

Achilles tendon rupture; Assessment of non-operative treatment

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This review has been accepted as a thesis together with four previously published papers by University of Copenhagen 15th of November 2013 and defended on 10th of January 2014

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Dan Med J 2014;61(4):B4837

The four original papers are:

I. Barfod KW, Nielsen F, Helander KN, Mattila VM, Tingby O, Boesen A, Troelsen A. Treatment of acute Achilles tendon rupture in Scandinavia does not adhere to evidence based guidelines. A cross-sectional questionnaire-based study of 138 departments. *American Journal of Foot and Ankle Surgery*. 2013;52(5):629–633.

II. Barfod KW, Bencke J, Lauridsen HB, Ban I, Ebskov L, Troelsen A. Non-operative, dynamic treatment of acute Achilles tendon rupture: The influence of early weight-bearing on clinical outcome. A blinded, randomized, controlled trial. Submitted manuscript.

III. Barfod KW, Bencke J, Lauridsen HB, Dippmann C, Ebskov L, Troelsen A. Non-operative, dynamic treatment of acute Achilles tendon rupture: The influence of early weight-bearing on biomechanical properties of the plantar-flexor muscle-tendon complex. A blinded, randomized, controlled trial. Submitted manuscript.

IV. Barfod KW, Riecke AF, Boesen A, Hansen P, Maier JF, Døssing S, Troelsen A. Validation of a Novel Ultrasound Measurement of Achilles tendon Length and Elongation. Submitted manuscript.

ABBREVIATIONS

ASA	American Society of Anesthesiologists
ATRS	Achilles tendon Total Rupture Score
ICC	Intraclass correlation Coefficient
MDC	Minimal Detectable Change
MRI	Magnetic Resonance Imaging
PROM	Patient Reported Outcome Measure
RCT	Randomized Controlled Trial
RSA	Roentgen Stereophotogrammetric Analysis
SEM	Standard Error of the Measurement
US	Ultrasound

1 INTRODUCTION

'This tendon, if bruised or cut, causes the most acute fevers, induces choking, deranges the mind, and at length brings death'
Hippocrates

The Achilles tendon was named after the Greek hero Achilles, the central character and greatest warrior of Homer's Iliad. To protect Achilles from harm, his mother dipped him into the River Styx. However, his heel was left vulnerable, as it was not covered by water. During the Trojan War, Achilles was struck on his unprotected heel by a poisoned arrow and died⁴³. The Achilles tendon is also called the calcaneal tendon. The oldest known written record using the term 'Achilles tendon' is found in the work *Corporis Humani Anatomia*, published in 1693 by the Dutch anatomist Philip Verheyen²⁹.

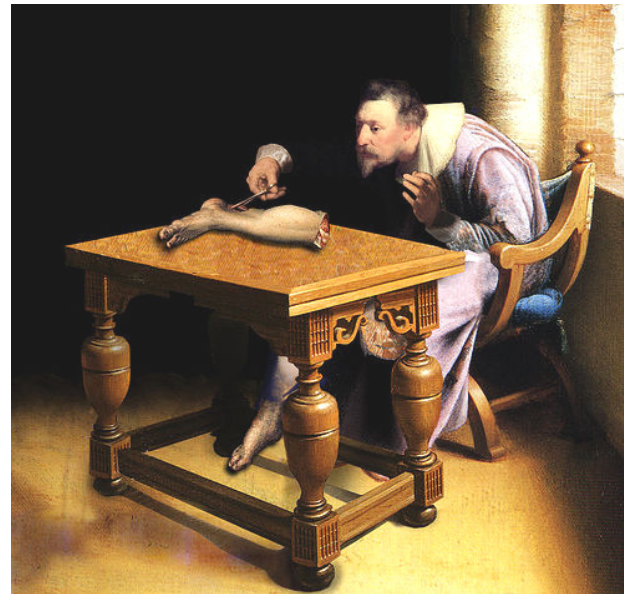


Figure 1: As a young man Philippe Verheyen had his lower limb amputated due to illness. It was preserved to be buried with him. In his older days he investigated his own limb to see if his phantom pain in fact originated from the actual amputated limb. Title: Philippe Verheyen Dissecting His Amputated Limb (1715-1730), Artist unknown. Source: Collection of Pieter Deheijde

Acute Achilles tendon rupture is, and has always been, a problem for the affected person and for society. It affects people in their most active years and follows them for the rest of their life. The area has been the focus of intense research over the past decades and treatment protocols have been continuously debated. Over the past five to ten years a shift towards non-operative treatment has been observed^{8,74}, notoriously raising the question: 'What is the optimal non-operative treatment protocol for acute

Achilles tendon rupture?’ It is my hope that this thesis will aid in illuminating this question.

2 THE ACHILLES TENDON

“If you can’t explain it simply, you don’t understand it well enough”
 Albert Einstein

2.1 ANATOMY

The Achilles tendon is the strongest and thickest tendon in the body. It transfers energy from the leg to the foot and is essential for walking, running and postural control. It serves to transmit force from the suralis muscle to the calcaneal bone.

2.1.1 The suralis muscle

As the name indicates, the suralis muscle consist of three parts: the gastrocnemius muscle containing two superficial heads and the soleus muscle containing the profound head (figure 2 and 3). The gastrocnemius muscle is two headed originating from the medial and lateral femur epicondyles, respectively, making the suralis muscle span two joints: the knee and ankle joint.



Figure 2: The anatomy of the Achilles tendon and the suralis muscle.

The muscle fibers are mainly type II and 6-8cm long, making them capable of explosive contractions used for jumping and running. They insert in a profound, gathered tendon sheet. The medial head is the most distal. The soleus muscle originates from the posterior site of tibia. The muscle fibers are 2-3 cm long and organized in a multipennat pattern. The soleus muscle consist mainly of type I fibers making it the workhorse in postural control and walking. The soleus muscle inserts in a superficial tendon sheet that gathers with the tendon sheet of the gastrocnemius muscle half way down the calf to form the Achilles tendon (figure 2 and 3).^{1,16,137}

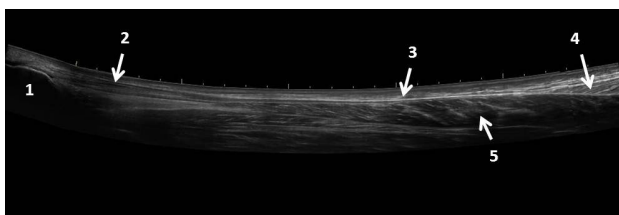


Figure 3: A panoramic ultrasound picture of the calf: 1) Calcaneus, 2) The Achilles tendon, 3) the convergence of the tendon sheets of the suralis and soleus muscles, 4) the gastrocnemius muscle, and 5) the soleus muscle.

2.1.2 The Achilles tendon

The Achilles tendon has a cross sectional area of approximately $\frac{1}{2}$ cm² (figure 2 and 3). It rotates 180° in supination before inserting at the calcaneal bone¹⁶. This spiraling of the tendon contributes to the elastic recoil of the tendon⁹³. The insertion in the calcaneal bone, the enthesis, has been estimated to be four times as strong as the mid substance of the tendon⁷⁵. The Achilles tendon is covered by a tendon sheet on the posterior/superior side of the tendon, but not at the anterior/inferior side. The plantaris tendon is found within the tendon sheet just medial to the Achilles tendon.

2.1.3 Architecture of the tendon

The Achilles tendon is built of collagen molecules in a complex matrix of left and right turned helices bound together by proteoglycans¹⁶. Type I collagen constitutes 95% of the total collagen. The remaining 5% consist of type III and V, mainly located to the enthesis and the epitenon.

The tendon is a hierarchical structure composed of collagen molecules, fibrils, fiber bundles, fascicles and tendon units that run parallel to the tendon’s axis (figure 4)¹¹⁶. Fibers and fascicles are enclosed by the epitenon, which is a fine, loose connective-tissue sheath containing the vascular, lymphatic, and nerve supply to the tendon¹³⁷. The dominant cell type is the fibroblast (tenoblasts and tenocytes), which align in rows between collagen fiber bundles and produce the collagen matrix.

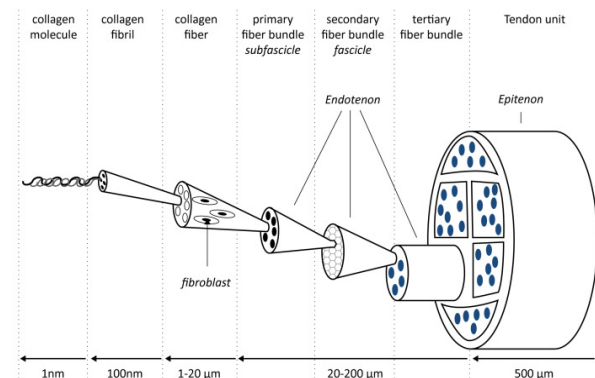


Figure 4: A schematic drawing of the tendon as a multi-unit hierarchical structure (modified from Wang et al., 2006)

2.1.4 The plantar flexor muscle-tendon complex

While the suralis muscle is by far the strongest plantar flexing muscle, also the plantaris muscle, the flexor hallucis longus, the flexor digitorum longus and the tibialis posterior muscle contribute to plantar flexion as they run behind the rotational axis of the ankle joint¹⁶. Due to this, some people are able to plantar flex the ankle after a total Achilles tendon rupture. Together, these five muscles and their respective tendons constitute the plantar flexor muscle-tendon complex.

2.1.5 Circulation

Vascularization of the Achilles tendon can be divided into three areas: the upper third, the middle third and the lower third; correspondent to the areas from where the tendon receives its blood supply: the musculotendinous junction, the paratenon and the osseotendinous junction^{1,128}. The upper and lower third are mainly supplied by the posterior tibial artery¹, whereas the middle third is supplied by the peroneal artery¹²⁸. It has been argued

that the mid portion of the Achilles tendon is especially susceptible to rupture due to its poor blood supply¹, however, newer studies using micro dialysis have shown blood supply in the Achilles tendon to increase proportionally with muscle tissue¹³⁷.

2.1.6 Innervation

Innervation of the Achilles tendon is found in the epitenon. The sensory branches originate from the contributing muscles and from the nearby cutaneous nerves⁹³. The suralis and the saphenous nerves run lateral and medial to the Achilles tendon leaving them exposed to injury during surgery on the Achilles tendon. The suralis muscle is innervated from the tibial nerve.

2.2 BIOMECHANICAL PROPERTIES

The Achilles tendon is remarkably strong and can withstand stresses that by far exceed those transmitted during daily activities and sports. It has been estimated that the peak force transmitted through the Achilles tendon during running is 9 kN, which is equivalent to 12.5 times the body weight⁵⁹. Our knowledge on biomechanical properties of tendons is mainly derived from animal models and cadaveric studies¹⁶. A typical tendon stress-strain curve is seen in figure 5.

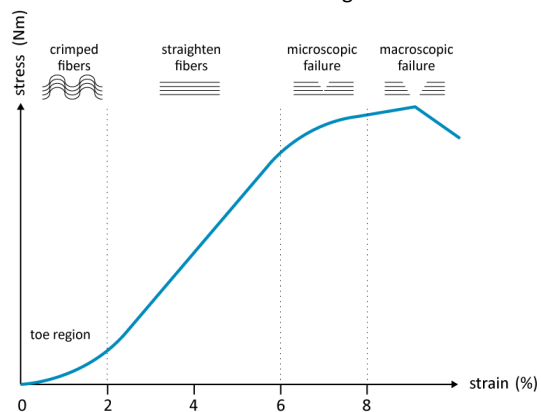


Figure 5: A schematic drawing of the stress-strain curve for the Achilles tendon (modified from Wang et al., 2006)

The first 2% of elongation represents the stretching-out of the collagen fibers¹³⁷. As all fibers become stretched the stress-strain curve becomes linear until the tendon starts failing and microscopic tearing occurs. Beyond a 8–10% strain, macroscopic failure occurs. The slope of the curve represents the tendon stiffness and is referred to as Young's modulus. Stiffness has been shown to be associated with the tendons efficiency in storing and releasing energy¹³⁵. The area under the loading stress-strain curve represents the tendons ability to store energy.

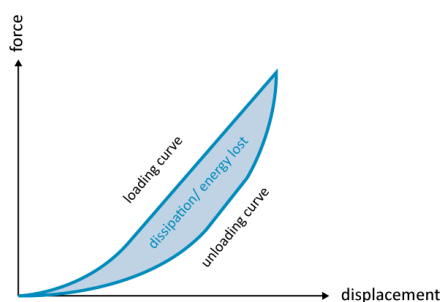


Figure 6: A schematic drawing of energy absorption in a tendon and energy lost during the coil-recoil process.

The area under the un-loading curve represents the tendons ability to release energy. The area between the two curves represents the energy lost in the coil-recoil process (figure 6). This ability to store and release energy is extremely important for the stretch-shortening cycle²², as it has been demonstrated that up to 60% of the work involved in repetitive jumping exercises is generated in the Achilles tendon¹³⁵. If the tendon is held maximally stretched, the tension will decline over time, a phenomenon referred to as torque relaxation (figure 7)¹⁸.

