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MAGNETIC RESONANCE IMAGING IN CHRONIC ACHILLES TENDINOPATHY

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*To
Ann-Christin and
our children
Donia, Nora and Adam*

ABSTRACT

The main objective of this thesis was to evaluate and monitor the morphological response following treatment interventions in patients with chronic Achilles tendinopathy by using different MRI-techniques. For this purpose, we investigated different types of sequences, including gadolinium contrast medium enhanced T1-WI images (CME T1-WI) and developed a precise method to measure tendon volume and mean intratendinous signal of the Achilles tendon.

Study I aimed at evaluating 15 patients with chronic painful Achilles tendinosis, before - and two years after - surgical treatment. There was marked regression of the intratendinous signal postoperatively. The most sensitive sequence for depicting an intratendinous lesion in this study was CME T1-WI images. They showed a regression of the intratendinous signal abnormality from 13/15 patients preoperatively to 4/15 postoperatively. The clinical outcome was excellent in 8, good in 5, fair in 1 and poor in 1 patient.

In **study II**, the early contrast agent enhancement in the dynamically enhanced MRI signal (DEMRI) was correlated to the histopathological findings in 15 patients with chronic Achilles tendinopathy. Early contrast enhancement (within the first 72 seconds) was seen in DEMRI in the symptomatic Achilles tendons with a significant difference compared to the asymptomatic contralateral tendons. Increased severity of tendon changes, including fiber structure abnormality, increased vascularity, rounding of nuclei and increased amount of glycosaminoglycans, correlated to CME.

In **study III**, we developed a computerized 3-D seed growing MRI-technique to measure tendon volume and mean intratendinous signal. This technique showed an excellent inter- and intra-observer reliability. The technique was also used to prospectively follow up the tendon adaptation and healing described in studies IV-VI.

In **study IV**, using serial MRI during a period of one year we evaluated the biological effect of tendon repair following iatrogenic tendon injury by five transversal ultrasound-guided core-biopsies employing a needle technique in chronic Achilles tendinopathy. Alterations found during healing, such as tendon volume and intratendinous reactive changes could be monitored by MR imaging, and subsided as noted in the seven and twelve months follow-up.

In **study V**, we evaluated the effect of treatment with three months daily-performed heavy loaded calf muscle strength training program in 25 patients who had been suffering from chronic painful Achilles tendinopathy. The tendon volume decreased with 14%, and the mean intratendinous signal with 23%. The clinical outcome was improved.

In **study VI**, we revealed tendon adaptation immediately following calf muscle strength training. An MRI examination within 30 minutes of the performed exercises resulted in increased total tendon volume (12%) and mean intratendinous signal (31%).

In conclusion, MRI-techniques can be used as an adjunct to clinical evaluation by monitoring morphological effects following different treatment interventions, thereby adding evidence in clinical studies on patients with chronic Achilles tendinopathy.

LIST OF PUBLICATIONS

This thesis is based upon the following six papers, which will be referred to by their roman numerals:

- I. **MRI evaluation of chronic Achilles tendinosis. A longitudinal study of 15 patients pre-and two years postoperatively.**
Shalabi A, Kristoffersen-Wiberg M, Aspelin P, Movin T
Acta Radiologica 42: 269-276, 2001.
- II. **Dynamic contrast-enhanced MR imaging and histopathology in chronic Achilles tendinosis. A longitudinal MR study of 15 patients.**
Shalabi A, Kristoffersen-Wiberg M, Aspelin P, Papadogiannakis N, Movin T
Acta Radiologica 43: 198-206, 2002.
- III. **Reliability in the assessment of tendon volume and mean intratendinous signal of the Achilles tendon on MRI. A methodological description.**
Shalabi A, Movin T, Kristoffersen-Wiberg M, Aspelin P, Svensson L
Submitted for publication.
- IV. **Tendon injury and repair following core-biopsies in chronic Achilles tendinosis evaluated by serial MR imaging.**
Shalabi A, Svensson L, Kristoffersen-Wiberg M, Aspelin P, Movin T
Accepted for publication in British Journal of Sports Medicine (BJSM), 2003.
- V. **Eccentric training of the gastrocnemius-soleus complex in chronic Achilles tendinopathy results in decreased tendon volume and intratendinous signal as evaluated by MRI.**
Shalabi A, Kristoffersen-Wiberg M, Svensson L, Aspelin P, Movin T
Accepted for publication in American Journal of Sports Medicine (AJSM), 2003.
- VI. **Immediate Achilles tendon adaptation following strength training of Gastrocnemius-soleus complex evaluated by MRI.**
Shalabi A, Kristoffersen-Wiberg M, Aspelin P, Movin T
Submitted for publication.

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LIST OF ABBREVIATIONS

AUC	Area Under Curve
CDV	Color Doppler Velocity
ECM	Extra-Cellular Matrix
FA	Flip Angle
FOV	Field of View
FSE	Fast Spin Echo
GAGs	Glycosaminoglycans
GE	Gradient Echo
Gd	Gadolinium
Gd CME	Gadolinium Contrast Medium Enhancement
MHz	Megahertz
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NMR	Nuclear Magnetic Resonance
PD	Proton Density
PGs	Proteoglycans
RF	Radio Frequency
ROI	Region of Interest
SE	Spin Echo
T	Tesla
TR	Repetition Time
TE	Echo Time
US	Ultrasonography

1 INTRODUCTION

1.1 HISTORY



Figure 1. The goddess Thetis dipped his son - Achilles – into the river Styx. Mother Thetis held Achilles by his foot and dipped his entire body, excepting the heel (illustrated by Peter Rubens (1577-1640) etching of Bernard Baron 1724).

The name Achilles tendon has a specific history. Achilles, a Greek hero, was the son of king Peleus and the goddess Thetis. Thetis wanted her son to become a hero, strong and invulnerable. She dipped him into the river Styx in Hades, so that he might become safe from all harm and invulnerable to weapons. Mother Thetis held Achilles by his foot (heel) and dipped his entire body, excepting the heel, which remained dry and unprotected and thus vulnerable (Figure 1). Achilles was wounded by an arrow shot by the Trojan prince Paris piercing his vulnerable heel, during the Trojan War (Figure 2). He died from his wound.

There is a second version of this history. According to Homer, Achilles killed the Trojan hero “Hector” in the Trojan War, pierced his heel tendons and dragged his corpse around the city walls after his chariot for twelve days (Grimal, 1986, Martinelli & Maffulli, 2000). Therefore, it was speculated that the name of the heel tendon should be “Hector tendon” instead of the medical name used today “Achilles tendon”.

From these legends, the anatomical medical terms “chorda Achilles or “tendo Achilles” were adopted during the 17th century (Couch, 1936).



Figure 2. Achilles was wounded by an arrow shot by the Trojan prince Paris piercing his vulnerable heel during the Trojan War.

The first report of an Achilles tendon rupture in the literature was written by Ambroise Paré “the father of surgery,” in 1575 (Malgaigne, 1840), and was followed by reports from the French surgeon Jean Louis Petit 1722 (Petit, 1724) and the Swede Olof af Acrel in Stockholm (1759). Reports of Achilles pain conditions, with suggestions of treatment, were first reported by Albert, in Vienna 1893, who described the retrocalcaneal bursitis (White, 1913). Patrik Haglund, the professor of orthopedic surgery at Karolinska Institutet, Stockholm described the treatment of achillo-bursitis and exostosis of tuber calcanei (1928) - a pain condition, now known as the “Haglund disease” or “Haglund’s deformity”.

1.2 BACKGROUND

The painful mid-portion Achilles tendon is among the most frequently injured tendons of the body, with a variety of types of traumatic and overuse conditions affecting it. The exact etiology of painful Achilles tendon disorders is still unknown and believed to be multifactorial. These conditions are common and are frequently imaged. The condition is frequently seen in athletes, but also in physically inactive individuals (Kvist, 1991, Åström & Rausing, 1995, Rolf & Movin, 1997).

The mechanism of pain in chronic Achilles tendon problems has not been scientifically clarified (Khan et al., 2000). The pathophysiology of Achilles tendon disorder is complex, and the nomenclature is irregularly applied. Although the pathological term “tendinosis” has been used for more than two decades to describe the collagen degeneration in the tendinopathy, many clinicians still use the term “tendinitis”, implying that the painful Achilles tendon condition is inflammatory (Puddu et al., 1976). Tendinosis is an intra-tendinous degeneration and histologically there is non-inflammatory intratendinous collagen degeneration with fibre disorientation and thinning, hypercellularity, scattered vascular ingrowth and increased amounts of interfibrillar glycosaminoglycans (GAGs) (Jozsa & Kannus, 1997, Khan & Maffulli, 1998, Åström & Rausing, 1997, Movin et al., 1997). The term “tendinopathy” is a generic descriptor of the clinical conditions in and around the tendons (Maffulli et al., 1998).

Pain condition in the mid-portion of the Achilles tendon “achillodynia” has been studied in a previous thesis, with the focus on the causes (pathohistology) of this painful common condition. Ljungqvist (1968) analyzed 24 patients with fusiform swelling located 2-10 cm proximal to the tendon insertion, after they were treated surgically. Kvist (1991) concluded that the paratenon was responsible for the symptoms, while the thesis on achillodynia by Åström (1997) found that the tendon itself could be the cause of the painful condition.

Movin (1998) studied 94 patients with long-standing pain and tenderness of the Achilles tendon, 1,5-7 cm proximal to the calcaneal insertion, with respect to etiology, pathoanatomy and evaluation of diagnostic methods. Koivunen (1995) studied 379 patients with normal Achilles tendons for evaluation of normal anatomy with respect to tendon thickness using ultrasound (US), Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS).

Fahlström (2001) investigated injuries in badminton players with particular focus on injuries and painful conditions in the Achilles tendon, and recommended treatment with eccentric calf-muscle training for patients with painful chronic Achilles tendinosis located at the 2-6 cm level in the tendon, excepting patients with distal Achilles tendon pain.

A recent thesis by Öhberg (2003) evaluated sonographic methods (grey-scale US and color Doppler velocity, CDV) in the investigation of chronic painful condition of the mid-portion of the Achilles tendon. He concluded that the neovascularization demonstrated by color Doppler was found in close relation to the region with structural tendon changes that was demonstrated by grey-scale US, and was very likely the source of pain in the chronically painful tendon.

The chronic tendinosis is commonly accompanied by poor healing of the tendon lesion, which may explain the long-lasting symptoms.

Achilles tendinosis is primarily treated non-operatively. This treatment may include anti-inflammatory drugs, physiotherapy and orthotic devices (Kvist, 1991). If the conservative treatment fails, surgical treatment is justified in chronic cases (Kvist & Kvist, 1980, Nelen et al., 1989, Rolf & Movin, 1997, Schepsis & Leach, 1987). The rationale for longitudinal internal splitting of the tendon during surgical treatment is to induce a healing response (Leadbetter et al., 1992). However, the postoperative healing process and its outcome in chronic Achilles tendinosis is poorly investigated.

To obtain rigorous scientific evidence for therapeutic interventions, empirical evidence has to be combined with a biological rationale. Many plausible hypotheses on treatment effects lack objective scientific evidence of effectiveness. Modern imaging techniques have the potential of non-invasively evaluating tendon matrix adaptation, thereby - beside clinical outcome studies - adding evidence to the suggested therapeutic methods.

The biological rationale in the treatment of chronic Achilles tendinosis is unclear. Empirical data give support to eccentric training and surgical treatment as useful methods (Alfredsson, 2003, Kader et al., 2002).

The proper evaluation of different treatment strategies, the ability to image the internal substance of the tendon, and the ensuing healing process requires an objective imaging modality. In clinical practice, US may be the first choice in chronic Achilles tendon disorders (Neuhold et al., 1992). However, in research, MRI is recommended, as the images can be evaluated more easily in a standardized manner (Movin, 1998).

MRI is the method of choice in all studies in this thesis. The importance and ability of MRI in monitoring and following up tendon healing have gained increasing interest. The healing process after surgically repaired Achilles tendon rupture has been recorded in MRI studies (Karjalainen et al., 1997). The development of repair scar tissue after harvesting the central third of the patellar tendon has also been studied using serial MRI investigations (Kartus et al., 2000).

- The aims of this thesis were to evaluate and monitor the morphological response following treatment interventions in patients with chronic Achilles tendinopathy by using different MRI-techniques.

2 THE NORMAL ACHILLES TENDON

2.1 ANATOMY

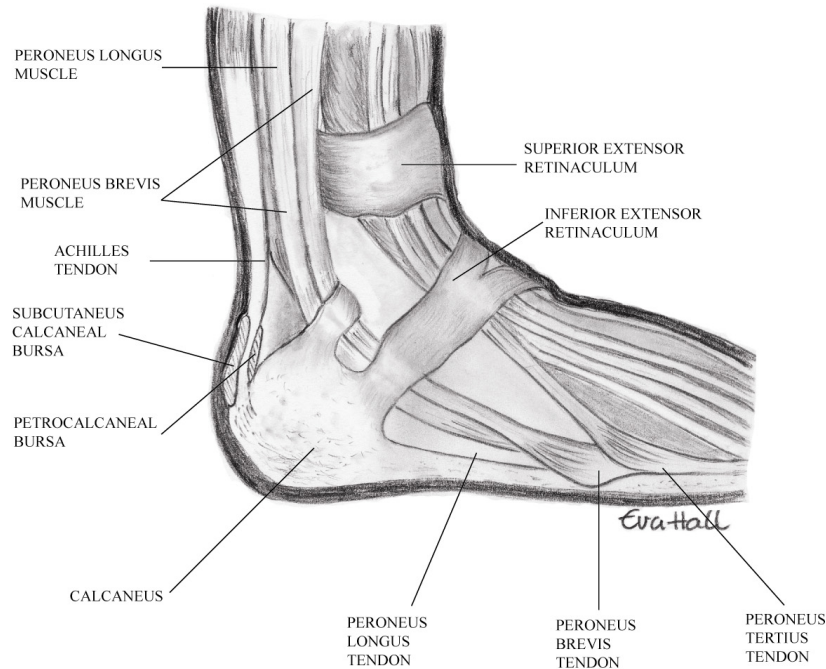


Figure 3. Schematic lateral view of the foot and ankle.

The Achilles tendon is the strongest, largest and thickest tendon in the human body, approximately 15 cm in length. The Achilles tendon originates in the mid region of the leg and is formed by the junction of the two heads of the gastrocnemius muscle and the soleus muscle (Soma et al., 1994). The bulk of the Achilles tendon is derived from the gastrocnemius muscle (Figures 3 and 4). The larger medial head originates almost entirely from an area just proximal to the medial femoral condyle, and the smaller lateral head arises from both the posterior and lateral surfaces of the lateral femoral condyle. At the junction of the proximal and mid calf, the two heads of the gastrocnemius muscles and their tendons approximate the midline. The origin of the gastrocnemius tendon is gradual, occurring over a length of approximately 3-4 cm. The fibres of the medial head originate slightly lower than

those of the lateral head. The Achilles tendon is not formed until the soleus muscle inserts in the gastrocnemius tendon, approximately 3-4 cm more distally (Soma et al., 1994).

The plantaris muscle originates from the lateral meniscus and the lateral femoral epicondyle in close association with the lateral head of the gastrocnemius muscle. The plantaris tendon then crosses obliquely between the soleus and gastrocnemius muscles and continues just medial to the Achilles tendon. Various plantaris insertions are seen, but most fibres insert on the medial aspect of the superior calcaneal tuberosity or 1 cm anterior and medial to the Achilles tendon on the calcaneus, a distinct insertion point separate from that of the Achilles tendon. The plantaris tendon is lacking in approximately 7% of all people (Cummins et al., 1946). The Achilles-plantaris complex is termed the “triceps-surae complex” (Salmons et al., 1995).

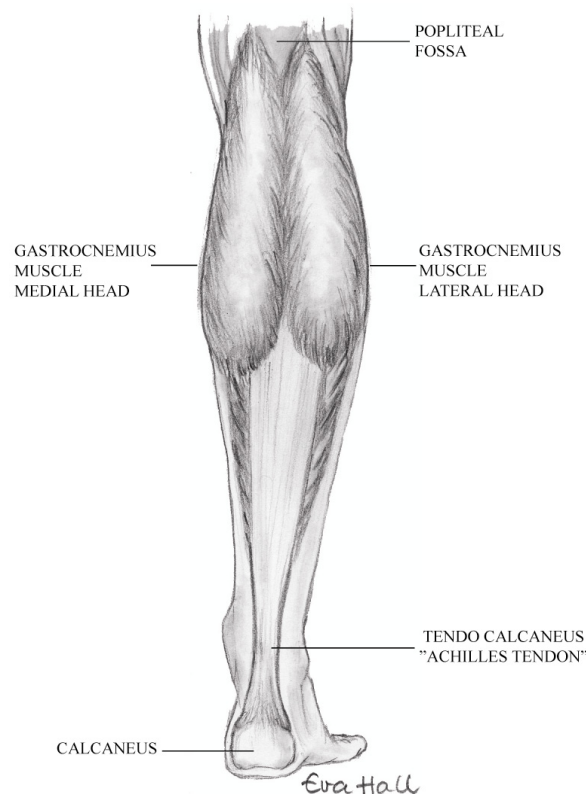


Figure 4. Schematic posterior image of the lower leg showing the gastrocnemius (medial and lateral heads) and soleus muscles forming the Achilles tendon.

The Achilles tendon lacks a synovial sheath. Instead it is surrounded by the paratenon, a multi-layered non-synovial tissue, which acts as an elastic sleeve allowing free movements of the tendinous structures (Lang, 1960).

The Achilles tendon is almost completely enclosed within a paratenon, which has both visceral and parietal layers (Salzman et al., 1994). The paratenon is analogous to a synovium in that it provides nutrition for the tendon; however, since the Achilles tendon does not change its axis of motion, there is no need for a lubrication function of the synovium.

Two layers of filmy fibrous tissue, with fine internal mesotendal blood vessels, make up the paratenon (Gould et al., 1980). The interwoven fibres of the paratenon allow it to stretch up to several centimetres in length during tendon movement and provide a certain degree of tendon gliding (Salzman et al., 1994). As the Achilles tendon descends, the fibres rotate laterally approximately 90°. Therefore, the gastrocnemius fibres insert laterally into the posterior calcaneus, whereas the soleus fibres insert medially (Root et al., 1977).

The insertion site of the Achilles tendon into the calcaneus is an enthesis and is intimately related to the only true anatomic bursa in the ankle, the retrocalcaneal bursa (Frey et al., 1982). The retrocalcaneal bursa is horseshoe shaped, filled with synovial fluid, and surrounded anteriorly by Kager's fat pad. The function of the retrocalcaneal bursa is to protect the distal Achilles tendon from frictional wear against the posterior part of the calcaneus (Reinherz et al., 1991).

2.2 FUNCTIONAL ANATOMY

The gastrocnemius, soleus and plantaris muscles act to flex the foot (Grumbine NA et al., 1990). The gastrocnemius muscle is also a knee flexor. The muscle is active in walking, jumping, and running, and for these purposes is composed predominantly of type II fibres (Fugl-Meyer et al., 1979). The soleus muscle has more of a stabilizing effect on the foot for standing and consists primarily of type I fibres (Garrett et al., 1984). Consequently, muscle fibre atrophy of the soleus occurs more rapidly than does that of the gastrocnemius muscle, making the soleus muscle a more sensitive indicator of atrophy resulting from complete tear or denervation (Booth et al., 1977).

2.3 BLOOD SUPPLY

The Achilles tendon receives its blood supply in three regions: at the musculotendinous junction, along its length and in the region of its insertion, and at the bone-tendon junction (Carr & Norris, 1989, O'Brien, 1997, Tuite et al., 1997), (Figure 5).

The blood supply in the musculotendinous junction arises from vessels in the muscles. Anteriorly, the tendon is attached to a richly vascularized tissue, where vessels can enter the tendon. These vessels, coming from the anterior surface of the paratenon, make up the majority of the blood supply to the mid-portion of the tendon and are considered to be the most important vessels to the tendon (Barfred, 1973). The lower third of the tendon receives its blood supply from vessels in the bone-tendon junction. The endotenon network carries blood vessels, nerves and lymphatics to the deeper portions of the tendon (Józsa & Kannus, 1997B). Mesotendal vascular anastomoses provide tendon nourishment. Findings are

controversial regarding the vascularity in the mid-portion of the Achilles tendon. The blood supply has been reported to be poor in the mid-portion of the tendon, at the 2-7 cm level proximal to the tendon insertion, which also is the part of tendon most prone to rupture (Lagergren et al., 1959, Hastad et al., 1959, Carr & Norris, 1989). However, recent studies have lead to contradictory results. Åström et al. (2000) studied the blood flow *in vivo* in the human Achilles tendon by Laser Doppler flowmetry and found that - besides a lower perfusion at the calcaneal insertion - there was an even distribution of blood flow in the tendon. Kannus & Józsa (1991) found that blood flow in the Achilles tendon decreases after the third decade of life. A recent study confirmed that peritendinous blood flow at rest was lower in older subjects than in younger and middle-aged subjects. However, there was an increased peritendinous blood flow during exercise, independent of age (Langberg et al., 2001).

