey VS, Dvorak HF. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. *Science* 1983;219(4587):983-5.

-
220. Ferrara N. Molecular and biological properties of vascular endothelial growth factor. *J Mol Med* 1999;77(7):527-43.
 221. Neufeld G, Cohen T, Gengrinovitch S, Poltorak Z. Vascular endothelial growth factor (VEGF) and its receptors. *FASEB J* 1999;13(1):9-22.
 222. Pufe T, Petersen W, Tillmann B, Mentlein R. The angiogenic peptide vascular endothelial growth factor is expressed in foetal and ruptured tendons. *Virchows Arch* 2001;439(4):579-85.
 223. Petersen W, Pufe T, Kurz B, Mentlein R, Tillmann B. Angiogenesis in fetal tendon development: spatial and temporal expression of the angiogenic peptide vascular endothelial cell growth factor. *Anat Embryol (Berl)* 2002;205(4):263-70.
 224. Alfredson H, Lorentzon M, Backman S, Backman C, Lerner UH. cDNA-arrays and real-time quantitative PCR techniques in the investigation of chronic Achilles tendinosis. *J Orthop Res* 2003;21(6):970-5.
 225. Adams GR. Invited Review: Autocrine/paracrine IGF-I and skeletal muscle adaptation. *J Appl Physiol* 2002;93(3):1159-67.
 226. Heinemeier K, Langberg H, Olesen J, Kjaer M. Role of TGF-beta1 in relation to exercise-induced type I collagen synthesis in human tendinous tissue. *J Appl Physiol* 2003;95(6):2390-7.
 227. Petersen W, Varoga D, Zantrop T, Hasselpflug J, Mentlein R, Pufe T. Cyclic strain influences the expression of the vascular endothelial growth factor (VEGF) and the hypoxia inducible factor 1 alpha (HIF-1alpha) in tendon fibroblasts. *J Orthop Res*.2004 Jul;22(4):847-53. 2004;22(4):847-53.
 228. Arnoczku SP, Tian T, Lavagnino M, Gardnet K, Schuler P, Morse P. Activation of stress-activated protein kinase (SAPK) in tendon cells following cyclic strain: the effects of strain frequency, strain magnitude, and cytosolic calcium. *J Orthop Res* 2002;20(5):947-52.
 229. Ip YT, Davis RJ. Signal transduction by the c-Jun N-terminal kinase (JNK) - from inflammation to development. *Curr Opin Cell Biol* 1998;10(2):205-19.
 230. Wall ME, Faber J, Yang X, Tsuzaki M, Banes AJ. Norepinephrine induced calcium signaling and expression of adrenoceptors in avian tendon cells. *Am j Physiol* 2004;287(4):912-8.
 231. Franke E, Sood A, Kenamond C. ATP stimulates an increase in intracellular calcium in human tendon cells via purinergic receptors. ATP temporally blocks gap junction signalling. *Orthopaedic Research Society*. 1998. p. 23.
 232. Cavaillon JM. Pro- versus anti-inflammatory cytokines: myth or reality. Review. *Cell Mol Biol* 2001;47(4):695-702.
 233. Fu SC, Wang W, Pau HM, Wong YP, Chan KM, Rolf CG. Increased expression of transforming growth factor-beta1 in patellar tendinosis. *Clin Orthop Relat Res* 2002;Jul(400):174-83.
 234. Alfredson H, Forsgren S, Thorsen K, Lorentzon R. In vivo microdialysis and immunohistochemical analyses of tendon tissue demonstrated high amounts of free glutamate and glutamate NMDAR1 receptors, but no signs of inflammation, in Jumper's knee. *J Orthop Res* 2001;19(5):881-6.
 235. Rolf C, Fu SC, Pau A, Wang W, Chan B. Increased cell proliferation and associated expression of PDGFR β causing hypercellularity in patellar tendinosis . *Rheumatology* 2001;40(3):267-73.
 236. Riley GP, Curry V, Degroot J. Matrix metalloproteinase activities and their relationship with collagen remodelling in tendon pathology. *Matrix Biol* 2002;21:185-95.
 237. Fu SC, Chan BP, Wang W, Pau HM, Chan KM, Rolf CG. Increased expression of matrix metalloproteinase 1 (MMP-1) in 11 patient with patellar tendinosis. *Acta Orthop Scand* 2002;73(6):658-

- 62.
238. Millar AW, Brown PD, Moore J. Results of single and repeat dose studies of the oral matrix metalloproteinase inhibitor. *Br J Clin Pharmacol* 1998;45:21-6.
239. Ireland D, Harrall R, Curry V, Holloway G, Hackney R, Hazleman BL et al. Multiple changes in gene expression in chronic human Achilles tendinopathy. *Matrix Biol* 2001;20:159-69.
240. Vasko MR, Campell WB, Waite KJ. *J Neurosci* 1994;14:4987-97.
241. Broome CS, Miyan JA. Neuropeptide control of bone marrow neutrophil production. A key axis for neuroimmunomodulation. *Ann.NY Acad.Sci* 2000;917:424-34.
242. Monneret G, Pachot A, Laroche B, Picollet J, Bienvenu J. Procalcitonin and calcitonin gene-related peptide decrease LPS-induced tnf production by human circulating blood cells. *Cytokine* 2000;12(6):762-4.
243. Kjaer M. Role of extracellular matrix in adaptation of tendon and skeletal muscle to mechanical loading. *Physiol Rev* 2004;84(2):649-98.
244. Kvist M. Achilles tendon injuries in athletes. *Sports Med* 1994;18(3):173-201.
245. Vailais AC, Vailais JC. Physical activity and connective tissue. In: Bouchard C, Stephard RJ, Stephens T, editors. *Physical activity, fitness and health*. Champaign,I.L.; 1994. p. 372-6.
246. Eyre DR, Paz MA, Gallop PM. Ccross-linking in collagen and elastin. *Ann Rev Biochem* 1984;53:717-48.
247. Enna CD, Dyer RF. Tendon plasticity: a property applicable to reconstructive surgery of the hand. *Hand* 1976;8:118-24.
248. Prockop DJ, Kivirikko KI. Collagens. Molecular biology, diseases, and potentials for therapy. *Annu Rev Biotherm* 1995;64:403-34.
249. Riley G. Chronic tendon pathology: molecular basis and therapeutic implications. *Expert Rev Mol Med* 2005;7(5):1-25.
250. Riley G, Harrall RL, Constant CR, Chard MD, Cawston TE, Hazleman BL. Tendon degeneration and chronic shoulder pain: changes in the collagen composition of the human rotator cuff tendons in rotator cuff tendinitis. *Ann Rheum Dis* 1994;53(6):359-66.
251. Benjamin M, Ralphs JR. Fibrocartilage in tendons and ligaments - an adaptation to compressive load. *J Anat* 1998;193:481-94.
252. Angelillo M, Blazina ME, Alanaatu A. Ligament structure, chemistry and physiology. In: Daniel D, editor. *Knee ligaments. Structure function, injury and repair*. New York: Raven Press; 1990. p. 77-91.
253. Jozsa L, Reffy A, Balint JB. Polarization and electron microscopic studies on the collagen of intact and ruptured human tendons. *Acta Histochem* 1984;74(2):20-215.
254. Woo SLY, Gomes MA, Woo YK, Akeson WH. Mechanical properties of tendons and ligaments. II. The relationship between immobilization and exercise on tissue remodelling. *Biorheology* 1982;19:397-408.
255. Langberg H, Skovgaard D, Petersen Bülow J, Kjaer M. Type I collagen turnover in the peritendinous connective tissue after exercise determined by microdialysis. *J Physiol* 1999;15(521):299-306.
256. Butler DL, Goods ES, Noyes FR. Biomechanics of ligaments and tendons. *Exerc Sports Sci Rev*