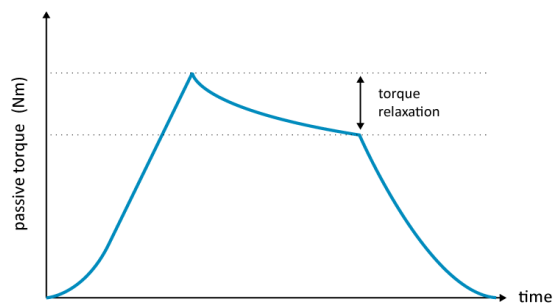


Figure 7: A schematic drawing of the phenomenon torque relaxation.

2.3 HEALING AFTER RUPTURE

Tissue turnover in the Achilles tendon is an extremely slow process. It has been shown that the core of the Achilles tendon is formed before the age of 20 and essentially not renewed thereafter⁴⁰. In contrast, the periphery of the tendon is able to respond to mechanical forces by altering its structure, composition, and mechanical properties. An adaptation mediated by the fibroblasts through biochemical signaling¹³⁷. Tendon repair can be described in three overlapping phases: 1) the inflammatory phase, 2) the proliferative phase, and 3) the remodeling phase (figure 8). In the inflammatory phase, the bleeding caused by the rupture leads to hematoma and activation of platelets and neutrophils, which again leads to the release of growth factors, chemotactic factors and vasoactive factors. The vascular permeability is increased, inflammatory cells are recruited and a tendon granuloma is produced^{6,32}. In the proliferative phase, angiogenesis allows for vascular and neuronal ingrowth in the granuloma. The fibroblasts produce collagen (mainly type 3) and the mechanical strength of the granuloma gradually increases. After 10 to 14 days a tendon callus has been produced gluing the torn tendon ends together. Production of collagen type 1 gradually takes over and the callus reaches its largest size. The large transverse area of the tendon compensates for its weak composition. In the remodeling phase, the randomly deposited collagen fibers are resorbed and replaced to produce better architecture and cross-linking. The remodeling phase starts one to three months after rupture and lasts for several years^{6,32,66,112}.

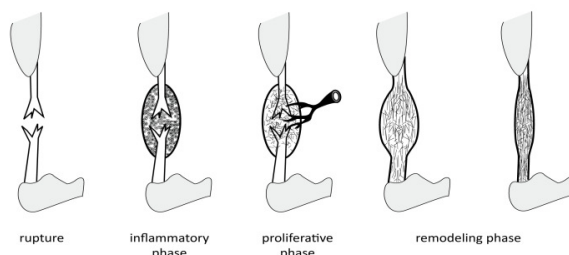


Figure 8: A schematic drawing of the three healing phases of an Achilles tendon (modified from Aspenberg et al., 2007)

2.3.1 Stimulation by mechanical loading

It is well described that mechanical loading improves tendon repair^{6,34,119,66,73}. Clinical studies looking at flexor tendons have found controlled early motion to increase strength and avoid adhesions after surgical repair^{34,119}. Animal studies have shown a three times increased strength of Achilles tendons rehabilitated with controlled early motion compared to the immobilized ones⁷³. Eliason et al. have shown that growth factors in the tendon callus are influenced by loading of the tendon^{32,30}. They found more than 150 genes up regulated or down regulated three hours after one loading episode, and conclude that as little as five minutes of loading each day can improve the strength of the healing tissue³¹. Thus, it seems reasonable to believe that early loading of the tendon under controlled conditions will affect tendon healing beneficially.

2.3.2 Stimulation by growth factors

This leads to the question whether mechanical loading can be replaced by drugs. Several growth factors have been shown to stimulate tendon repair in animal models⁶; among those platelet-derived growth factors^{10,42}, fibroblast growth factors²⁵, vascular endothelial growth factors¹⁴⁵ and insulin-like growth factors⁶³. For those to be applied in the treatment of acute Achilles tendon rupture several questions need to be answered concerning time and dose of application and safety issues. In an attempt to short-cut those considerations some clinicians have started treatment with platelet concentrate derived from the patient's own blood, as platelets contain a number of growth factors¹³⁴. Animal studies have shown promising results¹³⁴, but the present clinical studies have not shown any effect of platelet derivatives¹⁰⁶.

2.6 ETIOLOGY OF RUPTURE

There is little agreement on the etiology of acute Achilles tendon rupture. Several theories have been suggested⁸⁶:

- 1) Tendon degeneration has been suggested to predispose rupture as histological studies have shown degenerative changes in specimens obtained from rupture sites^{5,68}
- 2) The collagen fibrils have been found to decrease with age, and therefore age has been suggested as a predisposing factor¹²⁰
- 3) Corticosteroids injected into rabbit tendons caused necrosis and delayed healing⁷. Furthermore, the anti-inflammatory response of corticosteroid might mask the symptoms of micro-lesions and make people continue high activity even though the tendon is damaged¹². However, prospective and retrospective studies have not been able to show causality between the use of corticosteroid and acute Achilles tendon rupture^{70,36}
- 4) Fluoroquinolones have been associated with acute Achilles tendon rupture. Intracellular changes and a decrease in fibril diameter have been found in rats treated with fluoroquinolones^{109,110,111}, and a large cohort study looking at 6.4 million people found the use of quinolones to be strongly associated with an increased risk of Achilles tendon rupture (odds ratio 2.0)¹⁴³
- 5) Avascularity and heat necrosis have also been suggested as possible predisposing factors^{1,142}

- 6) Finally Barfred demonstrated that healthy tendons ruptured when maximal stress was applied in combination with supination of the calcaneus and oblique loading of the tendon⁹

2.7 EPIDEMIOLOGY OF RUPTURE

Acute Achilles tendon rupture is a frequent injury that typically occurs among young active adults. The incidence is 11 to 37 per 100,000 person-years and the male:female ratio is 5:1^{45,65,74,82}. A bimodal age distribution has been proposed with a maximum incidence of sports injuries in the fourth decade of life followed by a second, but lower, peak of other injuries in the eighth decade⁸². The latest Danish incidence study published in 1998 showed an increase in incidence from 18 per 100,000 person-years in 1984 to 37 per 100,000 person-years in 1996. 74% of the ruptures were sports-related and 89% of those occurred in racket and ball games⁴⁵.

2.8 DIAGNOSIS OF RUPTURE

Patients with acute Achilles tendon rupture typically present with a history of sudden pain in the Achilles tendon accompanied by a loud snapping sound. The patient often feels he/she was kicked or hit by something, though the spectators can tell it was not the case. The rupture often occurs in push off with extended knee. The clinical examination reveals a palpable gap at the site of the rupture, typically 4-5cm above calcaneus. The ability to push off during walking and to plantar flex against resistance is weak or absent^{69,85,93}.

A number of clinical tests have been described, of which Thompsons test (the calf squeeze test) and Matles test have the best sensitivity (0.96 and 0.88 respectively) and specificity (0.93 and 0.85 respectively)⁶⁹. Thompsons test is performed with the patient lying prone and the feet hanging freely, while the calf is squeezed from side to side and plantar flexion of the foot is observed. The test is positive if plantar flexion is absent¹³⁰. Mattles test is performed with the patient lying prone, the knees are bent 90 degrees and the position of the ankles and feet is observed during flexion of the knee. The test is positive if the foot on the affected side falls into neutral or into dorsiflexion⁷².

Ultrasound (US) and Magnetic Resonance Imaging (MRI) are used as diagnostic tools in some regions²⁰. However, the high sensitivity and specificity of Thompsons and Mattles tests taken into consideration, one should be careful not to be misled by the imaging modalities. US and MRI examinations are not recommended for routine use²⁶. The diagnosis of acute Achilles tendon rupture is primarily clinical⁶⁹.

3 TREATMENT OF ACUTE ACHILLES TENDON RUPTURE

*The whole problem with the world is
that fools and fanatics are always so certain of themselves
but wiser people so full of doubts
Bertrand Russel*

The first description of acute Achilles tendon rupture was done by Ambroise Paré (1510-1590). He described the treatment and prognosis as follows: "...This mischance may be amended by long lying and resting in bed and repelling medicines applied to the part....neither must we promise to ourselves or to the patient certain or absolute health. But on the contrary at the beginning of the disease we must foretell that it will never be so cured, and that some relics may remain..."⁵⁸. In 1736 Jean Louis Petit started

treating patients in equinus position. The patient was treated prone with the knees flexed and the feet plantar flexed. A slipper on the foot was attached to the thigh with pins to maintain plantar flexion. The bandages were removed and reapplied after eight and 15 days. Healing was advanced at 22 days and weight-bearing commenced ten days later⁵⁸.

The first published series describing acute Achilles tendon rupture was published by Qenu and Stoianovitch in 1929¹⁰⁰. They compared the results of 29 non-operatively treated and 39 operatively treated patients, thereby starting an ongoing discussion of whether to treat operatively or non-operatively. During the past fifty years an increased awareness of acute Achilles tendon rupture and treatment modalities developed, and a range of different treatment protocols have been described⁵⁷. The historical diversity of published results and recommendations has led to considerable variation in treatment protocols between departments treating this injury⁸.

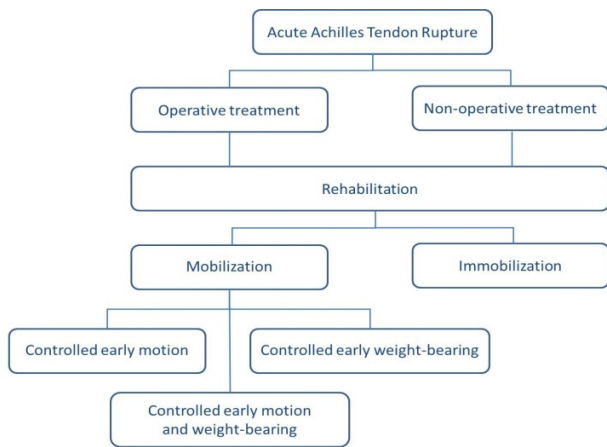


Figure 9: A flow diagram to visualize the different treatment and rehabilitation protocols after acute Achilles tendon rupture.

Treatment of acute Achilles tendon rupture can be divided into two main categories: Operative and non-operative treatment (figure 9). Rehabilitation can be immobilizing or mobilizing. In this thesis, treatment protocols allowing mobilization before the end of the fourth week are categorized as mobilizing. Mobilization can be divided into controlled early motion and early weight-bearing. Some confusion exist concerning terminology as the term dynamic rehabilitation by some authors refers to the overall term 'mobilization' and by others to 'controlled early motion'. In paper I-III dynamic rehabilitation refers to controlled early motion. Over the past decade a change in treatment of acute Achilles tendon rupture from operative and immobilizing treatment towards non-operative treatment using controlled early motion has taken place⁷⁴.

3.1 OPERATIVE VS. NON-OPERATIVE TREATMENT

The first known open repair of an acute Achilles tendon rupture was performed in 1888 by Polaillon⁵⁸. Since then a variety of open, minimally invasive, and percutaneous surgical techniques have been developed and described³. Surgical techniques are, however, not addressed in this thesis. Since the early 80ies, 12 randomized controlled trials (RCT's) and 7 meta-analyses comparing operative and non-operative treatment have been published (table 1).

Table 1

	Nn	Mobilization	RR-rate (%)	Rec. Operation	Bhandari 2002 ¹²	Khan 2005 ⁸⁶	Lothman 2010 ⁸⁷	Jiang 2012 ⁸⁵	Jones 2012 ⁸⁸	Wilkins 2012 ¹³⁸	Sordocanu 2012 ¹³⁷
Nistor 1981 ²⁹	105	No	2/5	No	X	X	X	X	X	X	X
Coffi 1993 ²²	111	No	3/7	Yes	X	X	X	X	X	X	X
Thormann 1995 ²⁸	50	Yes	?	Maybe	X						X
Schroeder 1997 ²⁰⁹	112	Yes	0/0	Yes		X	X	X	X		X
Majewski 2000 ⁷¹	73	?	?	?	X						X
Möller 2001 ⁸⁴	112	No	1/11	Yes	X	X	X	X	X	X	X
Twaddle 2007 ¹⁴⁴	47	Yes	7/1	No			X	X	X	X	X
Metz 2008 ⁷⁸	83	Yes	3/5	Maybe			X	X	X	X	X
Willis 2010 ¹⁴⁵	144	Yes	2/5	No				X	X	X	X
Nilsson-Helander 2010 ⁸⁷	75	Yes	2/6	No				X	X	X	X
Keating 2011 ²⁵	80	Yes	7/14	No				X			
Olsson 2013 ⁸²	100	Yes	0/5	Yes							
RR-rate (operative vs. non-operative)					3% vs. 13%	4% vs. 13%	5% vs. 12%	4% vs. 10%	4% vs. 11%	4% vs. 9%	RR 0.4
Infection-rate (operative vs. non-operative)					5% vs. 0%	4% vs. 0%	4% vs. 0%	3% vs. 0%	4% vs. 0%	2% vs. 0%	NA
Total complication rate (other than RR)					NA	24% vs. 8%	29% vs. 8%	17% vs. 7%	17% vs. 6%	NA	RR 3.9

Table 1: RCT's (Y-axis) and meta-analyses (X-axis) comparing operative and non-operative treatment of acute Achilles tendon rupture. The left side of the table shows the individual RCT's conclusions. The right side of the table shows the meta-analyses, which studies they included and their overall conclusion. No=Number of patients, RR=Re-rupture, Rec=Recommend. (*) operative / non-operative. Modified after Tengberg et al.¹²⁵ and Olsson⁸².