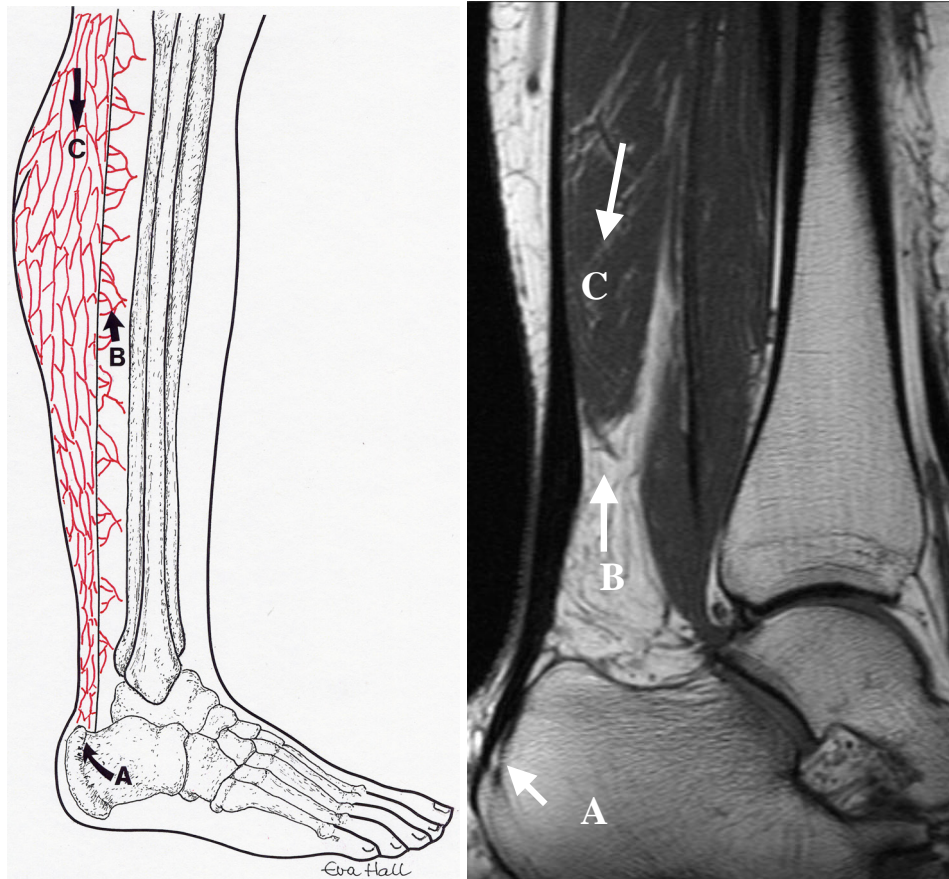


Figure 5. Schematic image of the lower leg (left) and T1-WI MR-image (right) illustrating that the Achilles tendon receives its blood supply in three regions: at the bone-tendon junction (A), along its length and in the region of its insertion (B), and at the musculotendinous junction (C).

2.4 NERVE SUPPLY

The Achilles tendon is innervated by nerves of the attaching muscles and by small fascicels from cutaneous nerves, in particular the sural nerve (Stilwell, 1957).

Inside the tendon, nerves follow the vascular channels that run longitudinally along the tendon. The numbers of both nerve fibres and nerve endings are relatively low in large tendons, such as the Achilles tendon, and many nerve fibres terminate in the sensory nerve endings on the tendon surface or in the paratenon (Figure 6). The major nerve fascicles contain myelinated or un-myelinated afferent axons and terminate in fine afferent nerve endings (Józsa & Kannus, 1997).

There are four types of receptors inside the tendon: The pressure and stretching sensors (Ruffini corpuscles), pressure sensors which adjust the movement (Vater-Pacini corpuscles), tension receptors (Golgi tendon organs) and the free nerve endings or pain receptors (Józsa & Kannus, 1997b, O'Brien, 1997).

Glutamate is a well-known and potent modulator of pain in the human central nervous system, but its function in the peripheral nervous system is unknown (Dickenson et al., 1997). However, neurotransmitter glutamate has been found in human Achilles tendons by using microdialysis technique (Alfredson et al., 1999). Further, the glutamate NMDAR1-receptors were found in close relation to nerve structures in tendinosis (Alfredsson et al., 2001).

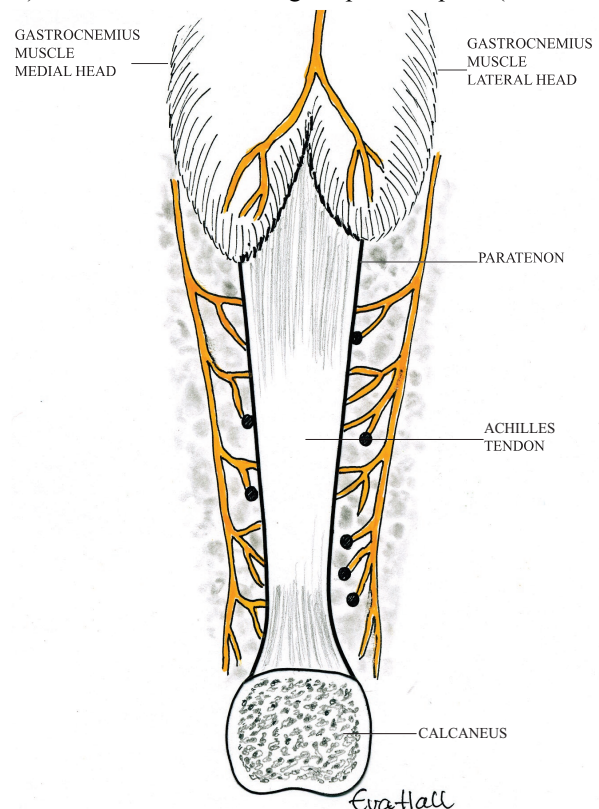


Figure 6. Nerve supply of the Achilles tendon.

2.5 BIOMECHANICS

The Achilles tendon has higher maximum rupture force and stiffness with a larger cross sectional area in men than in women (Józsa et al., 1997), while tendons in younger individuals have significantly higher tensile rupture stress and lower stiffness (Thermann et al., 1995).

The mechanical properties of the tendons have been studied by *in vitro* tensile tests. At rest, tendon fibres and collagen fibres have a wavy pattern, which disappears when under slight stress when the tendon is stretched by about 2%, corresponding to straightening of the fibres in the toe region of the stress-strain curve (Józsa & Kannus, 1997b). With less than about 4% elongations, the tendon can return to its original length when the tensile force is released, and the tendon resumes its normal wavy pattern. However, if the strain exceeds approximately 4%, the tendon fibres are damaged, and at strain level approximately 8% the tendon ruptures (Józsa & Kannus, 1997b).

In vivo, the tendon forces have been demonstrated to be very individual and values are well above the range of the single load of ultimate tensile strength, demonstrating the limited value of *in vitro* tests for *in vivo* situations (Józsa & Kannus, 1997). The load imposed on the Achilles tendon was measured using a “buckle”-type of transducer implanted in the Achilles tendon under local anesthesia. Forces reached up to 9 KN during running, corresponding to 12.5 times the body weight, 2.6 KN during slow walking, and less than 1 KN during cycling (Komi et al., 1987, 1990 and 1992).

Elastic behavior of the human tendomuscular system during jumping was investigated by determination of the *in vivo* Achilles tendon force. A buckle-type transducer was implanted, under local anesthesia, around the right Achilles tendon of an adult subject. The changes in tendon length were estimated assuming a stiffness constant calculated from the tendon architecture. The percentages of elastic energy stored in the Achilles tendon during jumping were 23%, 17% and 34% of the total calf muscle work in the squat jump, the counter movement jump, and hopping, respectively (Fukashiro et al., 1995).

2.6 METABOLISM

The normal Achilles tendon has enzyme chains for the three pathways of energy metabolism, the aerobic Krebs cycle, the anaerobic glycolysis, and the pentose phosphate shunt (Hess et al., 1989, Józsa & Kannus, 1997). The metabolic pathways for production of energy change from an aerobic cycle in younger persons to anaerobic glycolysis in older age. The metabolic rate is low in the tendon, allowing it to tolerate low oxygen conditions, e.g. longstanding increased tension, without risking ischemia or necrosis. However, the disadvantage of low metabolic rate is the slow rate of recovery, e.g. the healing process after tendon injury.

2.7 TENDON ULTRASTRUCTURE

The tendon is a connective tissue structure composed of few, scattered cells, closely packed collagen fibres and a non-collagenous extracellular matrix of proteoglycans and glycoproteins (ECM). The collagen fibres are as long as the tendon; where they anastomose with each other, they do so at acute angles. The cell responsible for the elaboration of the collagen and the ECM, as well as maintenance of the integrity of the tendon, is the “tenocyte” or “tenoblast” (Hall, 1965).

2.7.1 Cells

The tendon contains relatively few cells. Tendon fibrocytes (or tenocytes) have longitudinally oriented, thin, flat nuclei, and a cytoplasm with a well-developed rough endoplasmic reticulum, intertwined between the collagen fibres. These cells constitute 90 – 95% of the cellular mass, the remaining 5 – 10% being chondrocytes located at the tendon insertion, synovial cells at the tendon surface and vascular cells. The synovial tenocytes have a well-developed capability of repairing a tendon injury, while the internal tenocytes appear to have a less efficient capability of repair (O’Brien, 1997).

2.7.2 Collagen

In human tendons, approximately 30% of the total mass of the tendon is dry mass, of which 65 – 75% is collagen type I and 2% is elastin, embedded in an extracellular proteoglycan matrix (Józsa & Kannus, 1997b). Collagen is responsible for the structural integrity and for resisting the tensile force applied to the tendon (Kvist, 1994, Józsa & Kannus, 1997b, O’Brien 1997, Tuite et al., 1997). The function of elastin is not entirely clear, but it may contribute to the recovery of the wavy configuration of the collagen fibres after stretching of the tendon (Józsa & Kannus, 1997b).

The tendon consists of densely packed fibres of collagen that extend over its entire length, and are arranged parallel to its long axis. Amino acids join to form an ***α-chain*** with a left-handed helix of the collagen molecule. The α -chains are surrounded by a thin layer of matrix (proteoglycans and glycosaminoglycans, GAGs). Three α -chains form the right-handed helix of the collagen molecule. The collagen molecules link to form a triple-helical polypeptide chain, called “tropocollagen molecules” or “***microfibrils***” (Józsa & Kannus, 1997b, Kickendall & Garrett, 1997, O’Brien, 1997, Tuite et al., 1997, Kannus, 2000). The microfibrils are stabilized and held together by electrostatically bonded chemical cross-linking. Cross-links are important for the tensile strength of collagen, to allow for increased energy absorption and increased resistance to proteases. The microfibrils aggregate progressively in units to form ***collagen fibrils***. The collagen fibrils are not straight, but rather “wavy”, in the rested, non strained state and are oriented longitudinally as well as horizontally, crossing each other and forming a spiral providing a good buffer capacity against forces during movement. A branch of collagen fibrils forms a collagen fibre, which is

the basic element of a tendon. The endotenon, which is a fine sheath of connective tissue, invests each collagen fibre and binding the fibres together. The collagen fibres are grouped together in “*primary bundles*” or “*subfascicles*” which in turn are assembled into larger “*secondary bundles*” or “*fascicles*” (Józsa & Kannus, 1997b, Kickendall & Garrett, 1997, O’Brien, 1997, Tuite et al., 1997, Kannus, 2000). The secondary bundles further form “*tertiary bundles*” (Schneider, 1959) which together comprise *the tendon* (Figure 7).

The tendon bundles are surrounded by a woven meshwork of loose connective tissue, “the peritenoneum internum” or “endotenon”. This tissue holds the bundles together, permitting some movement of bundles in relationship to each other and carrying all the blood vessels, lymphatics and nerves. It has elastic fibres (Hirai, 1959), which tend to draw the tendon bundles into a wavy structure when relaxed. At the musculotendinous junction, there is an intimate relationship between the sarcomeres and the collagenous fibril bundles, although there is no direct continuity (Boyd, 1960). Each group of muscle fibres enclosed in the perimysium continues as a secondary bundle (or fascicle) and the perimysium continues with the endotenon (Edwards, 1946).

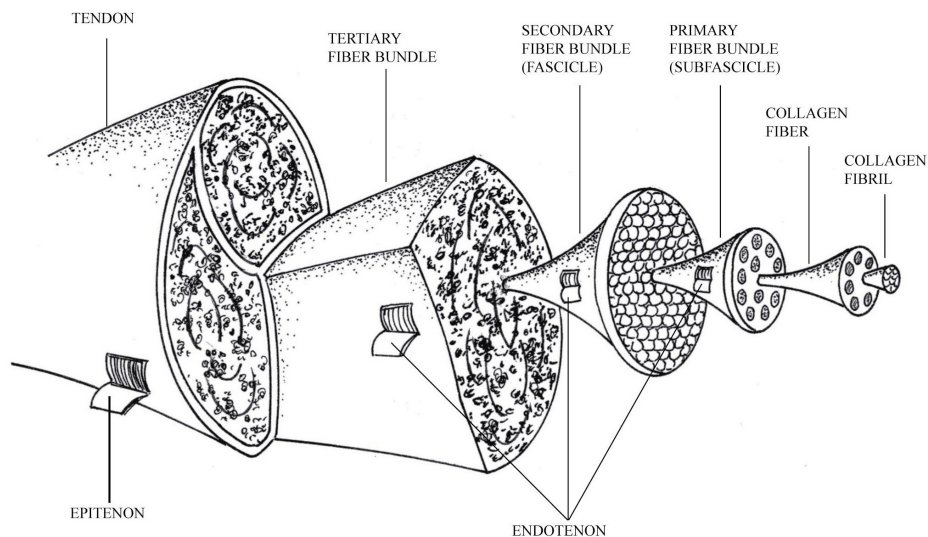


Figure 7. Schematic image of the tendon ultrastructures.

The whole tendon is surrounded by a fine connective tissue sheath, “the peritenoneum externum” or “epitenon”, which is continuous with the endotenon along its inner surface. Surrounding the tendon is a loose, fatty, areolar tissue, “the paratenon”. Its mechanical function is to allow the tendon to glide freely against the surrounding tissue (Tuite et al., 1997). The paratenon together with the epitenon is called “the peritendon” (Józsa & Kannus, 1997b).

2.7.3 Proteoglycans

Proteoglycans (PGs) are macromolecules composed of a protein core at which at least one glycosaminoglycan (GAG)-chain is covalently attached via the end. PGs may occur intercellularly, at the cell surface, or in the extracellular matrix (ECM). There are two major PGs in the ECM, the large aggregating PGs and the small intestinal PGs. The large aggregating PGs contain aggrecan and versican, providing mechanical support and regulating cell migration and aggregation. The small intestinal PGs include decorin, biglycan and fibromodulin, which modulate or inhibit collagen fibrillogenesis and regulate cell growth (Kjellén & Lindahl, 1991).

The GAGs consist of a disaccharide repeat of hexosamine and either a hexuronic acid or a galactose residue. The GAGs are highly negatively charged, making the PGs strongly hydrophilic and attracting osmotically active cations, forcing water into the matrix, and also enabling a rapid diffusion of water-soluble molecules into and out of the cells. The amount and composition of the PGs within the tendon differ between regions exposed only to tensional forces and those under both tensional and compressive forces. The tensional segment contains small intestinal PGs, up to 90% of the total PGs, including dermatan sulphate, and the remaining 10% are large PGs rich in chondroitin sulphate (Vogel & Heinegård, 1985).

3 PAINFUL ACHILLES TENDON DISORDERS

3.1 NOMENCLATURE AND PATHOLOGY

The etiology of painful Achilles tendon disorders is multifactorial. The symptoms are frequently seen in runners (Kvist, 1991, Rolf & Movin, 1997), but are also seen in non-athletes (Åström & Rausing, 1995, Rolf & Movin, 1997). The nomenclature used in the literature to describe chronic tendon disorders is confusing. The terms tendinitis, tendonitis, tendinopathy, tenopathy, tendinosis, paratenonitis, tenosynovitis, tendovaginitis, and peritendinitis are used to describe the clinical entities (Åström & Rausing, 1995, Järvinen, 1997). The classification by Puddu includes paratenonitis, paratenonitis with tendinosis, tendinosis and tendonitis (Puddu et al., 1976). The authors suggested an inflammatory response within or around the tendon as being responsible for experienced pain. However, the histopathological examination of the paratenon in chronic Achilles tendon disorders shows no or only slight inflammatory reaction (Kvist, 1987, Åström & Rausing, 1995) and the tendon tissue contains no inflammatory cell infiltrates in chronic cases (Åström & Rausing, 1995, Movin et al., 1997). In the histopathological survey of surgically treated patients, by Åström and Rausing, histology was considered abnormal in one-third of the evaluated paratendinous biopsies, compared to 144 out of 155 tendon biopsies. These findings suggest that inflammation, defined as an inflammatory cell infiltration, is not responsible for the symptoms (Åström & Rausing, 1995). The tendon changes in chronic Achilles disorder are characterized by an altered fiber structure, tenocyte nuclear reactions, neovascularity and increased non-collagenous matrix (Åström & Rausing, 1995, Movin et al., 1997). Therefore, the use of the term “tendinitis” has been criticized. Chronic Achilles tendinopathy or tendinosis has become widely accepted in the recent literature on the subject, considering degenerative changes seen in the tendon tissue (Khan et al., 1996, Teitz et al., 1997).

There are two theories about the cause of the rupture of the Achilles tendon, the “vascular” and the “mechanical”. The vascular theory implies impaired vascular supply and blood flow due to ageing, disease processes, or trauma, which may lead to chronic degeneration of the tendon, and occurrence of tendon rupture with or without minimal excessive loads being applied. The tendon rupture according to this theory is the clinical “end-stage” of a degenerative process in the tendon tissue. The mechanical theory, on the other hand, suggests that the rupture is the result of acute over-loading of a normal tendon (Järvinen, 1997).

The majority of Achilles tendon ruptures occur in individuals over 25 years of age in situations where a relatively sedentary individual renews an active athletic lifestyle. In these instances, where the tendon fails, histological studies have confirmed pre-existing degenerative changes within the tendon tissue (Kannus & Józsa, 1991).

3.2 CLINICAL ASSESSMENT

The clinical assessment should be performed by a proper collection of patient history and a clinical physical examination. The patient history should include the onset of symptoms, level of physical activity, type of footwear and previous treatment. Negative tiptoe and calf squeeze tests rule out neglected total Achilles tendon ruptures. The localization of tenderness and involvement of tendon tissue form the basis for a clinical classification of painful conditions in the Achilles tendon: the muscle-tendon junction (proximal), the mid-portion and the tendon insertion (distal) (Movin et al., 1998). By imaging, the clinical classification can further be divided into the involvement of the tendon tissue proper (Movin et al., 1998) and reveal if the tendon is enlarged or has an intratendinous lesion (Archambault et al., 1998).

3.2.1 Proximal pain at the muscle-tendon junction

Proximal pain at the muscle-tendon junction has been reported to be relatively uncommon (Williams, 1986), although it is considered to be the weakest point in the muscle-tendon and therefore susceptible to strain injuries (Józsa & Kannus, 1997b). The injury often occurs during running or jumping. Many conditions should be considered in the differential diagnosis, such as deep venous thrombosis, ruptured Baker cyst and muscle rupture or hematoma in the calf muscle.

3.2.2 Mid-portion pain condition

The mid-portion of the Achilles tendon is the most common part afflicted by the chronic pain condition (Figure 8). Excessive load with repetitive micro trauma has been regarded as the major causal factor; however, sedentary and elderly persons also present with Achilles tendon problems (Åström and Rausing, 1995, Rolf and Movin, 1997, Fahlström et al. 2003). Overuse injuries involving the Achilles tendon are common, especially among runners. The majority of these injuries occur in middle-aged male athletes (Clement et al., 1981, James et al., 1978). Common etiologic features, other than overstraining, include overpronation, poor gastrocnemius-soleus flexibility and strain, and improper footwear (Alfredson et al., 2002).