- 1978;6:125-81.
257. Sommer HM. The biomechanical and metabolic effects of a running regime on the Achilles tendon in the rat. *Int Orthop* 1987;11(1):71-5.
 258. Birch HL, McLaughlin L, Smith RK, Goodship AE. Treadmill exercise-induced tendon hypertrophy: assessment of tendons with different mechanical functions. *Equine Vet J Suppl* 1999;30:222-6.
 259. Rosager S, Aagaard P, Dyhre-Poulsen P, Neergaard K, Kjaer M, Magnusson SP. Load-displacement properties of the human triceps surae aponeurosis and tendon in runners and non-runners. *Scand J Med Sci Sports* 2002;12(2):90-8.
 260. Kongsgaard M, Aagaard P, Kjaer M, Magnusson P. Structural Achilles tendon properties in athletes subjected to different exercise modes and in Achilles tendon rupture patients. *J Appl Physiol* 2004;96:861-4.
 261. Kjaer M. Matrix loaded and unloaded: can tendons grow when exercised? *J Appl Physiol* 2007;102:515.
 262. Ulreich N, Kainberger F, Huber W, Nehrer S. Achilles tendon and sport. *Radiologe* 2002;42(10):811-7.
 263. Huang TF, Perry SM, Soslowky LJ. The effect of overuse activity on Achilles tendon in an animal model: a biomechanical study. *Ann Biomed Eng* 2004;32(3):336-41.
 264. Legerlotz K, Schjerling P, Langberg H, Brüggemann GP, Niehoff A. The effect of running, strength, and vibration strength training on the mechanical, morphological, and biochemical properties of the Achilles tendon in rats. *J Appl Physiol* 2007;102(2):564-72.
 265. Langberg H, Rosendal L, Kjaer M. Training-induced changes in peritendinous type I collagen turnover determined by microdialysis in humans. *J Physiol* 2001;534(1):297-302.
 266. Kjaer M, Langberg H, Miller BF, Boushel R, Crameri R, Koskinen S et al. Metabolic activity and collagen turnover in human tendon in response to physical activity. *J Musculoskelet Neuronal Interact* 2005;5(1):41-52.
 267. Koskinen SOA, Kjaer M, Mohr Y, Biering Sørensen F, Suuronen T, Takala TES. Type IV collagen and its degradation in paralyzed human muscle: effect of functional electrical stimulation. *Muscle Nerve* 2000;23(4):580-9.
 268. Langberg H, Ellingsgaard H, Madsen T, Jansson J, Magnusson P, Aagaard P et al. Eccentric rehabilitation exercise increases peritendinous type I collagen synthesis in humans with Achilles tendinosis. *Scand J Med Sci Sports* 2007;17:61-6.
 269. scott JE, Orford CR. Dermatan sulphate-rich proteoglycan associates with rat tail-tendon collagen at the d band in the gap region. *Biochem J* 1981;197(1):213-6.
 270. scott JE, Orford CR, Huges EW. Proteoglycan-collagen arrangements in developing rat tail tendon. An electron microscopical and biochemical investigation. *Biochem J* 1981;195(3):573-81.
 271. scott JE. Collagen--proteoglycan interactions. Localization of proteoglycans in tendon by electron microscopy. *Biochem J* 1980;187(3):887-91.
 272. Ippolito E, Natali PG, Postacchini F, Accinni L, Martino C. Morphological, immunochemical, and biochemical study of rabbit achilles tendon at various ages. *J Bone Joint Surg Am* 1980;62(4):583-98.
 273. Noyes FR, Grood ES. The strength of the anterior cruciate ligament in humans and Rhesus monkeys. *J Bone Joint Surg Am* 1976;58(8):1074-82.

274. Magnusson P, Beyer N, Abrahamsen H, Aagaard P, Kjaer M. Increased cross-sectional area and reduced tensile stress of the Achilles tendon in elderly compared with young women. *J Gerontol A Biol Sci Med Sci* 2003;58(2):123-7.
275. Pang BS, Ying M. Sonographic measurement of achilles tendons in asymptomatic subjects: variation with age, body height, and dominance of ankle. *Ultrasound Med* 2006;25(10):1291-6.
276. Centrella M, McCarthy TL, Canalis E. Platelet-derived growth factor enhances deoxyribonucleic acid and collagen synthesis in osteoblast-enriched cultures from fetal rat parietal bone. *Endocrinology* 1989;125(1):13-9.
277. Virag JA, Rolle ML, Reece J, Hardouin S, Feigl EO, Murry CE. Fibroblast Growth Factor-2 Regulates Myocardial Infarct Repair. Effects on Cell Proliferation, Scar Contraction, and Ventricular Function. *Am J Pathol* 2007;171(5):1431-40.
278. Kwon YB, Kim HW, Roh DH, Yoon SY, Baek RM, Kim JY et al. Topical application of epidermal growth factor accelerates wound healing by myofibroblast proliferation and collagen synthesis in rat. *J Vet Sci* 2006;7(2):105-9.
279. Boushel R, Langberg H, Olesen J, Gonzales-Alonzo J, Bulow J, Kjaer M. Monitoring tissue oxygen availability with near infrared spectroscopy (NIRS) in health and disease. *Scand J Med Sci Sports* 2001;11(4):213-22.
280. Kalliokoski KK, Langberg H, Ryberg AK. The effect of dynamic knee-extension exercise on patellar tendon and quadriceps femoris muscle glucose uptake in humans studied by positron emission tomography. *J Appl Physiol* 2005;99(3):1189-92.
281. Magnusson P, Hansen P, Kjaer M. Tendon properties in relation to muscular activity and physical training. *Scand J Med Sci Sports* 2003;13(4):211-23.
282. Yoon JH, Halper J. Tendon proteoglycans: biochemistry and function. *J Musculoskelet Neuronal Interact* 2005;5(1):22-34.
283. Robbins JR, Evanko SP, Vogel KG. Mechanical loading and TGF-beta regulate proteoglycan synthesis in tendon. *Arch Biochem Biophys* 1997;344(2):203-11.
284. Jozsa L, Kannus P, Balint JB, Reffy A. Three-dimensional ultrastructure of human tendons. *Acta Anat* 1991;142(4):306-12.
285. Ernst S, Langer R, Cooney CL, Sasisekharan R. Enzymatic degradation of glycosaminoglycans. *Crit Rev Biochem Mol Biol* 1995;30(5):387-444.
286. Movin T, Gad A, Reinholt FP, Rolf C. Tendon pathology in long-standing achillodynia. Biopsy findings in 40 patients. *Acta Orthop Scand* 1997;68(2):170-5.
287. Khan KM, Maffulli N, Coleman BD, Cook JL, Taunton JE. Patellar tendinopathy: some aspects of basic science and clinical management. Review. *Br J Sports Med* 1998;32(4):346-55.
288. Karlsson J, Kalebo P, Goksor LA, Thomee R, Sward L. Partial rupture of the patellar ligament. *Am J Sports Med* 1992;20(4):390-5.
289. Karlsson J, Lundin O, Lossing IW, Peterson L. Partial rupture of the patellar ligament. Results after operative treatment. *Am J Sports Med* 1991;19(4):403-8.
290. Raatikainen T, Karpakka J, Puranen J, Orava S. Operative treatment of partial rupture of the patellar ligament. A study of 138 cases. *Int J Sports Med* 1994;15(1):46-9.
291. Khan KM, Bonar F, Desmond PM, Cook JL, Young DA, Visentini PJ et al. Patellar tendinosis (jumper's knee): findings at histopathologic examination, US, and MR imaging. *Radiology*

