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EFFECTS OF EARLY FUNCTIONAL MOBILIZATION AFTER ACUTE ACHILLES TENDON RUPTURE REPAIR

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Effects of Early Functional Mobilization after Acute Achilles Tendon Rupture Repair

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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Till Annette,

Den här boken blev skriven tack vare dig! Nu till minne av dig! Du trodde på mig och gav dig inte, vilket jag är dig evigt tacksam för! Du fanns där som stöd hela vägen, in i det sista.... Jag skulle klara detta, och trots att du inte fick uppleva slutet på min resa, så har jag hela tiden känt ditt stöd, din värme, din omtänksamhet, din beslutsamhet, boken är nu klar! Önskar så att jag fick dela den med dig!

ABSTRACT

Background: Patient outcome after Achilles tendon rupture (ATR) varies greatly, and complications such as deep venous thrombosis (DVT) and tendon elongation are common. Although accelerated rehabilitation is considered safe, the optimal content of the rehabilitation protocol is still unknown. Immediate early functional mobilization (EFM) could possibly be a way to reduce the risk of complications and improve outcome.

Aim: The overall aim of this thesis was to investigate whether EFM could reduce the risk of complications and improve outcome in individuals after surgical treatment of acute ATR.

Methods: A total of 149 ATR patients treated with a standardized surgical protocol were postoperatively randomized to either EFM (immediate full weightbearing and ankle motion in an orthosis) or standard treatment (ST, non-weightbearing plaster cast for 2 weeks). The incidence of DVT was examined by means of compression duplex ultrasound at 2 and 6 weeks postoperatively. Self-reported loading, steps and pain were recorded as well as evaluations of plantar pressure measurement, ultrasound imaging of the muscle-tendon morphology, clinical assessments, questionnaires, gait analysis, and functional outcome at different time points over the first postoperative year.

Results: EFM did not increase the risk of re-ruptures and infections compared to ST. EFM versus ST showed no difference in the incidence of DVT at 2 or 6 weeks. Risk factors for exhibiting a DVT postoperatively were older age and BMI >26, as well as low loading (≤50%) the first week after surgery in the EFM group. More experience of pain during activity was associated with lower degree of loading. Suffering from a DVT postoperatively resulted in inferior patient-reported outcome up to a year after ATR repair.

Patients in the EFM group reported higher general health and vitality compared to ST at 6 months postoperatively. The two groups exhibited no differences in functional outcome, neither at 6 months nor at one year.

EFM resulted in more pronounced tendon elongation at 2 weeks compared to ST. At later time points, no significant differences in elongation were found. However, tendon elongation of more than 3 cm resulted in inferior outcome in the heel-rise test at one year. No significant differences in muscle atrophy between groups were observed, although a trend for increased atrophy was seen in the ST group. The soleus atrophy seemed to be persistent at one year postoperatively.

No significant differences in gait patterns between groups were observed at 8 weeks or at 6 months.

Conclusions: EFM after ATR repair does not increase or reduce the risk of DVT, re-rupture and infection in the short term or tendon elongation and muscle atrophy in the long term, but EFM resulted in enhanced general health and vitality in the medium term outcome. Higher loading in the EFM group was associated with a lower risk of DVT. Suffering a DVT results in inferior patient-reported outcome and exhibiting excessive tendon elongation leads to impaired functional outcome at one year.

SAMMANFATTNING

Bakgrund: Utfallet efter hälseneruptur är mycket varierande och komplikationer så som djup ventrombos (DVT) och senförlängning är vanliga. Även om en mer accelererad rehabilitering har ansetts vara säker, är det optimala innehållet i rehabiliteringsprotokollet fortfarande okänt. Omedelbar tidig funktionell mobilisering (EFM) skulle kunna vara ett möjligt sätt att minska risken för komplikationer och förbättra resultatet.

Syfte: Det övergripande syftet med denna avhandling var att undersöka om EFM kunde minska risken för komplikationer och förbättra återhämtningen av funktion hos individer som har genomgått kirurgisk behandling efter akut hälseneruptur.

Metod: Totalt 149 patienter med akut hälseneruptur behandlades med standardiserad öppen kirurgi och ingick i en randomiserad kontrollerad studie. Efter operation lottades patienterna till antingen EFM (tidig funktionell mobilisering med full belastning direkt) eller standardbehandling (ST; underbensgips och avlastning i 2 veckor). Förekomsten av DVT undersöktes med ultraljud vid 2 och 6 veckor efter operation. Självrapporterad belastning, antal steg per dag och smärta rapporterades, samt mätning av belastning, ultraljudsmätning av muskel-senkomplexet, kliniska mätningar, frågeformulär, gånganalys, och funktionella resultat utvärderades vid olika tidpunkter under det första året efter operation.

