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The chronic painful Achilles tendon
Sonographic findings and new methods for treatment

by

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Abstract

The aim of the present thesis was to evaluate sonographic methods for investigation of the chronic painful Achilles tendon. In a prospective study on patients with chronic painful mid-portion Achilles tendinosis, grey-scale ultrasound (US) showed a decreased tendon thickness and a “normalized” structure in the majority of patients successfully treated with eccentric calf-muscle training. By combining US with colour Doppler examination (CDV), a neovascularisation was shown in the region with structural tendon changes in all painful tendons, but not in any of the pain-free normal tendons. In a small pilot study, the sclerosing agent Polidocanol was injected towards the neovessels under US and CDV guidance. The majority of the patients became pain-free and had no remaining neovessels, while the patients with remaining pain had remaining neovessels. The combined findings from US, immuno-histochemical analyses of biopsies, and diagnostic injections, showed that the patients were temporarily pain-free after US and CDV guided injections of local anaesthesia towards the region with neovessels, and biopsies from the region with tendon changes and neovascularisation showed nerve structures in close relation to blood vessels. The presence of neovessels was shown also in patients with chronic pain in the Achilles tendon insertion, and it was found that treatment with sclerosing injections cured the pain in the majority of patients. A good result of treatment was associated with no remaining neovessels.

In a prospective study on patients with chronic mid-portion Achilles tendinosis treated with eccentric training, CDV after treatment showed no remaining neovessels in the majority of the pain-free patients. In the patients with remaining tendon pain there were remaining neovessels.

In conclusion, the findings in this thesis indicate that neovessels and accompanying nerves might be the source of chronic Achilles tendon pain. Sclerosing injections towards the neovessels, and eccentric training, seem to have a potential to cure the pain.
Abbreviations

CDV            Colour Doppler Velocity
CDE            Colour Doppler Energy or Power Doppler.
GAGs           Glucose-amino-glycans
MHz            Mega Hertz
MRI            Magnetic Resonance Imaging
NSAID          Non-Steroidal Anti-Inflammatory Drugs
PGE$_2$        Prostaglandin E$_2$
US             Ultrasound
VAS            Visual Analogue Scale
XR             X-ray, plain film radiography
Original papers

The thesis is based upon the following papers, which will be referred to by their Roman numerals:


V. Öhberg L, Alfredson H. Effects on neovascularisation behind the good results with eccentric training in chronic mid-portion Achilles tendinosis? Submitted.

Introduction

History

The name Achilles tendon originates from the Greek mythology. Achilles was a son of Peleus and Thesis. His mother, Thesis, who wanted him to be invulnerable, dipped him into the river Styx, the river of hate, separating the world of the living from the world of the dead. The purpose was to dip the whole body into the sacred water of Styx, and become invulnerable. Unfortunately, his heel remained dry, and therefore his heel was unprotected. In the war against the Trojans, an arrow wounded Achilles in his unprotected heel. Achilles died from the wound in the heel.

Anatomy and functions

The Achilles tendon is the strongest tendon in the human body (Józsa and Kannus 1997), and tendon forces equalling 12 times the body weight have been recorded (Komi et al. 1992). The Achilles tendon is a part of the gastrocnemius-soleus complex. The gastrocnemius muscle is divided into a medial and a lateral head, originating at the posterior, nonarticulated, surfaces of the medial and the lateral femoral condyles. The soleus muscle is originated from the posterior aspect of the fibular head, upper 1/4 – 1/3 of the posterior surface of the fibula, middle 1/3 of medial border of the tibial shaft, and from the posterior surface of a tendinous arch spanning over the two sites of bone origin. The aponeuroses from the three muscle bellies of the gastrocnemius and soleus muscles join and form the Achilles tendon. The fibres in the tendon spiral up to 90 degrees from the proximal to the distal end at the insertion on the calcaneal tuberosity. Consequently, fibres originally positioned posterior in the proximal part of the tendon become lateral, lateral fibres become anterior, anterior fibres medial, and medial fibres posterior, at the distal end of the tendon (Józsa and Kannus 1997). The distal portion of the Achilles tendon attaches to the mid-posterior calcaneus by a stiff fibrocartilaginous expansion. The osteo -
tendinous junction involves a gradual transition from tendon to fibrocartilage and bone (Józsa and Kannus 1997). Close to the insertion of the tendon are the subcutaneous calcaneal and retrocalcaneal bursae (Fig 1).

The Achilles tendon is surrounded by a peritendinous sheet (paratenon), with thin gliding membranes that reduce friction and permits free movement of the tendon against surrounding tissues (Józsa and Kannus 1997). The basic elements of tendons are cells, collagen, and ground substance (extracellular matrix). The natures of the different components are as follows (Józsa and Kannus 1997):

1. Cells: Tenoblasts and tenocytes comprise 90 – 95 % of the cellular elements in the tendon. The remaining 5 – 10 % includes chondrocytes at the insertion, and synovial cells of the tendon surface. The tenoblasts are immature cells with varying form especially in children. As the children grow older, most of the tenoblasts transforms to mature tenocytes. These cells are flat, spiderlike, and sparsely situated between the collagen fibrils. Both the tenoblasts and the tenocytes are producing procollagen, as well as the ground substance.

2. The collagen, which constitute 65 – 75 % of the dry mass in human tendons, is produced by tenocytes, and arranged in hierarchical levels of complexity. The smallest elements are tropocollagen, a triple-helix polypeptide chain. Tropocollagen molecules are stabilised and held together by electrostatic chemical cross-linking bonds. These chains unite into fibrils, (Fig 2) which are visible in electron microscope. A bunch of fibrils are united to collagen fibres aligned from end to end in a tendon. A fine sheath of connective tissue called the endotenon enfolds each collagen fibre and binds the fibres together. A group of fibres forms a primary fibre bundle (subfascicle), and a group of primary fibre bundles forms a secondary fibre bundle (fascicle). Groups of secondary fibre bundles unit to form tertiary bundles forming the tendon. Each group of bundles is surrounded by the endotenon. The tendon is covered by the epitenon, a fine, loose connective tissue sheet that is extending deeper in the tendon forming the endotenon. The vascular, lymphatic, and nerve supply of the tendon is following the epitenon and the endotenon into the depths of the tendon. Superficially, the epitenon is surrounded
Fig 1 Schematic image of a foot.
a: Achilles tendon. b: Subcutaneous bursa. c: Retrocalcaneal bursa.
d: Calcaneus

Fig 2: Schematic image of the different structures in a tendon
by the paratenon, a loose areolar connective tissue composed of collagen fibrils, some elastic fibrils, and an inner lining of synovial cells.

3. The ground substance consists of proteoglycans and glycoproteins, produced by the tenocytes. Proteoglycans are composed of a protein core with one or more glycosaminoglycans (GAGs) covalently attached. They are large, negatively charged hydrophilic molecules, which can entrain water up to 50 times their weight, and are mostly entrapped between collagen fibrils and fibres. Human tendons act as connections between muscles and bone, transmitting the muscular force to bone, and make movements possible. The maximum force to the tendon fibres is transmitted parallel to the long axis of the tendon. The collagen fibrils in the resting, non-strained state are wavy or crimped. The fibres are orientated both longitudinally, as well as transverse and horizontal, with the longitudinal fibrils also crossing each other forming spirals and plaits. This complex ultra structure of the tendon provides a good buffer capacity against longitudinal, transversal, horizontal, and rotational forces. When the tendon is stretched about 102 % of its length, the wavy configuration of the tendon fibres disappears. When the tendon is stretched to approximately 104 %, the tendon is able to return to its original length when the tensile force is released, and the tendon is also able to resume its normal wavy appearance. If the strain exceeds approximately 104 %, the tendon fibres are damaged, and if the strain exceeds a level of 108 % the tendon will rupture (Józsa and Kannus 1997).

The purpose of the ground substance in the tendon is to provide the collagen fibrils to resist high compressive and tensile forces with high capacity, and to improve the elasticity of the tendon. The proteoglycans also enable rapid diffusion of water-soluble molecules, gases, and migration of cells. There is also some evidence that the ground substance may be the modulating medium that prompts cells to change their pattern of protein synthesis in response to load (O’Brien 1997).
**Blood supply**

Tendons receive their blood supply from three sites (O’Brien 1997, Tuite et al. 1997): (1) From vessels coming from the muscle, (2) from vessels coming from the bone and periosteum in the osteotendinous junction, and (3) from vessels in tissue surrounding the tendon (paratenon, and mesotenon). The blood vessels are carried deep into the tendons by the endotenon (Hess et al. 1989, Józsa et al. 1991). The intratendinous network of vessels consists of longitudinally arranged vessels, where one artery is followed by two veins. The small arterioles and capillaries that originate from the longitudinal arteries form the microvascular units of the tendon tissue.