- 1996;200(3):821-7.
292. Åström M, Rausing A. Chronic Achilles tendinopathy. A survey of surgical and histopathologic findings. *Clin Orthop* 1995;316:151-64.
 293. Popp JE, Joseph S, Kaeding CC. Recalcitrant Patellar Tendinitis: Magnetic Resonance Imaging, Histologic Evaluation, and Surgical Treatment. *Am.J.Sports Med* 1997;25(2):218-22.
 294. Colosimo AJ, Bassett FH3. Jumper's knee. Diagnosis and treatment. *Orthop Rev* 1990;19(2):139-49.
 295. Fritschy D, Wallensten R. Surgical treatment of patellar tendinitis. *Knee Surg Sports Traumatol Arthrosc* 1993;1(2):131-3.
 296. Ferretti A, Ippolito E, Mariani P, Puddu G. Jumper's knee. *Am J Sports Med* 1983;11(2):58-62.
 297. Cook JL, Feller JA, Bonar SF, Khan KM. Abnormal tenocyte morphology is more prevalent than collagen disruption in asymptomatic athletes' patellar tendons. *J Orthop Res* 2004;22(2):334-8.
 298. Boesen MI, Koenig MJ, Torp-Pedersen S, Bliddal.H., Langberg H. Tendinopathy and Doppler activity: the vascular response of the achilles tendon to exercise. *Scand J Med Sci Sports* 2006;16(6):463-9.
 299. Hollinshead WH, Rosse C. Textbook of anatomy. 4th ed. Philadelphia: Harper & Row; 1985. p. 434-5.
 300. Fritschy D, deGautard R. Jumper's knee and ultrasonography. *Am J Sports Med* 1988;16(6):637-40.
 301. Bodne D, Quinn SF, Murray.W.T., Rudd S, Lewis K, Danies P et al. Magnetic resonance images of chronic patellar tendinitis. *Skeletal Radiol* 1988;17(1):24-8.
 302. Martens M, Wouters P, Burssens A, Mulier JC. Patellar tendinitis: pathology and results of treatment. *Acta Orthop Scand* 1982;53(3):445-50.
 303. Jozsa L, Reffy A, Kannus P, Demel S, Elek E. Pathological alterations in human tendons. *Arch Orthop Trauma Surg* 1990;110(1):15-21.
 304. Cetti R, Junge J, Vyberg M. Spontaneous rupture of the Achilles tendon is preceded by widespread and bilateral tendon damage and ipsilateral inflammation: a clinical and histopathologic study of 60 patients. *Acta Orthop Scand* 2003;74(1):78-84.
 305. Kålebo P, Sward L, Karlsson J, Peterson L. Ultrasonography in the detection of partial patellar ligament ruptures (jumper's knee). *Skeletal Radiol* 1991;20(4):285-9.
 306. Rolf C, Movin T. Etiology, histology, and outcome of surgery in Achillodynia. *Foot Ankle* 1997;18:565-9.
 307. Astrom M, Rausing A. Chronic Achilles tendinopathy. A survey of surgical and histological findings. *Clin Orthop* 1995;12:246-52.
 308. Ohberg L, Alfredson H. Ultrasound guided sclerosis of neovessels in painful chronic Achilles tendinosis: pilot study of a new treatment. *Br J Sports Med* 2002;36(3):173-5.
 309. Mourad K, King JB, Guggiana P. Computed tomography and ultrasound imaging of jumper's knee-patellar tendinitis. *Clin Radiol* 1988;39(2):162-5.
 310. Myllymaki T, Bondesteam S, Suramo I, Cederberg A, Peltokallio P. Ultrasonography of jumper's knee. *Acta Radiol* 1990;31(2):147-9.
 311. Davidsson L, Salo M. Pathogenesis of subcutaneous tendon ruptures. *Acta Chir Scand* 1969;135(3):209-12.

312. Yu JS, Popp JE, Kaeding CC, Lucas J. Correlation of MR imaging and pathologic findings in athletes undergoing surgery for chronic patellar tendinitis. *AJR Am J Roentgenol* 1995;165(1):115-8.
313. Paavola M, Kannus P, Jarvinen TA, Khan KM, Jozsa L, Jarvinen M. Achilles tendinopathy. *J Bone Joint Surg Am* 2002;84-A(11):2062-76.
314. Jozsa L, Reffy A, Kannus P, Demel S, Elek E. Pathological alterations in human tendons. *Arch Ortop Trauma Surg* 1990;110(1):15-21.
315. Galliani I, Burattini S, Mariani AR, Ricco M, Cassiani G, Falcieri E. Morpho-functional changes in human tendon tissue. *Eur J Histochem* 2002;46(1):3-12.
316. Tuoheti Y, Itio E, Pradhan RL, Wakabayashi I, Takahashi S, Minagawa.H. et al. Apoptosis in the supraspinatus tendon with stage II subacromial impingement. *J Shoulder Elbow Surg* 2005;14(5):535-41.
317. Scott A, Khan KM, Heer J, Cook JL, Lian O, Duronio V. High strain mechanical loading rapidly induces tendon apoptosis: an ex vivo rat tibialis anterior model. *Br J Sports Med* 2005;39(5):e25.
318. Yuan J, Murell GAC, Wei AQ, Wang M-X. Apoptosis in rotator cuff tendonopathy. *J Orthop Res* 2002;20(6):1372-9.
319. Alfredson H, Lorentzon R. Chronic tendon pain: no signs of chemical inflammation but high concentrations of the neurotransmitter glutamate. Implications for treatment? *Curr Drug Targets* 2002;3(1):43-54.
320. Martinoli C, Derchi LE, Pastorino C, Bertolotto M, Silvestri E. Analysis of echotexture of tendons with US. *Radiology* 1993;186(3):839-43.
321. Movin T, Kristoffersen-Wiberg M, Rolf C, Aspelin P. MR imaging in chronic Achilles tendon disorders. *Acta Orthop Scand* 1998;68(2):126-32.
322. Maffulli N, Regine R, Angelillo M, Capasso G, Filice S. Ultrasound diagnosis of Achilles tendon pathology in runners. *Br J Sports Med* 1987;21(4):158-62.
323. Movin T, Kristoffersen-Wiberg M, Shalabi A, Gad A, Aspelin P, Rolf C. Intratendinous alterations as imaged by ultrasound and contrast medium-enhanced magnetic resonance in chronic achillodynia. *Foot Ankle Int* 1998;19(5):311-7.
324. Maffulli N, Regine R, Carrillo F, Minelli S, Beaconsfield T. Ultrasonographic scan in knee pain in athletes. *Br J Sports Med* 1992;26(2):93-6.
325. Kannus P. Etiology and pathophysiology of chronic tendon disorders in sports. *Scand J Med Sci Sports* 1997;7(2):78-85.
326. Murphy DF, Connell DAJ, Beynon BD. Risk factors for lower extremity injury: a review of the literature. *Br J Sp Med* 2003;37(1):13-29.
327. Archambault.J.M., Wiley JP, Bray RC. Exercise loading of tendons and the development of overuse injuries. A review of current literature. *Sports Med* 1995;20(2):77-89.
328. Kettunen JA, Kujala UM, Kaprio J, Sarna S. Health of Master Track and Field Athletes: A 16-year Follow-up Study. *Clin J Sport Med* 2006;16(2):142-8.
329. Kannus P, Niitymaki S, Jarvinen M. Sports injury in elderly athletes: a three-year prospective, controlled study. *Age Ageing*. 1989;18:263-70.
330. Fahlstrom M, Lorentzon R, Alfredson H. Painfull conditions in the Achilles tendon region: a common