Resultat: EFM ökade inte risken för re-ruptur eller infektion jämfört med ST. Det fanns inga skillnader i DVT-incidensen mellan grupperna vid 2 eller 6 veckor. Riskfaktorer för DVT efter operation var högre ålder, BMI >26, och i EFM-gruppen, låg belastning (≤50%) första veckan efter operation. Mer smärta under aktivitet var associerad med en lägre grad av belastning. Patienter som hade haft en DVT postoperativt rapporterade sämre resultat på självskattningsformulären upp till ett år efter operation.

Patienterna i EFM-gruppen rapporterade bättre allmän hälsa och vitalitet jämfört med ST-gruppen vid 6 månader efter operation. Inga skillnader avseende funktionella tester sågs mellan grupperna, varken vid 6 månader eller ett år.

EFM-gruppen uppvisade en signifikant högre grad av senförlängning vid 2 veckor jämfört med ST-gruppen. Vid senare tidpunkter sågs inga signifikanta skillnader i senförlängning mellan grupperna. En senförlängning på mer än 3 cm resulterade i ett sämre utfall på tåhävningstestet vid ett år. Inga signifikanta skillnader i muskelatrofi sågs mellan grupperna, dock fanns en trend för ökad atrofi i ST-gruppen. Muskelatrofin av soleus verkade vara bestående vid ett år efter operation.

Inga skillnader i gångmönster sågs mellan grupperna, varken vid 8 veckor eller 6 månader.

Slutsats: EFM efter kirurgiskt behandlad hälseneruptur varken ökade eller minskade risken för DVT, re-ruptur eller infektion på kort sikt, och inte heller risken för senförlängning eller muskelatrofi på lång sikt men däremot ledde EFM till förbättrad allmän hälsa och vitalitet på medellång sikt. Högre grad av belastning i EFM-gruppen var förknippad med minskad risk för DVT. Att ha haft en DVT efter operation resulterade i sämre patientrapporterat utfall och en för stor senförlängning ledde till försämrad funktion vid ett år.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following papers and manuscript, which are referred to in the text by their Roman numerals.

I. Aufwerber S, Heijne A, Edman G, Silbernagel KG, Ackermann PW.
Early mobilization does not reduce the risk of deep venous thrombosis after Achilles tendon rupture: a randomized controlled trial.
Knee Surg Sports Traumatol Arthrosc. 2020;28(1):312-319. doi:10.1007/s00167-019-05767-x

II. Aufwerber S, Heijne A, Silbernagel KG, Ackermann PW.
High plantar force loading after Achilles tendon rupture repair with early functional mobilization.
Am J Sports Med. 2019;47(4):894-900. doi:10.1177/0363546518824326

III. Aufwerber S, Edman G, Silbernagel KG, Ackermann PW.
Changes in tendon elongation and muscle atrophy over time after Achilles tendon rupture repair – a prospective cohort on the effects of early functional mobilization.
Am J Sports Med. 2020;48(13):3296-3305. doi:10.1177/0363546520956677

IV. Aufwerber S, Naili JE, Silbernagel KG, Ackermann PW.
Effects of early functional mobilization on gait pattern after acute Achilles tendon rupture repair.
Manuscript

V. Aufwerber S, Heijne A, Edman G, Silbernagel KG, Ackermann PW.
Does early functional mobilization affect long-term outcomes after an Achilles tendon rupture? A randomized clinical trial.
Orthop J Sports Med. 2020;16;8(3):2325967120906522. doi:10.1177/2325967120906522

CONTENTS

LIST OF ABBREVIATIONS

3D	Three-Dimensional
ADL	Activities of Daily Living
ANOVA	Analysis of Variance
AT	Achilles Tendon
ATR	Achilles Tendon Rupture
ATRA	Achilles Tendon Resting Angle
ATRS	Achilles tendon Total Rupture Score
BMI	Body Mass Index
CDU	Compression Duplex Ultrasound
CI	Confidence Interval
CMJ	Countermovement Jump
CSA	Cross-sectional Area
DF	Dorsiflexion
DVT	Deep Venous Thrombosis
EFM	Early Functional Mobilization
EFOV	Extended Field of View
EMG	Electromyography
FAOS	Foot and Ankle Outcome Score
ICC	Intraclass Correlation Coefficient
IPC	Intermittent Pneumatic Compression
IQR	Interquartile Range
LG	Lateral Gastrocnemius
LMWH	Low Molecular Weight Heparin
LSI	Limb Symmetry Index
MDC	Minimal Detectable Change
MG	Medial Gastrocnemius
MRI	Magnetic Resonance Imaging
MTJ	Myotendinous Junction
MTU	Muscle-Tendon Unit
N	Newton