3.2.3 Distal pain at the tendon insertion

Distal pain at the tendon insertion has also been termed insertitis, inthesitis, insertion tendinopathy or tendonitis, tendo-periostitis and retrocalcaneal bursitis. This condition is relatively common in sports. In a study by Kvist (1991) during the period 1976-1986, 23% of their study group had insertional pain, of which 61% was described as insertiotendinitis, 21% had retrocalcaneal bursitis, and 18% had both conditions. There are two types of bursitis: retrocalcaneal - in the deep bursa between the bone and the tendon - and superficial in the bursa between the skin and the tendon (Järvinen et al., 1997). The superficial type is more often due to oversized or tight shoes and particularly to high heels (Hoppenfeld, 1976).

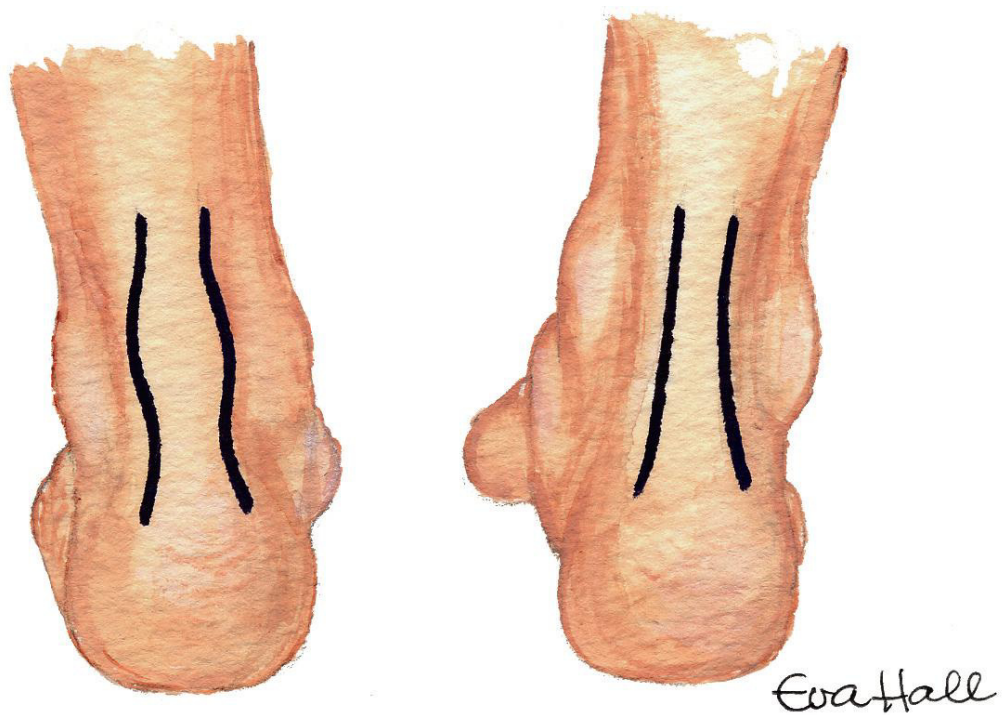


Figure 8. Schematic image of the feet showing the focal thickening of the mid-portion of the left Achilles tendon, at 2-7 cm level – a typical finding in chronic Achilles tendinosis. The right Achilles tendon is normal.

3.3 TREATMENT OF CHRONIC ACHILLES TENDINOSIS

Achilles tendinosis is primarily treated non-operatively with anti-inflammatory drugs, physiotherapy and orthotic devices (Kvist & Kvist, 1980). Most authors recommend a conservative treatment regimen as the initial strategy (James et al., 1978, Welsh & Clodman, 1980, Clement et al., 1984, Williams, 1986, Brody, 1987, Nelen et al., 1989, Kvist, 1991, Schepesis et al., 1994, Alfredson et al., 1998b). However, if the conservative treatment fails, surgical treatment is justified in chronic cases (Kvist, 1991, Nelen, 1989, Rolf and Movin, 1997). The rationale for longitudinal internal splitting of the tendon during surgical treatment is to induce a healing response (Leadbetter, 1992). However, the postoperative healing process in chronic Achilles tendinosis has so far been poorly documented.

3.3.1 Conservative treatment

The initial conservative treatment often consists of a combination of correction of presumed etiological factors - such as training errors, muscle weakness, poor flexibility and poor equipment - and a symptomatic regime using non-steroidal anti-inflammatory drugs, such as NSAIDs. The correction of biomechanical divergences has been considered one of the most important factors in the treatment of chronic Achilles tendon injuries (Kvist, 1994, Sandmerier & Renström, 1997). However, the scientific evidence for this statement is poor. The biomechanical divergences were not important in chronic Achilles tendinopathy (Åström, 1997). The effect of non-steroidal anti-inflammatory drugs in the treatment of chronic Achilles tendinosis is controversial, as the histopathological findings showed absence of inflammatory cells; consequently, the use of anti-inflammatory agents cannot be scientifically justified. A randomized study of anti-inflammatory drugs (Piroxicam) in the treatment of chronic Achilles tendinopathy showed no clinical effects (Åström & Weslin, 1992). Furthermore, Almekinder (1995) claims that NSAIDs may have potentially negative effects during the proliferative stage of healing, since the medication is associated with decreased DNA synthesis in tendon fibroblasts *in vitro*. A study by Alfredson (1999), using a microdialysis technique, demonstrated normal prostaglandin E2-levels and no signs of chemical inflammation in the painful Achilles tendon.

Other conservative medications include anticoagulation with intravenous injection of heparin - recommended in acute peritendinitis crepitation (Allenmark, 1992). Corticosteroid injection is not recommended because of the lack of proven efficacy, as well as concerns about the deleterious effects on the integrity of the tendon (Saltzman & Tearse, 1998).

3.3.2 Physiotherapy by “eccentric calf muscle training”

Different methods of physiotherapy, including stretching and strength training regimens have been suggested. Recently, heavy loaded eccentric calf muscle strength training has been popularized, providing a model shown to result in recovery of symptoms; it has been

recommended as a treatment alternative prior to surgical intervention (Stanish et al. 1986, Alfredson, 1996). Good clinical results (short- and midterm) have been reported following painful heavy-load eccentric calf muscle training in patients with chronic painful Achilles tendinosis at the 2-6 cm level in the tendon (Alfredson et al., 1998). Furthermore, the results were reproduced by Mafi (2001) in a randomized prospective study showing a significantly better result with painful heavy-load eccentric calf muscle training than with painful concentric training; the majority of the patients (82%) could return to previous loading activity without need for surgical treatment.

3.3.3 Surgical treatment

Nonsurgical treatment is not always successful and surgery may be required in about 25% of the Achilles tendinopathy patients (Kvist M, 1994). Surgical treatment is recommended after conservative methods of treatment have been exhausted, often tried for at least six months. However, long standing Achilles tendinopathy is associated with poor results of surgery; with a high rate of re-operation before reaching a satisfactory outcome (Maffulli et al., 1999).

The surgical intervention includes excision of fibrotic adhesions, removal of degenerated nodules, and the making of multiple longitudinal incisions in the tendon to detect intratendinous lesions, restore vascularity, and stimulate the remaining viable cells to initiate cell matrix response and healing (Rolf and Movin, 1997, Åström, 1997). The main surgical procedures are: open tenotomy with excision of abnormal tissue (no stripping of the paratenon), open tenotomy, with removal of abnormal tissue and stripping of the paratenon; open tenotomy with longitudinal tenotomy with or without paratenon stripping and percutaneous longitudinal tenotomy (Rolf and Movin, 1997, Nelen, 1989, Schepisis and Leach, 1987). Other surgical techniques include flexor hallucis transfers (Wilcox et al., 2000, Den Hartog, 2003).

3.3.4 Intervention treatment

Multiple percutaneous longitudinal tenotomies have been used in patients with isolated and well-defined nodular lesions (less than 2.5 cm long) after confirming the precise location of the lesion by US scanning (Maffulli et al., 1997, Testa et al., 1996). This procedure is simple and can be performed under local anesthesia, the patients being mobilized as soon as possible. Maffulli et al., 1997, reported that 77% (37/48 patients) showed excellent to good outcome at 1.5-5 years follow-up. More recently, US-guided percutaneous longitudinal tenotomy has been used in patients with a single and well-defined intratendinous lesion lacking paratenon involvement - with a relatively high rate of success (Testa et al., 2002). Further, US-guided sclerosing injections of neovessels in painful Achilles tendinosis have been tried in as a pilot study of new treatment methods (Öhberg and Alfredson, 2002). This treatment procedure showed promising short-term clinical results.

4 IMAGING MODALITIES

The Achilles tendon and the surrounding structures can be imaged using several imaging techniques. Conventional X-rays, Xeroradiography, Computed Tomography (CT), Ultrasonography (US) and Magnetic Resonance Imaging (MRI) have been used as diagnostic tools in Achilles tendon disorders. However, US and/or MRI are regarded as methods of choice in the diagnosis of changes in the Achilles tendon. US is inexpensive, non-invasive and harmless, but requires a meticulously performed examination. Potential advantages of MRI include multiplanar imaging, sensitivity in discriminating neighbouring normal from affected structures, and the ability to image the internal substance of the tendon and the ensuing healing process. MRI is the method of choice used in all studies in this thesis and will therefore be presented in detail.

4.1 CONVENTIONAL X-RAYS

Tissue contrast in the plain X-ray film radiographs and in other methods using X-rays is based on differences in the average electron density of the tissue. The first radiological diagnosis of Achilles tendon rupture, according to the literature, was reported already in 1914. Kager, (1939) described the loss of regularity of the hypodense fat triangle between the Achilles tendon, the dorsal calcaneal surface and the deep calf muscles in connection with Achilles tendon rupture.

Blomquist, (1961) described the X-ray appearance of Achilles tendons in cases of essential hypercholesterolemia as characterized by features of small, medium sized, large and calcified xanthomas. Blankenhorn and Meyers, (1969) standardized the position of the foot in the soft tissue X-ray technique for the diagnosis of Achilles tendon xanthomas. When radiological conditions are right, both anterior and posterior borders of the tendon are sharply outlined on the plain film and the point of maximal thickening of the tendon can be measured.

4.2 XERORADIOGRAPHY

Xeroradiography is a technique using photoconductors, electrostatic charges and xerographic type processing as methods of recording X-ray images. This technique has a better X-ray contrast acceptance capability than conventional X-rays films (Wolfe, 1973). It delineates soft tissue contours by edge effect, which was not possible with the earlier soft tissue radiological techniques. The border between the fibrous tissues of the tendon is distinctly visualized, and the measurements of the anterior-posterior diameter of the Achilles tendon become more exact (Seidl et al., 1983).

4.3 COMPUTED TOMOGRAPHY (CT)

CT offers excellent contrast resolution and density (attenuation) measurements of soft tissues. CT produces transaxial images of the tendon, and the muscle-tendon junction is easily identifiable (Michael and Holder, 1985).

4.4 ULTRASONOGRAPHY (US)

US is defined as sound having a frequency greater than what is audible by humans. Thus, any sound having a frequency greater than 16-20 kilohertz falls into the category of US. In medicine, most commonly used frequencies range from 1 to 15 megahertz (MHz) (McDicken, 1981). US examination of tendons requires high spatial and contrast resolution, achieved through a high frequency (5-15 MHz) providing the best combinations of field of view, resolution and depth of field with electronic focusing of the sound beam (Van Holsbeeck and Introcaso, 1991). US examination techniques became widely accepted for assessment of musculoskeletal diseases in the beginning of the 1980's (Moss and Mowal, 1983, Laine, 1984). There was a continuous development of US equipments and transducers to increase the spatial resolution for both superficial and deep structures. These developments made the US technique sensitive for different diagnostic procedures. Now it is possible to examine tendons, ligaments and muscle fibres with good reliability (Van Holsbeeck & Introcaso, 2001). The resolution of the image in US is dependent of the distance from the probe to the examined target. The US transducer is also of great importance in diagnostic examinations, and the resolution in musculoskeletal US increases with higher frequency of the transducer. For optimal musculoskeletal examinations, a transducer with a frequency of 5-15 MHz is required. Since most tendons are superficial, linear transducers are preferable due to the high resolution in a short distance from the transducer. Linear transducers provide optimal images, having their sound beam perpendicular to the tendon (Van Holsbeeck & Introcaso, 2001). The US also provides the study of blood flow using the color Doppler technique or color Doppler velocity (CDV), allowing visualization of the velocity and direction of blood flow.

Recently, Öhberg (2003) studied patients with chronic painful conditions of the mid-portion of the Achilles tendon by using grey-scale US and CDV and found that neovascularization could be demonstrated by color Doppler; he used US and CDV for guided sclerosing injections of the region with the aim of inducing neovascularization for treatment of patients with chronic Achilles tendinopathy.

4.5 MAGNETIC RESONANCE IMAGING (MRI)

4.5.1 How it all began

The interaction of nucleic magnetic moments (spins) with radiofrequency radiation in the presence of a strong magnetic field was demonstrated for the first time in the 1940's (Bloch et al., 1946, Purcell et al., 1946) and developed into a powerful research tool in chemistry and physics. Bloch and Purcell started the use of Nuclear Magnetic Resonance (NMR) in spectroscopy of chemical compounds during the 1950's and 1960's and they were awarded the Nobel Prize for physics in 1952. The so called Larmor relationship, which means that the angular frequency of precession of the nuclear spins is proportional to the strength of the magnetic field, was demonstrated earlier by Sir Joseph Larmor (Irish physicist, 1857-1942).

In 1970-71, Raymond Damadian demonstrated that T1 and T2 relaxation times (tissue parameters) could be measured *in vitro* by NMR, differing between pathological and normal tissues (Damadian, 1971). In 1974, a chemist, Dr. Ernst R.R., described the application of fourier transformation, a method of processing that converts the raw data that form the MR images into viewable and understandable images. Dr. Ernst was awarded the Nobel Prize for his contributions to the development in this field in 1991.

In the early 1970's Paul Lauterbur discovered the possibility of creating a two-dimensional image by introducing gradients in the magnetic field. By analysis of the characteristics of the emitted radio waves, he was able to determine their origin. This made possible the buildup of images of structures that could not be visualized with other methods.

Peter Mansfield discovered further possibilities to utilize gradients in the magnetic field. He showed how the radio signals could be mathematically analyzed, which made possible the development of a useful imaging technique. Mansfield also showed how images could be achieved extremely fast using magnetic resonance. This became technically possible in clinical medicine about a decade later.

Professor Paul C. Lauterbur and Professor Emeritus Sir Peter Mansfield were awarded the Nobel Prize in Medicine for their work, in 2003.

Today commercially available MR equipments offer spectroscopy packages where the detecting voxel can be localized with the aid of MR images to obtain spectra from the tissues of interest. The Magnetic Resonance Spectroscopy (MRS) technique provides tools for metabolic studies and chemical analysis of living systems. NMR spectra analyzed biochemically *in vitro* previously, can now be measured *in vivo*, and the chemical nature of tissues can be analyzed non-invasively.

4.5.2 The Basics

The "radiation" used in MRI is quite different from X-rays. It lies in the FM range (conventional radio- and TV-frequencies), is nine orders of magnitude smaller than the frequencies corresponding to X-rays and is considered biologically safe.

An atom of one element differs from an atom of another element in its internal structure. The human body hydrogen constitutes about 80% of all atoms in the body. Different nuclear compositions and numbers of surrounding electrons are reflected in different physical properties. The magnetic properties of the hydrogen nucleus - the proton - which is the basis of the magnetic resonance phenomenon are not easily perceived. Although these properties are not easily visualized, they are well defined and obey certain rules. With the use of radio waves, the magnetic properties permit the production of images of the human body that can furnish information about morphology and function of the human organism.

When placed in a strong magnetic field, all protons in the body are aligned to the field. Slightly more than 50% of them are aligned along the magnetic field and the remaining protons have an opposite direction. This small net magnetization allows measuring the net magnetic vector, making possible the acquisition of MR images. Radio frequency (RF) pulses together with different magnetic gradients are needed to produce images. The initial RF-pulse in the MRI sequence is the “excitation”. The net magnetic vector changes its original direction or “deflection”, when exposed to the RF-pulse. After excitation, when the RF-pulse is switched off, the magnetic vector returns to its original direction. This phenomenon is called “relaxation” and the relaxation time describes the rate at which the proton spin system returns to equilibrium after interaction with radio waves. There are two major types of relaxation, longitudinal and transverse (T1 and T2), and images can be T1-, T2- or Proton Density (PD) weighted.

The repetition time (TR) is the time between each excitation, while the echo time (TE) is the time after the emitted radio signal - “the echo” - is collected. The TR and TE influence the contrast in the final image and determine the image weighting T1, T2 or PD.

The TR determines the T1-relaxation of the image, while the TE determines the T2-relaxation of the image. A T1 weighted spin echo sequence has a short TR and a short TE while a T2 weighted spin echo sequence has a long TR and a long TE.

4.5.3 Contrast: Basic consideration

The dream of everybody involved in medical imaging is to be able to distinguish the structures of the object that is examined with such sharpness and accuracy that there is no room for speculation and the normal anatomy and pathological changes can be easily defined. This means that high contrast is a prerequisite for a good imaging method. Several definitions of contrast have been proposed during recent years. Contrast implies the relative difference of intensities of two adjacent regions within the examined object. Image signal intensity in MRI is not standardized; unlike CT it does not possess any correlate to Hounsfield units. The signal intensity of an MR image can represent a mixture between T1 and T2 values, flow, diffusion and perfusion. The most important factor for the signal intensity is the manner in which the nuclear spin system has been excited. The stronger the signal, the better the image

quality will be. However, signals can be distorted by noise. The aim in medical imaging is to get a combination of both best possible signal-to-noise ratio and the best possible contrast.

Voxel and pixel size influence spatial resolution - and thus contrast. All anatomical structures within one voxel add to its average signal intensity in the final image. The sometimes blurry features of these images are caused by the averaging of different structures. This is known as “partial volume effect”. The smaller the pixel size, the better the suppression of partial volume effects. However, the bigger the voxel size, the better the signal will be. In general, the signal-to-noise is the determining factor for the final voxel/pixel size (Rinck, 1993).

4.5.4 Contrast agents

The first experiences of using paramagnetic contrast agents were reported in the early 1980's. The paramagnetic electron has a stronger magnetic movement than that of the proton and causes a shortening of the relaxation times of the tissues due to the indirect effect on the local magnetic field at the atomic level. Two types of contrast agents have been used, positive contrast agents, mainly affecting the T1-value, and negative - mainly affecting the T2-value.

Many different gadolinium contrast agents (Gd CME) were developed in the 1990's. The most common used contrast agents are those with a fast passage through the vessels to the extracellular space. The mechanism of Gd CME is not fully clarified. The intravenous paramagnetic Gd CME shortens the T1, thereby increasing the signal from the nearby protons (Galtung Lihaug, 1996). In the musculoskeletal system, the Gd CME has mainly been used in the diagnosis of recurrent disk hernia, to depict synovitis in the arthritic joint and in the diagnosis of musculoskeletal tumours and infections (Cova et al., 1991, Erlemann et al., 1989 and 1993).

The application of gadolinium contrast medium (Gd CME) in tendons is limited. Movin et al. (1998) used Gd CME in patients with chronic mid-portion achillodynia and conclude that the intratendinous signal alterations were more obvious after a Gd contrast medium (Figure 9) and that Gd CME reveals greater sensitivity in demonstrating intratendinous changes than US.



Figure 9. Sagittal (A) and transversal (C) unenhanced T1-weighted images of the Achilles tendon revealed thickened fusiform-shaped mid-portion Achilles tendon. There was marked contrast agent enhancement with high signal alterations (white arrows) after contrast agent administration (B and D).

4.5.5 Sequences

MRI has been applied to the assessment of changes in the tendons and other structures in the foot and ankle. The position of the patient (supine versus prone) and position of the feet are influenced by the specific indications for the MRI examination.

MR images can be obtained in the sagittal, transaxial and coronal planes, or in a combination of these planes. At least two imaging planes - the sagittal and axial - with at least two different pulse sequences should be used to ensure proper assessment of both internal and external contour abnormalities and for the determination of the longitudinal extent of the tendon lesion (Kier at al., 1991). The most commonly employed MRI sequences are standard spin echo, multiplanar gradient recalled echo, and short tau inversion recovery (STIR) sequences. The modes of sequences used to examine tendons in the foot and ankle regions, especially the Achilles tendons in different international medical centres, are summarized in Table 1(Resnick, 1998).

Table 1. Examples of different MR-sequences used in the foot and ankle (modified from Internal Derangements of Joints: Advanced MR Imaging, 1998).