Most of the trials published before 2005 suggested better outcome after surgery due to a higher rate of re-rupture in the non-surgical group^{23,84,107}. Since then a number of high quality RCT's have opted in favor of non-operative treatment due to a non-significant difference in the rate of re-rupture and a significantly increased risk of other complications in the surgically treated group^{55,87,132,141}. In the same period two large prospective cohort studies looking at 945 and 487 patients, respectively, showed re-rupture rates of 2.8% and 6.6% in non-operatively treated patients^{11,136}. Looking at the meta-analyses we find compelling evidence that operative treatment yields a risk of re-rupture of 3-5% and non-operative treatment of 9-13%. Likewise operative treatment yields a risk of other complications of 27-34% and non-operative treatment of 3-8%. Looking at functional results some RCT 's have been able to show a slightly improved function after operative treatment^{23,87}, but this is not reflected in the meta-analyses^{48,49,57,117,139}.

3.2 MOBILIZATION VS. IMMOBILIZATION

The role of mobilization has been discussed since the early 1980s and has gained increasing popularity over the past decade^{8,27,74,80,104,122,132}. All RCT's comparing operative and non-operative treatment published after 2007 have used mobilization in both study groups. In 2007 Twaddle & Poon hypothesized that use of mobilization might be the most important factor in optimizing outcome in patients with Achilles tendon rupture and that surgery makes no difference to the outcome apart from increasing the risk of local infection¹³². Looking at the literature very little evidence exists concerning the use of mobilization in the treatment of acute Achilles tendon rupture. The shift towards mobilization has been driven by RCT's comparing operative and non-operative treatment protocols and not by trials comparing mobilization and immobilization^{55,78,87,92,117,132,141}. The low rate of re-rupture in both the operatively and non-operatively treated groups has been attributed to the early controlled rehabilitation regimes, though this has not been the research area of the trials.

In order to investigate the effect of mobilization one should look at trials designed for this purpose. Operatively treated and non-operatively treated patients must be investigated separately, as the baseline situation for the healing process is different. Also controlled early motion must be distinguished from controlled early weight-bearing, as it is unknown how the two variables affect tendon healing and how they interact.

3.2.1 Controlled early motion

Three RCT's have investigated the effect of controlled early motion in the treatment of acute Achilles tendon rupture (table 2)^{24,51,80}. The quality of the three trials was assessed to be medium by two independent reviewers using the Jadad score^{47,90}. No statistically significant differences were found in rate of re-rupture and other complications between the immobilized group and the group treated with controlled early motion. The studies argue for shorter sick leave, less tendon elongation, and better strength in the group treated with controlled early motion.

Table 2

Trials	Jadad score	No of patients	Treatment	Weight-bearing	Re-rupture Motion/Immobilization	Other complications Motion/Immobilization
Cetti 1994 ²¹	3	60	Operative	No	1/2	1/6
Mortensen 1999 ⁸⁰	3	71	Operative	No	1/2	1/0
Kangas 2003 ⁵¹	2	50	Operative	Yes	1/2	?

Table 2: Table showing RCT's comparing controlled early motion and immobilization.

3.2.2 Controlled early weight-bearing

One RCT has investigated the influence of controlled early weight-bearing in the treatment of acute Achilles tendon rupture (table 3)¹²¹. The study looked at health-related quality of life assessed with use of the RAND 36-Item Health Survey (RAND-36) as its primary outcome. Secondary outcomes were activity level, calf strength, ankle range of motion, return to sports and work, and complications. 98 patients (89%) completed the six-month follow-up. At six weeks the weight-bearing group had significantly better scores than the non-weight-bearing group in the RAND-36 domains of physical functioning, social functioning, role-emotional, and vitality scores ($p < 0.05$). Patients in the weight-bearing group also reported fewer limitations of daily activities at six weeks postoperative ($p < 0.001$).

Table 3

Trials	Jadad score	No of patients	Treatment	Motion	Re-rupture Motion/Immobilization	Other complications Motion/Immobilization
Suchak 2008 ¹²¹	3	110	Operative	Yes	0/0	8/11

Table 3: Table showing RCT's comparing controlled early weight-bearing and immobilization.

At six months, no significant differences between the groups were seen in any outcome. Suchak et al. concludes that no detrimental effect of weight-bearing from the second postoperative week was found in operatively treated patients.

3.2.3 Controlled early motion and weight-bearing

Three RCT's have investigated the combined influence of controlled early motion and weight-bearing in the treatment of acute Achilles tendon rupture (table 4). Saleh et al.¹⁰⁴ developed a new orthosis, the Sheffield splint, allowing both controlled early motion and weight-bearing which they tested against immobilization in cast. They found that the group treated with mobilization regained mobility and range of motion significantly quicker than the immobilized group. Costa et al.²⁷ also tested a new orthosis allowing both controlled early motion and weight-bearing against immobilization in cast. No significant differences were found. The trials were influenced by selection bias, as active people were operated and inactive people were treated non-operatively.

Table 4

Trials	Jadad score	No of patients	Treatment	Re-rupture Motion/Immobilization	Other complications Motion/Immobilization
Saleh 1992 ¹⁰⁴	1	40	Non-operative	1/1	?
Costa 2005 ²⁷	3	48	Non-operative	1/2	0/2
Costa 2005 ²⁷	3	48	Operative	2/0	6/7

Table 4: Table showing RCT's comparing the combined influence of controlled early motion and weight-bearing against immobilization.

3.3 REHABILITATION PROTOCOLS

The following are examples of rehabilitation protocols being used after both operative and non-operative treatment of acute Achilles tendon rupture:

3.3.1 Immobilizing rehabilitation protocols

A typical immobilizing treatment protocol has been described by Cetti et al.²³: A below-the-knee plaster cast with the foot in 20° of plantar flexion is worn for eight weeks. During this period no weight-bearing is allowed on the injured leg. After eight weeks the cast is removed and weight-bearing allowed. Alternatively the cast is changed after three to four weeks bringing the ankle in a neutral position or a brace is worn throughout the treatment period gradually bringing the ankle into neutral position.

3.3.2 Mobilizing rehabilitation protocols

Mobilizing treatment must be divided into 1) controlled early motion, 2) controlled early weight-bearing and 3) controlled early motion and weight-bearing.

3.3.2.1 Controlled early motion

Controlled early motion can be performed using a dynamic brace, allowing movement of the ankle, or using a removable brace, instructing the patient to remove the brace and exercise. A treatment protocol using a dynamic brace has been described by Nilsson-Helander et al.⁸⁷: Patients are treated with a below-the-knee cast with the foot in equinus position for two weeks, followed by an adjustable brace for the next six weeks. The brace is set at free plantar flexion motion with dorsiflexion limited to -30° the first two weeks, -10° the next two weeks, and +10° the last two weeks. Weight-bearing as tolerated is allowed after six to eight weeks.

A treatment protocol using a removable brace has been described by Twaddle et al.¹³²: Patients are treated with a removable brace for eight weeks. The foot is initially placed in equinus position by application of three wedges. Every second week a wedge is removed, slowly bringing the ankle to neutral. Patients are instructed to remove the brace for five minutes of every hour and, while sitting with the injured leg hanging, practice active ankle dorsiflexion and passive plantar flexion, letting the foot fall down as far as was comfortable. Particular emphasis was made of the importance of not dorsiflexing the ankle beyond the neutral position and remaining non-weight-bearing.

3.3.2.2 Controlled early weight-bearing

Controlled early weight-bearing without movement of the ankle is a widely used treatment protocol in Scandinavia⁸. Yet, it has not been possible to find a published description of this protocol. The following treatment protocol is used in hospitals in the area of Copenhagen: The patient is treated with a brace for six weeks when operatively treated and eight weeks when non-operatively treated. The foot is initially placed in equinus position by application of wedges in the brace and slowly brought to neutral by removal of the wedges. Full weight-bearing is allowed from day one.

3.3.2.3 Controlled early motion and weight-bearing

A treatment protocol using both controlled early motion and weight-bearing has been described by Möller et al.⁸⁴: The patient is treated with a below-the-knee plaster cast with the ankle in equinus for two weeks. After two weeks the cast is replaced with a brace and full weight-bearing and range of motion exercises are encouraged during weeks three to eight.

4 OUTCOME ASSESSMENT

'If you can measure that of which you speak, and can express it by a number, you know something of your subject, but if you cannot measure it, your knowledge is meager and unsatisfactory.'

William Thomson

Outcome denotes whether or not a patient benefits from the medical care provided³⁷. In order to evaluate patient outcome and compare treatment regimens valid, broadly accepted and clinically relevant outcome parameters are required.

4.1 PATIENT REPORTED OUTCOME MEASURES

Patient reported outcome measures (PROM's) have added a new dimension to clinical outcome evaluation. PROM's are important both for assessing individual patients in the clinic, for quality monitoring and research purposes. Traditional clinical methods for assessing outcome after Achilles tendon rupture may fail to detect the patient's perception of disability^{33,38,55,88,123}. Over the past decades numerous PROM's have been developed, but only the Achilles tendon Total Rupture Score is developed and validated for use after acute Achilles tendon rupture⁵⁴. The most widely used scores are presented in the following paragraphs.

4.1.1 Achilles tendon Total Rupture Score (ATRS)

The Achilles tendon Total Rupture Score consists of 10 items reflecting symptoms and physical activity after treatment of acute Achilles tendon rupture. The items are assessed using a Likert scale (range 0-10; 10 being the best possible score). It was developed and validated in 2007 by Nilsson-Helander et al.⁸⁸ It has since been translated to English and Danish and both versions have been validated^{33,53}. The ATRS was found to be a good and reliable PROM for measuring differences of more than 7 points between groups of patients. However, for assessing individual patients in the clinic, the ATRS showed serious limitations, as it cannot be expected to detect changes of less than 19 points when reassessing individual patients at several points³³.

4.1.2 Victorian Institute of Sports Assessment – Achilles (VISA-A)

The VISA-A questionnaire is a PROM validated for Achilles tendinopathy based on symptoms. It consists of eight questions that measure the domains of pain, function in daily living and sporting activity. The results range from 0 to 100, where 100 represents the ideal score¹⁰³. VISA-A has been used in validations of the ATRS^{88,53} and has been translated to and validated in Danish⁴⁶.

4.1.3 Physical Activity Scale (PAS)

The physical activity scale has been developed to be a simple alternative to measuring physical activity by diary. It is a self-reported questionnaire estimating the total physical activity on an average week-day. It is developed and validated in Danish¹⁴⁶.

4.1.4 Health related quality of life

A wide range of patient reported questionnaires to assess quality of life have been developed and validated. The most widely used are listed below this paragraph. Inspired from those a purpose made questionnaire was developed to investigate the health related quality of life during the initial eight weeks of treatment in study II (Annex A). Five items were assessed using a Likert scale (range 0-10; 10 being the best possible score). The items reflected: 1) limitations in daily living, 2) limitations in work situations, 3) limitations in social life, 4) affection of the patient mood, and 5) level of pain.

4.1.4.1 Short Form 36 (SF-36) and RAND-36

The SF-36 and RAND-36 are identical multi-purpose, short-form health surveys containing 36 questions^{39,124,138}. They measure eight health concepts summarized in two main scores: the physical component score and the mental component score. The questionnaires are thoroughly tested and validated^{39,124,138}.

4.1.4.2 EuroQOL (EQ-5D)

The EQ-5D essentially consists of a descriptive system comprising five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and a visual analogue scale where the person is to give an overall rating of self-rated health¹²⁷. The questionnaire is thoroughly tested and validated⁹⁷.

4.2 FUNCTIONAL TESTING

Functional testing is widely used in trials assessing the outcome after acute Achilles tendon rupture.

4.2.1 Heel-rise test

The heel-rise test is an endurance test where the number of standing unilateral heel raises, at a rate of 40/minute, is counted. Only heel lifts above 5 cm are counted^{83,85}.

4.2.2 Heel-rise work test

The heel-rise work test is an endurance test where the patient stands on one leg and lifts the heel up and down until exhaustion. The participants are allowed to place two fingertips per hand, at shoulder height, against the wall for balance. A frequency of 30 heel-rises per minute is kept. The participants are instructed to go as high as possible on each heel-rise and then lower the heel to the starting position before next heel-rise. The participants are asked to perform as many heel-rises as possible. The test is terminated when the patient stops, cannot maintain the frequency, or does not perform a proper heel-rise (<2cm)¹¹⁴. Silbernagel et al. have found a good validity of the heel-rise work test and greater ability to detect differences between the injured and the uninjured sides compared to the heel-rise test¹¹⁴.

4.2.3 Heel-rise height

The heel-rise height is measured under the same setting as the Heel-rise work test. The maximum heel-rise is recorded¹¹⁴. The decrease in heel-rise height has been hypothesized to be correlated to tendon lengthening¹¹⁵.

4.2.3 Single heel-rise test

The patient stands with the foot in neutral position. It is recorded whether the patient is able to make a single heel-rise on the injured leg. The heel-rise is acknowledged if the heel can be lifted at least 2 cm with stretched knee. It has been shown that the ability to do a heel-rise 12 weeks after rupture is correlated to

outcome. The heel-rise ability appears to be an important early achievement and reflects the general level of healing, which influences patient-reported outcome and physical activity⁹¹.