Nm	Newton meter
OR	Odds Ratio
OTJ	Osteotendinous Junction
PAS	Physical Activity Scale
PE	Pulmonary Embolism
PROM	Patient-reported Outcome Measure
PT	Physiotherapist
QoL	Quality of Life
RCT	Randomized Controlled Trial
ROM	Range of Motion
SD	Standard Deviation
SJT	Sargent Jump Test
SSC	Stretch-Shortening Cycle
ST	Standard Treatment
TSK-SV	Tampa Scale of Kinesiophobia-Swedish Version
US	Ultrasound
VAS	Visual Analogue Scale
VTE	Venous Thromboembolism
W	Watt

1 INTRODUCTION

1.1 BACKGROUND

Achilles tendon rupture (ATR) is a sports injury that affects otherwise healthy young to middle-aged people. The injury often requires prolonged rehabilitation, and many patients do not achieve fully restored function. The injury is common in ball and racket sports, and the incidence has increased in recent decades. This increase is believed to be due to a greater number of middle-aged people being more active in high-intensity sports. Men in their 30s to 50s are at higher risk of suffering an ATR than women (1–4). The injury can be treated either with or without surgery, and there is currently no consensus regarding which of these treatments is preferable. It was recently found that the risk of re-rupture is reduced through use of a more functional orthosis treatment compared to a longer period of plaster cast treatment. However, a recent systematic review suggested that it might not be the initial treatment that is of most importance, but rather the rehabilitation (5). Moreover, there is a wide variation in outcome following ATR irrespective treatment (6–8). Many patients suffer from both early complications, such as deep venous thrombosis (DVT) (9,10), and late stage complications including decreased strength and function, pain, and gait abnormalities several years after injury (7,8,11–16). Thus, although early functional mobilization (EFM) seems promising for the treatment of ATR, many questions regarding efficacy of treatment remain to be answered.

1.2 ACHILLES TENDON

1.2.1 Anatomy

The Achilles tendon (AT) is the thickest and strongest tendon in the human body. The AT consists of fibers from the posterior calf muscles, the triceps surae, and inserts at the dorsal part of the calcaneal bone. In addition, the plantaris tendon runs medial to the AT (17) and inserts distally in close proximity or into the AT. The plantaris muscle is absent in a small percent of individuals (18). The triceps surae muscles are composed of the superficial, two-headed gastrocnemius muscle and the deeper soleus muscle. The gastrocnemius muscle originates from the femoral condyles, and the medial head is larger and longer than the lateral head (Figure 1). The gastrocnemius has more type II fast-twitch fibers and is involved in more explosive contractions compared to the soleus. The soleus is a flat, pennate muscle that originates from the posterior surface of the tibia and fibula and runs farther distal than the gastrocnemius (Figure 1). The soleus has more slow-twitch type I fibers, which are postural fibers, than the gastrocnemius (19). The function of the gastrocnemius muscle is to perform plantar flexion at the ankle joint and flexion at the knee joint, while the soleus acts solely at the ankle joint to plantar flex and supinate the ankle (18).