Since tendons predominantly are extracellular tissue, with low metabolic requirements and rates, they have low blood supply compared to many other tissues, and it has been stated that the middle part of the Achilles tendon has a relatively poor vascularity (Józsa & Kannus 1997). However, in a recent study of the blood flow in human Achilles tendons, using Laser Doppler flowmetry (LD), it was shown that besides a lower perfusion at the calcaneal insertion, there was an even distribution of blood flow in the tendon (Åström 2000). An increase in peritendon blood flow during exercise have also been shown using microdialysis technique, Langberg (1998).

**Metabolism**

The tendon has three systems of energy metabolism; the aerobic Krebs cycle, the anaerobic glycolysis and the pentose phosphate shunt (Hess et al. 1989, Józsa & Kannus & 1997). In young people the metabolism is more aerobic, but with increasing age it changes to become more anaerobic.

The metabolic rate in a tendon is low, allowing for a long standing increased tension in the tendon without the risk for ischemia and necrosis. Simultaneously, because of the low metabolic rate, the tendons have a slow rate of recovery after activity and healing after injury.
Tendons has commonly been considered to be relatively inactive, but recently, using microdialysis technique Langberg et al. (1999 and 2000) have shown that peritendinous tissue is more metabolically active in response to activity than previously thought. Also, Boushel et al. (2000) have demonstrated a marked increase in metabolism in peritendinous space (Achilles tendon) during plantar flexion exercise in young individuals.

**Innervation**

Sensory nerves from the overlying superficial nerves or from nearby deep nerves supply the tendons. Most of the sensory nerves are located on the surface of the tendon. There are only few sensory nerve fibres inside the tendons, and they follow the vascular network in the endotenon. The nerves anastomose with each other via obliquely and transversely oriented nerve fibres, and finally terminate in the sensory nerve endings (Józsa & Kannus 1997).

There are four types of receptors inside the tendons: (1) Ruffini corpuscles – pressure and stretching sensors. (2) Vater-Pacini corpuscles – pressure sensors, reacting to acceleration and deceleration movements. (3) Golgi tendon organs – tension receptors. (4) Free nerve endings – pain receptors (Józsa & Kannus 1997, O’Brien 1997)

Using microdialysis technique, the neurotransmitter glutamate has recently been identified in human Achilles tendons (Alfredson et al. 1999). Glutamate is a potent modulator of pain in the human central nervous system, but its function in the peripheral nervous system is still mainly unknown (Dickenson et al 1997). Also, glutamate NMDAR1-receptors were found in close relation to nerve structures in tendinosis and normal tissue from Achilles tendons (Alfredson et al. 2001).
Diagnostics

**Clinical examination**

It is important to carefully collect the patient history, including onset of the symptoms, level of activities, training pattern, type of footwear, and previous treatment. It is also important to perform a proper clinical examination. We usually have the patient standing on his knees on the examination table, with the feet hanging outside the edge of the table. Thereby, the Achilles tendon is easy to access, and side-to-side comparisons can be done. Range of motion in the ankle joint is evaluated, and symptoms from the Achilles tendon are noticed. The Achilles tendon and the insertion into the calcaneus are inspected and palpated. Swollen areas, prominences, and tenderness should be recorded. It should be evaluated whether the superficial calcaneal and deeper retrocalcaneal bursae are swollen or tender.

The possibility of differential diagnoses such as; tenosynovitis or dislocations of the peroneal tendons, tenosynovitis of the plantar flexors, accessory soleus muscle, os trigonum, and radiating pain from lumbar nerve root entrapment, should also be carefully evaluated.

To classify the tendon pathology more precisely, different imaging techniques can be used.

**Imaging**

Three imaging modalities are used in the diagnosis of pathology in the Achilles tendon, i.e. diagnostic ultrasound US, magnetic resonance imaging (MRI), and plain film radiography (XR). US is the method of choice used in all studies in this thesis and will therefore be presented in detail. MRI and XR will only be briefly presented. The thickness and the structure of the Achilles tendon as well as the attachment to the muscles and the calcaneal bone can be visualized with both US and MRI. It is also possible to examine other structures in relation to the Achilles tendon, to diagnose other conditions responsible for pain in the Achilles tendon.
region using these methods. Skeletal changes in the calcaneus, calculi or loose bone fragments in the Achilles tendon insertion to the calcaneus, as well as major swelling of the tendon can, be visualized by XR, (Kalebo et al. 1990).

**Ultrasound**

US is a non-invasive and harmless method to examine the human body. The method was invented at the beginning of the last century. During the Second World War there was an intense work to develop radar and sonar systems to be used by the armed forces. Dussik (1942) was one of the first in the world using ultrasound in diagnostic purpose. Howry recorded the first cross-sectional ultrasonographic image with a 35-mm camera, and published the first studies of human tissue visualised by US (Howry 1952). The first systems could only show the anatomy in black and white, without grey scale, and only major organs and major pathology could be shown. One of the most important innovations in the development of the US technique was the scan converter that made it possible to develop the grey-scale (Kossoff et al. 1974). The first US equipments were static machines, where the transducer were attached to an arm connected to sensors indicating the position of the transducer on a screen. Static US images were produced when the examiner moved the transducer along the human body. Since every single slice had to be produced manually, it was very time consuming and difficult to learn the US technique. The static machines were followed by real time machines during the 1980\textsuperscript{th}. These machines were easier to handle and it was easier to learn the method, since there was a dynamic image visualising the human anatomy. In the first machines the spatial resolution was not high enough to be used in musculoskeletal ultrasound, especially not in the diagnosis of structural changes in tendons. During the digital development in 1980\textsuperscript{th} and 1990\textsuperscript{th}, there was a fast development of US machines and transducers, with increasing spatial resolution both at the surface as well as in the deep structures. This development has made the US technique sensitive and usable for different diagnostic procedures, i.e. it is now possible to
examine muscle fibres, tendons, and even ligaments, with good reliability (vanHolsbeek & Introcaso 2001).

**Equipment**

In modern digital US equipments there is a very efficient technology for both imaging and storage. The critical part in diagnostic US is the US probe (Meire et al. 1993 vanHolsbeck & Introcaso 2001). The resolution of the US technique has increased rapidly over the last two decades due to a technical development of both the piezo electrical crystals as well as computer capacity. Furthermore, the development has also lead to several dedicated probes, and it is very important to use the correct probe for a certain investigation. The resolution increases with higher frequency of the probe, but the penetration decrease. A lower frequency has consequently a good penetration but a bad resolution. A probe with the frequency 2 – 5 MHz is suitable for abdominal examinations. For musculoskeletal examinations the optimal frequency is 5 – 15 MHz. Furthermore, the resolution in the image is not only dependent of the frequency of the probe, but also of the distance from the probe to the examined structure. In musculoskeletal US, where the most important tendons to be examined are situated very superficial in the body, linear probes are preferable due to the high resolution in a short distance from the probe. It is also possible to hold the linear probe strictly along the tendon fibres, which is not possible with vector or curved probes that are best suited for abdominal investigations. Another disadvantage of the sector and vector probes is a narrow near field of view and near-field blurredness (Meire et al 1993, vanHolsbeek & Introcaso 2001). Linear transducer provides optimal images, having their sound beam perpendicular to the tendon throughout the imaging field (vanHolsbeek & Introcaso 2001). In modern scanners, it is, apart from routine adjustments, possible to select different frequencies, different focusing of the sound beam, and different field of views.
**Colour Doppler**

An important issue of the US technique is the possibility to study blood flow non-invasively with the aid of Doppler technique. The first blood flow studies using the Doppler technique was done in the late 50th in Japan, further developed by Reid et al (1972). With the first machines, continuous or duplex Doppler machines, the results were presented graphically. The next step in the development of the Doppler technique was the colour Doppler technique, which was presented in Japan by Omoto et al. (1984). Their approach of colour mapping is still in use today. The colour Doppler technique, or colour Doppler velocity (CDV), visualizes both the velocity and the direction of the blood flow. McDicken (1992) presented a new, even more sensitive method to study the movements of tissues (usually blood). This technique is called Power Doppler, or Colour Doppler Energy (CDE). Both CDV and CDE are very sensitive to show blood flow in small vessels. In larger vessels the angle of the probe against the vessels is more critical with CDV than CDE. With the aid of CDE it is not possible to show flow velocity or flow direction. Both colour Doppler techniques can be combined with pulsed Doppler technique, where the flow is presented graphically, and the flow direction and flow velocity can be estimated. It is also possible to characterise the flow, i.e.; it is possible to find out if it is arterial or venous flow. This characterisation can also be presented by sound effects.

In clinical situations, colour Doppler is widely used in different examinations of blood flow, e.g.; in cardiology, in the diagnosis of venous thrombosis (Theodorou et al. 2003), and in the diagnosis of atherosclerotic changes in the carotids and other arteries (Muller et al 2001). During the last years, the development has proceeded, and it is now possible to examine very small vessels in the near field with the aid of colour Doppler. It is even possible to visualize vessels with colour Doppler that are not visible with grey scale US. Also, it is possible to diagnose regions with decreased perfusion (Dogra et al. 2003). The high sensitivity of the CDV for low flow, combined with the high spatial resolution in dynamic grey scale
US, makes the method suitable for characterisation of structural and vascular changes in tendons.