INSTITUTION	PLANE	SEQUENCE	TR/TE (msec)	FOV (cm)	MATRIX	SLICE THICKNESS /GAP (MM)
UCSD (Univ. of California, San Diego)	Transaxial (localizer)	SE, Double echo	2000/20 2000/80	12	256 x 128	3-4/ (1)
	Sagittal	SE	600/20	12	256 x 128	3/ (1)
	Sagittal	FSE, Fat suppression	3000/20	12	256 x 128	3/ (1)
	Coronal	FSE, Fat suppression	3000/20	12	256 x 128	3-4/ (1)
BAYSIDE	Sagittal (localizer)	FSE	500/17	16	256 x 192	4 (0.5)
	Sagittal	FMPIR	5500/18	16	256 x 256	4 (0.5)
	Coronal	FSE, Double echo	6000/17 6000/102	15	256 x 128	4 (0.5)
	Transaxial	FSE, Double echo	6000/17 6000/102	15	256 x 256	4 (0.5)
JEFFERSON	Sagittal (localizer)	SE	500/min	20	256 x 192	4 (1)
	Transaxial	FSE, Fat suppression	5200/70	14	256 x 256	5 (1)
	Sagittal	FMPIR	5400/48	16	256 x 256	4 (1)
	Coronal	FMPIR	3000/38-48	16	256 x 256	4 (1)
	Transaxial	FSE	6000/40	16	256 x 512	4 (1)
MINNEAPOLIS	Coronal (localizer)	SE	300/20	24	256 x 192	5 (1)
	Sagittal	FSE, Double echo	4000/20 4000/100	12-14	256 x 192	3 (1)
	Coronal	FSE, Double echo	4000/20 4000/100	12-14	256 x 256	3 (1)
	Transaxial	FSE, Double echo	4000/20 4000/100	12-14	256 x 256	3 (1.5)
	Sagittal	FMPIR	3000/51	16	256 x 128	4 (1)

STANFORD	Sagittal (localizer)	SE	300/min	18	256 x 128	5 (1)
	Coronal	SE	300/min	12-14	256 x 192	3 (1.5)
	Coronal	FMPIR	5000/85	12-14	256 x 192	3 (1.5)
	Transaxial	SE	300/min	12-14	256 x 192	2
	Transaxial	FSE, Fat suppression	4000/108	12-14	256 x 192	3 (1.5)
	Sagittal	SE	300/min	12-14	256 x 192	3 (1.5)
CLEVELAND CLINIC	Sagittal	FMPIR	4000/30	12-14	256 x 192	3 (1.5)
	Transaxial	SE	200/12	20	256 x 128	10 (5)
	Sagittal Coronal (localizer)					
	Sagittal Coronal	SE	600/14	16	256 x 512	4 (1)
	Transaxial					
	Transaxial	SE, Double echo	2300/20 2300/80	14	256 x 128	4 (1)
OHIO STATE	Variable	STIR	6356/22	14	256 x 180	4 (1)
	Variable	Turbo SE	8000/130	14	256 x 150	4 (1)
	Transaxial (localizer)	SE, Double echo	2000- 3000/20-80	16	256 x 128	3 (1)
	Coronal	SE, Double echo	2000- 3000/20-80	16	256 x 192	3 (1)
	Sagittal	SE	600/15	16	256 x 256	3 (1)
	Sagittal	SE, Double echo	2000/20 2000/80	16	256 x 192	3 (1)
WEST HOLLYWOOD	Transaxial (localizer)	FSE	1764/17	16	256 x 160	5 (2.5)
	Sagittal	SE	800/min	12-14	256 x 192	3 (1)
	Coronal	SE, Double echo	2500/min 2500/70	12-14	256 x 160	3 (1)
	Transaxial	FSE, Seprate echo, Fat Suppressed	2000/15 2500/80	12-14	256 x 256	4 (0.5)
	Sagittal	3D GRE, Fat suppression SPGR	45/15; flipangle 30 degrees	12-14	256 x 192	1.5 (0)
Karolinska University Hospital/ Huddinge	Transaxial (localizer)	SE	15/6	18	256 X 256	3
	Sagittal	SE	550/20	18	256 X 512	3
	Transaxial	SE	730/20	20	256 X 512	3
	Sagittal	SE, 2D FLASH	460/10	18	410 X 512	3
	Sagittal	Turbo SE, Double echo	3500/17 3500/119	Rec. (5/8)	400 X 512	3
	Sagittal	SE, enhanced T1-WI	550/20	18	256 X 512	3
	Transaxial	SE, enhanced T1-WI	730/20	20	256 X 512	3

4.5.6 MRI features of the normal Achilles tendon

The normal Achilles tendon appears as a long, thin, hypointense structure in the sagittal image, and a flattened, hypointense structure with rounded lateral and medial margins in the transaxial image (Quinn et al. 1987). The normal Achilles tendon has a very low water content, which means that the tendon is hypointense - “black” - in all MRI sequences (Figures 10 and 12). The regular tendon structure is believed to induce changes in the rotational motion of the associated water molecules, which cause a marked reduction in the signal intensity. However, due to the anisotropic nature of the tendon tissue, the orientation of the tendon influences the signal intensity. A marked increase signal intensity (hyperintense) can be observed at 55° in relation to the static field, intermediate signal intensity at 45° and 65° and no signal at 0° and 90° (Erickson et al. 1991). This phenomenon called “the magic angle artefact” can be observed at the use of short TE (T1- or PD weighted sequences).



Figure 10. Sagittal and transversal T1-WI sequences of normal Achilles tendon. The tendon is thin in the sagittal image ((arrows) in A and has a concave-convex form in the transversal image (arrowheads) in B. There is no intratendinous signal alteration.

In a recent study by Oatridge (2003) of eight patients with chronic Achilles tendinopathy and five normal controls who were examined with the long axis of the tendon placed at 55 and 0 degrees to the main magnetic field, it was concluded that the use of magic angle MRI imaging improved the distinctness in the demonstration of signal changes in the Achilles tendon in chronic tendinopathy, and the STIR images obtained at the magic angle showed a more obvious signal change than those obtained at 0 degrees. Furthermore, the changes due

to contrast agent enhancement were much more evident on images obtained at 55 degrees than at 0 degrees.

4.5.7 Achilles tendon alterations on MRI

In tendinopathy, MRI demonstrates the diffuse or focal enlargement or thickening of the tendon and in most of the cases high signal lesions in both T1- and T2- sequences can be noticed (Quinn et al., 1987, Berquist, 1990) (Figures 11, 12 and 13). In trauma, the disruption of tendon structure is clear in total ruptures and in large partial ruptures. Smaller partial ruptures can be recognized as high intratendinous signal collections, or inhomogeneity of the signal, in both T1- and T2 weighted images (Quinn et al., 1987, Davies, 1991). The partial saturation techniques and short T1 inversion recovery sequences have been suggested to be more sensitive in detecting focal signal changes than spin echo sequences alone in the case of small alterations of tendon structure (Davies, 1991). The addition of a Gd contrast agent reveals more obvious intratendinous signal abnormalities, regarding size and intensity, on T1-weighted MR images in the Achilles tendon in patients with chronic achillodynia (Movin, 1998, Shalabi et al., 2001 and 2002).

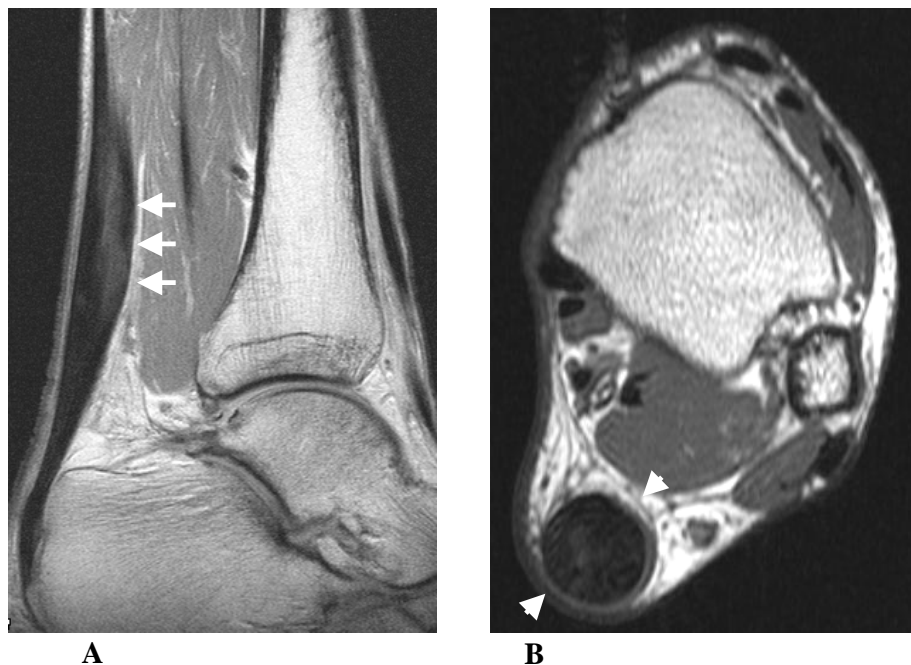


Figure 11. Sagittal (A) and transversal (B) PD-WI MR images of the right Achilles tendon in 36-year-old man with chronic Achilles tendinosis. The images show thickened fusiform-shaped Achilles tendon with high intratendinous signal alteration (tendinosis) at the mid-portion of the tendon (white arrows).

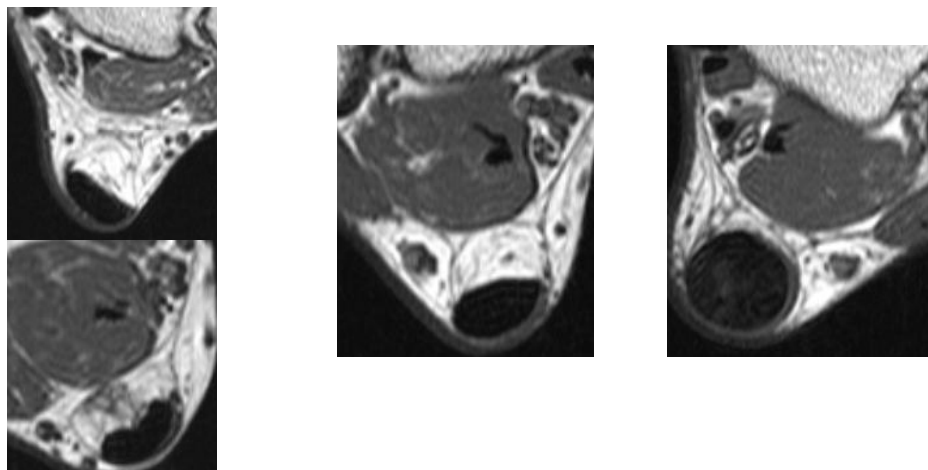
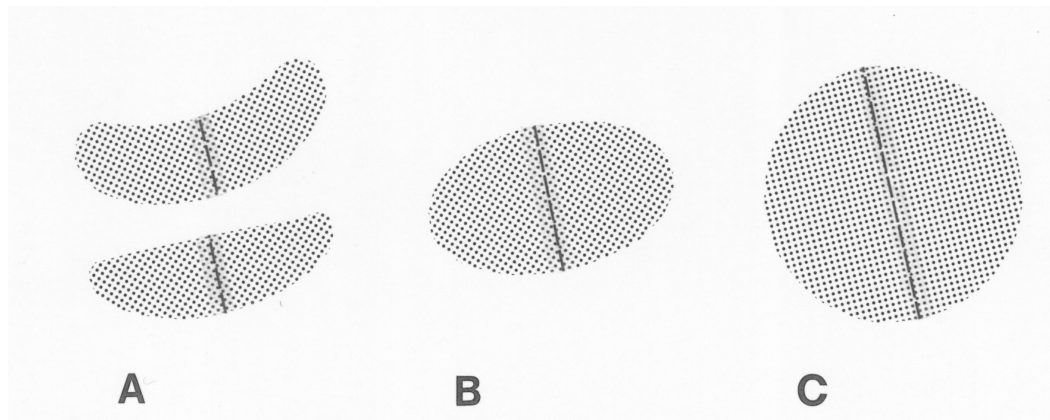


Figure 12. Schematic and transversal T1-WI imaging of Achilles tendon cross-section area: Normal and pathologic.

A. Concave-convex and plano-convex form: This form shows a normal finding. Cross-section area of the tendon is equal to or less than 6 mm.

B. and C. Ellipsoid and circular forms: Pathological alteration on Achilles tendon cross-section area in case of degenerative Achilles tendinopathy. The cross-section area is more than 6 mm.

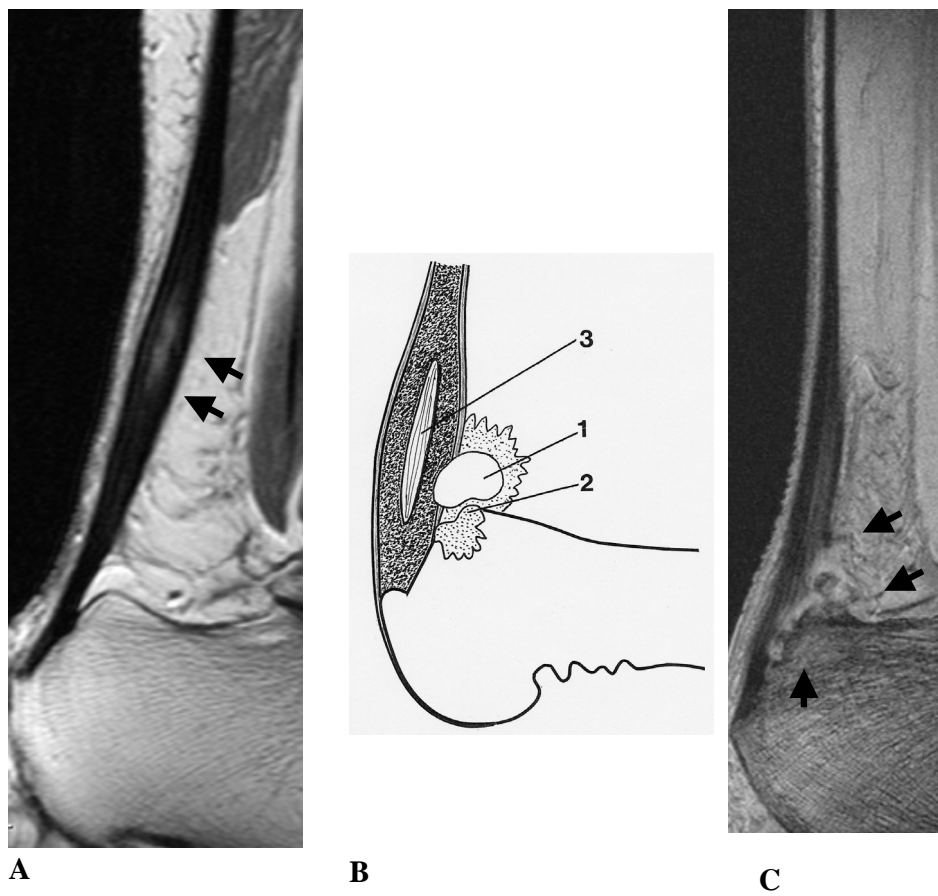


Figure 13. Sagittal MR imaging (A and C) and schematic (B) of pathological conditions of the Achilles tendon:

Retrocalcaneal bursitis (1) and erosion of the calcaneal tubersity (2) on sagittal FLASH gradient echo sequence (C), (black arrows).

Tendinosis (3) on sagittal T1-WI (A), (black arrows).

4.5.8 MRI classification of Achilles tendon pathology

The pathological alterations of the Achilles tendon have been classified according to MRI findings. Weinstabl et al. (1991) categorized the MRI findings of the thickened Achilles tendon into four types, where type I lacks structural changes, types II and III include intratendinous signal alterations, and type IV shows complete rupture (Table 2).

MRI classification by Pomeranz (1997) categorized grade 0 as a normal tendon, grades IA, IB and II as intratendinous signal alterations (tendinopathy), and grade III as complete rupture with retraction (Table 3).

There is a complete lack of MRI classification according to MRI-contrast agent enhancement. We have been using a four-point semi-quantitative grading scale for the evaluation of the enhancement of the intratendinous signal on gadolinium enhanced T1-WI (CME T1-WI), where grade 0 corresponds to the normal tendon (no enhancement), grade I mild contrast enhancement, grade II moderate and grade III severe contrast enhancement (Shalabi et al., 2001), (Table 4).

Table 2. MR classification of Achilles tendon pathology (Weinstabl et al., 1991)

Type I	Thickening of the tendon without structural change of tendon tissue
Type II	Thickening of the tendon with longitudinal and centrally located image changes
Type III	Thickening of the tendon with structural changes longitudinally and horizontally including the paratenon
Type IV	Thickening of the tendon with altered signal intensity and visible discontinuity

Table 3. Spectrum of tendon injury (Pomeranz, 1997)

Grade 0	Homogeneous hypointensity (normal) \pm peritendinous fluid
Grade I-A	T1 hypointense signal disappears on T2
Grade I-B	Intratendinous isointensity T1 (< 50% of the tendon), intratendinous iso - or hyperintensity T2
Grade II	Intratendinous isointensity T1 (> 50% of the tendon), intratendinous iso - or hyperintensity T2, attenuated size
Grade III	Tendon transaction with retraction and peritendinous T1 hypointensity, T2 hyperintensity

Table 4. The four point semi-quantitative grading of Achilles tendon pathology according to Gd-CME (gadolinium contrast medium enhancement).

Grade 0	No intra-tendinous contrast enhancement
Grade I	Mild intra-tendinous contrast enhancement
Grade II	Moderate intra-tendinous contrast enhancement
Grade III	Severe intra-and peri-tendinous contrast enhancement

4.5.9 Achilles tendon injury: Signs on MRI (Pomeranz, 1997)

- * Signal in T1-, T2- and PD-WI and relative change in signal between sequences
- * Tendon size (hypertrophy versus atrophy)
- * Peritendinous inflammation or masses
- * Extent of retraction (and potential apposition in the plantar flexion)
- * Status of torn edges
- * Presence or absence of hematoma
- * Proximal or distal extent of tear
- * Status of proximal musculature
- * Status of hindfoot, ankle joint and subtalar space

4.5.10 Achilles tendon injury: Pitfalls on MRI (Pomeranz, 1997)

- * Retrocalcaneal bursitis: Hypointense T1-WI
- * Tendinitis
- * Ganglion of the Achilles or posterior ankle joint: Hypointense T1-WI
- * Posterior talofibular rupture or injury
- * Hindfoot or sinus tarsi syndrome
- * Subtalar joint arthropathy or capsular cyst
- * Accessory soleus-muscle: Isointense with muscle
- * Hypercholesterolemic xanthoma: Variable hyperintense T1-WI
- * Kagel's fat pad hypertrophy: hyperintense T1-WI
- * Hematoma: hyperintense T1-WI
- * "Tennis leg": Myotendinous junction rupture of the medial head of the gastrocnemius muscle

5 AIMS OF THE PRESENT INVESTIGATION

The general aim of the present thesis is to evaluate and monitor the morphological response following treatment interventions in patients with chronic Achilles tendinopathy by using different MRI-techniques.

In the different papers the specific aims were:

- To evaluate the tendon disorder and its healing process by MRI, in patients with chronic painful Achilles tendinosis, before and two years after surgical treatment (study I).
- To evaluate the merit of dynamic contrast enhanced MR imaging and its correlation to histopathology and symptoms in chronic Achilles tendinosis (study II).
- To design a computerized 3-D seed growing technique for MRI to calculate Achilles tendon volume and mean intratendinous signal (study III).
- To evaluate the morphological response of transversal core-biopsies in patients with chronic Achilles tendinosis by serial MRI during a period of one year (study IV).
- To evaluate tendon volume and intratendinous signal in patients with chronic painful Achilles tendinosis by MRI, before and after three months of daily eccentric calf muscle strength training (study V).
- To evaluate tendon adaptation by MRI, in terms of tendon volume and intratendinous signal, immediately after gastrocnemius-soleus complex strength training in the Achilles tendon (study VI).

6 MATERIAL AND METHODS

6.1 SUBJECTS

The MRI-Achilles tendon study has been running at Huddinge University Hospital since 1992. The patients were referred to the orthopedic university clinic by general practitioners and by orthopedic surgeons. They have then been further referred for an MRI examination of the Achilles tendon by the orthopedic surgeons in the hospital. Totally 129 MR-examinations in 57 patients were performed between 1997 and 2002 (four patients received five MR-examinations, one patient four, one patient three and 51 patients two MR-examinations), resulting in 1878 sequences (bilateral) and 13146 MR-images for evaluation (Table 5). The extents of overlapping between the patients in all studies are presented in Table 6. All patients included in this thesis experienced pain and local tenderness at palpation of the mid-portion of the Achilles tendon, 2-7 cm proximal to the tendon insertion. The duration of symptoms, in terms of pain and functional impairment, lasted for at least 4 months.

Table 5. Number of Achilles tendon patients, number of patients with bilateral symptoms and number of healthy controls included in the studies. The age of the patients are presented as median and range. The number of MR-examinations and performed sequences (seq.) in every study are also presented in this table.