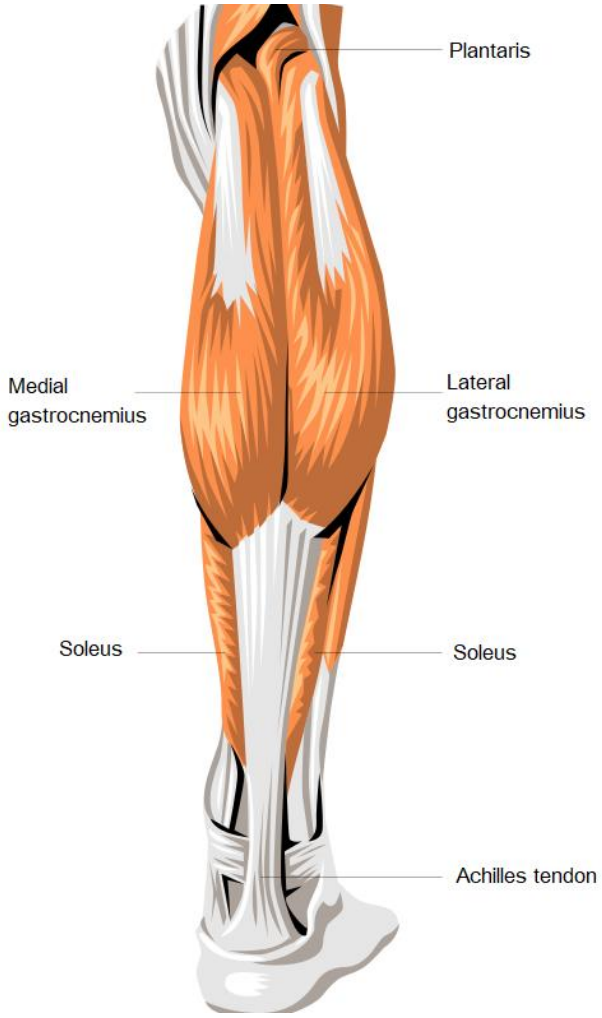

Figure 1. Anatomy of the posterior calf muscles and the AT *(from wpclipart.com).*

Tendons act as force transducers to transmit forces from muscle to bone (17). The AT is approximately 15 cm long (18). The gastrocnemius part of the tendon is longer (11−26 cm) than the soleus part (3−11 cm) (20). The proximal union of tendon and muscle is called the myotendinous junction (MTJ), while the distal union of tendon to bone is called the osteotendinous junction (OTJ) (21). The AT is flat at the MTJ and becomes rounded as it descends. About 4 cm proximal to the broad insertion on the calcaneus, it becomes flat again (17,19). The tendon twists 90 degrees to allow for elasticity and elongation so that energy can be released during motion (17). The tendon rotates laterally (clockwise in the left tendon and counterclockwise in the right) (22). The anteromedial portion of the tendon receives more fibers from the soleus, whereas the posterior portion receives them from the gastrocnemius (19).

1.2.1.1 Circulation and innervation

The tendon is primarily supplied from the recurrent branch of the posterior tibial artery. The tendon, itself, is mostly avascular and receives its blood supply from the MTJ, the surrounding connective tissue (paratenon) and the OTJ. The mid-portion (2–6 cm from the insertion) of the AT is less vascularized (18,23), and most of the blood supply at this site comes from the paratenon (23).

The tendon receives its nerve supply from sensory branches from the tibial nerve (18). The sural nerve crosses the AT distally and is vulnerable to injury during surgery (24).

1.2.1.2 Tendon structure and biomechanics

The tendon tissue is comprised of collagen, mostly collagen type I, and a small amount of elastin embedded in an extracellular matrix. The tendon is composed of fiber bundles (Figure 2). The collagen fibrils are grouped in parallel into fascicles (collagen fibers) and the fascicles are bundled and surrounded by connective tissue, the endotenon, to form the structure of the tendon, covered by the epitenon. The epitenon is further surrounded by the paratenon, and between the layers there is a layer of fluid reducing friction during tendon movement (17,18,21).

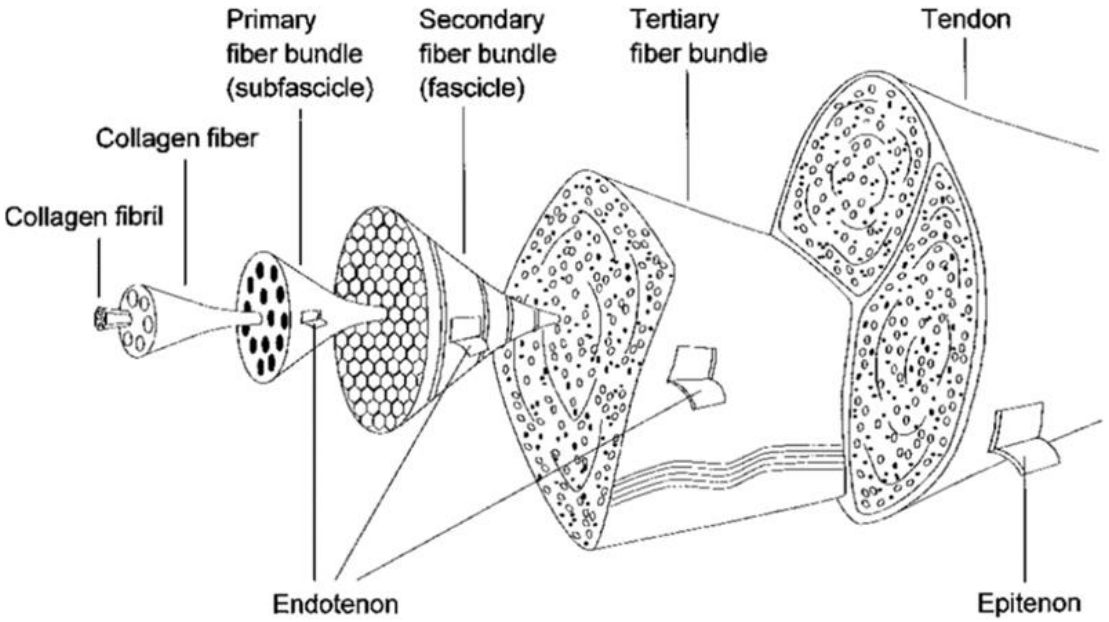

Figure 2. Organization of tendon structure *(from Kannus, P (21), reprinted with permission from John Wiley and Sons).*