During the last years, intravenous contrast material designed for US examinations, has been developed (Maresca et al. 1998, Correas et al. 2001). These contrast material consist of micro bubbles with the ability to pass through the capillaries in the human body. Using this contrast material it is possible to study the blood flow in tissues. The contrast examination is not combined with Doppler technique. Instead, it is a dynamic study of the contrast filling the capillaries and the arteries in human tissues. It is also possible to follow the venous phase, the venous wash out of micro bubbles. The method has mainly been used to diagnose and to characterize liver tumours (Albrecht et al. 2003).

**Sonographic Anatomy of the normal Achilles tendon**

The Achilles tendon is composed of parallel running fibres Fig 3) that are reflective by US (vanHolsbeeck & Introcaso 2001). The resolution of the fibre pattern is increased with increased frequency of the US probe (Fessel et al. 1998, Goodwin 2000, Martinoli et al. 1993 & 1999 & 2002).

![Us examination of a normal Achilles tendon. Note the echogenic fibril structure in the tendon.](image)

**Fig 3:** Us examination of a normal Achilles tendon. Note the echogenic fibril structure in the tendon.
In the longitudinal section, the normal Achilles tendon is equally thick or slightly thickened distally, with successively diminishing thickness proximally, where the Achilles tendon becomes a thin aponeurosis between the soleus and the gastrocnemius muscles (Goodwin 2000). The maximum thickness of the tendon has been estimated to 6.3 mm ± 0.5 mm in adults 18 – 30 years, and 6.9 ± 1.0 mm in adults older than 30 years (Koivunen-Niemela et al. 1995, Ying et al. 2003). In the transversal section the Achilles tendon is ovoid in shape.

The paratenon, surrounding the Achilles tendon, is demonstrated as a reflective line around the tendon. The normal retrocalcaneal bursa can be seen as a thin layer of fluid. The normal walls of the bursae are too thin to be identified by ultrasound (vanHolsbeeck et al. 1989). At the dorsal side of the tendon is the highly reflective skin and subcutaneous fat identified. Ventral to the Achilles tendon is the Kager’s fat pad, identified as a moderately echogenic, irregular, structure.

In the normal Achilles tendon, colour Doppler shows no vessels. The equipment is not sensible enough to register the blood flow in the intratendinous vessels. However, in rare occasions, it is possible to register some minimal vascular flow entering through the paratenon. Normally, a few small vessels can be seen in the fatty tissue in Kager’s fat pad.

**Ultrasound guided puncture**

A very important tool in the US technique is the possibility to perform US guided punctures. One of the pioneers was Holm (1972), who presented a method to use US as a guide in percutanously puncture procedures. All modern US machines today are equipped with puncture devices. They consists of software showing digital lines on the US monitor corresponding to a puncture guide attached to the transducer, keeping a puncture needle in exact position in the image of the examined structure, shown on the screen. A sterile rubber coat covers the transducer, and the puncture device is sterile to minimize the risk of infection. The puncture device makes it possible to perform US guided punctures in real time. As an example, the method is used to puncture small tumours in the liver and pancreas.
percutanously, or small lymph glands in the neck in order to receive tissue for cytological or histological diagnosis (Solbiati et al. 2001). The use of ultrasound guided puncture also minimizes the risqué for complications and increases the possibility to obtain a satisfactory tissue sample, compared to blind puncture (Nobili et al. 2003). Besides diagnostic punctures there are also therapeutic US guided interventions, i.e. drainage of fluid or infected collections, or injections of drugs percutanously into targets not palpable. When a very small structure is punctured it is important to localize the target exactly, and it is furthermore an advantage to connect the needle to a syringe with a connecting tube. The US physician is holding the needle, and an assistant the connected syringe. This procedure combines the dynamic US guidance with the sensitivity of the finger tips, and makes it possible to puncture very small structures. To get a good result, it is very important that there is a good collaboration between the physician and the assistant.

When very small superficial structure is punctured, it is usually not possible to connect a puncture device to the transducer, since the needle must be positioned almost parallel to the skin and very close to the transducer. Instead, the puncture can be performed either with the needle in the longitudinal plane, or in the transversal plane of the transducer. It is possible to puncture in real time also with this method, since the needle is seen in the tissue with US. This technique must be used, when US is used dynamically to puncture the small vessels anterior to the Achilles tendon, seen in chronic painful Achilles tendon conditions.

**MRI of the Achilles tendon**

MRI is a method well suitable to study the Achilles tendon (Soila et al 1999, Karjalainen et al. 2000, Schweitzer et al. 2000, Tuite et al. 2002). The normal tendon has low water content, resulting in no signals from the normal tendon. Consequently, the normal tendon is black in all sequences, and there are no detectable structures inside the tendon. When there are pathologic changes in the tendon there is increased water content, and consequently, structural changes.
within the tendon can be recognised. In recent MRI studies has an enhancement of gadolinium in the pathological structures been shown (Movin et al. 1998c, Schalabi et al. 2001&2002). Marshall et al. (2002) also showed, in a patient with chronic tendinopathy, a small rapidly enhancing focal area of enhancement next to the insertion of the tendon at the sites of blood supply, and also an early local contrast enhancement within the tendon.

When comparing MRI and US, MRI is more sensitive to small changes of signals in the tendon (Soila et al. 1999), but US shows more details in the tendon structure and has a higher sensitivity to diagnose small intratendinous calculi (Kamel. et al. 2003). On the other hand, MRI can show bone pathology, which is not possible with US (Karjalainen. et al. 2000). An MRI examination is more time consuming and more expensive than an US examination. It is furthermore not possible to perform a dynamic examination with MRI, which is possible with US.
Chronic Achilles tendon pain

In this thesis we have focused on the chronic painful condition in the Achilles tendon, and acute conditions will not be discussed.

Nomenclature in chronic painful conditions

In the literature, the nomenclature for chronic painful conditions in the Achilles tendon is often confusing, and not reflecting the pathology of the tendon disorders. The terms “tendinitis” and “tendonitis” are often used even though there is no inflammatory cell infiltration (Åström 1995, Maffulli et al. 1998, Movin 1998, Khan et al. 1999, Alfredson & Lorentzon 2000). In recent literature the term “tendinosis” has become widely accepted, and is being used for patients with a chronic painful condition in the midportion of the tendon and were imaging (US or MRI) show tendon abnormality corresponding to the painful area (Alfredson et al. 1998a+b, Khan et al. 1998, Teitz et al. 1997). The term “partial rupture” has also been used (Ljungqvist 1967, Denstad & Roaas 1979, Åström 1998) for an injury where a clearly discernible partial discontinuity is demonstrated at surgical exploration. In patients with a long duration of pain symptoms, where the clinical findings and imaging often are identical, “tendinosis” and “partial rupture” are difficult to distinguish from each other. In a study by Åström & Rausing (1995), it was shown, that when examining the histopathology in patients with chronic painful Achilles disorders, partial ruptures were always surrounded by non-inflammatory lesions (tendinosis). It is not known whether the tendon changes associated with tendinosis precede partial rupture or if the partial rupture initiates the tendinosis. Altogether, most likely, an acute onset of pain indicates a complete or partial rupture of the Achilles tendon, while a gradually onset of the pain should be named tendinosis.

The conditions can also be divided into proximal, mid-portion, and distal injuries.
**Proximal pain**

Chronic pain in the proximal (musculo-tendinous junction) part of the Achilles tendon is not very common (Williams 1986). It mainly appears as late symptoms after a total or partial rupture of the medial head of the gastrocnemius muscle. Chronic pain in the calf can be caused by scar tissue or an organized haematoma after a traumatic rupture. An important differential diagnosis is deep venous thrombosis. Other conditions that must be ruled out is ruptured Baker cyst, or muscle rupture with haematoma in the calf muscle. US combined with colour Doppler can be used in the diagnosis of muscle ruptures with haematomas (Aspelin et al.1992, Bianchi et al. 1998), ruptured Baker cysts (Langsfeld 1997) and deep venous trombosis (vanHolsbeeck & Introcaso 2001, Theodorou 2003). The diagnostic procedure will not be discussed in details.

**Mid-portion pain (2 – 6 cm from the calcaneal insertion)**

The midportion of the Achilles tendon is the most common part for the chronic painful condition. The condition is relatively common among elite and recreational athletes, especially in the age-group between 30 – 60 years (Kvist 1994). The aetiology and pathogenesis are unknown, but an association with overuse have been suggested. However, also non-active individuals have been shown to have this condition (Fahlström et al. 2003).

The typical patient has a gradual onset of stiffness and pain, and clinical examination show a tender swelling in the mid-portion of the tendon. Usually there is no skin reaction (Alfredson&Lorentzon 2000).