- problem in middle-aged competitive badminton players. *Knee Surg Sports Traumatol Arthrosc* 2002;10:57-60.
331. Clement DB, Taunton JE, Smart GW. Achilles tendinitis and peritendinitis: etiology and treatment. *Am J Sports Med* 1984;12:179-84.
 332. Alfredson H, Forsgren S, Thorsen K, Lorentzon R. High intratendinous lactate levels in painful chronic Achilles tendinosis. An investigation using microdialysis technique. *J Orthop Res* 2002;20:934-8.
 333. Goodship AE, Birch HL, Wilson AM. The pathobiology and repair of tendon and ligament injury. *Vet Clin North Am Equine Pract* 1994;10(2):329-49.
 334. Bestwick CS, Maffulli N. Reactive oxygen species and tendoninopathy: do they matter? *Br J Sports Med* 2004;38(6):672-4.
 335. Arancia G, Trovalusci CP, Mariutti G, Mondovi B. Ultrastructural changes induced by hyperthermia in Chinese hamster V79 fibroblasts. *Int J Hyperthermia* 1989;5(3):341-50.
 336. Brich HL, Wilson AM, Goodship AE. The effect of exercise-induced localised hyperthermia on tendon cell survival. *J Exp Biol* 1997;200(11):1703-8.
 337. Wilson AM, Goodship AE. Exercise-induced hyperthermia as a possible mechanism for tendon degeneration. *J Biomech* 1994;27(7):899-905.
 338. Beeharry D, Coupe B, Benbow EW, Morgan J, Kwok S, Charlton-Menys V et al. Familial hypercholesterolaemia commonly presents with Achilles tenosynovitis. *Ann Rheum Dis* 2006;65(3):312-5.
 339. Riley GP, Harrall RL, Cawston TE, Hazleman BL, Mackie EJ. Tenascin-C and human tendon degeneration. *Am J Pathol* 1996;149(3):933-43.
 340. Riley GP, Harrall RL, Constant CR, Cawston TE, Hazleman BL. Prevalence and possible pathological significans of calcium phosphate salt accumulation in tendon matrix degeneration. *Ann Rheum Dis* 1996;55:109-15.
 341. Cole AS, Cordiner-Lawrie S, Carr AJ, Athanasou NA. Localised deposition of amyloid in tears of rotator cuff. *J Bone Joint Surg (Br)* 2001;83(4):561-4.
 342. Nigg BM. The role of impact forces and foot pronation: a new paradigm. *Clin J Sport Med* 2001;11(1):2-9.
 343. James SL, Bates BT, Osternig LR. Injuries to runners. *Am J Sports Med* 1978;6(2):40-50.
 344. Williams D.S.3rd., McClay IS, Hamill J. Arch structure and injury patterns in runners. *Clin Biomech* 2001;16(4):341-7.
 345. Lorentzon R. Cause of injuries: intrinsic factors. In: Dirix A, Knuttigen HG, Tittel K, editors. *The Olympic book of sports medicine*. 1 ed. Boston.: Blackwell Scientific.; 1988. p. 376-90.
 346. Pufe T, Petersen W, Kurz B, Tsokos M, Tillmann B, Mentlein R. Mechanical factors influence the expression of endostatin--an inhibitor of angiogenesis--in tendons. *J Orthop Res* 2003;21(4):610-6.
 347. Basso O, Amis AA, Johnson DP. Biomechanical analysis of surgical procedures for patellar tendonitis. 2002.
 348. Schmidt MR, Hodler J, Cathrein P, Duewell S, Jacob HA, Romeo J. Is impingement the cause of jumper's knee? Dynamic and static magnetic resonance imaging of patellar tendinitis in an open-configuration system. *Am J Sports Med* 2002;30(3):388-95.

349. Johnson DP, Wakeley CJ, Watt I. Magnetic resonance imaging of patellar tendonitis. *J Bone Joint Surg Br* 1996;78(3):452-7.
350. Kaufman KR, Brodine SK, Shaffer RA, Johnson CW, Cullison TR. The effect of foot structure and range of motion on musculoskeletal overuse injuries. *Am J Sports Med* 1999;27(5):585-93.
351. Mahieu NN, Wityrouw E, Stevns V, Van Tiggelen D, Roget P. Intrinsic risk factors for the development of achilles tendon overuse injury: a prospective study. *Am J Sports Med* 2006;34(2):226-35.
352. Wityrouw E, Bellemans J, Lysens R, Danneels L, Cambier D. Intrinsic risk factors for the development of patellar tendonitis in an athletic population: a two-years prospective study. *Am J Sports Med* 2001;29(2):190-5.
353. Almekinders LC. Tendinitis and other overuse tendinopathies. *J Am Acad Orthop Surg* 1998;6:157-64.
354. Witvrouw E, Bellemans J, Lysens R, Danneels L, Cambier D. Intrinsic risk factors for the development of patellar tendinitis in an athletic population. A two-year prospective study. *Am J Sports Med* 2001;29(2):190-5.
355. Józsa L, Balint JB, Kannus P, Reffy A, Barzo M. Distribution of blood groups in patients with tendon rupture. An analysis of 832 cases. *J Bone Joint Surg Br* 1989;71(2):272-4.
356. Jozsa L, Kvist M, Balint JB, Reffy A, Jarvinen M, Lehto M et al. The role of recreational sport activity in Achilles tendon rupture. A clinical, pathoanatomical, and sociological study of 292 cases. *Am J Sports Med* 1989;17(3):338-43.
357. Kannus P, Natri A. Etiology and pathophysiology of tendon ruptures in sports. *Scand J Med Sci Sports* 1997;7(2):107-12.
358. Kujala UM, Jarvinen M, Natri A, Lehto M, Nelimarkka O, Hurme M et al. ABO blood groups and musculoskeletal injuries. *Injury* 1992;23(2):131-3.
359. Mokone GG, Gajjar M, September AV, Schweltnus MP, Greenberg J, Noakes TD et al. The guanine-thymine dinucleotide repeat polymorphism within the tenascin-c gene is associated with Achilles tendon injuries. *Am Orthop Soc Sports Med* 2005;33(7):1016-21.
360. Mokone GG, Schweltnus MP, Noakes TD, Collins M. The COL5A1 gene and Achilles tendon pathology. *Scand J Med Sci Sports* 2006;16(1):19-26.
361. Olivieri L, Gemignani G, Gherardi S, Grassi L, Ciompi MI. Isolated HLA-B27 associated Achilles tendinitis. *Ann Rheum Dis* 1987;46(8):626-7.
362. Riley G. The pathogenesis of tendinopathy. A molecular perspective. *Rheumatology (Oxford)* 2004;43(2):131-42.
363. Jozsa L, Kannus P. Tendon alteration in inherited disease. In: Jozsa L, Kannus P, editors. *Human tendons: anatomy, physiology and pathology*. Champaigns: Human Kinetics.; 1997. p. 390-402.
364. Webb JM, Bannister GC. Percutaneous repair of the ruptured tendo Achillis. *J Bone Joint Surg Br* 1999;81(5):877-80.
365. Holmes GB, Lin J. Etiologic factors associated with symptomatic achilles tendinopathy. *Foot Ankle Int* 2006;27(11):952-9.
366. Preston ET. Avulsion of both quadriceps tendons in hyperparathyroidism. *JAMA* 1972;221(4):406-7.
367. Carvès C, Duquenoy A, Toutain F, Trioche P, Zarnitski C, Le Roux P et al. Gouty tendinitis revealing