The collagen fibrils are crimped at rest, giving the tendon a wavy structure. Load on the tendon causes tensile stress and the fibrils are stretched. The tendon can be stretched around four percent of its length before the collagen fibers slides apart. At around eight percent of strain, the tendon ruptures (17,18) (Figure 3).

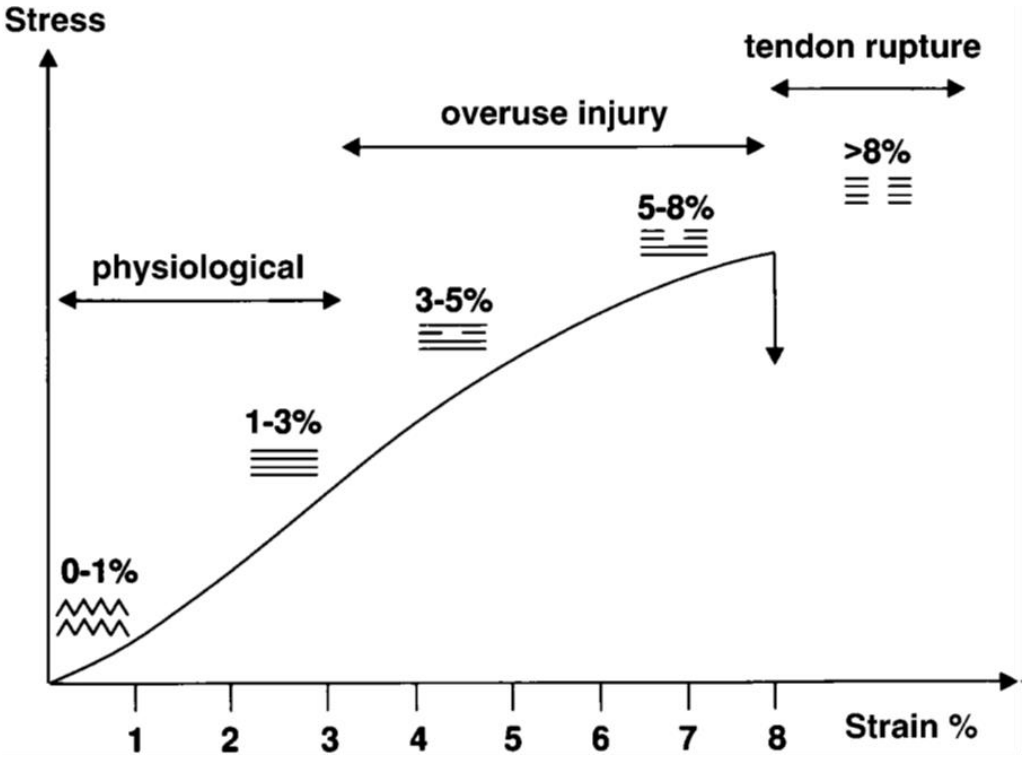

Figure 3. Stress-strain curve *(from Maffulli, N (17), reprinted with permission from Wolters Kluwer Health and John Wiley and Sons).*

1.2.2 Tendon healing

Tendon healing is usually divided into three overlapping stages (25). The inflammatory phase starts immediately after injury and occurs during the first week after the injury. A hematoma is present, and a pro-inflammatory response is released. The secondary phase is the proliferative phase, where repair is initiated. This phase starts after a few days and lasts for weeks. A mechanically inferior matrix of type III collagen is produced. The third and last phase is the remodeling phase, where more type I collagen is produced. A progressive organization and alignment of collagen fibrils into parallel bundles is achieved. This phase starts a month after injury and lasts for at least a year. The biomechanical properties of the repaired tissue do not recover completely (26).

The remodeling phase can be further divided into a consolidation stage and a maturation stage. The repair tissue shifts from cellular to fibrous and, during the consolidation stage, collagen-I synthesis is increased. During the maturation stage, the tissue becomes more scar-

like with decreased metabolism and vascularization and increased collagen bundle thickness (25,26).