**Histopathology**

Movin et al. (1997) has demonstrated changes in the collagen fibre structure and arrangement, and an increased amount of interfibrillar glycosaminoglycans (GAGs) in biopsies from the pathologic tendon (demonstrated with ultrasound). Furthermore, Åström et al. (1995) showed an irregular, hypervascular pattern, with
groups of thick-walled vessels distributed un-evenly in the hyper-cellular tissue in pathologic tendons. Some vessels had a nodular appearance, and some were running perpendicular to the collagen fibres.

**Pain mechanism**

The background to pain in this condition has been largely unknown. The absences of inflammatory cells in biopsies have indicated that this is a non-inflammatory condition, but still, in common praxis, it has been treated as inflammation (Leadbetter 1995, Kvist 1994, Józsa and Kannus 1997). However, recent studies using intra-tendinous microdialysis, and gene technological investigations of biopsies, clearly demonstrated that there is no chemical inflammation involved in the chronic stage of this condition (Alfredson et al. 1999 and 2003). Interestingly, in the microdialysis study, a significantly higher concentration of glutamate was shown in painful tendinosis tendons, in comparison to pain-free normal tendons. Glutamate is a well-known and potent modulator of pain in the human central nervous system (Dickenson et al 1997), but besides the finding of glutamate receptors in bone-tissue (Chenu et al 1998), it had never before been identified in the peripheral nervous system in humans. The role of glutamate in the chronic painful Achilles tendon is still not known.

Also, in another study using microdialysis technique significantly higher levels of lactate was shown in tendinosis tendons compared to normal tendons, and the lactate concentrations were at about the same level as in working muscle tissue (Alfredson et al. 2002). This finding indicates ischaemic conditions in tendinosis tendons, but whether this is associated with ischaemic pain is not known.

**Ultrasound**

In midportion chronic Achilles tendinosis there is usually a thickening of the tendon. In the longitudinal view, there is a spool-shaped thickening in the mid-portion of the tendon, or the tendon is thickened in its whole length (vanHolsbeeck & Introcaso 2001). In the transversal view, the tendinosis tendon is rounded or
oval. There are usually focal hypo-echogenic regions in the affected tendon (Åström et al. 1996, van Holsbeeck & Introcaso 2001, Kainberger et al. 1990, Gibbon et al. 2000). Generally it is very difficult to perform an exact measurement of the size of these hypo-echogenic regions, since they are diffusely demarked. The hypo-echoic regions inside the pathological tendon are most likely correlating to the increased amount of GAG’s that have been demonstrated in core biopsies (Movin et al. 1997).

**Conservative treatment**

Most of the proposed conservative treatment regimens for chronic painful Achilles tendinosis are not based on scientific evidence (Almekinders & Temple 1998, Khan et al. 1999, Alfredson & Lorentzon 2000). Often, biomechanical malalignments are suggested to be causative factors (Welsh and Clodman 1980, Schepsis and Leach 1987 Hess et al. 1989, Kvist 1991). However, Åström (1998) demonstrated in a study including 342 consecutive patients with chronic Achilles tendinopathy and 147 controls, that biomechanical “abnormalities” were not important in chronic Achilles tendinopathy, and questioned the value of orthotics in the treatment of this condition. Also, Lowdon et al. (1984) demonstrated in a randomized prospective study including 33 patients with sports induced Achilles tendinitis, that there was no benefit of treatment with viscoelastic heel pads. Commonly, the initial treatment is a combination of methods assaulting different presumed etiological factors, such as; training errors (James et al. 1978, Brody 1987) muscle weakness (Appel 1986), Renström 1988, Nicol et al. 1991), poor flexibility (Wallin et al. 1985, Kvist 1991), and poor equipment (Brody 1987, Jörgensen and Ekstrand 1988, Hess et al. 1989). Different methods of physiotherapy, including stretching and strength training programs have been utilized (Welch and Clodman 1980, Galloway et al. 1992, Sandmeier and Renström 1997). Considering strength training, good clinical short- and mid-term results with painful heavy-load eccentric calf muscle training has been reported on patients with chronic painful Achilles tendinosis at the 2 – 6 cm level in the tendon (Alfredson et al. 1998, Fahlström et al. 2003). The results were
reproduced in a randomised prospective study, where the results after painful eccentric calf-muscle training were significantly better than after painful concentric training (Mafi et al. 2001). The majority (82%) of these patients could return to pre-injury tendon loading activity.

Anti-inflammatory medications, NSAIDs and corticosteroid injections, are very often used as a complement to other conservative therapies. The effect has been debated by many authors (Åström & Westlin 1992, Almekinders et al. 1995, Shrier et al. 1996, Åström 1998), but with the recent research findings in mind (Alfredson et al. 1999 and 2003), that this is not an inflammatory condition, the use of anti-inflammatory medication cannot be justified in the chronic phase of this condition.

**Surgical Treatment**

If it is not possible to cure the patient conservatively, surgical treatment is used. It is a general opinion that approximately 25% of patients with chronic painful Achilles tendinosis are treated surgically, and the frequency of surgery increase with patients’ age, duration of symptoms, and occurrence of pathologic changes in the tendon (Kvist 1994). Different surgical techniques are used. Usually the hypertrophic parts of the paratenon and macroscopically abnormal tendon tissue are excised (Leadbetter et al. 1992, Schepsis et al. 1994, Alfredson et al. 1998a, Morberg et al., 1997, Movin et al 1997b). Recently Maffuli et al. (1997) have reported promising results using percutaneous multiple longitudinal incisions in the region with tendinosis. The short-time results after surgery has been reported to be good in 80 -100 % of patients. However, there are few prospective studies and few studies with a long-term follow-up. Leppilahti et al. (1991) reported excellent or good result in 29/52 patients operated for mid-portion tendinosis and followed during a 4-year period postoperatively. In a longer follow-up, ranging from 1-13 years, Schepsis et al. (1994) reported a satisfactory result in 67% of the patients. From that study it was concluded that there were signs of deterioration of the results of surgery, with time. In a 2-7 years follow-up report by Nelen et al. (1989) on 50 patients surgically treated for tendinosis, 40 patients (80%) had an excellent
or good result. Morberg et al. (1997) reported 80% excellent or good results in 25 patients surgically treated for chronic pain from a partial rupture in the midportion of the Achilles tendon, and with a follow-up period of 1.5-11 years. In a report by Movin et al. (1997) including 40 patients surgically treated for intratendinous pathology, 77% had excellent or good results at follow-up ranging from 1-4.2 years postoperatively. After percutaneous longitudinal tenotomy (Maffulli et al. 1997) 37 out of 48 patients (77%) had an excellent or good result at follow-up 1.5-5 years postoperatively.

The effect of surgery is debated. Many authors state, that surgery promotes a new repair process, and improves the vascularity in tendon (Leadbetter et al. 1992, Maffuli et al. 1997). However, the good results of quite different techniques might also indicate that the effect of surgery is simply caused by extended denervation. There are also other factors like the postoperative rehabilitation that might be of significant important for the result (Leadbetter et al. 1992, Sandmeier & Renström 1997). However, it is important to keep in mind that the background to the sometimes good results with surgical treatment has not been scientifically clarified. There are few well-designed studies with long-term follow-ups of well defined patient groups, and there are no randomized studies comparing different surgical methods.

**Distal pain (Achilles tendon insertional pain)**

The distal part of the Achilles tendon is also relatively common for the chronic painful condition, mainly in adult individuals. It can affect elite or recreational athletes, but also non-active individuals. The aetiology and pathogenesis have not been scientifically clarified, but there might be shoe-induced problems. The shoes can be either too tight or too big, or having too high heel-caps (Hoppenfeld 1976). The result can be mechanically induced injuries, such as friction induced subcutaneous or retrocalcaneal bursitis.

The condition is more complex compared to mid-portion pain, since the tendon, bursae, and bone (calcaneus), alone or in combination, can be involved (Järvinen et
A prominent posterior angle of the calcaneal bone, Haglund’s deformity, has been suggested to cause a painful “impingement” on the tendon with ankle dorsiflexion (Vega et al. 1984). Most often the symptoms start gradually, with pain during tendon loading activities. Clinical examination commonly shows a tender swelling of the insertion region of the Achilles tendon. The upper lateral or medial part of the calcaneus is often prominent and tender, and the patients have difficulties to wear shoes with heel-caps.