- glycogen storage disease Type Ia in two adolescents. *Joint Bone Spine* 2003;70(2):149-53.
368. Jozsa L, Kannus P. Tendon alterations in endocrinologic and metabolic diseases. In: Jozsa L, Kannus P, editors. *Human tendons: anatomy, physiology and pathology*. Champaigns: Human Kinetics.; 1997. p. 403-12.
369. Jozsa L, Kannus P. Tendon alteration in rheumatic diseases. In: Jozsa L, Kannus P, editors. *Human tendons: anatomy, physiology and pathology*. Champaigns: Human Kinetics.; 1997. p. 412-29.
370. Peiro A, Ferrandis R, Garcia L, Alcazar E. Simultaneous and spontaneous bilateral rupture of the patellar tendon in rheumatoid arthritis. A case report. *Acta Orthop Scand* 1975;46(4):700-3.
371. Lauzon C, Carette S, Mathon G. Multiple tendon ruptures at unusual sites in rheumatoid arthritis. *J Rheumatol* 1987;14(2):369-271.
372. Aydingöz U, Aydingöz O. Spontaneous rupture of the tibialis anterior tendon in a patient with psoriasis. *Clin Imaging* 2002;26(3):209-11.
373. Jakobsen LP, Knudsen TB, Bloch T. Spontaneous infrapatellar tendon rupture in a patient with systemic lupus erythematosus. *Ugeskr Laeger*. 2000;162(38):5088-9.
374. Pritchard CH, Berney S. Patellar tendon rupture in systemic lupus erythematosus. *J Rheumatol* 1989;16(6):786-8.
375. Qzgartas T, Yildiz C, Serdar M, Atesalp S, Kutluay T. Is high concentration of serum lipids a risk factor for Achilles tendon rupture? *Clin Chim Acta* 2003;331(1-2):25-8.
376. Hofmann GO, Weber T, Lob G. Tendon rupture in chronic kidney insufficiency--"uremic tendonopathy"? A literature-supported documentation of 3 cases. *Chirurg* 1990;61(6):434-7.
377. Kricun R, Kricun ME. Patellar tendon rupture with underlying systemic disease. *Am J Radiol* 1980;135:803-7.
378. Maffulli N, Irwin AS, Kenward MG, Smith F, Porter RW. Achilles tendon rupture and sciatica: a possible correlation. *Br J Sp Med* 1998;32(2):174-7.
379. Nigg B. Causes of injuries. Extrinsic. In: Dirix A, Knuttigen HG, Tittel K, editors. *The Olympic book of sports medicine*. 1. ed. Oxford: Blackwell Scientific Publications; 1988. p. 363-75.
380. Ferretti A. Epidemiology of jumper's knee. *Sports Med* 1986;3(4):289-95.
381. Ilfeld FW. Can stroke modification relieve tennis elbow? *Clin Orthop* 1992;276:182-6.
382. Kibler WB, Chandler TJ, Pace BK. Principles of rehabilitation after chronic tendon injuries. *Clin Orthop* 1992;11(3):661-71.
383. James SL. Running injuries to the knee. *J Am Acad Orthop Surg* 1995;3:309-138.
384. Brody DM. Running injuries. Prevention and management. *Clin Symp* 1987;39(3):1-36.
385. Khurana R, Torzillo PJ, Horsley M, Mahoney J. Spontaneous bilateral rupture of the Achilles tendon in a patient with chronic obstructive pulmonary disease. *Respirology* 2002;7(2):161-3.
386. Newham DM, Douglas JG, Leggs JS, Friend JA. Achilles tendon rupture: an underrated complication of corticosteroid treatment. *Thorax* 1991;46(11):853-4.
387. Chhajed PN, Plit ML, Hopkins PM, Malouf MA, Glanville AR. Achilles tendon disease in lung transplant recipients: association with ciprofloxacin. *Eur Respir J* 2002;19(3):469-71.

388. Malaguti M, Triolo L, Biagina M. Ciprofloxacin-associated Achilles tendon rupture in a hemodialysis patient. *J Nephrol* 2001;14(5):431-2.
389. Kannus P, Paavola M, Paakkala T, Parkkari J, Jarvinen T, Jarvinen M. Pathophysiology of overuse tendon injury. *Radiologe* 2002;42(10):766-70.
390. James SL, Bates BT, Osternig LR. Injuries to runners. *Am J Sports Med* 1997;6:40-50.
391. Bjordal JM, Lopea-Martins RAB, Iversen VV. A randomised, placebo controlled trial of low level laser therapy for activated Achilles tendinitis with microdialysis measurement of peritendinous prostaglandin E2 concentrations. *Br J Sports Med* 2006;40(1):76-80.
392. Hart DA, Frank CB, Bray RC. Inflammatory processes in repetitive motions and overuse syndromes: potential role of neurogenic mechanisms in tendon and ligaments. In: Gordon SLBSJFLJ, editor. *Repetitive motion disorders of the upper extremity*. Rosemont: American Academi of Orthopaedic Surgeons.; 1995. p. 247-62.
393. Arnoczku SP, Lavagnino M, Egerbacher M. The response of tendon cells to changing loads: implications in the etiopathogenesis of tendinopathy. In: Woo SL, Renström P, Arnoczku SP, editors. *Tendinopathy in athletes*. 1 ed. Blackwell Publishing.; 2007. p. 46-59.
394. Almekinders LC, Vellema JH, Weinhold PS. Strain patterns in patellar tendon and the implications for patellar tendinopathy. *Knee Surg Sports Traumatol Arthrosc* 2002;10(1):2-5.
395. Basso O, Amis AA, Race A. Patellar tendon fibert strain: their differential responses to quadriceps tension. *Clin Orthop* 2002;400:246-53.
396. Maganaris CN, Narici MV, Almekinders LC, Maffulli N. Biomechanics and pathophysiology of overuse tendon injuries: ideas on insertional tendinopathy. *Sports Med* 2004;34(14):1005-17.
397. Murell GA. Understanding tendinopathies. *Br J Sports Med* 2002;36(6):392-3.
398. Arnoczku SP, Tian T, Lavagnino M, Gardnet K, Schuler P, Morse P. Activation of stress-activated protein kinase (SAPK) in tendon cells following cyclic strain: the effects of strain frequency, strain magnitude, and cytosolic calcium. *J Orthop Res* 2002;20(5):947-52.
399. Backman C, Boquist L, Friden J, Lorentzon R, Toolanen G. Chronic achilles paratenonitis with tendinosis: an experimental model in the rabbit. *J Orthop Res* 1990;8(4):541-7.
400. Solowsku LJ, Carpenter JE, DeBano CM, Banerji I, Moalli MR. Development and use of an animal model for investigation on rotator cuff disease. *J Shoulder Elbow Surg* 1996;5:383-92.
401. Stone D, Green C, Rao U, Aizawa H, Yamaji T, Niyibizi C et al. Cytokine-induced tendinitis: a preliminary study in rabbits. *J Orthop Res* 1999;17(2):168-77.
402. Silver IA, Brown PN, Goodship AE, Lanyon LE, McCullagh KG, Perry GC et al. A clinical and experimental study of tendon injury, healing and treatment in the horse. *Equine Vet J Suppl* 1983;1:1-43.
403. Williams IF, McCullagh KG, Goodship AE, Silver IA. Studies on the pathogenesis of equine tendonitis following collagenase injury. *Res Vet Sci* 1984;36(3):326-38.
404. Sullo A, Maffulli N, Capasso G, Testa V. The effects of prolonged peritendinous administration of PGE1 to the rat Achilles tendon: a possible animal model of chronic Achilles tendinopathy. *J Orthop Sci* 2001;6(4):349-57.
405. Khan MH, Li Z, Wang JHC. Repeated exposure of tendon to prostaglandin-E2 leads to localized tendon degeneration. *Clin J Sport Med* 2005;15(1):27-33.

406. van der Linden PD, van Puijenbroek EP, Feenstran J. Tendon disorders attributed to fluoroquinolones: a study of 42 spontaneous reports in the period 1988-1998. *Acta Anaesthesiol Scand* 2001;45:235-9.
407. Williams RJ, Attia E, Wickiewicz TL, Hannafin JA. The effect of ciprofloxacin on tendon, paratenon, and capsular fibroblast metabolism. *Am J Sports Med* 2000;28(3):364-0.
408. Corps AN, Harral RL, Curry VA, Fenwick SA, Hazleman BL, Riley GP. Ciprofloxacin enhance the stimulation of matrix metalloproteinase 3 expression by interleukin-1beta in human tendon-derived cells. *Arthr Rheum* 2002;46(11):3034-40.
409. Characterization of fluoroquinolone-induced Achilles tendin toxicity in rats: comparisson of toxicities of 10 fluoroquinolones and effect of anti-inflammatory compounds. *Antimicrob Agents Chemother* 1998;41:2389-93.
410. Kashida Y, Kato M. Characterization of fluoroquinolone-induced Achilles tendin toxicity in rats: comparisson of toxicities of 10 fluoroquinolones and effect of anti-inflammatory compounds. *Antimicrob Agents Chemother* 1998;41(11):2389-93.
411. Almekinders LC, Banes AJ. An integrative therapeutic approach to tendinopathy: biomechanic and biological considerations. In: Woo SL, Renström P, Arnoczku SP, editors. *Tendinopathy in athletes*. 1 ed. Blackwell Publishing.; 2007. p. 160-9.
412. Kannus P. etiology and pathophysiolohy of chronic tendon disorders in sports. *Scand J Med Sci Sports* 1997;7(2):78-85.
413. Zamora AJ, Marini JF. Tendon and myo-tendinous junction in an overloaded skeletal muscle of the rat. *Anat Embryol (Berl)* 1988;179(1):89-96.
414. Blankstein A, Cohen I, Diamant L, Heim M, Dudkiewicz I, Israeli A et al. Achilles tendon pain and related pathologies: diagnosis by ultrasonography. *Isr Med Assoc J* 2001;3(8):575-8.
415. Cosgrove D, Meire H, Dewbury. *Clinical Ultrasound a comprehensive text. Abdominal and General Ultrasound*. Churchill Livingstone; 1993.
416. McGahan JP, Goldberg BB. *Diagnostic Ultrasound: a logical approach*. Lippincott-Raven Publishers; 1998.
417. Marcelis S, Daenen B, Ferra MA. In: Dondelinger RF, editor. *Peripheral Musculoskeletal Ultrasound Atlas*. New York: Thieme Medical Publishers; 1996.
418. Astrom M, Gentz CF, Nilsson P, Rausing A, Sjoberg S, Westlin N. Imaging in chronic achilles tendinopathy: a comparison of ultrasonography, magnetic resonance imaging and surgical findings in 27 histologically verified cases. *Skeletal Radiol* 2003;25(7):615-20.
419. Paavola M, Paakkala T, Kannus P, Järvinen M. Ultrasonography in the differential diagnosis of Achilles tendon injuries and related disorders. *Acta Radiol* 1998;39:612-9.
420. Weinberger EP, Adams MJ, Hollenberg GM. Color Doppler sonography of patellar tendinosis. *AJR* 1998;171:743-4.
421. Gisslen K, Alfredson H. Neovascularisation and pain in jumper's knee: a prospective clinical and sonographic study in elite volleyball players. *Br J Sports Med* 2005;37(7):423-8.
422. Fornage BD. Achilles tendon: US examination. *Radiology* 1986;159(3):759-64.
423. Fornage BD, Rifkin MD, Touche DH, Segal PM. Sonography of the patellar tendon: preliminary observations. *AJR* 1984;143(1):179-82.