Study	No of patients	Bilateral symptom	Asymptomatic tendons	Age (years)	Gender M/F	No of MR-examination	No of seq.
I	15	3	12	39 (27-48)	10/5	30	240
II	15	5	10	40 (27-79)	11/4	30	240
III	33	8	25	52 (29-70)	20/13	33	231
IV	10	6	4	48 (36-56)	7/3	35	245
V	25	8	17	51 (28-70)	16/9	50	350
VI	22	8	14	45 (28-57)	15/7	44	308

Study	No of patients
I	3
I+II	12
II	3
III	1
III+IV	3
III+IV+VI	4
III+V	13
III+V+VI	12
IV+VI	3
VI	3
Sum	57

Table 6. Number of patients appearing in each individual paper.

6.2 METHODS

6.2.1 Clinical Assessment

The clinical outcome of surgical treatment was evaluated from a questionnaire, levels of physical activity (Table 7), and a physical examination was performed by an independent observer.

The level of pain and functional impairment was graded by using the modified classification by Curwin and Stanish, 1984 (Curwin & Stanish, 1984, Rolf & Movin, 1997), where pain was categorized on a six-level scale and performance on a four-level scale (Table 8).

The protocol for the clinical examination included walking on tiptoes, palpation with localization of tenderness, Simmonds test (Simmonds, 1957), Matles test (Matles, 1975), and determination of vascular and nerve function distal to the surgical scar (*studies I and II*).

The clinical outcome was categorized as excellent (lack of symptoms), good (pain associated with extreme exertion only), fair (patients with symptoms in between poor and good) or poor (pain during daily activities or inability to participate in sports).

Table 7. Levels of physical activity

Level	Physical activity
I	Daily living, white collar work
II	Walking. Moderate work
III	Recreational running or heavy labor
IV	Competitive running

Table 8. Classification of outcome of surgery, modified from Curwin & Stanish, 1984 (Curwin & Stanish, 1984, Rolf & Movin, 1997).

Intensity	Level	Pain	Level	Performance
Mild	1	None	1	Normal
	2	With extreme exertion only, not intense	1	Normal
Moderate	3	Starts with activity, lasts for 1-2 hours after activity	2	Performance may be affected
	4	With any athletic activity, increase during activity	3	Performance level significantly decreased
Severe	5	Immediately upon any activity involving tendon. Sudden increase in pain if activity is continued, lasts for 12-24 hours afterwards	3	Performance markedly curtailed or prevented
	6	During daily activities	4	Unable to participate

6.2.2 Surgical technique (studies I & II)

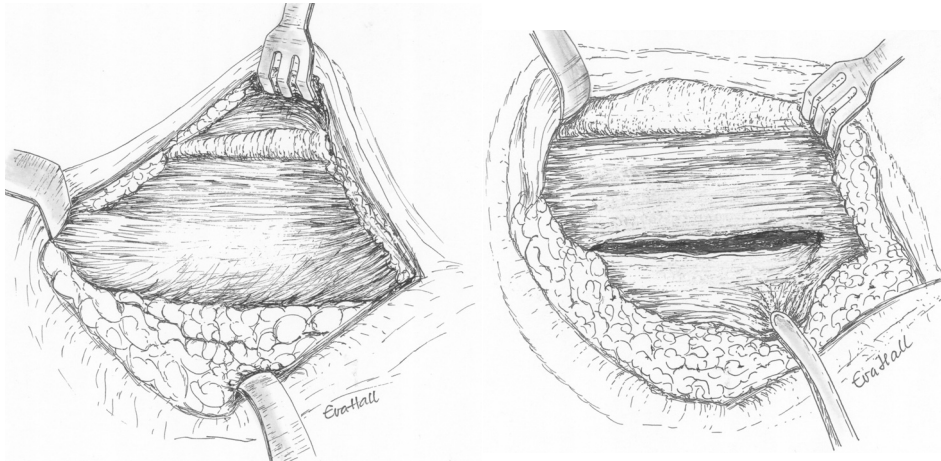


Figure 14. A thickened Achilles tendon with the intratendinous changes (left). Open tenotomy with longitudinal incisions in the tendon to detect the intratendinous lesion (right).

The criteria for surgical treatment were failure of conservative treatment and major subjective complaints together with localized tenderness on palpation. At surgery, we used a medial incision. Adhesions between the paratenon and the skin and the paratenon and the tendon, respectively, were excised. The tendon lesion was verified by longitudinal incision and characterized by an increased consistency at palpation, poorly defined fiber structure, and discoloration on inspection. The paratenon was excised if stiff and fibrotic, otherwise it was left open. Longitudinal tendon splitting was performed. Pathologically changed regions were excised. In no case was reinforcement flaps used (Figure 14).

The initial postoperative regime included treatment in an orthosis with the ankle in the neutral position for two weeks. Weight bearing was allowed during the immobilization time. Strengthening exercises supervised by a physiotherapist followed. Running exercises were allowed three months after surgery, provided the patient was free of symptoms.

6.2.3 US-guided core biopsies (study II)

Biopsies and US examinations were performed using an Acuson 128 real-time scanner with 5 or 7 MHz linear array transducers. US-guided core biopsies were taken from all 15 patients preoperatively with the free hand technique under sterile conditions and after use of local anesthetic infiltration of the skin (prilocain 5-10 ml 10 mg/ml, Astra, Sweden), using a MonoptyTM biopsy instrument (Bard Radiology, Covington, GA, USA). The diameter of the

needle was 1.2 mm and the needle throw was 22 mm. The specimens were taken from the centre of the lesion, which had a hypoechoic appearance. One to 5 (median 4) biopsies were obtained from the diseased hypoechoic areas.

6.2.4 Transversal US-guided core-biopsy (study IV)

Transversal US-guided core-biopsy examinations were made using an Acuson Sequoia 512 real-time scanner with a 13 MHz linear array transducer. The patient was placed in prone position, and US-guided core-biopsies were obtained from the hypoechoic areas in the Achilles tendon. Under sterile conditions, a local anesthetic of the skin, subcutaneous tissue and fascia - but not the tendon - was applied. An approximately two mm incision was made through the skin only.

The US-guided biopsies were obtained using a Bard instrument and Bard magnum biopsy needle™ (C.R. Bard, inc. Covington, GA, USA) with gradation and an etched tip. The diameter of the needle was 1.2 mm (14 gauges), the length of the needle 100 mm, and the length of the sample notch 19 mm.

After placing the needle inside the Bard instrument, it was inserted through the skin and fascia. The needle was then advanced to the surface of the Achilles tendon over the hypoechoic area; the trigger was then fired under ultrasonographic guidance.

The location of the hypoechoic area in the Achilles tendon was ensured by means of US before obtaining the biopsy; then, a continuous US-guidance was given during the whole procedure.

6.2.5 Histopathology (study II)

The samples obtained via the US core-biopsy technique had a diameter of 1.2 mm and were 10-17 mm in length. The specimens were fixed in buffered neutral formalin and embedded in paraffin. Staining was performed with hematoxylin and eosin (HE) for general evaluation and the Alcian Blue (PH 2.5)-Periodic Acid-Schiff method (AB/PAS) for detection of water-retaining glycosaminoglycan (GAG) - rich areas. Eight parameters were assessed: fiber structure, fiber arrangement, shape of nuclei, regional variations in cellularity, increased vascularity, decreased collagen stainability, mucoid score, and presence and/or extent of fibrosis or hyalinization (Figure 15).

These eight parameters were semi-quantitatively graded into a four-point scale (0 - III), where grade 0 was normal, grade I slightly abnormal, grade II moderately abnormal and grade III markedly abnormal (Movin et al., 1997). The protocol gave a maximum total tendon score of 24 for each specimen. As there was a median of four specimens obtained from the tendon lesion, the mean tendon score was used to quantify the severity of the tendon lesion.

The sections stained with AB/PAS were examined histomorphometrically to assess the volume density of GAG-rich areas, using a Reichert Jung projection microscope. Areas stained blue (GAG-rich area) and red (collagen) were calculated in a magnification of 122

times using a square lattice with 2 cm intercept placed on the projection screen with the intersection lines at an angle of 20 degrees to the longitudinal axis of the tendon fibers. The intersection points on GAG-rich areas and collagen, respectively, were registered. The whole specimen area was evaluated and the hits for all specimens in each patient were added, allowing calculation of the volume fraction of GAG-rich matrix areas, expressed as a GAG/collagen ratio.

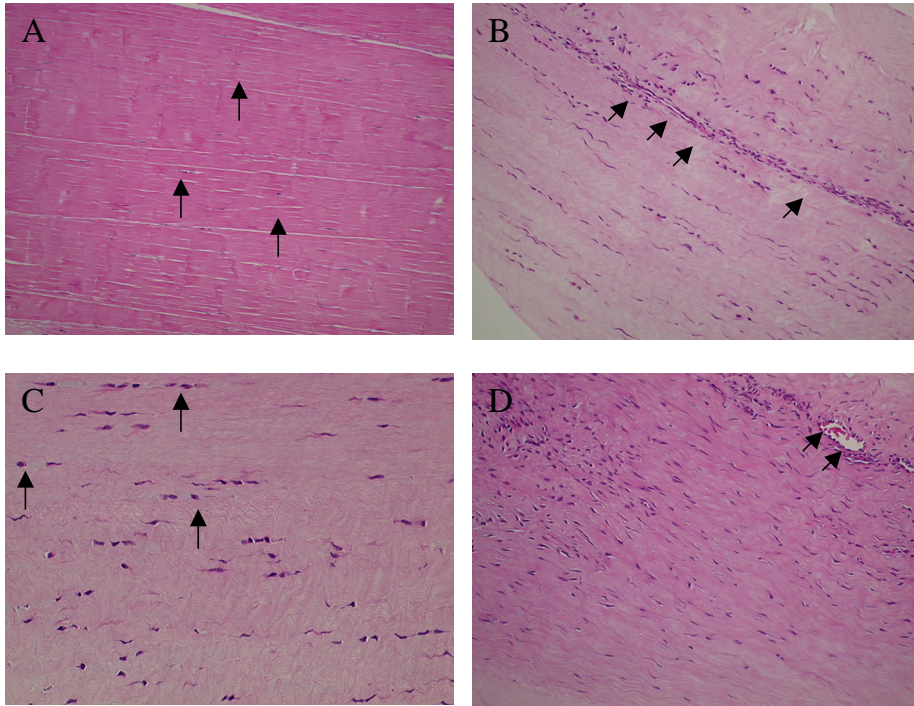


Figure 15. Histological sections from normal tendon tissue (A) show regular fiber arrangement and a few nuclei with flat shapes (black arrows). Figures (B-D) from a patient with chronic tendinosis, show hypercellularity, abnormally-looking nuclei with rounded shapes (arrows in B), irregular arrangement of fibers (arrows in C), and evidence of neovascularization (arrows in D). Hematoxylin and Eosin (original magnification x 200).

6.2.6 Calf muscle training (studies V & VI)

The patients saw a physiotherapist on two occasions and were interviewed by telephone once during the home exercise period.

At the first visit to the physiotherapy unit, prior to the first MRI-examination, a general evaluation was made including patient history and instructions for an eccentric 12-week home exercise program. The home exercise program was started the day the first MRI examination was performed. This eccentric exercise program followed the model developed by Alfredson et al. (1998). Eccentric loading of the calf with the knee straight and bent, with 3 sets and 15 repetitions, was performed twice a day for 12 weeks (Figure 16). The load was increased as tolerated by successively adding weight in a backpack. Patients were allowed to experience some pain, but were told to discontinue the exercise if pain became disabling. Running activity was allowed, even with minor discomfort, but pain was to be avoided.

Patients kept an exercise diary, where perceived pain during exercise was documented for each training session. At six weeks, the patients were interviewed by phone to make sure that the exercise program was in keeping with the guidelines. At this point, exercise load (weights in backpack) should have been added; if not the patients were encouraged to do so. If the patients had difficulties with the program in any way, they received an appointment for an extra visit to the clinic.

At 12 weeks, the patients saw the physiotherapist for a final follow-up regarding the subjective pain/functional performance. The exercise diaries were collected on this occasion. If patients at this time still experienced remaining symptoms, they were referred back to the orthopedic surgeon.

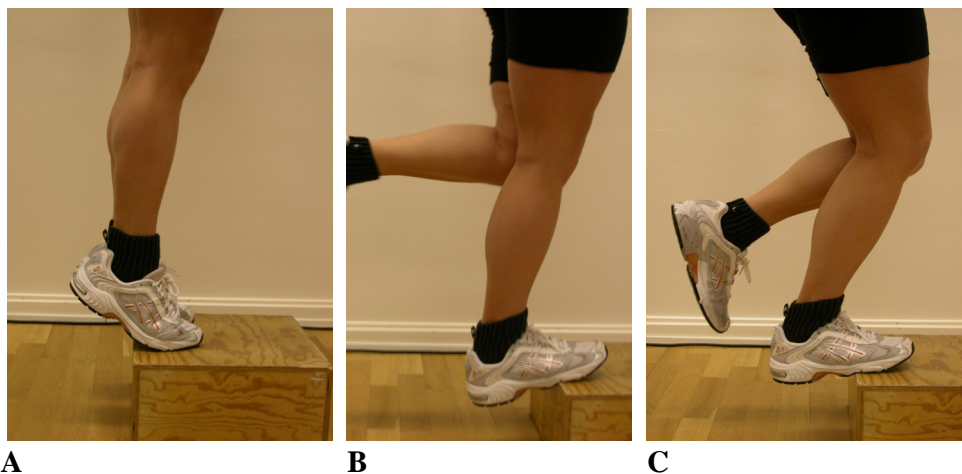


Figure 16. The exercise starts from an upright body position and standing with all body weight on the forefoot and the ankle joint in plantar flexion (A). On the injured side, the calf muscle was loaded eccentrically by lowering the heel with the knee straight (B) and with the knee bent (C). Three sets of 15 repetitions of each exercise were made twice daily for 12 weeks.

6.2.7 Statistical Methods

- * Statistical hypotheses regarding within-patient comparisons and changes between the pre- and postoperative MRI examinations and clinical outcome were tested applying Wilcoxon sign-rank tests (*studies I, II & IV*).
- * The non-parametric Spearman Rank Order Correlation test was applied to evaluate the correlation between the histopathological findings and the early contrast agent enhancement in dynamic MRI and contrast enhancement in static MRI (*study II*) and to evaluate the correlation between subjective pain, tendon volume and intratendinous signal after intervention (*study IV*).
- * Power analysis (two tails test) was performed to calculate the sample size of Achilles tendons required to allow accurate statistical judgments of the 3-D seed growing technique (*study III*).
- * Repeated measures ANOVA (Statistica 6.1) with a general linear model approach and the coefficient of variation were used to test the intra- and inter-observer reliability (*studies III and V*).
- * Student's *t*-test for paired samples was used to compare figures on tendon volume and intratendinous signal before and after intervention, and in the comparison between symptomatically treated and untreated healthy tendons (asymptomatic) (*studies V & VI*).
- * Confidence intervals were used for showing the difference between means of the symptomatic eccentrically heavy loaded tendon and the concentrically loaded contralateral side (*study VI*).
- * Variables of continuous and ordinal types are presented as mean and standard deviation.
- * A *p*-value of <0.05 was considered statistically significant.

6.2.8 Magnetic Resonance Imaging

MRI imaging was performed on a superconductive 1.5 T Magnetom SP 63, Siemens (studies I & II) and on a Magnetom Vision, Siemens (studies III-VI), using a commercially available CP-flexible 21 x 52-cm coil for all patients. Both Achilles tendons were examined simultaneously. Sagittal and transversal images were obtained with the patient in supine position, the feet in resting position in the coil with a maximum plantar flexion of 15 degrees. The coil was centred over the Achilles tendons. The slice thickness was 3 mm with a 0.3 mm gap in all sequences.

6.2.8.1 Sequences (studies I & II)

1. Transversal PD/T2-weighted spin-echo: TR/TE 2200/20 and 80 ms, 1 acquisition (acq), half fourier, time of acquisition (TA) 4.1 min, FOV 200 mm, matrix 192 X 256 with rectangular FOV.
2. Sagittal PD/T2-weighted turbo spin-echo: TR/TE 2500/19 and 93 ms, echo train length (ETL) 3, 1 acq, TA 3.40 min, FOV 200 mm, matrix 256 X 256.
3. Sagittal T1-weighted spin-echo: TR/TE 420/15 ms, 2 acq, TA 3.38 min, FOV 200 mm, matrix 256 X 256.
4. Transversal T1-weighted spin-echo: TR/TE 420/15 ms, 2 acq, TA 3.38 min, FOV 200 mm, matrix 256 X 512 with rectangular FOV.
5. The last two sequences were repeated after intravenous (I.V.) contrast agent was given.

6.2.8.2 Sequences (studies III-VI)

1. Transversal and sagittal T1-weighted spin-echo: TR/TE 730/20 and 550/20, 2 acq, TA 5.54 min and 4.45 min, FOV 200 mm and 180 mm and 160 x 512 (rec FOV 5/8) and 256 x 512 matrix, respectively.
2. Sagittal FLASH 2 D-gradient-echo: TR/TE 460/10 ms, 2 acq, TA 6.19 min, FOV 180 mm, 410 x 512 matrix.
3. Sagittal PD/T2-weighted turbo spin-echo: TR/TE 3500/17 and 119, 1 acq, TA 4.48 min, FOV 180 mm, 400 x 512 matrix.
4. In addition, the first two sequences were repeated after a contrast agent had been given I.V.

The contrast agents used in all MR-examinations were either 0.1 mmol/kg body weight (B.W) gadopentetate dimeglumine (Magnevist, Schering) or gadodiamide (Omniscan, Nycomed), injected as a bolus within 20 seconds and immediately after injection the catheter was flushed with saline. The sagittal and transversal T1-weighted sequences after gadolinium (Gd) contrast medium enhancement (CME) were performed within 10 min (CME T1-WI).

6.2.8.3 MRI evaluation

The following parameters were evaluated (**studies I & II**):

- * The presence, localization and volume of intratendinous signal alterations estimated on all sequences of the operated and the contralateral Achilles tendon.
- * The volume of the signal alteration was estimated by multiplying the anteroposterior, mediolateral and craniocaudal signal alteration diameters. Alterations $< 0.05 \text{ cm}^3$, corresponding to a signal alteration with a mean diameter less than 3 mm, were not considered significant.
- * The median length of maximal anteroposterior dimension and its distance from the tendon insertion were measured in the sagittal plane.
- * The enhancement of the intratendinous signal on CME T1-WI sequences was visually categorized using a four-point semi-quantitative grading scale.
- * The presence of peritendinous fluid or a retrocalcaneal bursa was noted.

6.2.8.4 Dynamic MRI (study II)

The dynamic series used were: Turbo FLASH in the sagittal plane (the same as SE sagittal series), with 6 mm slice thickness, TR/TE 9/4 ms, flip angle 8° , 1 acquisition, FOV 200, matrix 128 x 128 and TA 7.43 s. We chose this dynamic sequence because it was fast. These sequences had only three slices. We decided to place two slices in the symptomatic tendon and one in the contralateral asymptomatic tendon.

The contrast agent injection was started immediately after the first sequence in the dynamic series. When the contrast injection started, 8 dynamic sequences were performed with 9 s intervals. The time of dynamic contrast agent enhancement series was 72 s after the bolus contrast agent injection. In each patient, all contrast-enhanced dynamic images were subtracted from the first, precontrast turbo flash-image by using the subtraction function available on the MRI-unit. The subtraction was done to facilitate detection of the enhancement in the tendon lesion.

Measurements of the early contrast agent enhancements were performed using the region of interest (ROI) technique. The ROI circle had a diameter of 5 mm and was placed at the most enhanced tendon region in preoperative MRI-examination and at the same region in the postoperative MRI-examination. When no contrast agent enhancement was found, measurements were performed in the center of the tendon, at the same distances from the cranial and caudal insertions. All measurements were performed on sagittal images and compared with those of the contralateral tendons. Five measurements, every 18 s up to 72 s, formed the basis for evaluating the signal enhancement.