Painful conditions in the Achilles tendon insertion, often called insertion tendinopathy, are well-known to be difficult to treat (Kvist 1991). In the acute phase conservative treatment is recommended, but with chronic pain, surgery is often required (Kvist 1991 and 1994, Järvinen et al. 1997). There are several theories explaining the origin of pain in this condition. It is suggested that the retrocalcaneal bursae might be focus for a chronically inflammation (Kvist 1991 and 1994, Järvinen et al. 1997), and consequently could be a source for nociceptive pain. Also, an impingement between a spur or prominence of the upper posterior calcaneus, and a thickened or normal tendon, might mediate nociceptive pain from the bone (periosteum) and/or tendon. Furthermore, a partially or totally detached bone fragment, and maybe also calcifications, may cause pain. These different tissues alone, or together, might all be responsible for the painful condition. Therefore, in clinical praxis, it is often difficult to judge were to address the treatment. Importantly, the scientific evidences for these theories are missing, and there might be other sources for the pain.

**Histopathology**

The condition is commonly called insertion tendinitis, despite inflammatory cell infiltration has not been demonstrated in the tendon (Järvinen et al. 1997). In distal Achilles tendon pain there is often tendon changes defined as tendinosis. However, there might well also be a subcutaneous and retrocalcaneal bursitis, showing the classical signs of inflammation. A common finding is also calculi and loose bone
fragments in the distal tendon. Frequently, there are bony spurs at the attachment of the Achilles tendon into the calcaneus.

**Ultrasound**

In a case with isolated distal Achilles tendinosis, the tendon is thickened, and the structure is irregular. The tendon fibres are irregularly organised and separated by hypo-echoic areas (vanHolsbeeck & Introcaso 2001, Gibbon et al. 2000). Like in mid-portion Achilles tendinosis, it is usually difficult to measure the structural changes in the tendon. An enlarged subcutaneous or retrocalcaneal bursa, with thickened walls and increased content of fluid, can be found (Kainberger et al. 1990, vanHolsbeeck & Introcaso 2001, Gibbon et al. 2000). It is often more difficult to penetrate the tissue anterior to the distal tendon following surgery, and the frequency of the transducer must be reduced to improve penetration. This is most likely due to absorption of the sound waves in the scar tissue. Furthermore, there are often echogenic calculi inside the distal Achilles tendon at the insertion into the calcaneus. There is a characteristic acoustic shadow behind the high-echogenic calculi. Often there are well-demarcated bony spurs adjacent to the insertion of the Achilles tendon into the calcaneus (Kamel et al. 2003).

**Treatment**

The chronic painful condition in the Achilles tendon insertion is well known to be difficult to treat. Because of the relatively poor knowledge about the source of pain, it is often difficult to judge were to address the treatment in clinical praxis. An isolated bursitis can sometimes be successfully treated with a local injection of corticosteroids, but besides bursitis, the general opinion is that there are no indications for corticosteroids in this condition (Leach et al. 1983, Renström and Johnson 1985). Painful eccentric training has in a scientific study been shown to have a poor effect on this condition (Fahlström et al. 2003). Other types of strength training have, to our knowledge, not been scientifically evaluated.
When conservative treatments fail, surgical treatment is instituted. During surgery, the main question is from what tissue the pain comes? Is it from the tendon, the bursae, or bone (spurs, fragments, prominent deformity), alone, or in combination? Consequently, the surgical technique is varying. Some authors address the surgery towards a presumed impingement between the cranial part of the calcaneus and the tendon, and state that a resection of the upper cranial calcaneus is necessary. Some focus on the bursae, others focus the surgery on the distal tendon, while some address the surgery to the tendon, bursa and bone in combination (Järvinen et al. 1997). Importantly, the scientific evidence for treatment results following different surgical procedures except for pure bursitis is missing.
Aims

The general aim with the present thesis was to evaluate sonographic methods in the investigation of the chronic painful condition in the mid-portion of the Achilles tendon.

Specific aims were:

- To use grey-scale US to describe tendon thickness and structure in the chronic painful condition located in the mid-portion of the Achilles tendon, before and after treatment with eccentric training (paper I).

- To use grey-scale US combined with colour Doppler (CDV) technique to describe the chronic painful condition in the mid-portion of the Achilles tendon (paper II).

- To evaluate the combined findings from grey-scale US and colour Doppler examinations, immunohistochemical analyses of biopsies, and diagnostic injections, in the chronic painful condition in the mid-portion of the Achilles tendon (paper VI).

- To describe the colour Doppler findings in the chronic painful condition of the mid-portion Achilles tendinosis, before and after treatment with eccentric training (paper V).

- To evaluate the effects of a new US guided treatment method (papers III, IV), based on the findings in papers II and VI.
Methods

*Ultrasound scanning technique of the Achilles tendon*

The patient is placed in prone position with the feet hanging free below the foot-end of the examination table (Fig 4). The posture must be comfortable, avoiding tensions in the calf muscles.

![Fig 4: Patient in position prepared for US examination of the Achilles tendon.](image)

After a careful palpation of the Achilles tendon, a generous amount of contact gel is placed on the skin over the tendon, and the US examination is performed. A stand of pad can be used to position the tendon within the transducers field of view (Fornage et al. 1984). This stand-off pad can only be used when the thickness of the tendon is measured, and when the structure is evaluated. When colour Doppler examination is performed, the stand-off pad must be removed, since the sensibility of the method will be better without the stand-off pad (the stand-off pad absorbs or hinder the sound-waves).

A high quality US equipment must be used. (In the present studies an Acuson Sequoia - Siemens Medical Solution was used). A linear transducer with high frequency (13 – 15 MHz) is positioned parallel to the longitudinal axis of the tendon (Martinoli et al. 1999 & 2002, vanHolsbeeck & Introcaso 2001). It is
important to place the probe perpendicular to the tendon, parallel with the tendon fibres, to minimise artefacts. One important artefact in the classification of structural changes in tendons is anisotropy (Connolly et al. 2001 Martinoli et al. 2002), which arises when the probe is placed in an improper angle to the tendon, causing a low echogenic image even in a normal, high echogenic Achilles tendon. The artefact is caused when the reflected sound-beams from the tendons do not hit the probe, and consequently, the tendon structure will be shown as low echogenic. Anisotropy is especially a problem where tendons are in a curved position, i.e. the Achilles tendon insertion in the calcaneus.

The Achilles tendon is examined from the musculotendinous junction to the attachment into the calcaneal bone. The whole length of the tendon is evaluated in both longitudinal and transversal view (Fig 5), and the thickness and the structure of the tendon is visually evaluated. Following questions should be answered: Is the Achilles tendon thickened? Is it possible to distinguish the fibre structure of the tendon, or are the fibres disorganized? Are there any hypo- or hyper-echogenic regions in the tendon? During the examination also the structures adjacent to the tendon are examined. Are there any hypo- or hyper-echoic regions around the tendon?

A                                                               B

Fig 5: US examination of the Achilles tendon. A: Longitudinal scan.
B: Transversal scan. Note the generous amount of contact gel.

Is the structure of the fatty tissue in Kager’s fat pad normal? Is the retrocalcaneal bursa visible? If there are symptoms from the proximal part of the Achilles tendon,
or the calf muscle, the whole length of the calf, including the vessels and the aponeurosis, must be examined.

When the grey scale examination is completed, the study continues with colour Doppler examination of the tendon. CDV or CDE can be utilized. It is important to adjust the system to make it possible to measure very low flows, since the vessels related to tendons are very small and not even visible with grey scale US. It is also very important to minimize the movements of the transducer to avoid artefacts. The CDV examination must include both the Achilles tendon, as well as the surrounding structures. As an example, it is important to find out if there is increased vascularity inside or around the subcutaneous and retrocalcaneal bursae. To be able to perform a proper examination and to accurately evaluate the results, the operator must be experienced in how to handle the equipment, and how to optimise the technical settings of the machine.

**Ultrasound-guided injection**

The patient is placed in prone position with the feet hanging free below the foot-end of the examination table. The posture must be comfortable, avoiding tensions in the calf muscles. A generous amount of contact gel is placed on the skin, and the Achilles tendon is examined without a standoff pad. A careful US examination as described above is performed prior to the treatment. The thickness and the structure of the tendon is evaluated and registered. The Achilles tendon is also carefully examined with CDV to evaluate the extension of neovessels in the tendon, and the strategy for injection is determined. The skin is washed carefully with an antiseptic solution before injection. The leg is dressed with a sterile paper cover only leaving the Achilles tendon free. The injection is performed either with an injection
**Fig 6:** Dynamic US-guided puncture from the medial side of the Achilles tendon.

**Fig 7:** Dynamic US-guided injection of Polidocanol against vessel entering the Achilles tendon anteriorly.

**Fig 8:** After injection of Polidocanol. No remaining circulation in the neo-vessels.
needle attached to a syringe or with a thin connecting tube between the needle and the syringe. The latter procedure is preferred, since the targets to be punctured are very small, and it is easier to perform a correct puncture when the operator has full control over the procedure.