424. Miles CA, Firsey GA, Birch HL, Young DA. Factors affecting the ultrasonic properties of equine digital flexor tendons. *Ultrasound Med Biol* 1996;22(7):907-15.
425. van Holsbeeck MT, Introcaso JH. In: van Holsbeeck MT, Introcaso JH, editors. *Musculoskeletal ultrasound*. 2. ed. St. Louis.: Mosby; 2001.
426. Kälébo P, Allenmark C, Peterson L, Sward L. Diagnostic value of ultrasonography in partial ruptures of the Achilles tendon. *Am J Sports Med* 1992;20(4):378-81.
427. Lehtinen A, Peltokallio P, Taavitsainen M. Sonography of Achilles tendon correlated to operative findings. *Ann Chir Gynaecol* 1994;83(4):322-7.
428. Kamel M, Eid H, Mansour R. Ultrasound detection of knee patellar enthesitis: a comparison with magnetic resonance imaging. *Ann Rheum Dis* 2004;63:213-4.
429. Mathieson JR, Connell DG, Cooperberg PL, Lloyd-Smith DR. Sonography of the Achilles tendon and adjacent bursae. *AJR* 1988;151(1):127-31.
430. Nehrer S, Breitenseher M, Broder W, Kainberger F, Fellingner EJ, Imhof F. Clinical and sonographic evaluation of the risk of rupture in the Achilles tendon. *Arch Orthop Trauma Surg* 1997;116(1-2):14-8.
431. Ying M, Yeung E, Li B, Li W, Lui M, Tsoi CW. Sonographic evaluation of the size of achilles tendon: the effect of exercise and dominance of the ankle. *Ultrasound Med Biol* 2003;29(5):637-42.
432. Koivunen-Niemela T, Parkkola K. Anatomy of the Achilles tendon (tendo calcaneus) with respect to tendon thickness measurements. *Surg Radiol Anat* 1995;17(3):263-8.
433. Khan KM, Forster BB, Robinson J, Cheong Y, Louis L, Maclean L et al. Are ultrasound and magnetic resonance imaging of value in assessment of Achilles tendon disorders? A two year prospective study. *Br J Sports Med* 2003;37(3):149-53.
434. Peers KH, Brys PP, Lysens RJJ. Correlation between power Doppler ultrasonography and clinical severity in Achilles tendinopathy. *Int Orthop* 2003;27(3):180-3.
435. Kallinen M, Suominen H. Ultrasonographic measurements of the Achilles tendon in elderly athletes and sedentary men. *Acta Radiol* 1994;35(6):560-3.
436. Richards PJ, Dheer AK, McCall IM. Achilles tendon (TA) size and power Doppler ultrasound (PD) changes compared to MRI: a preliminary observationale study. *Clin Radiol* 2001;56(10):843-50.
437. Fornage BD. Achilles tendon: US examination. *Radiology* 2003;159(3):759-64.
438. Gibbon WW, Cooper JR, Radcliffe GS. Distribution of sonographically detected tendon abnormalities in patients with a clinical diagnosis of chronic achilles tendinosis. *J Clin Ultrasound* 2000;28(2):61-6.
439. Mahfeld K, Kayser R, Mahlfeldt A, Merk H. Ultrasound findings of the patellar tendon and its insertion sites. *Ultraschall Med* 1997;18(6):249-53.
440. Paavola M. Achilles tendon overuse injuries. Diagnosis and treatment. [dissertation]. University of Tampere, Finland; 2001.
441. Seddio C, Dettori E, Casoni S, Stanga C. Comparison of ultrasonography and magnetic resonance in the postoperative monitoring of complete subcutaneous rupture of the Achilles tendon. *Radiol Med (Torino)* 1997;94(1-2):47-51.
442. Archambault J.M., Wiley JP, Bray RC, Verhoef M, Wiseman DA, Elliott PD. Can sonography predict the outcome in patients with achillodynia? *J Clin Ultrasound* 1998;26(7):335-9.

-
443. Cook JL, Khan KM, Kiss ZS, Coleman BD, Griffiths L. Asymptomatic hypoechoic regions on patellar tendon ultrasound: A 4-year clinical and ultrasound followup of 46 tendons. *Scand J Med Sci Sports* 2001;11(6):321-7.
 444. Gisslen K, Gyulai C, Nordström P, Alfredson H. Normal clinical and ultrasound findings indicate a low risk to sustain jumper's knee patellar tendinopathy: a longitudinal study on Swedish elite junior volleyball players. *Br J Sp Med* 2007;41(4):253-8.
 445. Warden SJ, Brukner P. Patellar tendinopathy. *Clin Sports Med* 2003;22(4):743-59.
 446. Davies SG, Baudouin CJ, King JB, Perry JD. Ultrasound, computed tomography and magnetic resonance imaging in patellar tendinitis. *Ultrasound* 1991;43:52-6.
 447. Rasmussen OS. Sonography of tendons. *Scand J Med Sci Sports* 2000;10(6):360-4.
 448. Rockett MS, Waitches G, Sudakoff G, Brage M. Use of ultrasonography versus magnetic resonance imaging for tendon abnormalities around the ankle. *Foot Ankle In* 1998;19(9):604-12.
 449. O'Connor PJ, Grainer AJ, Morgan SR, Smith KL, Waterton JC, Nash AFP. Ultrasound assessment of tendons in asymptomatic volunteers: a study of reproducibility. *Eur Radiol* 2004;14(11):1968-73.
 450. Robson MD, Benjamin M, Gishen P, Byder G. Magnetic resonance imaging of the Achilles tendon using ultrashort TE (UTE) pulse sequences. *Clin Radiol* 2004;59(8):727-35.
 451. Gatehouse PD, Byder GM. Magnetic resonance imaging of short T2 components in tissue. *Clin Radiol* 2003;58(1):1-19.
 452. Warden SJ, Kiss ZS, Malara FA, Aoi AB, Cook J, Crossley KM. Comparative accuracy of magnetic resonance imaging and ultrasonography in confirming clinically diagnosed patellar tendinopathy. *Am J Sports Med* 2007;35(3):427-36.
 453. Erickson S. High-resolution imaging of the musculoskeletal system. *Radiology* 1997;205(3):593-618.
 454. Mersky H, Spear FG. The reliability of the pressure algometer. *Br J Clin.Psychol* 1964;3:130-6.
 455. Black J, Cook J, Kiss ZS, Smith M. Intertester reliability of sonography in patellar tendinopathy. *J Ultrasound Med* 2004;23(5):671-5.
 456. Shalabi A, Kristoffersen-Wiberg M, Aspelin P, Movin T. Immediate Achilles tendon response after strength training evaluated by MRI. *Med Sci Sports Exerc* 2004;36(11):1841-6.
 457. Shalabi A, Kristoffersen-Wiberg M, Svensson L, Aspelin P, Movin T. Eccentric training of the gastrocnemius-soleus complex in chronic Achilles tendinopathy results in decreased tendon volume and intratendinous signal as evaluated by MRI. *Am J Sports Med* 2007;32(5):1286-96.
 458. Shalabi A, Movin T, Kristoffersen-Wiberg M, Aspelin P, Svensson L. Reliability in the assessment of tendon volume and intratendinous signal of the Achilles tendon on MRI: a methodological description. *Knee Surg Sports Traumatol Arthrosc* 2005;13(6):492-8.
 459. Keele KD. Pain-sensitivity tests: The pressure algometer. *Lancet*. 1954:636-9.
 460. Ylinen J, Nykanen M, Kautiainen H, Hakkinen A. Evaluation of repeatability of pressure algometry on the neck muscles for clinical use. *Man Ther.* 2007;12(2):192-7.
 461. Dahl JB, Rosenberg J, Molke Jensen F, Kehlet H. Pressure pain thresholds in volunteers and herniorrhaphy patients. *Acta Anaesthesiol Scand* 1990;34(8):673-6.
 462. Jensen K, Norup M. Experimental pain in human temporal muscle induced by hypertonic saline,