In animal studies, early mobilization resulted in an increased speed of neuronal plasticity (27) and an upregulation of anabolic growth factors and pro-inflammatory substances as a sign of better tendon healing (28,29). Even short episodes of loading in the inflammatory phase are advantageous for the healing tendon if sufficient time for recovery is allowed (30). In the remodeling phase, controlled mobilization enhances healing (26,31).

Early mobilization following a strong surgical repair has been found to be safe (6) and promote tendon healing in humans (32). However, as yet there has been no investigation as to whether direct postoperative mobilization after tendon rupture is safe when it comes to tendon elongation and re-rupture risk, or has the possibility of improving patient-reported and functional outcome.

1.2.3 Biomechanics

The force on the AT peaks during push-off. The load on the AT has been measured as around 3 times body weight (2600N) during normal walking and up to 12.5 times body weight (9000 N) during running (33). The peak AT force during walking differs greatly between individuals (34). During jumping activities, the load on the AT differs between different jumping modalities, with forces up to 2–5 times body weight (for squat jump/ countermovement jump ≈ 2000 N and for hopping 4000 N) (33).

During running and jumping, both internal and external forces impact muscle work. Muscles are contracting both eccentrically and concentrically, and the combination of those contractions forms the stretch-shortening cycle (SSC). The SSC allows for greater force and power in the final concentric contraction as compared to a movement of solely a concentric contraction without the prestretch (i.e. the difference between a countermovement jump and a squat jump). The increased performance through SSC is referred to as a recoil of elastic energy stored in the muscle-tendon unit during the stretching phase (35,36).

A systematic assessment of human movement patterns can be performed by means of three-dimensional (3D) gait analysis using high speed cameras and force plates (37). Kinematic and kinetic data are obtained to quantify and describe gait patterns (37). Kinematics involves a description of movement independent of the forces causing the movement. Kinematic variables are linear and angular displacement, velocities, and accelerations. Kinetics are the forces causing the movement, both internal and external. The internal forces are derived from muscle activity and the ligaments, while the external forces arrive from external loads or the ground reaction force (38). Dynamic forces are termed “moments” and are expressed in Newton meter (Nm) and normalized to body weight (Nm/kg). Power is the joint moment times angular velocity and occurs when the muscle contraction changes from eccentric to

concentric, as in the end of the stance phase for the triceps surae. The unit for power is the watt (W) (39).