The syringe and the needle (including the connection tube) are filled with Polidocanol 5 mg/ml, (2 – 4 ml). The active substance in Polidocanol (Aethoxysklerol, Inverdia AB, Stockholm, Sweden) is an aliphatic, non-ionised nitrogen free substance with a sclerosing and local anaesthetic effects. Polidocanol has been widely used as sclerosing agent, with good clinical results in the treatment of varicose veins in the legs and oesophagus, haemorrhoids, telangiectasis, and gastroduodenal lesions (Guex 1993, Conrad et al. 1995, Winter et al. 2000). The probe is covered with a sterile coat and a sterile contact gel is located on the skin. The operator also wears sterile rubber gloves. The operator must be able to handle the functions of the US machine either with a foot pedal, or there must be an assistant handling the machine, since it is important to be able to shift momentary between grey scale and CDV when the puncture is performed. The puncture is always done from the medial side (Fig 6), to avoid a puncture of the sural nerve. The needle is positioned just below the Achilles tendon (Fig 6&7), and the puncture is performed dynamically with the aid of US. The needle tip is placed against/into the small vessels entering the anterior surface of the Achilles tendon. Puncturing of the tendon must be avoided, but the needle should be positioned adjacent to the surface of the tendon. During the whole procedure the positioning of the needle is continuously controlled with grey scale US and CDV. When the needle tip is in correct position a small amount (0.1 – 0.2 ml) of Polidocanol is injected, and the result is immediately visualized on the screen. If the position is correct, the injected substance is spread along the anterior surface of the Achilles tendon, and the circulation usually stops instantly in the vessels in the region. Usually, it is possible to find several vessels entering the Achilles tendon from one puncture of the skin. It is possible to alter the direction of the needle subcutaneously and reach several targets. If it is not possible to reach all vessels from one puncture, another punctures should be performed. It is important to
inform the patient that the puncture sometimes can be very painful, but that the pain usually diminishes because of the local anaesthetic effect of Policocanol. When there is no remaining circulation in the neovessels in the Achilles tendon the treatment is finished (Fig 8).

The local anaesthetic effect will last a few hours. For some days after the injection there is sometimes pain the region for injection, most likely due to a haemorrhage caused by the puncture. The patient is allowed to walk freely immediately after the procedure, and after one week more tendon loading activity is allowed. The effect of the treatment will follow successively, with diminishing pain, but the treatment must usually be repeated 1 – 5 times (mean 2 times) with 4 – 6 weeks interval.

**Statistical methods**

The SPSS packages (SPSS Inc., USA) version 7.5 – 9.0 for personal computer was used for descriptive statistics and statistical analysis.

Results are presented as means ± SD.

A non-parametric test for paired samples (Wilcoxon signed ranks test) was used to test differences over time.

A p-value less than 0.05 was considered significant.
Summary of papers

Paper I:

Eccentric training in patients with chronic Achilles tendinosis- normalized tendon structure and decreased thickness at follow-up

Aim
To use grey-scale US to prospectively study tendon thickness and tendon structure in patients with chronic painful mid-portion Achilles tendinosis treated with eccentric calf-muscle training.

Material and Methods
In this study 26 Achilles tendons in 25 patients with a long duration of pain-symptoms from the mid-portion of the Achilles tendon were included in the investigation. Grey-scale US was performed before and after the eccentric training regimen, and the thickness and the structure of the tendons were evaluated.
At follow-up, all patients answered a questionnaire assessing their satisfaction with the result of treatment, the level of present tendon loading activity, and tendon related symptoms.

Main results
All tendons with tendinosis showed a localised thickening including structural abnormalities (hypo-echoic areas and irregular structure) before treatment. At the follow-up, mean 3.8 years after treatment, the US examinations showed a significantly decreased thickness of the tendinosis tendons as well as a “normalised” structure in 19 of the 26 tendons. In 6 out of 7 tendons with remaining structural abnormalities, the patients experienced pain in the tendon during tendon loading activity. The non-treated, pain-free normal tendons were unchanged during the study period.
Conclusions

- Grey-scale US can be used to prospectively study Achilles tendon thickness and structure.
- Treatment with eccentric calf muscle training in patients with chronic mid-portion Achilles tendinosis seems to be associated with a localised (mid-portion) decrease in tendon thickness, signs of a “normalised” tendon structure, and pain relieve.
- Remaining structural tendon abnormalities seems to be associated with remaining pain from the tendon.

Paper II:

Neovascularisation in Achilles tendons with painful tendinosis but not in normal tendons: an ultrasonographic investigation

Aim

To use grey-scale US combined with colour Doppler examination to study vascularity in tendons from patients with chronic painful mid-portion Achilles tendinosis and in pain-free (normal) tendons.

Material and Methods

In this study, 21 patients (28 Achilles tendons) with chronic mid-portion Achilles tendon pain and 14 controls (20 Achilles tendons) with no history of Achilles tendon pain were included. The tendons were examined with grey-scale US, and thickness and structure of the tendons were evaluated. Blood flow was registered with CDV.
**Fig 9**: Achilles tendinosis. CDV shows neovessels before treatment.

**Fig 10**: Tendinosis. CDV six months after US-guided injection of Polidicanol. No remaining vessels in the Achilles tendon. No remaining pain.

**Fig 11**: Tendinosis. CDV two years after US-guides injection of Polidocanol. No remaining vessels in the Achilles tendon. No remaining pain.
Main results

Neovessels were seen inside and on the ventral side of the region with structural tendon changes in all Achilles tendons with chronic painful mid-portion tendinosis, but not in the normal pain-free tendons.

Conclusions

- High resolution grey-scale US combined with colour Doppler examination adds information about occurrence of a neovascularisation.

- There are neovessels in tendons with chronic painful mid-portion Achilles tendinosis, but not in pain-free, normal, tendons.

- There might be a correlation between the occurrence of neovessels and pain in patients with chronic painful mid-portion Achilles tendinosis.

Paper III:
Ultrasound guided sclerosis of neovessels in painful chronic Achilles tendinosis: pilot study of a new treatment

Aim

To evaluate whether a specific treatment, ultrasound and colour Doppler guided sclerosing therapy, addressed towards neovessels outside the region with structural tendon changes, would have any effect on the pain in chronic painful mid-portion Achilles tendinosis.
Material and Methods

Ten patients with chronic painful mid-portion Achilles tendinosis were treated by US and colour Doppler guided injections of Polidocanol against the neovessels entering the Achilles tendon from the anterior aspect. The effect on pain during Achilles tendon loading activity was evaluated using a visual analogue scale (VAS). The effect on the neovessels was registered using colour Doppler.

Main results

Neovascularisation was found inside and outside the ventral side of the region with structural tendon changes in all tendons with chronic painful mid-portion Achilles tendinosis. Before treatment, the mean VAS-score, evaluating the amount of pain during Achilles tendon loading activity, was 73.6 (range 39-89). At the six month follow up, 8/10 patients were satisfied with the treatment and mean VAS score had decreased to 8 (range 0-29), and in the majority of the tendons all neovessels had disappeared. In the 2/10 patients that not were satisfied with the treatment (remaining tendon pain), multiple neovessels remained.

Conclusion

- US and colour Doppler guided sclerosing therapy of neovessels in chronic painful mid-portion Achilles tendinosis seems to have a potential to cure the pain in the short-term perspective.


**Paper IV:**

Sclerosing therapy in chronic Achilles tendon insertional pain-results of a pilot study

**Aim**

To use US and colour Doppler guided sclerosing therapy to destroy the neovessels and most likely also nerves accompanying the vessels, but not addressing any treatment to the tendon, bursae, or bone, would affect chronic Achilles tendon insertional pain in order to receive a pain relieve.

**Material and Methods**

Eleven patients with chronic insertional Achilles tendon pain were treated by US and colour Doppler guided injections of Polidocanol against the neovessels entering the Achilles tendon from the anterior aspect. All patients had distal tendon pathology, 9 patients also had retrocalcaneal bursitis, and 4 patients had tendon pathology, retrocalcaneal bursitis, and calcaneal bone pathology (spurs, bone fragments). The effect on pain during Achilles tendon loading activity was evaluated using VAS.

**Main results**

Before treatment, all tendons showed thickening, structural abnormalities (hypoechoic areas and irregular structure), and neovessels in the distal Achilles tendon. Nine cases also had neovessels in close relation to the abnormal retrocalcaneal bursa, and four cases also had bony spurs, calcifications, or loose bone fragments in the tendon insertion. Before treatment, the mean VAS-score (pain during tendon loading activity) was 84 (range 64-100). After the treatment the mean VAS-score of the successfully treated patients (8/11) was decreased to 14 (range 3-40), and in
the three poor cases to 58 (range 49-74). Among the 3/11 patients that not were satisfied with the treatment, two had bone pathology.

**Conclusion**

- US and colour Doppler guided sclerosing therapy of neovessels in chronic Achilles tendon insertional pain seems to have a potential to cure the pain.

**Paper V:**

**Effects on neovascularisation behind the good results with eccentric training in chronic mid-portion Achilles tendinosis?**

**Aim**

To use grey-scale US and colour Doppler technique to prospectively investigate if eccentric calf-muscle training might have an effect on the neovessels demonstrated in chronic painful mid-portion Achilles tendinosis.