- potassium and acidity. *Cephalalgia* 1992;12(2):101-6.
463. Bendtsen L, Jensen R, Jensen NK, Olix ML. Muscle palpation with controlled finger pressure: new equipment for the study of tender myofascial tissues. *Pain* 1994;59(2):235-9.
 464. Pfeiffer-Jensen M. Computer controlled pressure algometry in human joints. A methodological study. Ph.D. thesis [dissertation]. Faculty of Health Science, University of Aarhus, Denmark; 1999.
 465. Fischer AA. Pressure algometry over normal muscles. Standard values, validity and reproducibility of pressure threshold. *Pain* 1987;30(1):115-26.
 466. Antonaci F, Sand T, Lucas GA. Pressure algometry in healthy subjects: inter-examiner variability. *J Rehabil Med* 1998;30(1):3-8.
 467. Maquet D, Croisier JL, Demoulin C, Crielaard J-M. Pressure pain thresholds of tender point sites in patients with fibromyalgia and in healthy controls. *Eur J Pain* 2004;8(2):111-7.
 468. Smidt N, van der Wind DA, Assendelft WJ, Mourits AJ, Deville WL, de Winter AF et al. Interobserver Reproducibility of the Assessment of Severity of Complaints, Grip Strength, and Pressure Pain Threshold in Patients With Lateral Epicondylitis. *Arch Phys Med Rehabil* 2002;83(8):1145-50.
 469. Oikarinen A, Viorio E, Zaragoza EJ, Palotie A, Chu ML, Uitto J. Modulation of collagen metabolism by glucocorticoids. Receptor-mediated effects of dexamethasone on collagen biosynthesis in chick embryo fibroblasts and chondrocytes. *Biochem Pharmacol* 1988;37(8):1451-62.
 470. Ledda-Columbano GM, Columbano A, Cannas A, Sinbula G, Okita K, Kayano K et al. Dexamethasone inhibits induction of liver tumor necrosis factor- α mRNA and liver growth induced by lead nitrate and ethylene dibromide. *Am J Pathol* 1994;145(4):951-8.
 471. Delany AM, Brinckerhoff CE. Post-transcriptional regulation of collagenase and stromelysin gene expression by epidermal growth factor and dexamethasone in cultured human fibroblasts. *J Cell Biochem* 1992;50(4):400-10.
 472. Blanco I, Krähenbühl S, Schlienger RG. Corticosteroid-associated tendinopathies: an analysis of the published literature and spontaneous pharmacovigilance data. *Drug Saf* 2005;28(7):633-43.
 473. Wise C. The rational use of steroid injections in arthritis and nonarticular musculoskeletal pain syndromes. *Bulletin on the Rheumatic Diseases*. 2003;52(1):1-7.
 474. Alexeeff M. Ligamentum patellae rupture following local steroid injection. *Aust N Z J Surg Y1 - 1986* 1996;56(9):681-3.
 475. Halpern AA, Horowitz BG, Nagel DA. Tendon ruptures associated with corticosteroid therapy. *West J Med* 1977;127:378-82.
 476. Cowan MA, Alexander.S., Alexander S. Simultaneous bilateral rupture of Achilles tendons due to triamcinolone. *Br Med J* 1961;1:1658.
 477. Stannard JP, Bucknell AL. Rupture of the triceps tendon associated with steroid injections. *Am J Sports Med* 1993;21(3):482-5.
 478. Leach R, Jones R, Silva T. Rupture of the plantar fascia in athletes. *J Bone Joint Surg Am* 1978;60(4):537-9.
 479. Subotnick S, Sisney P. Treatment of Achilles tendinopathy in the athlete. *J Am Podiatr Med Assoc* 1986;76:552-7.
 480. Read MTF. Safe relief of rest pain that eases with activity in achillodynia by intrabursal or

- peritendinous steroid injection: the rupture rate was not increased by the steroid injections. *Br J Sports Med* 1999;33(2):134-5.
481. Read MTF, Motto SG. Tendo achillis pain: steroid and outcome. *Br J Sp Med* 1992;26(1):15-21.
482. Haraldsson BT, Langberg H, Aagaard P, Zuurmond AM, van El B, Degroot J et al. Corticosteroids reduce the tensile strength of isolated collagen fascicles. *Am J Sports Med* 2006;34(2):1992-7.
483. Walsh WR, Wiggins ME, Fadale PD, Ehrlich MG. Effects of a delayed steroid injection on ligament healing using a rabbit medial collateral ligament model. *Biomaterials* 1995;16(12):905-10.
484. Unverferth LJ, Olix ML. The effect of local steroid injections on tendon. *J Sports Med* 1973;1:731-7.
485. Noyes F, Grood ES, Nussbaum NS, Cooper SM. Effect of intra-articular corticosteroids on ligament properties: a biomechanical and histological study in rhesus knees. *Clin Orthop Relat Res* 1977;123:197-209.
486. Kapetanos G. The effect of the local corticosteroids on the healing and biomechanical properties of the partially injured tendon. *Clin Orthop* 1982;163:170-9.
487. Hugate R, Pennypacker J, Saunders M, Juliano P. The effects of intratendinous and retrocalcaneal intrabursal injections of corticosteroid on the biomechanical properties of rabbit Achilles tendons. *J Bone Joint Surg Am* 2004;86(4):794-801.
488. Balasubramaniam P, Prathap K. The effect of injection of hydrocortisone into rabbit calcaneal tendons. *J Bone Joint Surg* 1972;54B:729-34.
489. Martin DF, Carlson CS, Berry J, Reboussin BA, Gordon ES, Smith BP. Effect of injected versus iontophoretic corticosteroid on the rabbit tendon. *South Med J* 1999;92(6):600-8.
490. Kennedy JC, Baxter R. The effects of local steroid injections on tendon: a biomechanical and microscopic correlative study. *Am J Sports Med* 1976;4:11-21.
491. Torricelli P, Fini M, Giavaresi G, Carpi A, Nicolini A, Giardino R. Effects of systemic glucocorticoid administration on tenocytes. *Biomed Pharmacother* 2006;60(8):380-5.
492. Wong MW, Tang YN, Fu SC, Lee KM, Chan KM. Triamcinolone suppresses human tenocyte cellular activity and collagen synthesis. *Clin Orthop Relat Res* 2004;421:277-81.
493. Wong MW, Tang YY, Lee SK, Fu BS. Glucocorticoids suppress proteoglycan production by human tenocytes. *Acta Orthop* 2005;76(6):927-31.
494. Wong MW, Tang YY, Lee SK, Fu BS, Chan BP, Chan CK. Effect of dexamethasone on cultured human tenocytes and its reversibility by platelet-derived growth factor. *J Bone Joint Surg Am* 2003;85(10):1914-20.
495. Matthews LS, Sonstegard DA, Phelps DB. A biomechanical study of rabbit patellar tendon: Effects of steroid injection. *J Sports Med* 1974;2:349-57.
496. Phelps D, Sonstegard DA, Mathews LS. Corticosteroid injection effects on the biomechanical properties of rabbit patellar tendons. *Clin Orthop* 1974;100:345-8.
497. Mackie JW, Goldin B, Foss ML, Cockrell JL. Mechanical properties of rabbit tendons after repeated anti-inflammatory steroid injections. *Med Sci Sports* 1974;6(3):198-202.
498. McWhorter W, Francis RS, Heckmann RA. Influence of local steroid injections on traumatized tendon properties: a biomechanical and histological study. *Am J Sports Med* 1991;19(5):435-9.