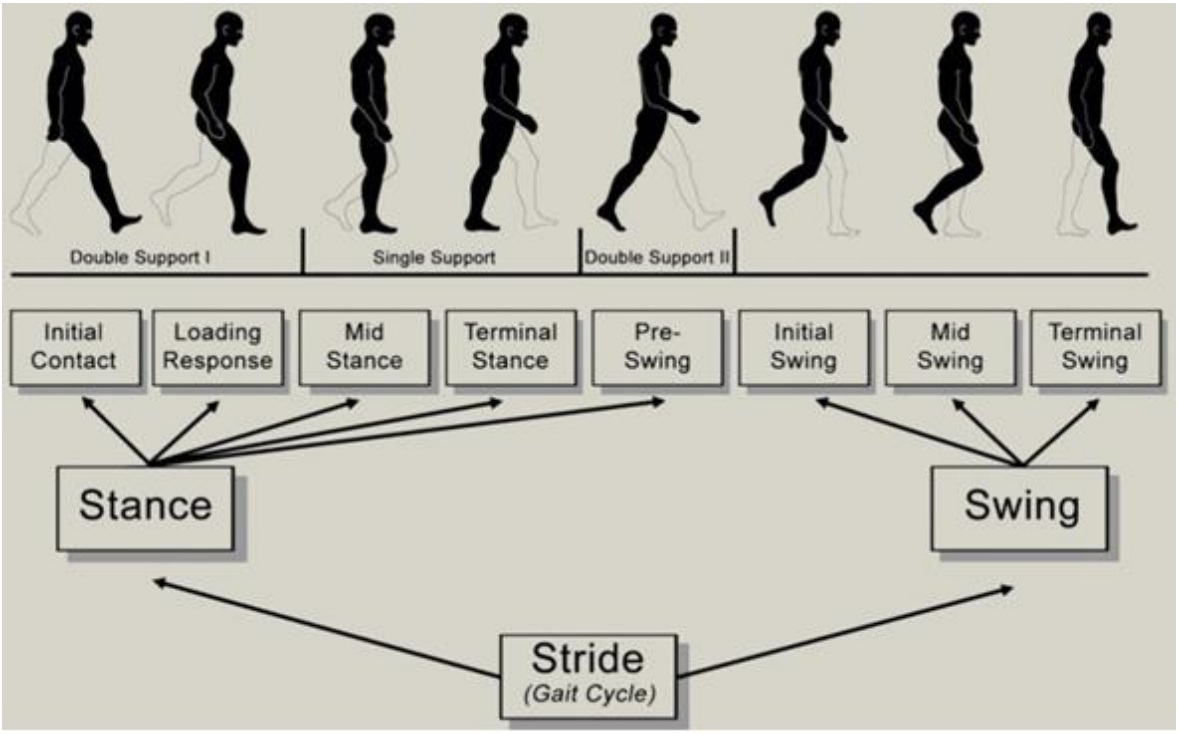

Figure 4. Phases of the gait cycle *(from Shah, K et al. (40), reprinted with permission from Elsevier).*

The gait cycle is divided into a stance phase (the first 60% of the gait cycle) and a swing phase (the remaining 40% of the gait cycle) for each leg (Figure 4). During gait, the triceps surae (i.e. the plantar flexors) is most active during terminal stance, both for stabilization and propulsion (19). The plantar flexors also provide ankle stability and contribute to knee stability. During stance phase, the activity in the plantar flexors begins at around 12% of the gait cycle and ends at around 50% of the gait cycle, when the body weight shifts onto the contralateral limb (41). The plantar flexors work eccentrically during stance phase, when the tibia is progressing over the foot to peak dorsiflexion, around 45% of the gait cycle. The work then shifts rapidly to concentric work and peaks before toe off at around 60% of the gait cycle (14,41). The soleus is most active in this phase to support the ankle during toe off (42). During normal gait, the plantar flexion force from the soleus muscle is almost double that of the gastrocnemius. The medial gastrocnemius contributes to more strength than the lateral gastrocnemius (43).

1.3 ACHILLES TENDON RUPTURE

1.3.1 Epidemiology

Achilles tendon rupture (ATR) is an injury that often occurs in recreational sports, especially ball and racket sports (44–46). The injury incidence has increased in recent decades, and is around 14–55/100,000 person-years (47,48). The peak incidence is in the third or fourth decade of life, and the injury is more than 3–4 times more likely in males than females (17,44–47). The incidence of ATR has shown a bimodal distribution, where a second peak occurs in the older age group of 70–80 years and is mostly non-sports related (2,49).

1.3.2 Etiology

The etiology of ATR is multifactorial and includes histological, biomechanical and genetic factors as well as medication and patient characteristics (50). Most patients sustaining an ATR have not had symptoms before the tendon ruptured, even though many tendons show degenerative changes in histopathologic studies (46). The AT is exposed to high forces during high-impact activities such as running and jumping (33). There are three main mechanisms of rupture. The first is pushing off on a weightbearing forefoot while extending the knee. The second is a sudden and unexpected ankle dorsiflexion, and the third is a forceful dorsiflexion of a plantar flexed foot (17).

1.3.3 Diagnosis

A patient with ATR frequently reports a history of sudden pain as well as a feeling compared to being kicked from behind at the time of injury. Sometimes with an audible snap. Weakness of the ankle and difficulties bearing weight on the affected leg are also reported (51). The diagnosis of an ATR is usually clinical. A gap might be palpated along the tendon, about 2 to 6 cm proximal to the insertion on the calcaneus. The Thompsons test, or calf-squeeze test, is performed with the patient prone on the examination table and feet hanging free outside the table. Squeezing the calf muscles produces a plantar flexion of the ankle if the tendon is intact, and is positive if no plantar flexion occurs (17). Another clinical test is the Matles test or knee-flexion test. The patient lies prone and actively flexes the knees to 90 degrees. If the injured foot is dorsiflexed or falling into neutral, an ATR can be diagnosed (17). Imaging is most often not necessary from a diagnostic perspective, but ultrasound (US) or magnetic resonance imaging (MRI) are most sensitive if imaging is needed (17).

1.4 TREATMENT

1.4.1 Surgical vs. non-surgical treatment

Modern orthopedic surgery aims to restore the patient's earlier capacity as soon as possible without subsequent complications related to surgery or immobilization. Today, patients have high expectations in terms of both low risk with surgery and early return to activity, both sports and work.