**Material and Methods**

In this prospective study 30 patients (45 tendons) with chronic painful mid-portion Achilles tendinosis, were included. All tendons were examined with high-resolution grey scale US combined with colour Doppler, before and after a 12 weeks eccentric calf-muscle training regimen (Alfredson et al. 1998).

**Main results**

Before treatment, there was local neovascularisation in the region with tendon changes (hypo-echoic areas, irregular fibre structure) in all tendons.
At follow up after treatment, there was a good clinical result in 40/45 tendons, and a poor result in 5/45 tendons. In 39/40 tendons with a good clinical result of treatment there was a normal tendon structure, and in 36/40 tendons there was no remaining neovascularisation. In 5/5 tendons with a poor result of treatment a remaining neovascularisation was seen, and in 2/5 tendons there were remaining structural abnormalities.

Conclusions

- In patients with chronic painful mid-portion Achilles tendinosis, a good clinical result after treatment with eccentric training seems to be associated with a “normalised” tendon structure and no remaining neovascularisation.

- Dynamic US and colour Doppler examination demonstrated direct effects on the neovessels (the flow stopped) during the eccentric load.

Paper VI

Is vasculo-neural ingrowth the cause of pain in chronic Achilles tendinosis?
- An investigation using US and colour doppler, immuno- histochemistry, and diagnostic injections

Aim

To study the possible importance of neovascularisation in chronic Achilles tendon pain, by evaluating the combined findings from grey-scale US and colour Doppler examinations, immunohistochemical analyses of biopsies, and the results of diagnostic injections.
Material and Methods

In this study, 25 Achilles tendons in 24 patients with chronic mid-portion Achilles tendinosis, and 20 tendons in 14 healthy controls with no history of Achilles tendon pain, were included. All tendons were examined with grey-scale US combined with colour Doppler. In all patients with painful tendinosis, under US and colour Doppler guidance, a local anaesthetic was injected in the area with neovascularisation outside the anterior part of the tendon. In 6 patients, biopsies was taken from the region with tendon changes and neovascularisation were processed for PGP 0.5 (a general nerve marker) immunohistochemistry.

Main results

In all tendons with painful tendinosis, but not in any of the pain-free normal tendons, there was a neovascularisation inside and outside the anterior part of the region with structural tendon changes. The pain during tendon loading activity was temporarily cured in all tendons, and the mean VAS-score for heel-raises decreased significantly from 75 to 6 mm following injection of local anaesthetic. The immunohistochemistry of the biopsies showed nerve structures in the vicinity of blood vessels.

Conclusion

- Colour Doppler examination showed a region with neovascularisation in close relation to the region with structural tendon changes, and findings from the injection of local anaesthetic support that the neovessels in the region might be the source of pain in chronic mid-portion Achilles tendinosis.
Discussion

Chronic Achilles tendinosis is a most often painful condition with unknown aetiology and pathogenesis, commonly seen among middle-aged recreational athletes (Kvist 1994, Tuite et al. 1997, Åström 1997, Movin 1998, Alfredson and Lorentzon 2000). Overuse has been suggested to be the primary causative factor, but the condition is also seen in physically non-active individuals (Åström 1997, Fahlström et al. 2003). The background to pain in chronic Achilles tendinosis has not been clarified (Khan et al. 2000b). For many years, despite the absence of inflammatory cell infiltrates in tendon tissue samples, an inflammatory component was considered to be involved. However, recent studies using microdialysis technique and gene technology have clarified that there is no chemical inflammation involved in the chronic stage of painful mid-portion Achilles tendinosis (Alfredson et al. 1999 and 2003). Instead, microdialysis studies showed high levels of the neurotransmitter glutamate and lactate in painful tendinosis tendons compared with pain-free normal Achilles tendons (Alfredson et al. 1999 and 2002). Glutamate is a well-known and potent modulator of pain in the human central nervous system, but had never before been identified in tendons. The possible role of glutamate or lactate in the pain mechanisms in painful tendinosis has not been clarified, but is focused in present research projects at the Sports Medicine Unit in Umeå, Sweden.

Chronic painful Achilles tendinosis has been known to be difficult to treat, but recently a specially designed painful eccentric calf-muscle training regimen has demonstrated to give very good clinical results (Alfredson et al. 1998, Mafi et al. 2001, Fahlström et al. 2003). The mechanisms behind the good results achieved with this method are not known, and development of methods suitable for prospectively studies of the tendons subjected to this treatment have been of high priority. US is well known to be a good tool for investigations of tendons. Grey-scale US has been shown to be a good and cost-effective method for examination of the Achilles tendon (Åström et al. 1996), and a high reliability to locate structural tendon abnormalities, such as tendinosis (Paavola et al. 1998). Grey scale
US alone has been used in most scientific studies evaluating Achilles tendon problems. During the last years, there has been a rapid development of the US techniques, with successively improved spatial resolution. Furthermore, Colour Doppler sonography is an established technique to study blood flow in main arteries and veins, and in tumours, Theodorou et al. (2003), Muller et al. (2001). Today it is possible to study blood flow, in vivo, in very small vessels. Altogether, these technical developments have increased the information about the pathology in the chronic painful Achilles tendon. In Paper I, grey-scale US was used to study tendon thickness and structure before and after treatment with eccentric calf-muscle training. The results showed that in the majority of the successfully treated patients the tendon thickness had decreased significantly, and the tendon structure looked “normalised”. Consequently, it seems that the eccentric training regimen has a potential to “normalise” the structural changes in the tendon, or at least is a part of a process leading to an US evaluated normalised tendon. In this study, due to practical reasons, the follow-up was performed 3-5 years after the 12 weeks eccentric training regimen. However, after 3 months of training the majority of patients were pain-free during Achilles tendon loading activity, indicating early effects on the pain mechanisms. In Paper I, we focused on patients with the combination chronic pain in the mid-portion of the Achilles tendon and corresponding structural tendon changes demonstrated with US. However, structural changes have also been demonstrated in the proximal part of pain-free patellar tendons (Khan et al. 1997, Cook et al. 2000a+b and 2001, Fredberg and Bolvig 2002). Furthermore, a spindle-shaped thickening in the mid-portion of the Achilles tendon has been shown not to correlate with tendon pain during activity (Fredberg and Bolvig 2002). It should be stressed that only thickness, not structural changes was, evaluated in that study. Fredberg and Bolvig (2002) followed a small group soccer players during one Danish soccer season, and found that only 5/11 of the tendons with a local thickening became symptomatic during the season. Also, in 4/11 of the asymptomatic tendons, the tendon thickness normalized during the season. Altogether, it seems that the findings of a spindle shaped thickening or
structural changes alone, not combined with pain during tendon loading activity, should be evaluated with caution and not render any specific treatment.

All our patients with chronic pain in the Achilles tendon are routinely examined with grey-scale US. Colour Doppler examination (CDV-technique), was in Paper II added to the grey-scale US. In consecutive patients referred for examination of chronic mid-portion Achilles tendon pain, we found a local neovascularisation inside, and outside the ventral part of the region with structural tendon changes in 28/28 tendons. In 20/20 pain-free tendons, there was a normal tendon structure and no local neovascularisation. There are only a few studies where CDV or CDE has been used to study tendons (Weinberg et al. 1998, Terslev et al. 2000, Richards et al. 2001, Khan et al. 2003, Peers et al. 2003, Zanetti et al. 2003). In the studies by Weinberg et al. (1998) and Terslev et al. (2000), US together with CDV or CDE, was used to study patellar tendinosis. Both studies showed structural tendon changes and neovessels in patients with jumper’s knee. Terslev (2000) showed that there was not always a positive correlation between pain symptoms and US findings. There were 4/14 asymptomatic patients with both structural changes and neovessels. Recently, CDV or CDE has been used to study chronic painful conditions in the Achilles tendon, and in a study by Peers et al. (2003), 22/25 of the chronic painful tendons with structural changes had a neovascularisation. Six patients with chronic painful Achilles tendons demonstrated a proliferation of vessels shown by power Doppler, and structural abnormalities demonstrated by both standard US and MRI (Richards et al. 2001). The findings in their studies, a neovascularisation in the tendons with structural changes and pain, are in line with the findings in our study. However, Khan et al. (2003) and Zanetti et al. (2003) did not find any correlation between the occurrence of neovascularisation and pain, in their studies on patients presenting with Achilles tendinopathy and Achillodynia. An explanation of the different results might be differences between the patient groups in the two studies. All patients in our study had structural tendon changes on US corresponding to a painful swelling localised in the mid-portion of the Achilles tendon, while only 37/57 tendons in the study by Khan et al. (2003), and 35/55 tendons in the study by Zanetti et al. (2003) had structural changes in the
tendons. To be included in our studies, it was not enough to have pain in the Achilles tendon (tendinopathy, Achillodynia), instead, there needed to be structural tendon changes on US corresponding to the painful region in the mid-portion of the tendon. It might be that the patients with “tendinopathy” and “Achillodynia” with normal US structure of the tendon had other diagnoses. Furthermore, in the study by Khan et al. (2003) MRI showed that in only 19/34 symptomatic tendons were there structural changes. This, again, raises the question about the diagnosis, since MRI is a very sensible method to show pathologic changes in tendons. Another important parameter to have in mind when evaluating studies using US and CDV/CDE is the influence of imaging technique. As an example, the position of the probe is very important since a wrong position of the probe might cause anisotropy, showing low echogenic regions, even when the tendon structure is normal. Another important factor is the importance of having relaxed calf muscles when the examination is performed, since a contraction of the muscles will reduce, or even stop the flow in the neovessels.