The area under curve (AUC) was used to measure the degree of early contrast agent enhancement. Early contrast agent enhancement was considered when the AUC was greater than 4. AUC was calculated by using the trapeziform method (Ashton M et al., 1984), in which the time-signal intensity (SI) curves were divided into four parallel trapeziform areas

(SI₀-SI₄). The four- trapezeform areas were calculated and the AUC was estimated by using the formula:

$$AUC = \frac{(SI_0 + SI_1 \times 0.3 \text{ min})}{2} + \frac{(SI_1 + SI_2 \times 0.3 \text{ min})}{2} + \frac{(SI_2 + SI_3 \times 0.3 \text{ min})}{2} + \frac{(SI_3 + SI_4 \times 0.3 \text{ min})}{2} - (SI_0 \times 1.2 \text{ min})$$

6.2.8.5 MRI-evaluation using the 3-D seed growing technique

The volume of the Achilles tendon at a distance of 2-12 cm proximal to its insertion was evaluated as a measure of intratendinous changes. To mask the volume of the tendon, a seed-growing algorithm was developed and implemented on a Hermes workstation (Nuclear Diagnostics AB, Sweden). The MRI-signal within the normal tendon was low and appeared dark in the sequences we used (T1-WI and PD-WI). The surrounding tissues - including muscle and fat - sent a more intense signal and appeared brighter in the images. It was more complicated to design a seed growing technique for masking a low signal volume than a high signal volume. Several extra steps and precautions had to be introduced to make the seed growing work

The 3-D seed growing algorithm itself relies on two inclusion criteria: absolute signal level and signal gradient. A voxel to be included was tested by checking neighboring voxels in a 3x3x3 cube. Each position in the cube had a weighting factor reflecting mainly how close the position was to the center position. However, the weighting factors were asymmetrical in order to handle different leakage probability in different directions.

Seven consecutive sagittal slices formatted as 512x512 matrices were acquired to cover each tendon. The pixel size was 0.35 x 0.35 mm² and the slice-to-slice distance 3.3 mm, giving a voxel volume of 0.35 x 0.35 x 3.3 mm³. The main steps in the procedure are illustrated in Figure 17. First, an optimal sagittal slice was selected, showing the tendon insertion; the insertion was then marked. Around the marked point, a circle with 2 cm radius is drawn to guide the selection of a point inside the tendon, 2 cm proximal to the tendon insertion. A circle with a 10 cm radius is drawn around this point and a level of 12 cm proximal to the tendon insertion can be marked. The desired 10 cm section of the Achilles tendon is thus demarcated. It was necessary to impose these fixed limits in order to restrict the seed growing procedure to the desired volume. The next step was to find the skin surface of the posterior border of the tendon. The signal outside the object was low and homogeneous; it was therefore easier for the algorithm to grow in the area outside the object and find the location of the skin than to grow the low-signal tendon directly from within the tendon. The tendon was now bounded by the skin and the 2 and 12 cm demarcations, and the final seed could be selected within the tendon. The full 3-D volume of the tendon was now grown with a minimum of leakage. To avoid leakage, fairly strict limits on the inclusion criteria were used. Thus, some manual corrections were needed to get the final result. This was especially true in the case of an enlarged tendon with a high internal signal level as a sign of severe tendinopathy. At this final stage, the volume in cm³, as well as the mean signal within the masked tendon, were displayed.

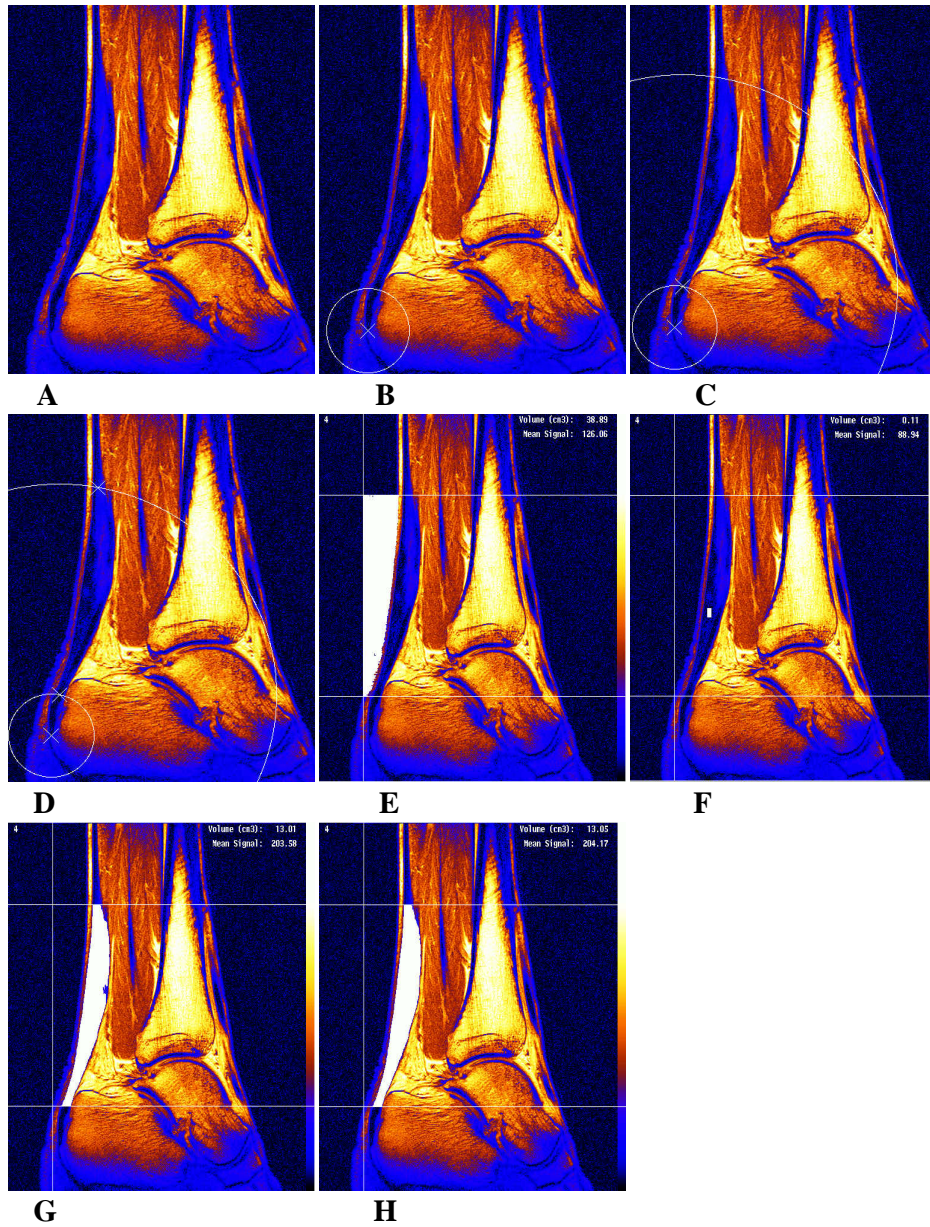


Figure 17. Sagittal PD-WI showing eight steps to perform the 3-D seed growing algorithm. A) Selecting the optimal sagittal slice. B) Marking of the tendon insertion. C) Marking a 2 cm distance above the tendon insertion using a circle with 2 cm radius. D) Setting a 10 cm mark using a circle with 10 cm radius. E) Marking the skin surface. F) Setting a seed inside the tendon. G) Growing the tendon region. H) Optionally manually correcting to get the final result

7 MAIN RESULTS

7.1 STUDY I

The main finding was the decrease of the intratendinous alterations or their elimination in all investigated MRI sequences in most of the 15 patients, two years following surgical treatment. The most sensitive sequence to depict an intratendinous lesion was the enhanced Gd-CME T1-weighted images followed by the unenhanced T1-WI and PD, and finally the T2-weighted sequences (Table 9).

There was a marked regression of the estimated volume of the intratendinous signal alteration from a median of 1.2 cm³ preoperatively to 0.0 cm³ postoperatively on CME T1-WI ($p = 0.001$). CME T1-WI showed a regress in intratendinous signal abnormality from 13 out of 15 patients preoperatively to 4 of 15 patients two years postoperatively (Table 10). However, the AP dimension remained unchanged at 9 mm, on both MRI occasions. The clinical outcome was excellent in eight, good in five, fair in one and poor in one patient.

When T1-WI was compared before and after Gd-CME on preoperative images, the signal abnormality was seen to a larger extent after Gd-CME ($p = 0.008$), a median of 0.27 cm³ prior and a median of 1.2 cm³ after Gd-CME, respectively.

Table 9. MRI in 15 surgically treated Achilles tendons. The number of tendons with signal alterations (SA) and the volume of the intratendinous signal alterations (ITS) are given pre-operatively and two years postoperatively.

	Preoperative (MRI I)			Postoperative (MRI II)			P-value
	Number of tendons with SA	Volume of ITS		Number of tendons with SA	Volume of ITS		
		Median	Range		Median	Range	
T1-WI	11	0.27	0 – 16.4	2	0	0 – 16.1	0.003
T2-WI	7	0	0 – 6.7	2	0	0 – 6.7	0.03
PD-WI	9	0.1	0 – 9.1	3	0	0 – 9.1	0.007
CME-T1WI	13	1.2	0 – 16.4	4	0	0 – 16.1	0.001

Table 10. Gd-contrast medium enhancement (CME-T1-WI) in the operated and contralateral Achilles tendon measured in a four point semi-quantitative grading (Table 4) (MRI I = preoperative, MRI II = 2 years postoperative).

Degree of CME	Number of the operated tendon		Number of the contralateral asymptomatic tendon		Number of the contralateral symptomatic tendon	
	MRI I	MRI II	MRI I	MRI II	MRI I	MRI II
0	2	13	8	9	2	2
I	7	2	4	2	1	1
II	5	0	0	1	0	0
III	1	0	0	0	0	0
Total	15	15	12	12	3	3

7.2 STUDY II

7.2.1 Dynamic MRI

Early contrast enhancement (first 72 s) in the dynamic MR series was seen in tendon lesions of the symptom-giving Achilles tendons; a significant difference was noted in comparison with asymptomatic contralateral tendons where no or mild enhancement was revealed ($p = 0.01$). In 12 out of 15 patients with $AUC > 4$, early contrast agent enhancement was seen within 72 s, preoperatively. The other 3 patients showed no (2 patients) or mild (one patient) early contrast agent enhancement. Postoperatively, 3 out of 15 operated tendons revealed early contrast agent enhancement. Two of these three patients had an unsatisfactory clinical outcome. Two years postoperatively, the intratendinous signal in the operated tendon had decreased from a median value of 85 preoperatively to 49 and the early enhancement evaluated by the AUC had decreased from 9 to 2, respectively ($p = 0.005$).

Table 11 summarizes the values for the intertendinous signal intensity of contrast agent enhancement at the start and after 72 s, and also the AUC in 15 operated and corresponding contralateral tendons (10 healthy and 5 with past history) preoperatively and two years following surgical treatment.

Categorization of the clinical outcome rated the patients from 8 for excellent, 4 for good, 2 for fair and 1 for poor.

Table 11. Area under curve (AUC) of the dynamic MR imaging (DEMRI) in 15 patients with chronic Achilles tendinosis and their corresponding contralateral side (10 patients with healthy tendons and 5 patients with a past history of chronic Achilles tendinosis) pre- (DEMRI I) and two-years postoperatively (DEMRI II). Absolute $T_{0\%}$ and absolute $T_{100\%}$ = the signal intensity of the ROI prior to and 72 s after contrast agent administration, respectively.

Patients	Number of patients	Absolute $T_{0\%}$		Absolute $T_{100\%}$		AUC	
		Median	Range	Median	Range	Median	Range
Operated DEMRI I	15	85	54 - 189	125	73 - 217	9	-2 - 83
Operated DEMRI II	15	49	24 - 99	51	30 - 102	2	-3 - 16
Healthy DEMRI I	10	71	40 - 168	72	42 - 174	2	-4 - 20
Healthy DEMRI II	10	65	30 - 131	71	40 - 136	1	-4 - 57
Past history DEMRI I	5	77	46 - 133	91	52 - 137	6	0 - 26
Past history DEMRI II	5	63	35 - 99	65	40 - 111	3	-1 - 9

7.2.2 Histopathology vs dynamic and static MRI

The early contrast agent enhancement (expressed as AUC) correlated to the severity of the total tendon pathology score ($p = 0.04$). Furthermore, increased occurrence of clusters of nuclei with a rounded outline correlated to increased AUC ($p = 0.005$). However, we found

no significant correlation to GAG/collagen ratio in the symptomatic tendon ($p = 0.67$) (Table 12). Furthermore, the semi-quantitative grading of contrast agent enhancement in static MR imaging was correlated to increased abnormality of the total tendon pathology score ($p = 0.01$), to clusters of nuclei with a rounded shape ($p = 0.02$) and to fiber structure ($p = 0.04$).

The median value of the total tendon pathology score was 16.75 (range 13–21.5). The median value of the GAG/collagen ratio was 0.38 (range 0–0.75). Characteristic histopathological changes were the alteration of fiber structure with total loss of fine structure and hyalinization, deterioration of collagen fibers, focal variations in cellularity - including regions of clusters of nuclei with a rounded shape - neovascularization, reduced stainability and increased amount of extracellular non-collagenous matrix. No specimen contained inflammatory cell infiltrates.

Table 12. Results of the semi-quantitative histopathological evaluation, with correlation to dynamic (DEMRI) and static MRI.

Histopathological parameters			Dynamic MR (AUC)		Static MR (semi-quantitative grading scale)	
	Median	Range	Spearman Rank Order Correlation R-value	Spearman Rank Order Correlation P-value	Spearman Rank Order Correlation R-value	Spearman Rank Order Correlation P-value
Fiber structure	2.5	1.5 – 3	0.43	0.11	0.53	0.04
Fiber arrangement	2.33	1.5 – 3	0.30	0.28	0.39	0.15
Fibrosis and hyalinization	2.25	1.5 – 3	0.39	0.16	0.44	0.09
Increased vascularity	1.5	0.5 – 2.5	0.11	0.68	0.01	0.73
Rounding of nuclei	1.75	1 – 3	0.68	0.005	0.72	0.002
Regional variations of cellularity	2	1 – 3	0.29	0.30	0.18	0.51
Decreased collagen stainability	2.5	1 – 3	0.36	0.19	0.39	0.15
Mucoid score	1.5	0 – 3	-0.02	0.92	0.16	0.57
Total score of tendon pathology	16.75	13 – 21.5	0.54	0.04	0.62	0.01

7.2.3 Dynamic vs static MRI

Larger AUC in DEMR correlated to higher categorization of contrast agent enhancement on the visual semi-quantitative grading on static MR images ($p = 0.04$). Two years postoperatively, the intratendinous signal evaluated on static MRI, in the operated tendon, had decreased from a median value of 85 preoperatively to 49, and the early enhancement evaluated by the AUC had decreased from 9 to 2, respectively ($p = 0.005$).

7.3 STUDY III

The computerized 3-D seed growing technique resulted in an excellent overall observer reliability of the MRI-measurements. For the tendon volume measurements, the T1-WI sequence was the best choice, with highest reliability ($R = 97.9\%$) and lowest coefficient of variation ($CV = 4.9\%$). Best result regarding measurements of the mean intratendinous signal was obtained for the PD-WI sequence with $R = 88.1\%$ and $CV = 8.9\%$. In general, reliability was higher for tendon volume than for mean intratendinous signal. For reliability, higher figures indicate more reliable estimates, whereas - for CV- lower values indicate more reliable estimates (Table 13). The same pattern was present when the coefficient of variation (CV) was studied. For the CV, lower figures indicate more reliable estimates. CV was 4.9% for tendon volume and 8.9% for mean intratendinous signal (Table 14).

Table 13. Contribution to total variance, from a repeated measures ANOVA design, for volume and mean intratendinous signal measurements and the two MRI data-sets (T1-WI and PD-WI). The column "Effect" shows the variance due to normal differences in tendon volume and mean intratendinous signal, i.e. the differences we would expect to find while looking at the Achilles tendons from different patients with different pathologic changes. The inter-observer (Observer) figures are generally about twice the intra-observer (Replicate) figures. The column Observer /Replicate shows the contribution to total variance from a combined Observer Replicate interaction.

	Effect	Observer	Replicate	Observer/ Replicate
Volume PD-WI	95.7%	2.3%	1.1%	1.0%
Volume T1-WI	97.9%	1.1%	0.5%	0.6%
Signal PD-WI	88.1%	5.7%	3.4%	2.8%
Signal T1-WI	82.1%	8.4%	4.5%	5.0%

Table 14. Overall mean figures, reliability (R) and coefficient of variation (CV) for volume and mean intratendinous signal measurements and two MRI data-sets (T1-WI and PD-WI). Higher R-figures indicate more reliable estimates. For the CV, smaller figures indicate more reliable estimates.

	Mean	Reliability	CV
Volume PD-WI	7.3	95.7%	7.5%
Volume T1-WI	7.0	97.9%	4.9%
Signal PD-WI	229	88.1%	8.9%
Signal T1-WI	103	82.1%	14.1%

7.4 STUDY IV

The main finding in our study was an initial increase followed by a gradual decrease of the tendon volume and intratendinous signal of the Achilles tendon after the transverse core biopsies. There was a significant decrease of tendon volume and intratendinous signal one year after the transverse core-biopsy procedure ($p < 0.05$)

One week after the biopsy procedure, MRI showed an increase of tendon volume (T1-WI) and mean signal intensity (PD-WI) with 29% and 30%, respectively ($p = 0.04$). During the follow-up process, tendon volume and mean signal intensity gradually decreased. One year after the biopsy procedure, the tendon volume had decreased with 20% and the intratendinous signal with 28% compared with the index MRI ($p = 0.04$) (Tables 15 and 16). However, in the untreated patients, both an increasing tendon volume (39%, $p = 0.06$) and intratendinous signal (37%, $p = 0.14$) were revealed at the one-year follow-up.

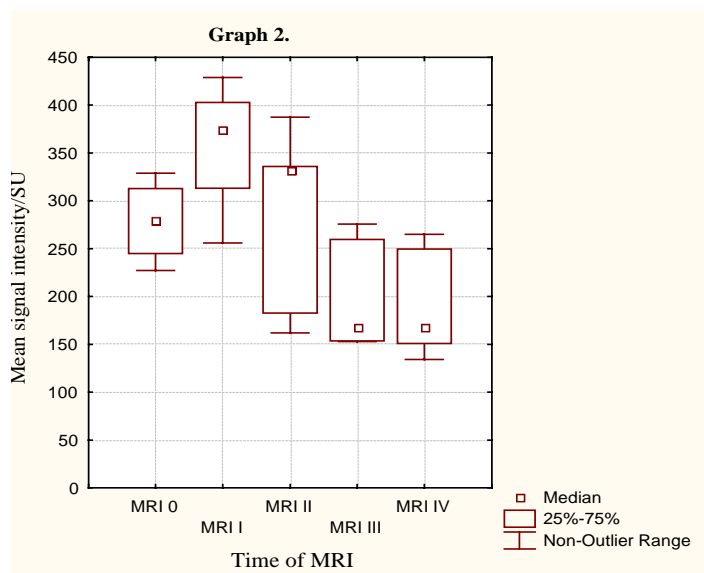
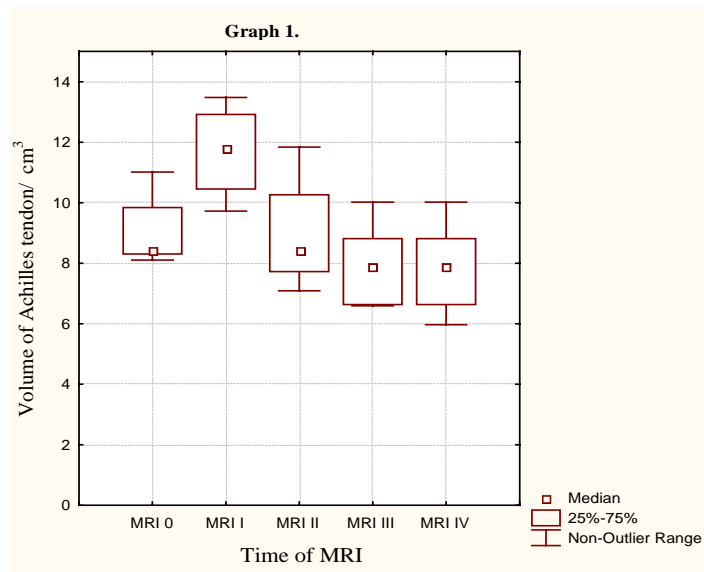
The clinical outcome at one year follow-up in the actively treated patients was categorized as good to fair. The pain level reduced - from median values of 5 (range 5-6) to 3 (range 2-4) - and the performance improved - from median values of 3 (range 3-4) to 2 (range 2-3) ($p = 0.02$ and 0.03 , respectively).

Table 15. MRI of the Achilles tendon before (MRI 0), one week after (MRI I) and one year after the transverse core-biopsy procedure (MRI IV). The tendon volume in cm^3 in five different sagittal MRI-sequences is presented. The table also shows the difference in the Achilles tendon volume in %, as well as in the biopsy group before, one week (Δ volume I), and one year after the biopsy (Δ volume II). The non-parametric Wilcoxon Matched pairs test was used.