4.2.4 Strength tests

Strength testing has been performed in different settings. Silbernagel et al. had the patients do concentric and eccentric toe-raise against increasing weight¹¹³. Möller et al. tested concentric and eccentric strength with the patient sitting with 90 degrees flexion in the hip and knee using an isokinetic dynamometer. Angular velocities of 30°/sec and 180°/sec were used. The reliability was found to be good⁸³. McNair et al. tested concentric strength at an angular velocity of 240°/sec⁷⁶.

4.2.5 Jump tests

In 2005 Silbernagel et al. described a test battery consisting of three jump tests: a counter movements jump, a drop counter movement jump and hopping¹¹³. The test battery was found to be reliable and able to detect differences in lower leg function between the injured and non-injured limb^{87,113}.

4.3 BIOMECHANICAL TESTING

Biomechanical testing is typically done using an isokinetic dynamometer^{76,83}. The patient is seated or lying with the hip and knee joint in a specified position. Positions between 0 and 90 degrees have been described for each joint^{76,83}. The subject's foot is strapped to the pedal of the dynamometer and he/she is asked to relax and not activate the lower limb muscles while the isokinetic dynamometer moves the ankle joint in dorsiflexion at an angular velocity of typically 5°/sec^{76,83}. The resistant torque is sampled by the isokinetic dynamometer and the matching torque and angle values are recorded.

4.3.1 Stiffness

Stiffness is the slope of the stress strain curve. Stiffness of the plantar flexor muscle-tendon complex increases with increasing dorsiflexion. It is, therefore, often reported in intervals like early, middle and late dorsiflexion⁷⁶.

4.3.2 Peak passive torque

Peak passive torque is the maximum torque exerted when stretching the passive plantar flexor muscle-tendon complex^{18,76}. It is usually reached in maximum dorsiflexion.

4.3.3 Energy stored during loading

The energy stored during loading is the area under the loading curve. It represents the energy absorbed by the plantar flexor muscle-tendon complex⁷⁶.

4.3.4 Torque relaxation

The torque relaxation is representative of the shock absorbing quality of the plantar flexor muscle-tendon complex. It is the fraction of energy stored after a period of relaxation, and can be expressed as a percentage: the persisting passive torque after a period of relaxation divided by the peak passive torque¹⁸.

4.3.5 Dissipation coefficient

The dissipation coefficient is another measure of shock absorbing quality. It is the fraction of energy released compared to the energy stored and can be calculated by dividing the energy lost in the coil-recoil process (the area between the loading and unload-

ing curves) by the energy stored during loading (the area under the loading curve)⁷⁶.

4.4 LENGTH MEASURES

A variety of methods have been developed to measure Achilles tendon length and elongation^{4,23,50,64,95,99,102,105,118,144}. The methods can be divided into four groups depending on modality: clinical, X-ray, ultrasound (US), and Magnetic Resonance Imaging (MRI).

4.4.1 Clinical

Clinically, the length of the Achilles tendon can be estimated by the spontaneous position of the ankle joint in the relaxed leg (figure 10). An Achilles tendon of normal length positions the ankle joint in 10-20 degrees of plantar flexion when the patient is lying prone with the knees flexed 90 degrees. An elongation of the tendon will make the foot fall into neutral or dorsiflexion⁷². Likewise, the height of a maximal heel-rise has been used to estimate elongation of the Achilles tendon^{91,115}.



Figure 10: Matles test

4.4.2 Radiological

X-ray allows for measurement of displacement of the torn tendon ends by implantation of radiological markers (figure 11)^{23,50}. The latest and best validated method is Roentgen Stereophotogrammetric Analysis (RSA) using tantalum beads as markers^{64,105}. Implantation of the markers is invasive and so far the technique has only been used to evaluate elongation after operative treatment.



Figure 11: RSA markers implanted in the Achilles tendon

4.4.3 Ultrasound

Ultrasound (US) has been established as an important and cost-effective tool in the diagnosis of tendon problems. It provides a fast investigation that can be performed by the surgeon. Three types of US based length measures have been described for the Achilles tendon.

Rees et al. developed a method combining video-based motion capture and US imaging¹⁰². Achilles tendon length was defined as the distance between the gastrocnemius muscle tendon junction and the tendon insertion at the calcaneus. Two retroreflective markers were placed on the back of the US probe and the markers were used to track the position of the probe. The measurement was validated by Silbernagel et al.¹¹⁵ It showed high reproducibility and a measurement error of < 1%. Panoramic ultrasound imaging allows the transducer to be moved along the patient's Achilles tendon, blending multiple images together to form one long image with an extremely wide field of view⁹⁹ (figure 3). The method is easy to perform and clinically applicable, but no validation of the measurement has been published^{95,118,144}. The authors of study IV have tested reliability of the measurement in a setting similar to the one used in study IV. The data has not been published yet, but showed an average

intra-rater reliability of ICC 0.84, SEM 0.94 and MDC 2.62 and inter-rater reliability of ICC 0.89, SEM 0.78 and MDC 2.15. Finally, Amlang et al. reported an US classification system to be used for individual treatment selection in patients with acute Achilles tendon rupture, looking at the degree of overlap of the torn tendon ends as a surrogate for tendon displacement and elongation⁴. This classification system is yet to be validated and correlated to the final outcome of treatment.

4.4.4 MRI

Magnetic Resonance Imaging (MRI) is also a non-invasive modality for tendon length measurement⁶⁰. In relation to US the setup is more demanding and expensive, as radiological assistance is needed to perform MRI measurements.

4.4.5 Strength in plantar flexion

Strength in the terminal part of plantar flexion can be used as a surrogate for tendon elongation. If tendon elongation is present one would expect strength to decline as plantar flexion increases and the suralis muscle loses its ability to contract further.

4.5 COMPLICATIONS

All published RCT's have reported the rate of complications^{23, 55,84,87,107,132,141}. Some studies have reported all complications and others only selected complications.

4.5.1 Re-rupture

The rate of re-rupture is the most common primary endpoint in the literature^{23, 55,84,87,107,132,141}. However, a clear definition of how re-rupture is defined is seldom given.

4.5.2 Infection

Infections can be divided into superficial and deep infections. Superficial infections are related to the skin, whereas deep infections involve the Achilles tendon.

4.5.3 Other complications

Other reported complications involve damage to the suralis nerve, adhesions between the tendon and the surrounding connective tissue, scar problems and deep vein thrombosis^{79,94}.

4.6 RETURN OF FUNCTION

In 2006 Costa et al.²⁷ concluded that the return to normal activities was the most important outcome measure as viewed by the patient and therefore claimed that it also should be the most important outcome measure for researchers.

4.6.1 Sick leave

The length of sick leave is of fundamental importance for the patient as well as for society. The measurement is usually self-reported through questionnaires or structured questioning at follow up^{27,84}.

4.6.2 Return to sport

Most acute Achilles tendon ruptures are acquired through sporting activities. The return to sports, and preferably a level of sporting activity similar to the one before the injury, is therefore an obvious outcome. The measurement is usually self-reported through questionnaires or structured questioning at follow up^{23,57}.

4.7 VALIDITY, RELIABILITY AND AGREEMENT OF MEASUREMENTS

Valid and reliable outcome parameters are cornerstones in proper research. Invalid outcome parameters may lead to wrong conclusions and unreliable outcome parameters may keep actual differences from being detected. Terminology within the field is confusing and imprecise, as it differs between papers and textbooks^{14, 44,52,62,123,133}. The following chapter is an outline of the terminology and concepts as they are understood and used in this thesis.

4.7.1 Validity

Validity can be divided into content, criterion and construct validity. Further description of this subdivision is out of the scope of this thesis. Generally speaking validity is the extent to which a measurement measures what it claims to measure (figure 12).

4.7.2 Assessment of validity

In order to assess if a measurement instrument actually measures what it claims to measure, one needs to know the real value of the object being measured. For example, if one would like to assess if an ultrasound measurement measures distances of tendons correctly, one needs to know the actual length of the measured tendons. If the actual length is not known, an alternative is to define a gold standard of measurement to validate the new measurement against. Validity can be expressed as the measurement error¹¹⁵:

$$\text{Measurement error} = \frac{\text{Actual length} - \text{measured length}}{\text{Actual length}}$$

4.7.3 Reliability and agreement

The term reliability, as used in the previous chapter (4.7.1), refers to the spread of data. It can be further subdivided into the terms reliability and agreement¹³³. Agreement is the extent to which a measurement measures the same at different occasions; it is related to the measurement error of the measurement itself. Reliability is the extent to which study objects can be distinguished from each other, despite measurement errors; it relates the measurement error of the measurement to the natural variability of the study population^{62,133}.

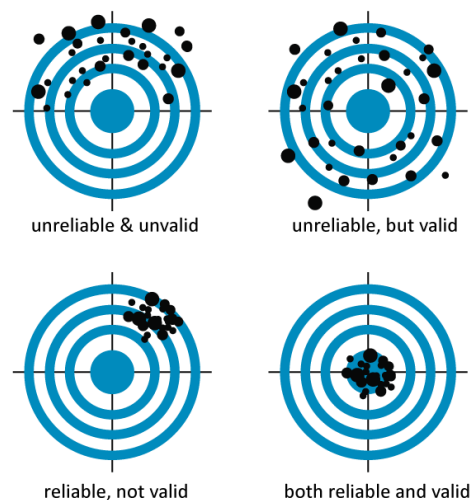


Figure 12: Diagram showing the difference between validity and reliability. (modified from Nevit Dilmen)

Figure 13 illustrates an example of 3 subjects (●, ■ and △) being measured five times. The distance between the five identical symbols represents the agreement of the measurement (the measurement error), which is not affected by the variability of the population. In contrast, reliability of a measurement is influenced by the variability of the study population. In a population represented by the subjects ● and ■ the measurement will have a good reliability, as the measurement error will not affect discrimination of the subjects. In a population represented by the subjects ■ and △ the measurement will have a poor reliability, as the measurement error will affect the ability to discriminate the subjects.



Figure 13: Diagram showing the difference between reliability and agreement. (Modified from de Vet et al. 2006)

Reliability is a characteristic of the performance of an instrument in a certain population sample. Agreement is rather a characteristic of the measurement instrument itself¹³³.

4.7.4 Assessment of agreement and reliability

4.7.4.1 Kappa-statistics

Agreement between categorical data is often assessed using kappa-statistics. The kappa-value tells the observed agreement as a percentage of agreement expected just by chance. A value of 1 indicates perfect agreement and a value of 0 indicates no agreement².

4.7.4.2 Intraclass correlation coefficient (ICC)

Reliability of a measurement can be assessed using the Intraclass Correlation Coefficient (ICC). The basic formula of the ICC is:

$$\text{Reliability} = \frac{\text{Variability between study objects}}{\text{Variability between study objects} + \text{Measurement error}}$$

If the measurement error is small, compared to the variability between persons, the ICC approaches 1. This means that the discrimination of the persons is hardly affected by the measurement error, and thus the reliability is high. If the measurement error is large, compared to the variability between persons, the ICC value becomes smaller¹³³.

4.7.4.3 Standard error of measurement (SEM) and minimal detectable change (MDC)

Agreement of a measurement can be assessed by calculating the standard error of the measurement (SEM) and the minimal detectable change (MDC). The SEM is used to assess the agreement between groups of data. It can be derived from the ICC: SEM = standard deviation $\times \sqrt{1 - \text{ICC}}$ ¹³³. The MDC is used to assess agreement between data of the individual subjects. It can be derived from the SEM: MDC = 1.96 $\times \sqrt{2} \times \text{SEM}$. Agreement parameters are expressed on the actual scale of measurement, and are therefore easily interpretable¹³³.

4.7.4.4 The Bland-Altman method

Agreement can be assessed graphically using the Bland-Altman plot^{14,15}. The plot shows the difference between measurements plotted against the average of measurements (figure 14).

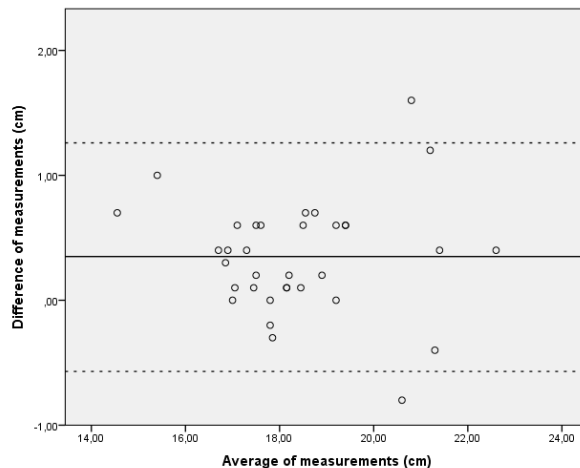


Figure 14: Bland-Altman plot showing difference against mean

The mean shows if there is a systematic difference between measurements and the 95% limits of agreement show the spread of data in the sampled distribution. The limits of agreement are calculated as the mean ± 1.96 standard deviations. The visual presentation of data makes it possible to detect skewed distributions and correlation between measurement error and the scale of the measurement.