The findings in our study raised questions because most commonly neovascularisation has been considered to be a positive part of the healing response (Leadbetter et al. 1992, Ferrara 1999). On the other hand, these patients had had a long duration of pain symptoms, and if this neovascularisation was a part of the normal healing response it seems that it was not good enough to cure the pain. How can the neovascularisation be explained? It is likely that something in the region with structural tendon changes (tendinosis) is triggering vascular ingrowth. In a recent study by Pufe et al. (2001), hypoxia and growth factors were possible stimulators of neovascularisation in cultured rat tenocytes. Interestingly, Alfredson et al. (2002) have recently demonstrated high levels of lactate in Achilles tendons with chronic painful tendinosis, compared to normal pain-free Achilles tendons. Therefore, theoretically, hypoxia might potentially stimulate neovascularisation in chronic Achilles tendinosis. Also, the high concentrations of glutamate demonstrated in chronic painful Achilles tendinosis tendons (Alfredson et al. 1999), might possibly be a trigger for vascular ingrowth.
To evaluate the importance a local neovascularisation had for chronic pain in the Achilles tendon, in Paper VI, we combined the findings from US and CDV examinations, immunohistochemical analyses of biopsies, and the results of injections of a local anaesthetic. We found that if local anaesthetic was injected locally against the neovessels entering the structurally changed Achilles tendon, the patients were temporarily pain-free during heel raises. Furthermore, using the pan-neuronal marker PGP 9.5 immunohistochemistry on biopsies taken from the region with structural tendon changes, nerve structures were demonstrated in the vicinity of blood vessels. This was not an unexpected finding, as it is well known that nerves usually “travels with” blood vessels. From this study it was concluded that there is a vasculo-neural ingrowths in the structurally changed part of the tendon that possibly can explain the pain suffered from chronic painful mid-portion Achilles tendinosis tendons.

In Paper III the hypothesis that the region with neovessels (vessels + accompanying nerves) is responsible for the pain was evaluated by, US and CDV guided injection of the sclerosing substance Polidocanol to destroy the neovessels. The injections were given in very close relation to the neovessels in the region anterior of the ventral part of the tendon where the vessels entered the region with structural tendon changes. The immediate effect was a closure of the vessels entering the tendon. After the injection the patients were temporarily pain-free because of the anaesthetic effect of Polidocanol. The results at the 6-months follow-up showed that after a mean of 2 injections (treatments), the majority of the patients were satisfied and had no Achilles tendon pain during tendon loading activity. US and CDV examination showed that these patients had no remaining neovessels inside the region with structural tendon changes. In patients with remaining tendon pain during activity, remaining neovessels were seen. These results indicating that the neovessels and accompanying nerves have a crucial role in the pain mechanism. However, the follow-up was short, the group of patients was small, and there was no control group. Recently, a 2-year follow-up of these patients showed that the same 8 patients were still pain-free and satisfied, and had no neovessels. Furthermore, the tendon structure was normalised (non-published...
We have now treated more than 70 patients (1-5 injections/treatments with the sclerosing agent Polidocanol) with chronic painful mid-portion tendinosis, and about 80% of the patients are satisfied and pain free. Also, we have a present ongoing randomised blinded study evaluating the results of injections of a sclerosing or a non-sclerosing substance. So far only 1/70 patients have suffered from any complication possibly related to the sclerosing injections. It was a patient who sustained a total Achilles tendon rupture at the end of an 800 meter race, six weeks after his second injection. The rupture was localised in the proximal part of the tendon, not in the distal part were he had received the injections. Theoretically, if the treatment causes an impaired local vascularity in the tendon there might be an increased risk for tendon injury. However, the neovessels might not be a part of the normal circulation, but instead be considered as “pathological”. Furthermore, the injections are given outside the tendon, under US and CDV, and only a small region is injected. The trauma using sclerosing injections is minimal compared to surgical treatment, where excision of tendinosis tissue or multiple longitudinal incisions is performed. Follow ups are continuously performed on all treated patients. Furthermore, we routinely take biopsies from the tendinosis tissue and the tissue surrounding the tendon in patients who have had a poor result of injections and are treated surgically. Preliminary results of two cases (the only cases that have needed surgical treatment during the last two years) that each had received 5 injections of Polidocanol, showed minor atrophy in the fat tissue on the ventral side of the tendon.

By using grey-scale US and CDV, we found neovessels entering the tendon from the ventral side, also in patients with chronic pain in the Achilles tendon insertion. In some patients there were also vessels in relation to an enlarged and pathologically changed retrocalcaneal bursa. Treatment of this condition is known to be difficult, and often there are difficulties to decide if the treatment should be addressed to the tendon, bursae, bone, or all these tissues in combination. In a small non-controlled pilot-study (Paper IV), we tested the hypothesis that it was the region with neovascularisation in the insertional part of the Achilles tendon that was source of the pain. As described in Paper III, US and CDV guided injections
of the sclerosing agent Polidocanol were given towards the region with neovessels entering the ventral surface of the tendon. The results showed that sclerosing the region with neovessels outside the pathologically changed Achilles tendons, close to the bursal walls and bone (spurs, calcifications, fragment), allowed the majority of these patients to return to pain-free tendon loading activity. Absence of neovessels after treatment correlated well with reduced pain from the Achilles tendon insertion. In a few patients with tendon, bone, and bursal pathology in combination, there was remaining pain in the tendon insertion after treatment. These patients had remaining neovessels. In one patient with remaining pain after treatment, there were no remaining neovessels, but a loose bone fragment. Naturally, it is unlikely that this therapy would help patients with considerable bone pathology causing mechanical problems, such as large spurs or loose bone fragments. The results are interesting, but studies on larger groups of patients are needed to be able to draw any conclusions on what type of distal pathology this therapy might be best suited. Anyhow, the results again indicate that the region with neovessels is involved in the pain mechanism, and submits additional information of importance for decisions about treatment of this chronic condition. In Paper V, the primary aim was to use grey-scale US and CDV technique to study the occurrence of a neovascularisation before and after treatment with eccentric training, and to relate the findings to the clinical results of the treatment, in patients with chronic painful mid-portion Achilles tendinosis. For that study, observations in Paper II was of significant importance. During the US and colour Doppler examination, passive dorsiflexion in the ankle stopped the flow in the neovessels. This finding raised questions whether the good clinical effects demonstrated with painful eccentric training might be due to effects on the region with neovascularisation? In Paper V, the results showed that before treatment there was a local neovascularisation in the region with tendon changes in all tendons. At follow-up after treatment, there was a good clinical result (no tendon pain during activity) in 90% of the tendons, and a poor result in 10% of the tendons. In the majority of the tendons with a good result, there was no remaining neovascularisation, but in a few tendons a minor neovascularisation remained. In
all tendons with a poor result there was a remaining neovascularisation in the
tendon. Altogether, these findings again indicate that the region with
neovascularisation might be the source of pain in this condition. It is difficult to
explain exactly how the eccentric exercises may influence on the region with
neovessels, but a possible explanation might be the repeated occlusion of the
vessels during the heel-drop. The vessels travel from the soft fatty tissue anterior to
the Achilles tendon, into the hard tendinosis tissue, and there might possibly be a
“breaking point” between the soft and hard tissues. Theoretically, during the
“eccentric heel drop”, when the tendon is stretched, there might possibly be a
mechanical trauma to the neovessels and accompanying nerves. It is tempting to
believe that the severe local pain these patients experience in the region with
tendinosis during the period with eccentric training, especially during the first 2
weeks of treatment, might be due to interference with nerves accompanying the
neovessels.
Conclusion

Sonographic methods (grey-scale US and CDV) have provided important information about the chronic painful Achilles tendon, leading to a better understanding of the pain mechanism, as well as to a new treatment method. However, since the methods are sensible to investigator technique, it is fundamental to stress the importance of an experienced radiologist. The neovascularisation demonstrated by colour Doppler, found in close relation to the region with structural tendon changes that was demonstrated by grey-scale US, has been demonstrated to be a very likely source of pain in the chronic painful Achilles tendon. Treatment with US and CDV guided sclerosing injections of the region with neovascularisation has shown promising short-term clinical results.
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