	MRI 0	MRI I	Δ volume I	P-value	MRI IV	Δ volume II	P-value
T1-WI	9.83	12.65	+29%	<0.05	7.87	-20%	<0.05
T2-WI	10.40	12.76	+23%	<0.05	7.96	-23%	<0.05
PD-WI	10.02	12.55	+25%	<0.05	7.69	-23%	<0.05
GE-WI	9.97	13.09	+31%	<0.05	6.95	-30%	<0.05
CME T1-WI	9.53	12.43	+31%	<0.05	7.52	-21%	<0.05

Table 16. MRI intratendinous signal alteration in signal units (SU) before (MRI 0), one week after (MRI I), and one year after the transverse core-biopsy procedure (MRI IV). The intratendinous signal alteration in five different sagittal MRI-sequences are presented. The table shows the difference in the Achilles tendon signal intensity in % in the biopsy group before, one week after (Δ signal I) and one year after the biopsy (Δ signal II). The non-parametric Wilcoxon Matched pairs test was used.

	MRI 0	MRI I	Δ signal I	P-value	MRI IV	Δ signal II	P-value
T1-WI	104	141	+36%	<0.05	68	-34%	<0.05
T2-WI	101	122	+21%	<0.05	76	-25%	<0.05
PD-WI	270	350	+30%	<0.05	194	-28%	<0.05
GE-WI	227	305	+34%	<0.05	151	-33%	<0.05
CME T1-WI	151	217	+43%	<0.05	95	-37%	<0.05



Graph 1 and 2. The volume of the Achilles tendon measured on T1-WI images (Graph 1) and the medial signal intensity of the Achilles tendon measured on PD-WI images (Graph 2) in a serial MRI; An index examination was undertaken before the ultrasound guided core-biopsy (MRI 0), then one week (MRI I), three months (MRI II), seven months (MRI III) and one year (MRI IV) after the biopsy procedure.

7.5 STUDY V

The main finding in this study was the significant decrease of tendon volume and intratendinous signal in all MRI-sequences, three months after eccentric calf muscle strength training ($P < 0.05$).

The eccentric training resulted in a 14 % (mean) decrease of tendon volume measured on T1-WI, from $6.6 (\pm 3.1) \text{ cm}^3$ to $5.8 (\pm 2.3) \text{ cm}^3$ ($p < 0.05$). The intratendinous signal in the symptomatic Achilles tendon measured on PD-WI decreased with 23 % (mean), from 227 (± 77) signal units (SU) to 170 (± 83) SU ($p < 0.05$). The most sensitive sequence to depict an intratendinous signal alteration was the PD-WI sequence, followed by the FLASH GE-WI, the CME T1-WI, the T2-WI, and lastly the unenhanced T1-WI sequences. All sequences showed a significantly decreased signal after training intervention (Table 17A and 17B).

The clinical outcome following three months of eccentric calf muscle strength training in the 25 patients was categorized as excellent in 10, good in 3, fair in 4 and poor in 8 patients. Three months of eccentric calf muscle training resulted in reduced pain - from median values of 5 (range 2 - 6) to 3 (range 1 - 6) - and improved performance - from median values of 4 (range 1 - 4) to 3 (range 1 - 4) ($p < 0.01$ and 0.001, respectively).

Table 17A. MRI intratendinous signal (mean and standard deviation) of the Achilles tendon in 25 patients before (MRI I) and after three months of eccentric calf muscle strength training (MRI II). Table A shows the tendon volume in cm^3 and table B the intratendinous signal alteration in signal units (SU) in five different sagittal MRI-sequences. Student's paired t-test was used.

Table 17A (Tendon volume)					
	MRI I		MRI II		P-value
	Mean (cm^3)	SD	Mean (cm^3)	SD	
T1-WI	6.55	3.07	5.78	2.31	0.02
CME T1-WI	7.20	2.42	6.33	2.82	0.03
PD-WI	7.38	2.91	6.36	2.61	0.02
GE-WI	7.47	4.39	6.68	3.90	0.03
T2-WI	7.62	2.12	6.57	1.86	0.0001

Table 17B (Intratendinous signal alteration)					
	MRI I		MRI II		P-value
	Mean (SU)	SD	Mean (SU)	SD	
T1-WI	75	22	62	20	0.005
CME T1-WI	130	54	96	47	0.0007
PD-WI	227	77	170	83	0.004
GE-WI	215	78	186	93	0.03
T2-WI	83	16	69	12	0.0006

The inter- and intra-observer reliability of the MR measurements shows excellent reliability. Tendon volume and mean intratendinous signal were calculated using a new seed growing technique showing 99.3% and 96.6% intra-observer reliability, respectively (Table 18 A-D).

Table 18A. Inter-observer reliability for total tendon volume			
	Mean	Reliability (R)	Coefficient of variation (CV)
First replicate*	7.28	98.6%	3.9%
Second replicate**	7.17	96.2%	5.3%

Table 18B. Intra-observer reliability for total tendon volume			
	Mean	Reliability (R)	Coefficient of variation (CV)
First observer***	7.35	99.3%	2.5%
Second observer****	7.11	97.6%	4.6%

Table 18C. Inter-observer reliability for mean intratendinous			
	Mean	Reliability (R)	Coefficient of variation (CV)
First replicate*	172.63	94.6%	7.1%
Second replicate**	164.80	78.0%	12.4%

Table 18D. Intra-observer reliability for mean intratendinous signal			
	Mean	Reliability (R)	Coefficient of variation (CV)
First observer***	175.22	96.6%	5.7%
Second observer****	162.21	83.5%	11.5%

*MR-measurement between the first reading of the first and second observer

**MR-measurement between the second reading of the first and second observer

***MR-measurement between the first and second reading of the first observer

****MR-measurement between the first and second reading of the second observer

7.6 STUDY VI

The immediate response to eccentric loading of the symptom-giving tendons resulted in a 12% increase of the tendon volume - evident on T2-WI ($p<0.001$) and a 31% increase of the intratendinous signal - evident on PD-WI ($p<0.001$) (Graphs 1 and 2). The corresponding sequences on the contralateral concentrically loaded tendons showed an increase of 17% of tendon volume ($p<0.001$) and an increase of 27% of the intratendinous signal ($p<0.001$) (Tables 19A and 19B).

There was no significant difference in the mean of the increased tendon volume and the intratendinous signal between eccentrically heavily loaded symptom-giving tendons and the concentrically loaded contralateral tendons.

Table 19. MRI of the eccentrically heavy loaded symptomatic tendons (group A) and the concentrically loaded contralateral tendons (group B), before (MRI I) and immediately after a standardized training program (MRI II). The total tendon volume in cm^3 (Table 19A) and the intratendinous signal in signal units (Table 19B) at three different sagittal MRI-sequences are presented. The tables show the difference in the Achilles tendon volume in % (Δ Volume) and intratendinous signal (Δ Signal), before and after strength training, using Student's *t*-test. The difference in the mean of the increased total tendon volume and intratendinous signal before and after strength training, between groups A and B (95% confidence interval, CF), are also presented.

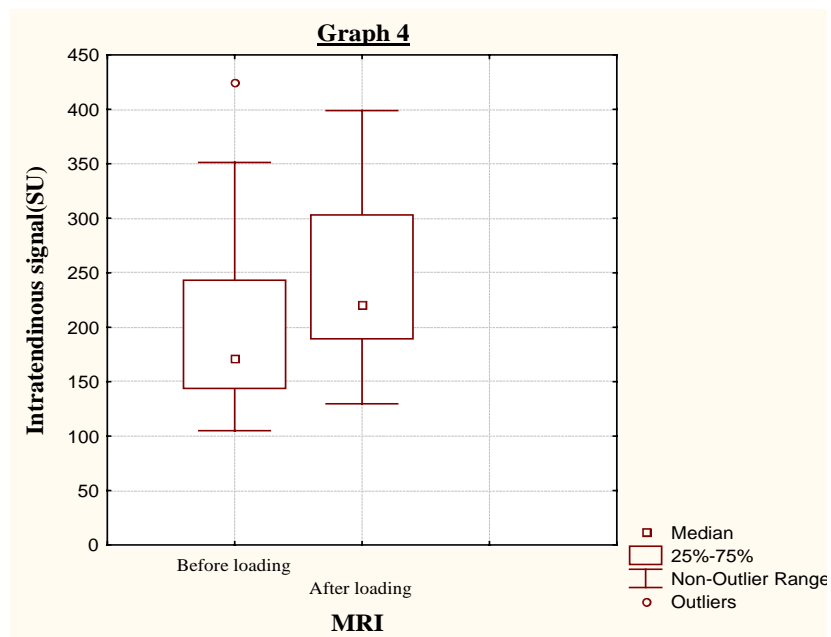
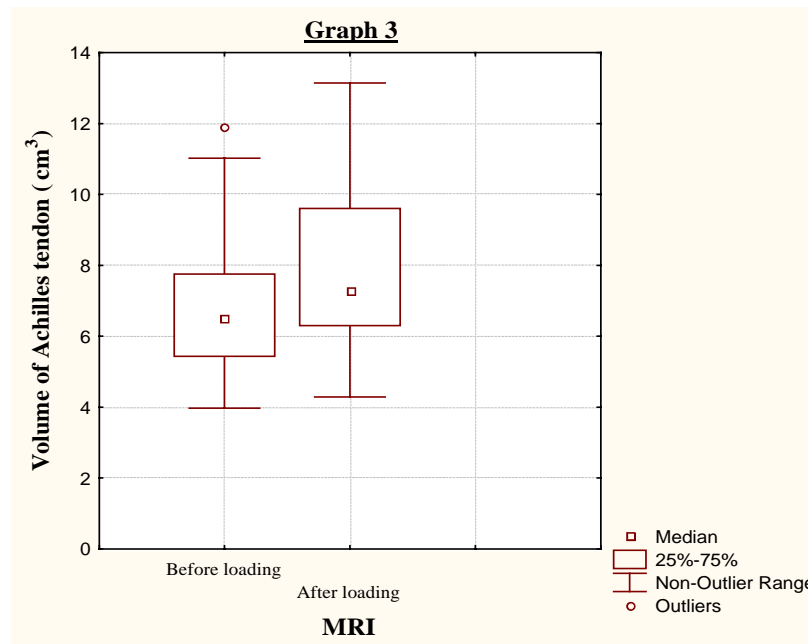
Table 19A. Total volume.

	Eccent. loaded symptomatic tendons (group A, nr = 22)					Concent. loaded contralateral tendons (group B, nr = 22)					Comparison A & B
	MR	MR	Δ	Δ 95%	P-	MR	MR	Δ	Δ 95%	P-	P- figure
	I	II	Volume	CF	figure	I	II	Volume	CF	figure	
T2	7.8	8.8	12 %	0.63-1.35	<0.001	6.1	7.0	17 %	0.58-1.30	<0.001	N.S.
PD	7.1	8.3	18 %	0.90-1.45	<0.001	5.2	5.8	14 %	0.49-0.90	<0.001	N.S.
GE	7.4	8.4	14 %	0.64-1.39	<0.001	5.0	5.9	18 %	0.67-1.09	<0.001	N.S.

Table 19 B. Intratendinous signal.

	Eccentrically loaded symptomatic tendons (group A, nr = 22)					Concentrically loaded contralateral tendons (group B, nr = 22)					Comparison A & B
	MR	MR	Δ	Δ 95%	P-	MR	MR	Δ	Δ 95%	P-	P- figure
	I	II	Signal	CF	figure	I	II	Signal	CF	figure	
T2	80	93	16 %	7-17	<0.001	78	91	15 %	5-18	<0.001	N.S.
PD	221	278	31 %	45-75	<0.001	170	211	28 %	33-53	<0.001	N.S.
GE	207	243	22 %	29-50	<0.001	141	180	31 %	32-48	<0.001	N.S.

Graph 3 and 4. Tendon volume, measured on T2-WI (graph 3) and mean intratendinous signal, measured on PD-WI (graph 4) of all 44 Achilles tendons before and immediately after strength training.



8 SUMMARY OF PAPERS

8.1 STUDY I

MRI evaluation of chronic Achilles tendinosis. A longitudinal study of 15 patients pre- and two years post-operatively.

Objectives

To evaluate patients with chronic painful Achilles tendinosis, before and two years after surgical treatment. The primary objective was to evaluate the tendon disorder and its healing process with MRI, including gadolinium contrast medium enhancement on T1-weighted images (CME T1-WI). The secondary objective was to evaluate the outcome of surgery in terms of subjective symptoms and clinical examination.

Main Results

There was a marked regression of the estimated volume of the intratendinous signal alteration from a median of 1.2 cm³ preoperatively to 0.0 cm³ postoperatively on CME T1-WI ($p = 0.001$). CME T1-WI showed a regression in intratendinous signal abnormality from 13 out of 15 patients preoperatively to 4 out of 15 patients two years postoperatively. However, the AP dimension remained unchanged at 9 mm, on both MRI occasions. The clinical outcome was excellent in eight, good in five, fair in one and poor in one patient.

Conclusion

Surgical treatment of chronic Achilles tendinosis and ensuing tissue healing resulted in a decrease or elimination of the intratendinous signal alteration, and correlated well to an improved clinical outcome two years postoperatively.

8.2 STUDY II

Dynamic contrast-enhanced MR imaging and histopathology in chronic Achilles tendinosis. A longitudinal MRI-study of 15 patients.

Objectives

To evaluate early contrast agent enhancement in dynamic gadolinium contrast agent enhanced MR imaging (DEMRI) in patients with chronic painful Achilles tendinosis. To correlate DEMRI to the histopathological findings in core biopsy tendon specimens obtained by ultrasound guiding. To correlate DEMRI to symptoms preoperatively and two years following surgical treatment, and to correlate DEMRI with static MRI.

Main Results

Early contrast enhancement (during the first 72 s) was seen in DEMRI in tendon lesions of the symptom-giving Achilles tendons; there was a significant difference to the asymptomatic contralateral tendons - in which no or only mild enhancement was noted ($p = 0.01$). Increased severity of histologically revealed changes in tendons (including i.a. fiber structure abnormality, increased vascularity, rounding of nuclei and increased amount of glycosaminoglycans) was correlated to both dynamic and static signal enhancement ($p = 0.04$ and 0.01 , respectively). Two years following surgical treatment, the signal alterations showed regression of early contrast enhancement (AUC decreased from 9 preoperatively to 2 post-operatively) ($p = 0.005$). The clinical outcome was rated by the patients to excellent (8), good (4), fair (2) and poor (1).

Conclusion

Patients with chronic painful achillodynia showed an early contrast agent enhancement corresponding to the tendon lesion. Increased enhancement correlated to increased severity of tendon histopathology and patient symptoms. Contrast agent enhancement decreased two years following surgical treatment.

8.3 STUDY III

Reliability in the assessment of tendon volume and mean intratendinous signal alterations of the Achilles tendon on MRI. A methodological description.

Objectives

To introduce a method for accurately and objectively evaluating volume and mean intratendinous signal within the Achilles tendon using MRI.

Main Results

The computerized 3-D seed growing technique resulted in an excellent overall observer reliability of the MRI-measurements. The reliability (R) regarding tendon volume measurements was highest for the T1-WI sequence ($R = 97.9\%$). For the mean intratendinous signal, the PD-WI sequence showed the highest reliability ($R = 88.1\%$). The same pattern was present when the coefficient of variation (CV) was studied. For the CV, lower figures indicate more reliable estimates. CV was 4.9% for tendon volume and 8.9% for mean intratendinous signal.

Conclusion

A computerized 3-D seed growing technique to monitor and evaluate the volume of the Achilles tendon and mean intratendinous signal, using MRI, shows an overall excellent reliability regarding inter- as well as intra-observer reliability. This method can be used in

studies to evaluate morphological effects following surgical and/or non-surgical treatment interventions directed toward the Achilles tendon.

8.4 STUDY IV

Tendon injury and repair following core-biopsies in chronic Achilles tendinosis evaluated by serial MR imaging.

Objectives

To evaluate the morphological response of transversal core-biopsies in patients with chronic Achilles tendinosis, using serial MRI, during a period of one year.

Main Results

One week after the biopsy procedure, MRI showed an increase of tendon volume (T1-WI) and mean signal intensity (PD-WI) with 29% and 30%, respectively ($p = 0.04$). During the follow-up period, tendon volume and mean signal intensity gradually decreased. One year after the biopsy procedure, the tendon volume had decreased with 20% and the intratendinous signal with 28% compared with the index MRI ($p = 0.04$). The untreated patients, however, revealed both an increasing tendon volume (39%, $p = 0.06$) and intratendinous signal (37%, $p = 0.14$) at the one-year follow-up. The clinical outcome after one year in terms of pain level and performance was improved in the treated patients, while none of the untreated patients was improved.

Conclusion: Five transverse ultrasound-guided core-biopsies induced a lesion in the diseased Achilles tendon. Alterations during healing, such as tendon size and intratendinous reactive changes, could be monitored by MR imaging. The tendon alterations imaged by MR had subsided one year after core-biopsies were taken.

8.5 STUDY V

Eccentric training of the gastrocnemius-soleus complex in chronic Achilles tendinopathy results in decreased tendon volume and intratendinous signal as evaluated by MRI.

Objectives

To evaluate patients with chronic painful Achilles tendinopathy, before and immediately after three months of daily eccentric calf muscle strength training. To use MRI to evaluate tendon volume and intratendinous signal alterations, and to evaluate the outcome of eccentric calf

muscle strength training in terms of subjective pain and disability - and correlation to the MRI findings.

Main Results

The eccentric training resulted in a 14 % (mean) decrease of tendon volume measured on T1-WI, from 6.6 (\pm 3.1) cm³ to 5.8 (\pm 2.3) cm³ ($p < 0.05$). The intratendinous signal in the symptomatic Achilles tendon measured on PD-WI decreased 23 % (mean), from 227 (\pm 77) signal units (SU) to 170 (\pm 83) SU ($p < 0.05$). The clinical outcome was categorized as excellent in 10, good in 3, fair in 5 and poor in 8 patients.

Conclusions

Eccentric training resulted in decreased tendon volume and intratendinous signal, and was correlated to an improved clinical outcome. MRI techniques can be used as an adjunct to clinical evaluation by monitoring morphological effects in clinical treatment studies of Achilles tendinopathy.

8.6 STUDY VI

Immediate Achilles tendon adaptation following strength training of gastrocnemius-soleus complex, evaluated by MRI.

Objectives

To evaluate the immediate tendon response by MRI following gastrocnemius-soleus complex strength training in patients with chronic Achilles tendinosis, in terms of tendon volume and intratendinous signal intensity.

Main Results

The immediate response of eccentric loading on the symptomatic tendons resulted in a 12% increase of the tendon volume, evident on T2-WI ($p < 0.001$), and a 31% increase of the intratendinous signal evident on PD-WI ($p < 0.001$). The corresponding sequences on the contralateral concentrically loaded tendons showed an increase of 17% of tendon volume ($p < 0.001$) and an increase of 27% of the intratendinous signal ($p < 0.001$). There was no significant difference in the mean of the increased tendon volume and the intratendinous signal between the eccentrically heavily loaded symptomatic tendons and the concentrically loaded contralateral tendons.

Conclusions

Both eccentric and concentric loading of the Achilles tendon resulted in increased total tendon volume and intratendinous signal. This increase may be explained by a higher water content and/or hyperemia in the Achilles tendon during, and/or immediately after, strength training of the gastrocnemius-soleus complex.

9 GENERAL DISCUSSION

9.1 MRI

The ability to image the internal structures of the tendon, the proper evaluation of different treatment strategies, and the ensuing healing process require an objective imaging modality. In clinical practice, US may be the first choice concerning chronic Achilles tendon disorders (Neuhold et al., 1992). However, MRI has a clear advantage over US, as the images more easily can be evaluated in a standardized manner in longitudinal studies (Movin, PhD thesis, 1998). The literature suggests that MRI and US are superior to other imaging modalities in the detection and evaluation of intratendinous changes (Åström et al., 1996, Movin et al., 1998). MR imaging can provide important information about the pathologic state of the Achilles tendon, and these imaging findings can provide information that is useful in patient treatment (Schweizer and Karasick, 2000).

MRI-techniques of different designs were the methods of choice in all studies of this thesis. These techniques enabled us to distinguish between various intratendinous physiologic and pathologic alterations.

9.1.1 Static and dynamic contrast agent enhancement (studies I-II)

The enhanced T1-WI was the best sequence depicting an intratendinous lesion; the Gd-contrast agent increased the signal intensity and size of the lesion depicted on T1-WI preoperatively (**study I**). Further, the addition of the Gd-contrast agent made it possible to reveal lesions not detected on other sequences. The literature on the application of Gd CME on tendons is limited (Movin et al., 1998a, Movin et al., 1998b, McLoughlin et al., 1995).

Movin et al. (1998) used Gd CME in patients with chronic mid-portion Achillodynia and concluded that the intratendinous signal alterations were more obvious after Gd contrast agent was used (Movin et al., 1998a) and that Gd CME depicted a larger size of the intratendinous abnormality than US (Movin et al., 1998b). McLoughlin et al. (1995) studied 15 patients with patellar tendonitis by gadolinium-enhanced MR imaging and graded the patellar abnormality, based on findings in the enthesial region at MR imaging. Oatridge et al. (2003) showed that changes due to contrast agent enhancement were much more evident on images obtained using the magic angle phenomenon.