5 AIMS

*Aim at the sun, and you may not reach it;
but your arrow will fly far higher
than if aimed at an object on a level with yourself.*
Joel Hawes

Over the past decade a change in treatment of acute Achilles tendon rupture away from operative and immobilizing treatment towards non-operative treatment using controlled early motion occurred^{8,74}. This thesis addresses the question: 'What is the optimal non-operative treatment protocol for acute Achilles tendon rupture?'

5.1 AIM OF THE THESIS

The aim of this PhD thesis was to evaluate non-operative treatment of acute Achilles tendon rupture, in order to pave the way for national and international treatment guidelines concerning acute Achilles tendon rupture.

5.2 AIMS OF THE STUDIES

5.2.1 Study I: Treatment of acute Achilles tendon rupture in Scandinavia

The aim of this survey was to investigate whether departments treating acute Achilles tendon rupture in Scandinavia adhere to the latest evidence.

5.2.2 Study II: The influence of early weight-bearing on clinical outcome

The aim of this blinded, randomized, controlled trial was to compare patient reported and functional outcome in patients randomized to immediate weight-bearing or non-weight-bearing in a non-operative treatment protocol for acute Achilles tendon rupture using controlled early motion.

5.2.3 Study III: The influence of early weight-bearing on biomechanical outcome

The aim of this blinded, randomized, controlled trial was to compare the biomechanical properties of the plantar flexor muscle-tendon complex of both limbs in patients randomized to early weight-bearing or non-weight-bearing. Both groups were treated non-operatively using controlled early mobilization.

5.1.4 Study IV: A Novel Ultrasound Measurement of Achilles tendon Length and Elongation

The aim of this study was to develop and validate a method which can determine Achilles tendon length and elongation accurately in a clinical setting using standard US equipment. In order to do so we had the following specific aims:

- 1) US identification of the anatomical landmarks and development of the specific measurement
- 2) Assessment of the intra-rater reliability
- 3) Assessment of the inter-rater reliability
- 4) Assessment of the validity by comparison with MRI

Comparison of the tendon length of both legs of the same subject

6 SUBJECTS AND METHODS

*'I hate definitions!'
Benjamin Disraeli*

In this chapter the methodology used in study I-IV is described. Outcome parameters and statistical methods are discussed and critically assessed. A thorough discussion of methodological considerations is done in chapter 7.

6.1 STUDY DESIGN, SUBJECTS, MATERIAL AND ETHICAL CONSIDERATIONS

6.1.1 Study I: Treatment of acute Achilles tendon rupture in Scandinavia

6.1.1.1 Study design

The study was conducted as a questionnaire based cross-sectional study investigating: 1) the use of surgical treatment, 2) the use of dynamic rehabilitation, and 3) the use of weight-bearing.

6.1.1.2 Subjects

All orthopedic departments treating acute Achilles tendon rupture in Denmark, Sweden, Norway and Finland were identified. Only public hospitals were included as private hospitals according to the experience of the authors play a negligible role in treatment of acute Achilles tendon rupture in Scandinavia. Data were collected in the period from October 2011 to October 2012.

6.1.1.3 Material

A questionnaire was developed in Danish and translated by bilingual speakers into Swedish, Norwegian and Finish (Annex B). The questionnaire was divided into four parts. Part one investigated

Achilles tendon rupture diagnostics, how choice of treatment was made and to what degree the patients were involved in the decision making process (four questions). Part two investigated which patients were recommended surgical treatment, which surgical technique was used and what kind of post-surgical regimen was offered (seven questions). Part three investigated what kind of non-surgical treatment was offered (three questions). Part four consisted of three patient cases where preference of surgical or non-surgical treatment had to be chosen.

6.1.1.4 Ethical considerations

Our survey did not make use of patients or animals and as such no ethical consideration were made in regard to those.

6.1.2 Study II: The influence of early weight-bearing on clinical outcome

6.1.2.1 Study design

This was a blinded, randomized, controlled, superiority trial with participants individually randomized to one of two parallel groups. The trial was designed in accordance with the Consort requirements; no changes were made to the trial design after commencement of the trial.

6.1.2.2 Subjects

Sixty patients were included in the trial. Patients with acute Achilles tendon rupture referred to the orthopedic department of Copenhagen University Hospital Hvidovre from April 2011 to March 2012 were assessed for eligibility. Diagnosis was based on a medical history with a clear snap of the Achilles tendon and a clinical examination with a palpable gap and positive Thompsons test^{1,30}.

All patients aged 18 to 60 years who were expected to be able to follow the treatment protocol and give written consent in Danish were eligible for inclusion if randomization could be done within 4 days of the rupture. Exclusion criteria were previous Achilles tendon injury, corticosteroid injections within the last 6 months, ASA-score of three or more, medical history of arterial insufficiency in the legs and rupture within 1 cm of calcaneus. 29 patients from the intervention group and 27 from the control group were included in the one-year analysis, all belonging to their original assigned groups. The groups were comparable at all parameters except for height with the non-weight-bearing group being three cm taller.

6.1.2.3 Material

All patients were treated with controlled early motion and randomized to either immediate weight-bearing or non-weight bearing.

Intervention

The intervention group was allowed full weight-bearing from day one. Crutches were recommended but not obligatory the first two weeks of treatment. The control group was instructed not to bear weight for the first six weeks of treatment. The last two weeks full weight-bearing was allowed

Standard treatment protocol used in both groups

In the emergency department an ankle orthosis (DJO Nextstep Contour2 Walker) with three wedges of 1.5cm was applied, fixat-

ing the ankle in equinus position (20-30 degrees of plantar flexion). The orthosis was worn for eight weeks gradually bringing the ankle to neutral position by removing a wedge every second week (table 5).

Table 5: Treatment protocol

Week 1 and 2
Orthosis with three wedges.
The orthosis could not be removed at any time.
Intervention group: Weight-bearing allowed, crutches were recommended.
Control group: No weight-bearing.
Week 3 and 4
Orthosis with two wedges.
Controlled early motion in both groups.
Intervention group: Full weight-bearing.
Control group: No weight-bearing.
Week 5 and 6
Orthosis with one wedge.
Controlled early motion in both groups.
Intervention group: Full weight-bearing.
Control group: No weight-bearing.
Week 7 and 8
Orthosis without wedges.
Controlled early motion in both groups.
The orthosis could be removed at night.
Intervention group: Full weight-bearing.
Control group: Full weight-bearing.
Week 9 to 16
Visit to physiotherapist three times a week.
Standardized rehabilitation protocol with room for individualization

Patients were seen in the outpatient clinic after two and eight weeks. The patients were instructed not to remove the orthosis at any time during the first two weeks. After two weeks the first wedge was removed and controlled early motion begun: Patients were instructed to remove the orthosis at least five times a day sitting on the edge of a table with both legs hanging (figure 15). Gravity plantar flexed the foot and the patient actively dorsiflexed the foot to a horizontal position. Patients were instructed to do this in series of 25 repetitions. The orthosis was not to be removed inbetween exercises from week three to six. The last two weeks of treatment the orthosis could be removed at night.

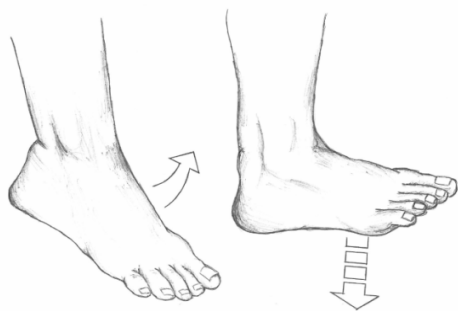


Figure 15: Controlled early motion. Gravity plantar flexed the foot, where upon the patient actively dorsi flexed the foot to a horizontal position. Patients were instructed to do this in series of 25 repetition five times a day. Drawing by Ilija Ban, MD

6.1.2.4 Ethical considerations

We believe that the potential benefits for the patients enrolled in the study (better functional outcomes, improved health-related well-being and economic savings) exceed the potential inconven-

iences (additional follow-up audits and possible risks/side effects).

The study was conducted in accordance with the principles of the Helsinki Declaration. The study was approved by the Regional Ethical Review Board. All participants received oral and written information concerning the trial before written consent was obtained. Patients were covered by Hvidovre University Hospital patient insurance.

6.1.3 Study III: The influence of early weight-bearing on biomechanical outcome

6.1.3.1 Study design

This study is based on data from a blinded, randomized, controlled trial with participants individually randomized to one of two parallel groups (study II).

6.1.3.2 Subjects

The study population was the same as described in study II (chapter 6.1.2.2). 26 patients from the intervention group and 20 from the control group were included in the one-year analysis, all belonging to their original assigned groups.

6.1.3.3 Material

The treatment protocol and the intervention was the same as described in study II (chapter 6.1.2.3). Follow up was done in the Gait analysis laboratory at Hvidovre Hospital.

Measurement of passive tension in the plantar flexor muscle-tendon complex was performed using an isokinetic dynamometer. A motor (Caldercraft Electric Motors, model 26) was driven by a DC power amplifier (model 2708; Brüel & Kjær, Naerum, Denmark) and could deliver maintained torques up to 80Nm and peak torques up to 120Nm. An electro-goniometer, connected to the footplate, measured the angle of the ankle joint and a torque meter measured the torque exerted on the footplate. This apparatus was developed and found to produce highly reproducible measurements of passive and reflex-mediated torque around the ankle joint by Sinkjær et al.^{131,140}. Before testing in the isokinetic dynamometer the patient warmed up on a stationary bicycle for 5 minutes. For the measurement, the patient was positioned with the foot strapped to a pedal in 10 degrees of plantar flexion and the knee and hip fixed in 90 degrees flexion. Patients were asked to relax and not activate their calf muscles as the ankle was passively moved into dorsiflexion by the pedal at an angular velocity of 5 °/sec. The isokinetic dynamometer rested for 2 seconds at maximal dorsiflexion before the pedal was returned to the starting position at the same velocity. The resistant torque was sampled at a frequency of 1000Hz. Patients who had a ROM exciding 20 degrees of dorsiflexion were tested in the range from 10 degrees plantar-flexion to 20 degrees dorsiflexion. Seven patients had a range of motion below 20 degrees of dorsiflexion, they were tested in the range from 20 degrees plantar-flexion to 10 degrees dorsiflexion. Ten repetitions were performed on each limb. The unaffected limb was tested before the affected. Strength was measured using the same isokinetic dynamometer setting. The patient was asked to relax as the dynamometer dorsiflexed their ankle to 10 or 20 degrees of dorsiflexion, respectively. The dynamometer rested for three seconds and the patient was encouraged to deliver maximal plantar-flexion power without activating the thigh while the dynamometer plantar flexed the foot 40 degrees from the starting position with a speed of 6.7°/s. Five repetitions were performed on each limb. The unaffected

limb was tested before the affected. Standardized verbal encouragement was provided to ensure maximal effort⁷⁷.

6.1.3.4 Ethical considerations

The ethical considerations were the same as described in study II (chapter 6.1.2.4).

6.1.4 Study IV: A Novel Ultrasound Measurement of Achilles tendon Length and Elongation

6.1.4.1 Study design

The study was done as a cross-sectional study comparing the investigated measures twice within a certain period of time.

6.1.4.2 Subjects

Both legs of 19 uninjured persons (8 males and 11 females) were studied. Their mean age was 43.4 years (SD 10.7, range 26-63). Average height was 175cm (SD 9, range 158-192) and average weight was 76.8kg (SD 12.9, range 58-110). They all had right as their dominant side.

6.1.4.3 Material

Definition of landmarks

Achilles tendon length was defined as the distance between the tendon insertion at the calcaneus and the medial gastrocnemius muscle tendon junction, as previously described by Rees et al.¹⁰² (figure 16).

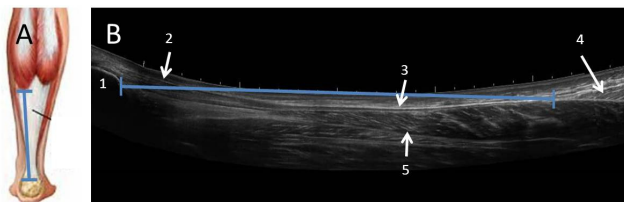


Figure 16: The blue line represents the distance measured by the novel ultrasound measure. (A) A posterior view of the calf. (B) A panoramic ultrasound picture of the calf: 1) Calcaneus, 2) The Achilles tendon, 3) the tendon sheet of the suralis muscle, 4) the gastrocnemius muscle, and 5) the soleus muscle.

First, the anatomical landmarks were identified and marked, then the distance between them was measured. The distal landmark was the posterior and most superior corner of the calcaneus in the midline, which on sagittal US examination was identified as the point where the cortical bone and its underlying shadow ended (figure 17). The proximal landmark was the distal tip of the medial gastrocnemius head, which was defined as the most distal point where the muscular fibers inserted into the v-shaped convergence of the deep crural fascia (figure 17).