499. Koenig MJ, Torp-Pedersen S, Qvistgaard E, Terslev L, Bliddal H. Preliminary results of colour Doppler-guided intratendinous glucocorticoid injection for Achilles tendonitis in five patients. *Scand J Med Sci Sports* 2004;14(2):100-6.
500. Kane D, Greaney T, Bresnihan B, Gibney R, FitzGerald O. Ultrasound guided injection of recalcitrant plantar fasciitis [see comments]. *Ann Rheum Dis* 1998;57(6):383-4.
501. DaCruz DJ, Geeson M. Achilles paratendonitis: an evaluation of steroid injection. *Br J Sports Med* 1988;22:64-5.
502. Fredberg U, Bolvig L. Jumper's knee. Review of literature. *Scand J Med Sci Sports* 1999;9(2):66-73.
503. Lambert MA, Morton RJ, Sloan JP. Controlled study of the use of local steroid injection in the treatment of trigger finger and thumb. *J Hand Surg Br* 1992;17(1):69-70.
504. Murphy D, Failla JM, Kotz R. Steroid versus placebo injection for trigger finger. *J Hand Surg [Am]* 1995;20(4):628-31.
505. Fleisch SB, Spindler KP, Lee DH. Corticosteroid injections in the treatment of trigger finger: a level I and II systematic review. *J Am Acad Orthop Surg* 2007;15(3):166-71.
506. Price R, Sinclair H, Heinrich T, Gibson T. Local injection treatment of tennis elbow - hydrocortisone, triamcinolone and lignocaine compared. *Br J Rheumatol* 1991;30(1):39-44.
507. Thonks JH, pai SK, Murai SR. Steroid injection therapy is the best conservative treatment for lateral epicondylitis: a prospective randomised controlled trial. *Int J Clin Pract* 2007;61(2):240-6.
508. Petri M, Dobrow R, Neiman R. Randomized, double-blind, placebo-controlled study of the treatment of the painful shoulder. *Arthritis Rheum* 1987;30:1040-5.
509. Adebajo AOP, Nash P, Hazleman BL. A prospective double blind dummy placebo controlled study comparing triamcinolone hexacetonide injection with oral diclofenac 50 mg TDS in patients with rotator cuff tendinitis. *J Rheumat* 1990;17:1207-10.
510. Koester MC, Dunn WR, Kuhn JE, Spindler KP. The efficacy of subacromial corticosteroid injection in the treatment of rotator cuff disease: A systematic review. *J Am Acad Orthop Surg* 2007;15(1):3-11.
511. Buchbinder R, Green S, Youd JM. Corticosteroid injections for shoulder pain. *Cochrane Database Syst Rev* 2003;CD004016.
512. Arroll B, Goodyear-Smith F. Corticosteroid injections for painful shoulder: a meta-analysis. *Br J Gen Pract* 2005;55(512):224-8.
513. Eustace JA, Bresnihan B, Gibney RP, Brophy DP, FitzGerald O. Comparison of the accuracy of steroid placement with clinical outcome in patients with shoulder symptoms. *Ann Rheum Dis* 1997;56(1):59-63.
514. Jones A, Regan M, Ledingham J, Patrick M, Manhire A, Doherty M. Importance of placement of intra-articular steroid injections. *BMJ* 1993;307(6915):1329-30.
515. Zingas C, VanHolsbeeck M., Failla JM. Injection accuracy and clinical relief of de Quervain's tendinitis. *J Hand Surg (Am)* 1998;23(1):89-96.
516. Huskisson EC. Measurement of pain. *Lancet* 1974;2(7889):1127-31.
517. Scott J, Huskisson EC. Graphic representation of pain. *Pain* 1976;2(2):175-84.
518. Cook JL, Khan KM, Kiss ZS, Purdam CR, Griffiths L. Prospective imaging study of asymptomatic

- patellar tendinopathy in elite junior basketball players. *J Ultrasound Med* 2000;19(7):473-9.
519. Khan KM, Cook JL, Kiss ZS, Fehrmann MW, Harcourt P, Tress BM et al. Patellar tendon ultrasonography and jumper's knee in female basketball players: a longitudinal study. *Clin J Sport Med* 1997;7(3):199-206.
 520. Paavola M, Kannus P, Paakkala T, Pasanen M, Jarvinen M. Long-term prognosis of patients with achilles tendinopathy. An observational 8-year follow-up study. *Am J Sports Med* 2000;28(5):634-42.
 521. Nussbaum EL, Downes L. Reliability of clinical pressure-pain algometric measurements obtained on consecutive days. *Phys Ther* 1998;78(2):160-9.
 522. Delaney GA, McKee AC. Inter- and intra-rater reliability of the pressure threshold meter in measurement of myofascial trigger point sensitivity. *Am J Phys Med Rehabil* 1993;72(3):136-9.
 523. Cathcart S, Prichard D. Reliability of pain threshold measurement in young adults. *J Headache Pain* 2006;7(1):21-6.
 524. Shalaby M, Almekinders LC. Patellar tendinitis: the significance of magnetic resonance imaging findings. *Am J Sports Med* 1999;27(3):345-9.
 525. Arner O, Lindholm A, Orell SR. Histologic changes in subcutaneous rupture of the Achilles tendon; a study of 74 bcases. *Acta Chir Scand* 1959;116:484-90.
 526. Jonsson P, Alfredson H. Superior results with eccentric compared to concentric quadriceps training in patients with jumper's knee: a prospective randomised study. *Br J Sports Med* 2005;39(11):847-50.
 527. Ohberg L, Alfredson H. Sclerosing therapy in chronic Achilles insertional pain - results of a pilot study. *Knee Surg Sports Traumatol Arthrosc* 2003;11:339-43.
 528. Aspenberg P, Virchenko O. Platelet concentrate injection improves Achilles tendon repair in rats. *Acta Orthop Scand* 2004;75(1):93-9.
 529. Virchenko O, Grenegaard M, Aspenberg P. Independent and additive stimulation of tendon repair by thrombin and platelets. *Acta Orthop* 2006;77(6):960-6.
 530. Zhang F, liu H, Stile MP, Pang Y, Oswald TM, Beck J et al. Effect of vascular endothelial growth factor on rat Achilles tendon healing. *Plast Reconstr Surg* 2003;112(6):1613-9.
 531. de Mos M, van El B, Degroot J, Jahr H, van Schie HT, van Arkel ER et al. Achilles Tendinosis: Changes in Biochemical Composition and Collagen Turnover Rate. *Am J Sports Med* 2007;35(9):1549-56.
 532. Terslev L, Qvistgaard E, Danneskiold-Samsøe B, Bliddal.H. Estimation of inflammation by Doppler ultrasound: quantitative changes after intra-articular treatment in rheumatoid arthritis. *Ann Rheum Dis* 2003;62(11):1049-53.