The mechanism behind contrast agent enhancement in tendon lesions is not fully understood. When the contrast agent reaches and is distributed within the intravascular and interstitial extracellular compartments, an increased vascularity and/or vascular permeability, or increased volume of interstitial stroma, may explain the contrast enhancement in pathologically changed tissue as apposed to in the surrounding normal tissue (Bone et al., 1998).

To better understand the mechanism of contrast agent enhancement in chronic Achilles tendinosis, we studied how the dynamic Gd-contrast agent enhanced MR imaging (**study II**).

In this study, the principle finding was the early contrast agent enhancement noted, within 72 s in dynamic MR imaging of chronic Achilles tendinosis. Thus, a vascular disturbance may be considered in chronic tendinosis.

Dynamic Gd-contrast agent enhanced MR imaging has recently evolved as an important method for evaluating various diseases of the musculoskeletal system, especially musculoskeletal tumors (Cova et al., 1991, Bonnerot et al., 1992, Erlemann, 1993). The early effect of the Gd-contrast agent appears within seconds after intravenous injection, almost synchronous with the arterial enhancement. The contrast-enhanced MR images readily show differences between viable and necrotic tumors (Shapeero et al., 1992). Dynamic MRI is thus a method of physiologic imaging, evaluating the early kinetics of the Gd-contrast agent. Since the sequences are performed during and immediately after a bolus injection of the contrast agent, they reflect the early contrast distribution in the capillaries and interstitial tissue. This technique thus provides information about tissue vascularity, perfusion and capillary permeability (Brasch et al., 1992, Verstraete et al., 1994). On the other hand, the standard static Gd-contrast agent enhancing MR images are performed several minutes after the injection of the contrast agent. At the point in time when the images are obtained, the contrast agent has equilibrated between the blood vessels and the interstitial spaces. This is why these “static” standard MR images mainly give a spatial resolution of the anatomy and pathologic changes (Erlemann, 1993, Fletcher et al., 1992).

9.1.2 MR-sequences

Different echo sequences can be used in the evaluation of the condition of the Achilles tendon. T1 weighted image (WI) is the most commonly used sequence in any MRI examination protocol. The tendon anatomy as well as tendon borders and limits, are most sharply demarcated on the T1-WI sequence. The addition of Gd contrast agent to this sequence improves the imaging of the abnormal intratendinous signal by discriminating between the symptomatic and healthy tendons, which may be of clinical importance (Movin et al., 1998a). Movin et al. (1998a) showing that MR imaging of symptomatic tendons (n=25) on enhanced T1-WI images revealed an intratendinous signal abnormality that was intermediate or high in 24 out of 25 symptomatic tendons, compared to 20 on PD-WI images, and 12 on T2-WI images. These findings are in agreement with our findings in studies I-II, as Gd CME was the most sensitive sequence depicting intratendinous signal.

The T2-/PD-WI spin-echo sequences can depict the abnormal composition within the tendon as a high or intermediate signal alteration. However, a shorter echo time has been noted to increase the sensitivity, depicting intratendinous alterations when gradient echo sequences (GRE) have been used (Koblik & Freeman, 1993, Reiff et al., 1995). Khan et al. (1996) showed that T2 gradient echo sequences revealed a larger area of high signal intensity in the patellar tendon than either T1-WI or T2-WI fast spin-echo sequences. This has been shown also in achillodynia patients. Karjalainen et al. (2000) used T1-weighted gradient-echo

MR imaging in the evaluation of 100 symptomatic patients and concluded that a more specific diagnosis and prognosis can be made with the use of MR imaging than with clinical examination alone (Karjalainen et al., 2000). Soila et al. (1999) concluded that by using T1-weighted gradient-echo (fast low-angle shot, FLASH) and short inversion time inversion recovery (STIR) sequences, heterogen signal intensity was seen in 45 out of 100 asymptomatic Achilles tendons (Soila et al., 1999). Furthermore, GRE sequences may reveal intratendinous signal alterations in up to 75% of the proximal patellar tendon without corresponding symptoms (Reiff et al., 1995) and in 45% of the asymptomatic Achilles tendons (Soila et al., 1999). Thus, the variability and high sensitivity on GRE sequences may be a potential source of diagnostic misinterpretation.

The use of magic angle MR imaging was found to improve the demonstration of signal changes in the Achilles tendon in chronic tendinopathy. The STIR images obtained at the magic angle, 55 degrees, showed a more obvious signal change than those obtained at 0 degrees. Furthermore, the changes due to contrast agent enhancement were much more evident on images obtained at 55 degrees than at 0 degrees (Oatridge et al., 2003).

Li et al. (2003) investigated the effect of varying the echo time (TE) figures and angle of the bovine Achilles tendon to the main magnetic field on the signal intensity observed with the magic angle phenomenon in tendons among most commonly used MR pulse sequences, including conventional spin echo (CSE), fast spin echo (FSE) and gradient echo (GRE) sequences. The magic angle phenomenon occurs in CSE, FSE and GRE sequences in differing degree, appearing most severe in CSE, intermediate in FSE, and weakest in the GRE sequence. In addition, the tendon signal changes produced by the magic angle phenomenon could be greatly reduced by increasing the TE to above a certain critical level in all three sequences. These critical TE levels, differed between CSE (40 msec), FSE (70 msec), and GRE (30 msec) sequences (Li et al., 2003).

9.1.3 3-D seed growing technique (studies III-VI)

The computerized 3-D seed growing technique showed excellent overall inter- and intraobserver reliability of the results regarding tendon volume and mean intratendinous signal. Limitations of this technique were i.a. the necessity of importing the MRI-data to a Hermes workstation after the MRI examination was performed. Furthermore, this technique required a specially designed software program to facilitate the standardization of the measurements. The manual work time for measurement was approximately 2 minutes per sequence that was analyzed.

The standardization of US measurements has obvious difficulties and standardization of cross section areas and AP-diameters with high precision is very difficult - even for the experienced radiologist. Another pitfall in US examination is the position of the probe, which is very important since a faulty position might cause anisotropy (Grrass et al., 1988). The relaxation of the calf muscles when the US examination with CDV/CDE is performed also

important, as a contraction of the muscles may reduce the blood flow in the neovessels (Öhberg, 2003).

The standardization of the investigation MRI-protocol, factors such as position of the feet in the coil, the magnetic field, the type of sequences used and exertion must all be considered. In our studies, all paired MRI examinations were performed with the same machine, the same position of the feet in the coil, the same sequences, and without exertion - disregarding walking prior to examinations at MRI unit. Using this technique, the highest reliability when measuring tendon volume and intratendinous signal was achieved with the T1-WI and PD-WI sequences, respectively.

9.2 TENDON PATHOLOGY

The mid-portion of the Achilles tendon is among the most frequently injured tendons of the body. The morphological response following different treatment interventions has been studied in this thesis.

9.2.1 Studies I-II

The response to surgical treatment and tendon healing was evident by the elimination of intratendinous alterations at a two-year follow-up. The mechanism of pain in chronic Achilles problems has not been scientifically clarified (Khan et al., 2000). Recent studies using intratendinous microdialysis and gene technological investigations showed an absence of chemical inflammation in the chronic stage and a significantly increased concentration of neurotransmitter glutamate in painful Achilles tendinosis, compared to the pain-free normal tendons (Alfredson et al., 1999 and 2003). However, the role of glutamate - which is a potent modulator of pain in the human central nervous system - in the chronic painful Achilles tendon is still unknown. In another study by Alfredson (2002), higher levels of lactate were demonstrated in Achilles tendinosis than in normal tendons, indicating presence of ischemia.

The correlation between early contrast enhancement and the histopathological total tendon score of the tendon specimens obtained by US-guided core biopsy in study II indicates that the enhancement may be a result of several factors.

The findings in this study show that the contrast enhancement was correlated to an increased presence of cell nuclei that had acquired a rounded shape. This may reflect a change of the ability of tenocytes to synthesize matrix substances such as collagens, proteoglycans and non-collagenous proteins. Thus, the rounded tenocyte nuclei may be a confounding factor without specific effect on the Gd-enhanced signal intensity.

Typical histopathological findings in painful Achilles tendinosis are derangement of collagen fibers, increased amounts of non-collagenous matrix (seemingly glycosaminoglycans-GAGs), and increased vascularity and cellularity (Åström & Rausing, 1995, Movin et al., 1997). Lowered fluid content in the tendon may result from reduced levels of GAGs (known for their extreme water-binding capacity) - a common finding in Achilles tendinosis.

The early contrast enhancement led our thoughts concerning the cause to a vascular disturbance or vascular leakage. Öhberg et al. (2001) found neovascularization in the area with Achilles tendon changes using gray-scale US combined with color Doppler examination. The vascularized area seen by color Doppler disappeared when the tendon was tensed, suggesting a pump mechanism (Öhberg et al., 2001). Furthermore, a pilot study of US-guided sclerosis of the neovessels with polidocanol has been reported as an effective treatment in chronic Achilles tendinosis (Öhberg et al., 2002).

9.2.2 Study IV

The tendon healing occurs in three phases: an inflammatory stage, a reparative or collagen-production stage - and finally - a remodelling or maturation stage influenced by normal loads. Inflammation occurs during the first three days after injury, collagen synthesis is seen within the first week and the collagen content increases through the first four weeks. Collagen maturation and functional linear realignment is usually seen around two months after injury (Gelberman et al., 1987).

Our design in this study is a description of the tendon healing process. The iatrogenic acute small Achilles tendon lesion resulted in increased tendon volume and intratendinous signal after one week, corresponding to the inflammatory phase of the normal healing process. This signal then decreases but is still evident on MRI after three months and disappeared or further diminished at seven month and one year MRI-examination (maturation phase). These findings describe the healing process evaluated by MRI.

Studies dealing with the healing process of the Achilles tendon are sparse, especially those of non-rupture etiology. A case report using MRI evaluation with a 6 months follow-up of an intratendinous Achilles tendon lesion with acute clinical onset reported regression of the lesion following non-surgical treatment (Nicolaisen et al., 1997).

With regard to ruptured Achilles tendons, Karjalainen et al. (1997) described the MRI appearance following surgical repair, with high-intensity signal areas at the rejoined tendon ends at 6 weeks and 3 months believed to correspond to the healing response. These areas of high-intensity signal diminished in size - or disappeared completely - after 6 months.

In the surgically repaired total rupture, the maximal tendon dimension occurred after 3 months, followed by a decrease (Karjalainen et al., 1997). These findings are in agreement with the observation in the present study of the tendon lesion induced by the biopsies and its subsequent repair in chronic Achilles tendinosis, resulting in early increase of tendon volume and intratendinous signal intensity followed by a gradual decrease.

9.2.3 Study V

The biological effect of eccentric training in Achilles tendinopathy is unclear. The reduced tendon volume and intratendinous signal on MRI may speculatively be a result of reduced fluid content in the tendon or a consequence of improved healing with collagen deposition.

Loading could influence the shape and function of tendons. The tendon cells generally respond to “windows” of augmented loading by increased matrix synthesis and modifications of their production of matrix components. There is a direct influence of eccentric loading in Achilles tendinopathy on the cells. Tendon cells have the potential to communicate with one another via cell processes and gap junctions and thus can be expected to use direct cell/cell communication to detect and/or coordinate their load responses (McNeilly et al., 1996). It is thus tempting to speculate that loading of the cells between the deranged fibres in tendinosis tissue may induce a healing response; if so, the notion supports the theory that eccentric loading in Achilles tendinopathy results in improved healing with collagen deposition and restoration of the matrix component.

The tensile loading of the tendon may speculatively “squeeze out” fluid, or the fluid may be reduced by vascular mechanisms. Thus, the Achilles tendon effect by eccentric loading on nerves and vessels, e.g. by obliteration or nerve stimulation, may speculatively explain reduced pain and the resolution of the intratendinous changes.

Ingrowth of nerves and vessels in chronic Achilles tendinosis may contribute to pain and tenderness, and further be of importance in the repair of the tendon matrix. However, intratendinous levels of the neurotransmitter glutamate showed no significant difference before and after three months of eccentric training, while the treatment successfully reduced tendon pain (Alfredson et al., 2003). Because substance P and other neuropeptides have been detected in the tendon, there are indications for a neurogenic factor. Nerve endings and mast cells in the matrix exist as functional units in the tendon matrix. The release of neuropeptides such as substance P (SP), and calcitonin gene related peptide (CGRP) stimulate the degranulation of the mast cells, releasing a parade of agents modulating a variety of cell activities in the matrix (Hart et al., 1995, Riley, 2003).

Our findings on MRI with decreased tendon volumes and mean intratendinous signals following eccentric loading give evidence for an improved tendon structure and tendon composition indicating healing of the tendon lesion.

9.2.4 Study VI

The immediate Achilles tendon adaptation following loading with an increase in tendon volume and intratendinous signal may be explained by hyperemia and/or higher water content in the tendon during, and/or immediately after strength training of the gastrocnemius-soleus complex.

The Achilles tendon receives its blood supply along the whole length of the musculo-tendinous region, and in the region for its insertion (Carr et al., 1989). Anteriorly, the tendon is attached to a richly vascularized tissue, which is considered most important to the Achilles tendon (Barfred et al., 1973). Human data suggest that the blood flow during rest is evenly distributed in healthy Achilles tendons (Åström et al., 1994). However, chronic Achilles tendinosis is associated with increased blood flow in the painful region (Åström et al., 1994).

The blood flow associated with the tendon increases up to 7-fold during exercise, independent of the age of the individual (Boushel et al., 2000, Langberg et al., 2001). It has further been observed that the blood flow around the tendon during exercise only reaches 20% of its maximal flow capacity observed during reactive hyperemia (Boushel et al., 2000). These data suggest that the Achilles tendon blood flow may be remarkably low during rest. The alterations of Achilles tendon blood flow during - and immediately after - eccentric training may thus contribute to the observed increased tendon volume and altered tendon composition.

The fibrillar collagen is embedded in a hydrophilic extracellular matrix consisting of proteoglycans and glycoproteins. The non-collagenous extracellular matrix contributes in important ways to the mechanical integrity of the tendon. Proteoglycans are complex macromolecules consisting of a protein core with at least one GAG-chain, such as dermatan sulfate, chondroitin sulfate or heparan sulfate. Large proteoglycans like versican and aggrecan provide mechanical support and are strongly hydrophilic, thereby attracting osmotically active cations, forcing water into the matrix, and also enabling rapid diffusion of water - soluble molecules- and migration of cells. The GAGs may trap water in amounts as much as 50 times their own weight (Wolfe, 1993). Increased amounts of GAGs are - along with increased vascularity and altered fiber structure and arrangement - the characteristic morphological features in chronic Achilles tendinosis (Movin et al., 1997). In healthy Achilles tendons, the amounts of GAGs are low within the tendon itself, higher in the paratenon. The water binding potential of the proteoglycans can hypothetically be important to explain the immediately increased tendon volume and increased tendon signal in the Achilles tendon following eccentric strength training.

9.3 CLINICAL OUTCOME

The variety in the results of clinical outcome studies depends on several factors, such as poor study design, diagnostic criteria and validity, selection bias, treatment methods - such as the surgical technique - and the rehabilitation programs. The methods that form the biases of scientific articles can have a considerable impact on the reported outcome for surgery of Achilles tendinopathy (Tallon et al., 2001).

Surgical treatment of patients with chronic Achilles tendinopathy in our prospective **studies I-II** was satisfactory, as 13 of 15 patients (87%) showed improved and satisfactory clinical outcome. Table 20 exemplifies the clinical outcome following surgical treatment in patients with chronic Achilles tendinopathy.

Table 20. Survey of surgical results of mid-portion Achillodynia in the literature.
RS = Retrospective study, PS = Prospective study

Authors	Type of study	Year	No of patients	Age/ year	Diagnosis	Surgical technique	Satisfactory results (%)
Ljungqvist	RS	1968	24	37	Partial rupture	Excision/flaps	100
Kvist & Kvist	RS	1980	201	27	Paratendonitis	Fascia release	97
Schepesis & Leach	RS	1987	24	29	Tendinitis	Fascia release/ Excision	92
Nelen et al.	RS	1989	93	30	Peritendinitis	Fascia release/ Excision	86
			26	30	Tendinosis	Excision	73
			24	30	Tendinosis	Excision/flaps	87
Rolf & Movin	RS	1997	18	37	Peritendinitis	Fascia release/ Excision	72
			21	42	Tendinosis	Excision	76
			19	40	Paratendonitis + Tendinosis	Fascia release/ Excision	78
Maffulli et al.	RS	1999	14	34	Tendinosis	Excision/longitudinal incision	36
Shalabi et al.	PS	2001	15	39	Tendinosis	Longitudinal Excision	87

The clinical outcome reported in **study IV**, one year after intervention using US-guided core-biopsy was improved in terms of pain level and performance in the treated patients (4/6), while none of the untreated patients was improved. The notion that use of needling or intervention US-guided core-biopsy could be regarded as potential treatment options remains to be further studied and evaluated in larger prospective series; since our study was limited to a small number of patients.

Eccentric loading reported in **study V** showed that 13/25 (52%) of the patients improved in terms of subjective pain and disability. Results of uncontrolled studies have suggested that eccentric loading is effective in the treatment of tendon pain (Table 21) (Alfredson et al. 1996, Silbernagel et al., 2001, Stanish et al., 2000).

Two randomized studies have shown that eccentric calf muscle training gives satisfactory subjective short-term results. Mafi et al. randomized 44 patients to treatment with either an eccentric or a concentric training regimen for the calf muscles. The results showed

that - after the eccentric training regimen - 82% of the patients (18/22) were satisfied and had resumed their previous activity level, compared to 36% of the patients (8/22) who were treated with the concentric training regimen (Mafi et al., 2001).

Silbernagel et al. randomized 44 Achilles tendons with proximal achillodynia. The treatment protocol with eccentric overload showed improvements in plantar flexion, and reduction in pain at palpation and during walking compared to the control group. 23 out of 44 patients had pain during activity prior to treatment. One-third of these patients (8/23) experienced a satisfactory result after three months of eccentric and concentric loading (Silbernagel et al., 2001).

The results of an unpublished long-term study by Öhberg et al. (2003) on 26 Achilles tendons with tendinosis evaluated by US showed that 19/26 (73%) tendons normalized after a mean of 3.8 years following a 12-week eccentric training regime. The clinical results showed 22 patients with excellent clinical outcome, and 4 patients who were not satisfied.

Our short-term study showed a morphological response and an improved tendon composition on MRI, following three months of eccentric training.

Table 21. Survey of results of eccentric loading in mid-portion Achilles tendinosis in the literature. ST = Prospective short-term study, LT = Prospective long-term study

Authors	Type of study	Year	Number of tendons	Age/ year	Diagnosis	Type of loading	Results (%)
Alfredson et al.	ST	1996	15	44	Tendinosis	Eccentric	100
Mafi et al.	ST	2001	22	48	Tendinosis	Eccentric	82
			22	48	Tendinosis	Concentric	36
Shalabi et al.	ST	2003	25	51	Tendinosis	Eccentric	52
Öhberg et al.	LT	2003	26	50	Tendinosis	Eccentric	84

10 FINAL REMARKS AND CONCLUSIONS

The overall conclusion is that MRI-techniques can be used as an adjunct to clinical evaluation by monitoring morphological effects following different treatment interventions, thereby adding evidence in clinical studies on patients with chronic Achilles tendinopathy.

In the different papers the specific conclusions were:

- Surgical treatment of chronic Achilles tendinosis and ensuing healing resulted in a decrease - or elimination - of the intratendinous signal alteration, correlating to an improved clinical outcome two years postoperatively.
- Patients with chronic painful achillodynia showed an early contrast agent enhancement corresponding to the tendon lesion. Increased enhancement correlated to increased severity of tendon histopathology and patient symptoms. Contrast agent enhancement decreased two years following surgical treatment.
- The computerized 3-D seed growing MRI-technique to monitor and evaluate the volume of the Achilles tendon, and the mean intratendinous signal, showed an excellent inter- and intra-observer reliability.
- Five transverse ultrasound-guided core-biopsies induced a lesion in the diseased Achilles tendon. The tendon volume and mean intratendinous signal imaged by MRI had subsided at the seven and twelve month's follow-up.
- Three months of daily-performed eccentric training of the calf muscle resulted in decreased tendon volume and mean intratendinous signal, along with improved clinical outcome.
- The tendon volume and mean intratendinous signal were increased 30 minutes after eccentric and concentric loading of the Achilles tendon. This adaptation on the part of the tendon may be explained by a higher water content and/or hyperemia.

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