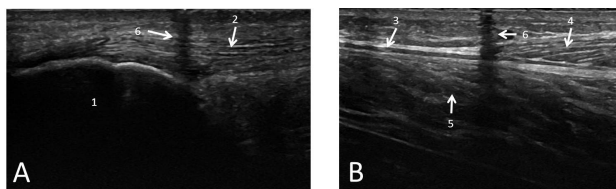


Figure 17: Sagittal US pictures showing (A) the insertion of the Achilles tendon at the calcaneus and (B) the muscle-tendon junction. (A) The distal landmark, the posterior-superior corner of calcaneus, is seen as the point where the cortical bone and its underlying shadow ends. (B) The proximal landmark is the distal tip of the medial gastrocnemius head (the insertion of the most distal muscle fibers into the deep fascia). 1) Calcaneus, 2) The Achilles tendon, 3) the tendon sheet of the suralis muscle, 4) the gastrocnemius muscle, 5) the soleus muscle, and 6) the posterior

acoustic shadowing of the needle of a 21 gauge needle projecting the landmark to the skin.

Setup

Participants were positioned in a prone position with the knee flexed 10 degrees. Anteriorly to (below) the ankle joint a triangle shaped foam pad was placed with the feet resting relaxed against it (figure 18). Using a goniometer the ankle joint was positioned in 10 degrees of plantar flexion by adjustment of the foam pad. Participants were positioned identically for US and MRI investigations.

The predefined anatomical landmarks were identified using longitudinal imaging. A needle was placed between the probe and the surface of the skin, and the posterior acoustic shadow created by the needle on the US image was centered over the landmark (figure 17). The position of the needle, thus representing the landmark, was then marked on the skin (figure 18). The direct distance between landmarks was measured with a tape measure following the curves of the leg.

Reliability-testing of the US measurement was performed using three different US scanners: GE Healthcare Logiq S8, Logiq 9 and logiq P5. Frequency was set to 15 MHz and focus was dynamically adjusted by the US operator. After each scan the marks on the skin were removed in order to secure blinding of results between investigators.

The novel US measurement was validated by three independent US-investigators with two to five years of experience within musculoskeletal US. MR-images were evaluated by two independent investigators, both specialized in musculoskeletal MRI. All investigators were blinded to the results of the other investigators and to their own previous results. Inter- and intra-rater reliability for the novel US measurement was determined for the three independent US investigators on two occasions with three weeks between scans. Within the following two months, MRI examinations were performed.



Figure 18: Positioning of the study subjects. Participants were positioned in a prone position with the knee flexed 10 – 20 degrees. The ankles rested on a triangular foam pad. Using a goniometer the ankle joint was positioned in 10 degrees of plantar flexion by adjustment of the foam pad (A). With a marker the point where the US probe and the needle crossed was marked on the skin (B+C). The distance between landmarks was measured with a tape measure following the curves of the leg (D).

6.1.4.4 Ethical considerations

There are no known side-effects or risks associated with the performed UL and MRI investigations. We believe that the potential benefits for coming generations of patients with acute Achilles tendon rupture exceed the potential inconveniences for the study subject.

The study was conducted in accordance with the principles of the Helsinki Declaration. The study was approved by the Regional Ethical Review Board. All participants received oral and written information concerning the trial before written consent was obtained.

6.2 CRITICAL ASSESSMENT OF OUTCOMES

A variety of outcomes have been used for assessment of acute Achilles tendon rupture. The following guidelines for choosing appropriate outcomes have been suggested³⁷: 1) the measure must be quantifiable, 2) the measure should be relatively easy to define and use, 3) the measure should lend itself to standardization and validation, and 4) the measure should be clinical relevant.

6.2.1 Study I: Treatment of acute Achilles tendon rupture in Scandinavia

6.2.1.1 Outcome parameters in study I

The following four outcomes were assessed in the study:

1) The use of surgical treatment

Departments were asked which of the following statements was most correct:

- a) In principle all patients are recommended surgery
- b) Healthy and active people under the age of 60 are recommended surgery
- c) Active sportsmen and people with excessive demands to their Achilles tendons are recommended surgery
- d) Only patients with delayed diagnosis, patients treated with corticoid-steroid, patients with sharp lesions and a few other cases are recommended surgery

2) The use of controlled early motion

Departments were asked if their treatment protocol allowed movement of the ankle joint from week three of treatment.

3) The use of controlled early weight-bearing

Departments were asked when partial and full weight-bearing was allowed.

4) The level of experience of the performing surgeons

Departments were asked if the operations were performed by specialist in orthopedic surgery or by any surgeon.

6.2.1.2 Critical assessment of the outcome parameters in study I

The chosen outcomes were investigated using a purpose made questionnaire. The questionnaire was developed in Danish and translated to Swedish, Norwegian and Finish. The Swedish and Norwegian translations were approved by the first author who is able to read and understand both languages. The questionnaire was not validated concerning construct, content or criterion validity¹²³. Nor was the reliability and agreement of the questionnaire tested⁶². As such, we do not know if the questionnaire measured what it intended to measure.

6.2.2 Study II: The influence of early weight-bearing on clinical outcome

Most RCT's presented in chapter 3 have used the re-rupture rate as their primary outcome parameter. It is debatable if the re-rupture rate is a good primary outcome, as it does not contain information concerning the functional outcome and the patient's

own perception of the outcome^{27,33,87,121}. In 2002 Pajala et al. investigated the outcome after 23 re-ruptures and nine deep infections and concluded that the outcome after a simple re-rupture without infection is satisfactory, whereas the outcome after a deep infection often is devastating⁹⁴.

6.2.2.1 Outcome parameters in study II

We decided to follow the recommendation by Silbernagel et al.¹¹⁴ and use a combination of patient reported outcome and functional outcome. Our primary outcome parameter was the Achilles tendon Total Rupture Score (ATRS) at one year follow up. Secondary outcomes were 1) the Heel-rise work test, 2) re-rupture rate, 3) length of sick leave, 4) time to return to sports, and 5) quality of life during treatment.

6.2.2.2 Critical assessment of the outcome parameters in study II

Whether to use doctor reported or patient reported outcomes is an ongoing discussion. Re-rupture and infection rate are doctor reported outcomes; they are quantifiable, easy to use and easily standardized. The ATRS is a patient reported outcome; it is quantifiable, easily standardized and relatively easy to use. The question is which of the outcome measures is the most clinical relevant.

We have chosen to use the ATRS as our primary outcome as we find the patients' perception of his/her injury to be the most important criteria of success of a given treatment. Critics of PROM-assessment argue that results are influenced by the sociocultural context, the shape and application of the questionnaire, by the patients' familiarity in answering the questionnaire and by the patients' relationship with the clinician/researcher^{67,98}. The ATRS it is developed and validated for use after acute Achilles tendon rupture and found to have good validity, reliability, internal consistency and responsiveness^{33,53,88}. Still, the construction of the questionnaire can be questioned. The questionnaire investigates 10 items with a possible score between zero and 10, it is thus possible to achieve a total sum score of maximum 100⁸⁸. It is common practice in sociology and psychology to add together ordered items to sum-scores and then use these sum-scores for subsequent analyses. It is however questionable if the added item-scores represent the same value, and as such if the sum-score is a valid measurement²¹. Another problem concerning the ATRS is the lack of clear analysis guidelines. Finally, the Danish validation of the ATRS showed an SEM of 7 and an MDC of 19; meaning that differences below 7 points cannot be measured with the ATRS.

Sick leave and time-to-return-to-sport was registered retrospectively at six and 12 months follow up; though there is a risk of recall bias.

Quality of life during treatment was measured using a purpose made 5 item questionnaire. The questionnaire was not validated concerning construct, content or criterion validity¹²³. Nor was the reliability and agreement of the questionnaire tested⁶². It would have added a dimension of validity to the study if a validated quality of life questionnaire had been used.

6.2.3 Study III: The influence of early weight-bearing on biomechanical outcome

No primary outcome was determined a priori as the study was based on data from study II. We did, however, suggest a primary outcome post-hoc, based on the availability of data from previous studies^{18,76}.

6.2.3.1 Outcome parameters in study III

We suggested peak passive torque as primary outcome parameter at one year follow up. Secondary endpoints were 1) stiffness in early, middle and late dorsiflexion, 2) energy stored, 3) torque relaxation and 3) the maximal strength.

6.2.3.2 Critical assessment of the outcome parameters in study III

The used outcome parameters have all been described and used in a range of experimental and clinical studies^{17,18,76,81}. The question is, however, to what degree we are measuring the biomechanical property of the Achilles tendon and to what degree the surrounding tissue (the plantar flexor muscles, the ankle joint and the loose connective tissue) influences the measurements.

6.2.4 Study IV: A Novel Ultrasound Measurement of Achilles tendon Length and Elongation

6.2.4.1 Outcome parameters in study IV

Intra- and inter-rater reliability and agreement was tested using the ICC, SEM and MDC. Furthermore a graphical evaluation using the Bland-Altman method was used. Validity of the novel ultrasound was tested against MRI measurements and the measurement error was calculated. Comparison of the two limbs was done using ICC, SEM and MDC.

6.2.4.2 Critical assessment of the outcome parameters in study IV

It is an ongoing discussion whether to use reliability parameters like ICC or to use the Bland-Altman method^{14,62,133}. We chose to present both, which some might consider unnecessary additional material.

Proportions of agreement could have given additional information. It would have been interesting to know the proportion of measurements lying within e.g. 5mm from each other and it would be interesting to know the proportion of persons having a discrepancy between the length of the left and right Achilles tendons above e.g. 10mm.

Validity was assessed by comparing the UL-measurements with the MRI-measurements. The actual length of the tendon is not known and as such the calculated measurement error might be misleading.

6.3 STATISTICS

The Statistical methods used in this thesis are outlined in table 6.

6.3.1 Paper I - statistical considerations

Two-way tables with Fisher's exact test were used for analysis as cells had expected values below 5.

6.3.2 Paper II - statistical considerations

The ATRS was considered a continuous score. One could argue that it is a categorical, ordinal score, but it does not affect the statistical testing as the results were not normally distributed and the Wilcoxon signed rank test was used.

6.3.3 Paper III - statistical considerations

The paired t-test was used for evaluation within groups of data. It was also used for comparison between the right and left leg of subjects, as data from the two sides of a person were considered to be connected.

6.3.4 Paper IV - statistical considerations

The statistical considerations concerning the use of the Bland-Altman method and ICC, SEM and MDC are described in chapter 4.7.

Tabel 6

Statistical Methods	Paper I	Paper II	Paper III	Paper IV
Type of data				
Categorical, ordinal and dichotomous	X	X	X	X
Continuous, normally distributed		X		
Continuous, not normally distributed		X		
Sample size calculation				
Made a priori		X		X
Made post hoc			X	
Comparison within groups				
Wilcoxon signed rank test (Continuous, not normally distributed data)		X		
Paired t-test (Continuous, normally distributed data)			X	
Comparison between groups				
Fischer's exact test (Dichotomous data)	X	X	X	
Un-paired t-test (Continuous, normally distributed data)		X		
Paired t-test (Continuous, normally distributed data)			X	
The Mann-Whitney U test (Continuous, not normally distributed data)		X		
Change over time				
Two way ANOVA (Continuous, not normally distributed data)			X	
Validity, agreement and reliability				
The Bland-Altman method				X
ICC, SEM and MDC				X

Table 6: Showing the statistical methods used in the four trials. The significance level for all significance tests was set to 0.05, two tailed.

7 METHODOLOGICAL CONSIDERATIONS

There are only a handful of ways to do a study properly but a thousand ways to do it wrong
Sackett

In the attempt to produce research of the highest quality, it is of outmost importance to choose the correct study design and setup in order to avoid bias and fulfill the aim of the study^{2,35}. The following chapter is an attempt to 1) assess the methodological problems encountered in this thesis, 2) discuss the possible induced bias, and 3) explain how bias has been or should be controlled.

7.1 BIAS

Bias refers to the presence of systematic error in the design, conduct, analysis or publication of a study^{35,37,96}. More than 70 different types of bias have been described and several classification systems proposed, the most common distinguishing between information, selection and confounding bias^{28,35}. Information bias refers to errors of assessment and measurement of the studied population (figure 19). Selection bias refers to factors influencing who is included in the study population. Confounding bias refers to factors that determine who is exposed to the studied intervention and influences the generalizability of the study results^{35,37}. The terminology and division of bias into categories varies by discipline and among authors.

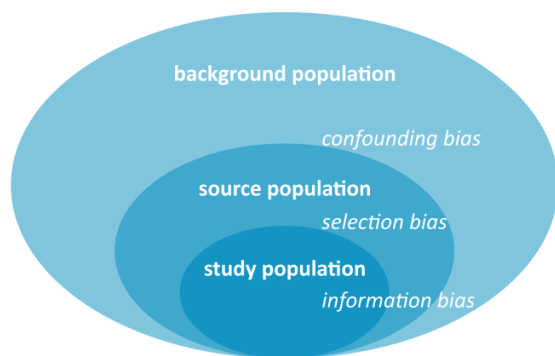


Figure 19: Schematic illustration of the relationship between information, selection and confounding bias and the study, source and background population. Modified from Gerhard et al.

7.1.1 The randomized controlled trial

The RCT has been developed to produce groups who are identical in all matters except for the intervention under investigation. Ideally it would lead to unbiased conclusions.

In reality bias is always present in research studies, the question is how much bias exists and to what extent it influences the drawn conclusion³⁵. The Cochrane group has published guidelines for design of RCT's in order to minimize risk of bias⁴¹, the main components are shown in table 7.

Table 7

Component	Type of bias	Description	How to control
Randomization	Selection bias	Systematic differences between baseline characteristics of the groups that are compared	Stringent randomization procedures Computer generated and concealed randomization
Blinding	Detection bias	Systematic differences between groups in how outcomes are determined	Blinding of investigators
	Performance bias	Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest	Blinding of patients, health personnel
Incomplete outcome data	Attrition bias	Systematic differences between groups in withdrawals from a study	Study design should consider how to avoid dropout Use of intention to treat analysis or Available case analysis
Selective outcome reporting	Reporting bias	Systematic differences between reported and unreported findings	All outcomes are reported
Baseline imbalance	May indicate selection bias May raise questions related to effect estimate	An imbalance in baseline characteristics may indicate flaws in randomization An imbalance in prognostic factors leads to the question of whether the effect estimate is because of the treatment effect or because of the difference in prognostic factors	Stringent randomization procedures Population size above 400 Stratification for a few important prognostic factors in small trials Regression analysis to adjust for observed imbalances
Early stopping	Early stopping bias	Trials are stopped at a point when the treatment effect is high at random when an insufficient number of outcome measures have been achieved	Well defined primary endpoint and when to investigate it
Academic	Academic bias Detection	A bias towards finding the same result if the clinical trial is repeated in a new group of patients	Publication of the trial protocol Honestly concerning previous publications and convictions
Source of funding	Detection bias Performance bias Reporting bias Early stopping bias	See descriptions above. The results tend to become favorable to the sponsor's product	Declaration of source of funding

Table 7: Showing the main components to minimize risk of bias in RCT's proposed by the Cochrane group. Modified from Gerhard et al. 2008.

7.2 STUDY I: TREATMENT OF ACUTE ACHILLES TENDON RUPTURE IN SCANDINAVIA

The aim of study I was to investigate the used treatment protocols in Scandinavia at a given time. For that an observational, prospective, cross-sectional study design was chosen, and data were collected through a questionnaire based survey. This design introduces a range of information bias.

The risk of *recall bias*; that the person who filled out the questionnaire did not recall or due to positive or negative emotions did over or under estimate the answer. It is an inherent part of a

questionnaire based cross-sectional study. In order to control for recall bias a prospective design investigating the actual treatment over a given period of time could be chosen.

Also the risk of *language bias* was present. Translation and cultural differences might have led to different interpretation of the questions in different parts of Scandinavia. To better control for language bias a proper validation of the questionnaire could be made in each country. Alternatively an English questionnaire could have been used. However, it might also be differently interpreted across Scandinavia and a validation would be needed to investigate this matter.

Some of the questions were designed as ordinal scales and others as nominal scales. *Misclassification bias* might have been introduced if the scales were not intuitively understood and the questions overlapping. Again the solution to better control for misclassification bias would be a proper validation of the questionnaire. The survey was designed to investigate the used treatment protocols in orthopedic departments across Scandinavia and did not consider the size of the respective departments. As such, the design did not allow for quantitative considerations concerning the number of patients receiving a given treatment. If one was interested in the number of patients receiving a given treatment a retrospective or prospective register study could be chosen. The prospective being the least biased of the two in this matter. The aim of the study was to investigate the treatment in Scandinavia and as all departments in Scandinavia were included in the source population it equals the background population. Therefore no confounding bias was present. If one would like to generalize the results outside of Scandinavia an analysis of possible confounding bias should be performed.

The high response rate of 93% minimizes the risk of selection bias. Still it is possible that the remaining 7% did not respond due to a systematic difference in their treatment protocols, which would lead to unrecognized selection bias.

7.3 STUDY II AND III: THE INFLUENCE OF EARLY WEIGHT-BEARING ON CLINICAL AND BIOMECHANICAL OUTCOME

The aim of study II and III was to investigate the effect of an intervention. For that an experimental, prospective, longitudinal design was chosen: a blinded, randomized, controlled, clinical trial. The randomized study design is the best design to prevent bias as unknown factors affecting the trial are expected to be equally distributed between groups. The randomized setup is logistically demanding and time consuming. The following is a systematic review of the components listed in table 7.

Inclusion and exclusion criteria were chosen according to existing literature. Age, delayed presentation, treatment with corticosteroid and severe medical illness were considered to be probable confounding variables and controlled for. Thus, the study can be generalized to a population of 18 to 60 year old persons without severe medical illness and without prior use of corticosteroids. Randomization was done by the book and no selection bias was recognized. The procedure would have had more credibility if the randomization sequence had been computer generated. No baseline imbalance was found except for a small difference in height. A larger sample size would most probably have eliminated this difference.

The investigators were blinded to the intervention, whereby we have controlled for detection bias. Patients and healthcare personal could not be blinded due to the type of intervention and as such performance bias might be present. The intervention taken into consideration, it is not possible to control for performance

bias as blinding of patients and healthcare personnel is not possible.

In paper II data from 56 of 60 patients were analyzed, in paper III data from 46 of 60 patients were analyzed. In order to reduce attrition bias, available-case-analysis was performed. In paper II and III it is stated that intention-to-treat-analysis was used. This is incorrect as no imputation of data was performed, only the available cases were analyzed.

All outcomes stated in the trial protocols are reported and sought published. No reporting bias was present. The trial was stopped according to the trial protocol thereby minimizing the risk of early stopping bias. The research group had no previous publication concerning the topic of interest. The risk for Academic bias is therefore low.

The trial was funded by Hvidovre University Hospital, though a minor contribution was received from a company fabricating orthoses. The company had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Furthermore the study result, whether positive or negative, did not have substantial implication for the firm. The risk of bias due to the source of funding is therefore considered minimal. It should also be considered if the lack of difference found between the intervention and control groups could be due to lack of compliance. We intended to register the extent to which the allocated regimens were followed by implantation of pressure sensors in the orthoses. The sensors were custom made to measure the number of steps taken. Unfortunately the pressure sensors broke during treatment and we were not able to measure the difference in weight-bearing between groups. Patients and health personnel were not informed about the malfunction of the pressure sensors. A degree of sham-effect is therefore expected. The large variation of data in study III makes one consider if the setup was imprecise. If seating of subjects in the isokinetic dynamometer lead to unrecognized bias or the isokinetic dynamometer functioned probably. However, the isokinetic dynamometer was used according to standard instructions and other studies performed on the same machine in the same period of time did not lead to excess spread of data. We therefore conclude that the spread of data is caused by an actual diversity in study population.

7.4 STUDY IV: A NOVEL ULTRASOUND MEASUREMENT OF ACHILLES TENDON LENGTH AND ELONGATION

The aim of study IV was to develop and validate a novel UL measurement. For that an observational, prospective, cross-sectional study design was used. We consider the study population to be static and data to be collected at a prolonged point in time. One can discuss the optimal time interval between test and re-test. The interval should be long enough for the investigators to forget their previous measurement but at the same time sufficiently short for the study subject to remain static. We decided for an interval between tests of three weeks, as we expected the length of an uninjured Achilles tendon to remain constant over time. When designing an observational study one would like the study population to reflect the background population in order to be able to generalize the results. The size of the study population in paper IV taken into consideration a kind of selection bias must be expected. All the investigated persons were health personal, aged 26 to 63 years, without prior Achilles tendon problems who volunteered to participate. They probably differ from the background population in a range of unrecognized ways, but it is of

less importance in the chosen setup where the left and the right sides were compared.

The next source of possible bias was the study setup. Positioning of the study subjects and execution of the measurements were done according to a written study protocol and agreed upon by the investigators just before measurement. Still some kind of bias must be expected as the measurement was personalized by the investigators and a learning curve effect is possible. Study subjects rotated between investigators positioned in the same room using three different US-scanners. Though no communication concerning the measurements was allowed between investigators they might have influenced each other. Finally, the measurement required visible marks to be made on the leg with a marker. The marks were removed between tests, but in some cases a vague mark persisted which might have influence the measurement of the following investigators.

It is difficult to control for the bias connected to the study setup. However, the risk of bias could possibly have been reduced study subjects had been positioned by the same person for all investigators. The risk of learning curve could have been reduced by a thorough training in the measurement before the study period. Finally the same scanner could have been used by all three investigators and scans could have been done in isolated rooms with time enough between scans to allow for proper removal of the marks.

8 SUMMARY OF RESULTS

Experience is that marvelous thing that enables you to recognize a mistake when you make it again.
Franklin Jones

8.1 STUDY I: TREATMENT OF ACUTE ACHILLES TENDON RUPTURE IN SCANDINAVIA

The questionnaire was returned by 138 of 148 departments (response rate: 93%). In Norway 73% of departments recommend operative treatment to all patients. This is significantly different from the remaining Scandinavian countries ($P < 0.001$) where only 9 – 18% recommends surgery to principally all patients. Some 92% of departments in Norway, 83% in Denmark and 65% in Sweden recommend surgical treatment for active people under the age of 60; this is only the case in 30% of departments in Finland ($P < 0.001$). Controlled early motion was used significantly less in Denmark 22% (5/23), Norway 38% (17/45) and Sweden 28% (11/40) compared to Finland 58% (15/26) ($P=0.015$). Two weeks after surgery 57% – 92% of departments across Scandinavia allow partial or full weight-bearing and it increases to 82% - 100% after 4 weeks. There is a significant difference between countries in educational level of performing surgeons. In Sweden 73% of departments answered that surgery was performed by a specialist in orthopedic surgery in the vast majority of cases. This is significantly different ($p = 0.001$) from Denmark (22%), Norway (19%) and Finland (41%).

8.2 STUDY II: THE INFLUENCE OF EARLY WEIGHT-BEARING ON CLINICAL OUTCOME

Thirty patients were randomized to each group; 29 and 27, respectively, were analyzed. There were no statistically significant differences between the weight-bearing and the non-weight-bearing groups at 12 months, except from a better health-related quality of life in the weight-bearing group ($p=0.009$). Mean ATRS at 12 months was 73 weight-bearing and 74 non-weight-bearing

($p=0.81$). The Heel-rise-work-test showed a total work performed of the injured limb compared to the uninjured limb of 53% weight-bearing and 58% non-weight-bearing ($p=0.37$) at 12 months. There were three re-ruptures in the weight-bearing group and two re-ruptures in the non-weight-bearing ($p=1.0$). The weight-bearing group returned to work averagely six days earlier and resumed sport 38 days earlier compared to the non-weight-bearing group, this was not statistically significant.

8.3 STUDY III: THE INFLUENCE OF EARLY WEIGHT-BEARING ON BIOMECHANICAL OUTCOME

Thirty patients were randomized to each group; 26 and 20, respectively, were analyzed. There were no significant differences between the weight-bearing and the non-weight-bearing groups. Compared to the unaffected limb, peak passive torque was significantly lower for the affected limb at six months (91%, $p=0.01$), but not at 12 months (98%, $p=0.51$). Stiffness was significantly lower for the affected limb during the early part of dorsiflexion at six months (67%, $p<0.001$), and remained inferior at 12 months (77%, $p<0.001$). Irrespectively of group, a statistically significant decrease in the ability to store energy was seen in the affected limbs at both six (74%, $p<0.001$) and 12 months (82% $p<0.001$) follow up. Likewise, a statistically significant increase in torque relaxation was found in the affected limbs at both six (114%, $p<0.001$) and 12 months (111% $p<0.001$) follow up. The strength was significantly lower in the affected compared to the unaffected limb at both six (82%, $p<0.001$) and 12 months (93%, $p=0.009$).

As a surrogate for tendon elongation we looked at strength throughout range of motion. If tendon elongation was present one would expect strength to decline in the end of plantar flexion. As seen from figure 20 no difference between groups were found.

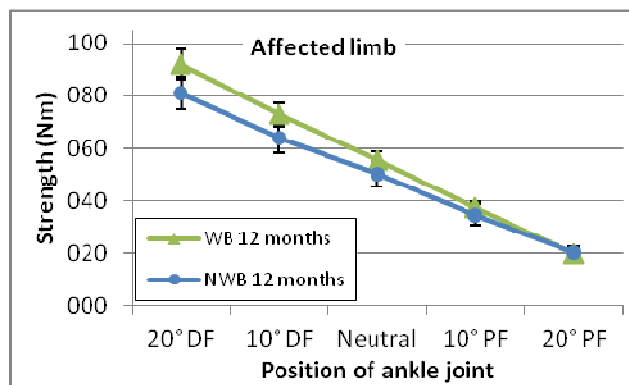


Figure 20: Strength throughout range of motion in the affected leg of the weight-bearing (WB) group and the non-weight-bearing (NWB) group.

8.4 STUDY IV: A NOVEL ULTRASOUND MEASUREMENT OF ACHILLES TENDON LENGTH AND ELONGATION

The intra-rater evaluation of the novel US measurement showed excellent reliability (ICC 0.96) and an acceptable agreement (SEM 3.7mm and MDC 10.3mm). The inter-rater evaluation showed a systematic difference between US observers of 2.1mm – 4.5mm ($p=0.001-0.036$); reliability was excellent (ICC 0.97) and agreement acceptable (SEM 3.3mm and MDC 9.3mm). Validity was evaluated by comparison with MRI measurements. UL measurements were on average 3.8mm longer than US ($p=0.001$); the measurement error was 2%. No statistically significant difference in length was found between the left and the right Achilles ten-

don. However, a rather large spread of data was found; agreement SEM 4.1mm and MDC 11.5mm.

9 DISCUSSION

*All who drink of this treatment recover in a short time,
except those whom it does not help, who all die.
It is obvious, therefore, that it fails only in incurable cases.*
Galen

The aim of this PhD thesis was to evaluate non-operative treatment of acute Achilles tendon rupture, addressing the question: 'What is the optimal non-operative treatment protocol for acute Achilles tendon rupture?'

Through the four papers of this thesis we have investigated 1) the status of treatment across Scandinavia and if departments adhere to the latest evidence, 2) the influence of immediate weight-bearing on patient reported and functional outcome, 3) the influence of immediate weight-bearing on biomechanical properties of the plantar flexor muscle-tendon complex, and 4) the validity and reliability of a novel ultrasound measurement of Achilles tendon Length and Elongation.

9.1 TREATMENT

9.1.1 Operative vs. non-operative treatment

There is increasing evidence supporting non-operative treatment as a safe and recommendable treatment for acute Achilles tendon rupture (chapter 3.1)^{55,87,132,141}. The meta-analyses reveal convincing evidence that non-operative treatment yields a 2-3 times increased risk of re-rupture and a 4-5 times decreased risk of other complications^{48,49,57,117,139}. Looking at functional results no clinical relevant differences are found in the meta-analyses^{48,49,57,117,139}. The few studies that have assessed the patient perception through a PROM have not found any differences either^{55,87}.

However, no evidence of difference is not equivalent with evidence of no difference. All studies performed so far have been superiority studies, and as such they are not able to claim non-inferiority of a given treatment. Furthermore, one could argue that the trials lack ability to show the actual differences between operative and non-operative treatment due to imprecise outcome parameters. Also it could be argued that the actual differences between treatment protocols are hidden in the heterogenic study populations. It is likely that a subgroup of the study populations would benefit from operative treatment and another subgroup from non-operative treatment. Dynamic ultrasound and Amlangs ultrasound classification have been suggested for use as selection tools to divide patients in subgroups, but no assessment of the measurements ability to predict final outcome has been made^{4,61}.

Considering the present literature the decision to treat operatively or non-operatively relies on an assessment of the severity of complications, in particular re-rupture and deep infection. The only published assessment of severity of complications was performed by Pajala et al.⁹⁴ They concluded that the outcome after a simple re-rupture without infection was satisfactory, whereas the outcome after a deep infection often was devastating. The severity of complications taken into consideration, our humble conclusion is that the literature favors non-operative treatment as the standard treatment for acute Achilles tendon rupture.

9.1.2 Departments in Scandinavia treat operatively

In Norway 3 out of 4 departments treat all patients operatively. In Denmark and Norway 9 out of 10 departments, in Sweden 7 out of 10 and in Finland 3 out of 10 departments use operative treatment as their standard protocol for active people under the age of 60. According to the literature, this puts patients in increased risk of complications without clear functional benefits^{48,49,57,117,139} and as such does not adhere to the latest evidence.

9.1.3 Controlled early motion vs. immobilization

Controlled early motion has been investigated in a number of experimental trials^{6,19,31} and a few RCT's^{24,51,80} (chapter 3.2.1). Furthermore controlled early motion has been used as standard treatment protocol in a number of RCT's testing operative vs. non-operative treatment^{55,78,87,92, 117,132, 141}. The trials have not found clear positive or negative effects of controlled early motion, but tend to favor the mobilizing regimen. Also, the arguments used in chapter 9.1.1 concerning precision of the used outcome parameters and heterogeneity of the study population are valid here.

9.1.4 Departments in Scandinavia use of controlled early motion to some extent

Controlled early motion is used in 20% – 60% of departments in Scandinavia; the least in Denmark and the most in Finland. One could argue that the spread use of controlled early motion is in accordance with the emerging evidence which might favor controlled early motion.

9.1.5 Controlled early weight-bearing vs. immobilization

Controlled early weight-bearing has been investigated in one RCT looking at operatively treated patients¹²¹ and been part of the standard treatment protocol in a number of other trials^{27,104} (chapter 3.2.2). The RCT found a positive impact on health related quality of life during treatment. No other effects were found. Also, the arguments used in chapter 9.1.1 concerning precision of the used outcome parameters and heterogeneity of the study population are valid here.

9.1.6 Departments in Scandinavia use controlled early weight-bearing

Partial or full weight-bearing after surgical and non-surgical treatment is allowed in the majority of departments across Scandinavia within the first 2 – 4 weeks. Considering the little evidence on the subject no conclusion can be drawn in regard to whether departments adhere to the latest evidence.

9.2 CONTROLLED EARLY WEIGHT-BEARING

The role of weight-bearing is of fundamental importance as it influences not only the quality of treatment but also the patient's ability to take care of him/herself. This ability is an essential part of most health related quality of life scores^{39,124,127} and as such, when using a PROM, it is expectable to find an improved quality of life during treatment in the weight-bearing group, as it was done by Suchak et al.¹²¹

The evidence concerning controlled early weight-bearing, as discussed in chapter 9.1.5-6, does not allow for proper conclusions; especially concerning non-operative treatment, where no RCT's have been performed. Anyway, controlled early weight-bearing is used as the standard treatment in the majority of hospitals across Scandinavia, probably due to the obvious advantages concerning the patient's ability to take care of him/herself and

the patients improved quality of life. The wide-spread use of controlled early rehabilitation can to some extent be considered a rough test of safety, as major complications most probably would have been recognized. However, the most probable complication associated with controlled early weight-bearing, namely tendon elongation, cannot be expected to be recognized outside a controlled clinical setup.

In this thesis we investigated the influence of immediate weight-bearing on patient reported and functional outcome in study II and on biomechanical properties of the plantar flexor muscle-tendon complex in study III. No differences were found between the weight-bearing and the non-weight-bearing groups except for the expected difference in quality of life.

Again it is important to emphasize that no evidence of difference is not equivalent with evidence of no difference. The trials were not designed as a non-inferiority trials and as such they cannot claim immediate- and non-weight-bearing to be equally effective in the treatment of acute Achilles tendon rupture. Also the arguments used in chapter 9.1.1 concerning precision of the used outcome parameters and heterogeneity of the study population are valid here.

9.3 LENGTH-MEASUREMENT

Elongation of the Achilles tendon after acute rupture is well known and associated with inferior clinical outcome^{50,78,81,115}.

Therefore, it is desirable to identify the group of patients in high risk of elongation in the acute or early phase after acute Achilles tendon rupture in order to individualize and thus optimize their treatment. A clinically applicable, accurate and easy to perform method for evaluating Achilles tendon length and elongation is needed for this purpose.

A range of length measures have been described in chapter 4.4^{4,23,50,64,95,99,102,105,118,144}, but they do not fulfill the above mentioned criteria. The aim of this study was to develop and validate a method which can determine Achilles tendon length and elongation accurately in a clinical setting using standard US equipment.

The first question that arises is whether it makes sense to investigate the length of a ruptured tendon. Does a ruptured tendon have a length or is it merely two flowing tendon ends. With the novel UL measurement we chose two anatomical landmarks at the periphery of the tendon. One could say that instead of investigating the tendon itself, we investigated if changes were made to the working length of the suralis muscle in relation to the calcaneal bone. When the tendon ruptures, the position of the proximal end of the Achilles tendon varies with knee flexion and contraction of the Triceps surae muscle and the position of the distal end of the Achilles tendon varies with the position of the ankle joint^{101,108}. It is therefore paramount for a measurement of the ruptured Achilles tendon to use a standardized position of the ankle and knee joint.

The validity of the measurement compared to MRI was acceptable (error 2%). The length assessment methods are different in US and MRI and as such a difference must be expected. MRI has not been validated for this specific length measure, thus it could be argued that our validity test is invalid. However, MRI was considered to be the best available non-invasive modality to use as gold standard concerning Achilles tendon length.

The reliability and agreement of the novel US measurement was comparable with the more advanced and logistically more demanding methods described in chapter 4.4^{102,115}. For comparison between groups of non-injured subjects, differences of more than

4mm can be detected. For repeated assessment of individual subjects, differences of more than 10mm can be detected. If the findings by Silbernagel et al.^{115,125} of an average elongation after ATR of 2.5-3.5cm holds to be true, the precision of the novel US measurement is fully acceptable. Finally, the large variation in length between the right and the left side in healthy people introduces an error in all measurements using the healthy leg as reference. We do not see an alternative reference value, but it is important for clinicians and researchers to be aware of this additional error.

10 CONCLUSION

*Life is the art of drawing sufficient conclusions
from insufficient premises.
Samuel Butler*

Non-operative treatment using controlled early weight-bearing after acute Achilles tendon rupture is safe. It may be the standard of care in national and international treatment guidelines concerning acute Achilles tendon rupture.

10.1 TREATMENT DOES NOT ADHERE TO EVIDENCE BASED GUIDELINES.

Operative treatment and controlled early weight-bearing is the preferred treatment protocol for acute Achilles tendon rupture in Scandinavia. This is in contrast with the latest evidence, which may favor non-operative treatment as the standard treatment for acute Achilles tendon rupture.

10.2 CONTROLLED EARLY WEIGHT-BEARING IS SAFE

It seems reasonable to recommend immediate weight bearing in a non-operative, dynamic treatment protocol as a safe treatment modality for acute Achilles tendon rupture. Immediate weight-bearing improves health related quality of life during treatment and does not seem to have detrimental effect on patient reported and functional outcome and on biomechanical properties of the plantar flexor muscle-tendon complex.

10.3 THE NOVEL UL MEASUREMENT IS VALID AND RELIABLE

The novel US measurement showed good validity, reliability and agreement. For comparison between groups of non-injured subjects differences of more than 4mm can be detected. For repeated assessment of individual subjects differences of more than 10mm can be detected. A measurement error of 2% was found. No systematic difference in length of the right and left Achilles tendon was found, but a rather large variation. Due to this an error of 5mm is introduced when looking at groups of patients using the uninjured side as reference and an error of 13mm for repeated assessment of individual subjects.

11 PERSPECTIVE AND FUTURE RESEARCH

'The more you know, the more you realize you know nothing.'
Socrates

The best treatment of acute Achilles tendon rupture has been discussed for a century. This thesis is a small step on the road of evidence.

An unacceptable diversity of treatment protocols is seen in Scandinavia. Future research should aim at developing a uniform treatment algorithm.

RCT's have focused on operative vs. non-operative treatment. There is a need for better investigation of the influence of rehabilitation. Future trials should investigate the area of controlled early motion and the combination of controlled early motion and weight-bearing.

An unacceptable fraction of patients acquiring an acute Achilles tendon rupture do not return to their pre-morbid level of function. We do not know why and we are not able to predict who will re-rupture and who will heal in elongation. If this subgroup could be identified in the acute phase of rupture or early phase of treatment, e.g. by US measurements, we might be able to individualize and improve their treatment. Future research should focus on identifying measures to identify this subgroup.

The novel US measurement should be tested in a population with Achilles tendon rupture and it should be correlated to final outcome. The same should be done for other US measurements like Amlangs US classification system⁴.

All RCT's published to date have considered patients the same and used re-rupture as the primary outcome. Future research could stratify people according to their risk profiles and use validated outcome measures.

SUMMARY

Background: Acute Achilles tendon rupture is a frequent and potentially disabling injury. Over the past decade a change in treatment of acute Achilles tendon rupture away from operative towards non-operative treatment has taken place. However, the optimal non-operative treatment protocol remains to be clarified, particularly the role of weight-bearing during early rehabilitation. Also, there is a need for a clinically applicable and accurate measurement to detect patients in risk of developing Achilles tendon elongation.

Purpose: The aim of this PhD thesis was to evaluate non-operative treatment of acute Achilles tendon rupture.

Methods: In study I, a cross sectional survey was performed investigating the chosen treatment protocols across Scandinavia. In study II, the effect of immediate weight-bearing on patient reported and functional outcomes was investigated in a randomized controlled trial (RCT). In study III, the effect of immediate weight-bearing on the biomechanical properties of the plantar flexor muscle-tendon complex was investigated in an RCT. In study IV, validity, reliability and agreement of a novel ultrasound measurement of Achilles tendon length and elongation was tested.

Results: Study I found surgery to be the preferred treatment in 83% of departments in Denmark, 92% in Norway, 65% in Sweden, and 30% in Finland ($p < 0.001$). Study II and III showed no statistically significant effects of controlled early weight-bearing at one year follow up except from a better health-related quality of life in the weight-bearing group ($p=0.009$). Compared to the unaffected limb, the affected limb had decreased stiffness (77%, $p<0.001$) and strength (93%, $p=0.009$) of the plantar flexor muscle-tendon complex. Study IV showed excellent intra-rater reliability (ICC 0.96, SEM 3.7mm and MDC 10.3mm), inter-rater reliability (ICC 0.97, SEM 3.3mm and MDC 9.3mm) and validity (measurement error 2%).

Conclusion: Treatment algorithms across Scandinavia showed considerable variation, though operative treatment and controlled early weight-bearing was the preferred treatment in

Denmark, Norway and Sweden. Immediate weight-bearing was found to be safe and recommendable in non-operative treatment of acute Achilles tendon rupture. The novel ultrasound measurement showed excellent reliability and acceptable validity and agreement.

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