Achilles tendon ruptures can be treated either with or without surgery. There are several systematic reviews and meta-analyses comparing surgical and non-surgical treatment following ATR (52–56). The advantage of surgery is the lower risk of re-rupture compared to non-surgical treatment (52,53,55–57). Re-rupture rate is also the most studied primary outcome after ATR (52–54,57–60). Surgery may also allow for a faster return to work (55). The disadvantages of surgery are the risk of other complications, including wound infection, nerve injury and scar formation (5,52–55,57), that may result in prolonged rehabilitation and delayed return to sports and work. In the long term, there seems to be no difference in outcome between treatment methods (6,8,61).

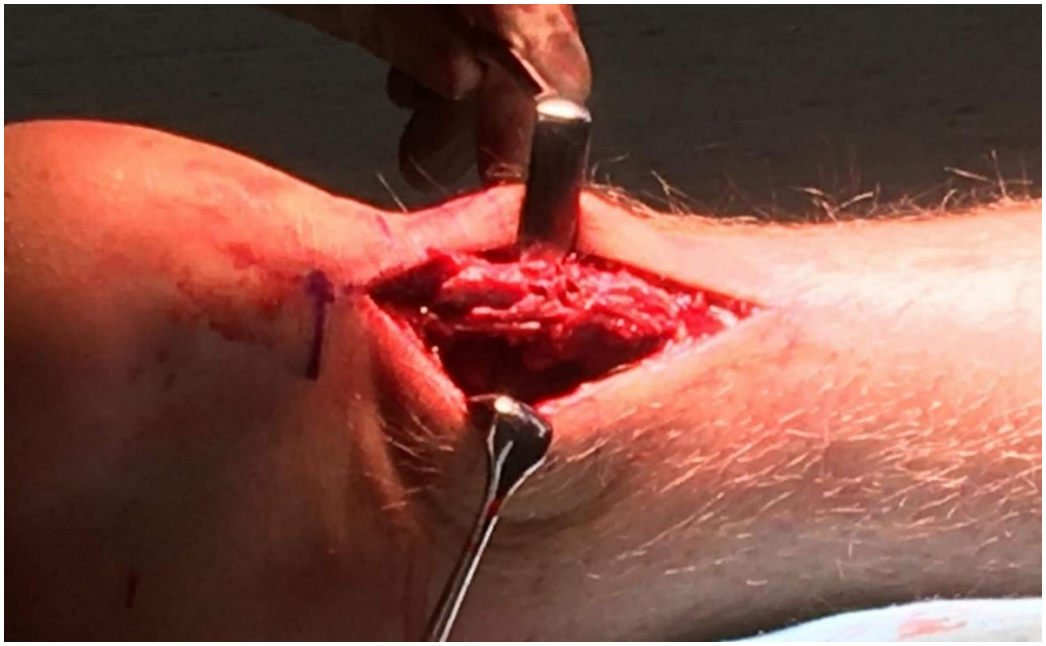

Figure 5. Open surgical repair after ATR.

1.4.2 Mobilization vs. immobilization

Immobilization of the ankle joint by limiting dorsiflexion is used during AT healing. Below-knee plaster cast in equinus position, approximately 30 degrees of plantar flexion, was previously used for an extended period of eight weeks following ATR. Recently, functional rehabilitation, i.e. mobilization with weightbearing in an orthosis, in both surgically and non-surgically treated ATR has shown a lower re-rupture rate (5,7,58,59,62,63). It has been

suggested that functional rehabilitation is of more importance for outcome than the initial use of surgery or not (5).

Different kinds of orthoses have been used for immobilization in research studies (64). Some studies have used orthoses fixed at the ankle joint (6,9), while others have used more dynamic orthoses with adjustable range of motion (7,61,65–67). Heel-wedges are commonly used in the orthosis to provide a sufficient degree of plantar flexion, allowing approximation of the tendon ends (68). The purpose of orthosis treatment is to restrict dorsiflexion in order to prevent elongation of the tendon during healing (64).

Elevation of the heel in the orthosis has been shown to reduce the strain on the tendon through decreased plantar flexor muscle activity (69,70) in both healthy subjects and patients during walking (71). Conversely, a study involving healthy subjects showed that the strain on the AT was higher when walking in an orthosis locked in plantar flexion than when walking barefoot, but with lower activity in the soleus muscle (72). However, these studies used different kinds of orthoses, which could account for the variation in results. Furthermore, studies have shown that the degree of plantar flexion was reduced in rigid orthoses provided with heel wedges compared to equinus casts (73,74). Although, the degree of plantar flexion was greater and more similar to an equinus cast when using an orthosis with an external wedge (VACOped) (68). Thus, the choice of and treatment with orthosis after Achilles tendon rupture is not simple, but seems essential for optimal healing conditions.

1.4.3 Early functional mobilization

Controlled early motion exercises postoperatively may enhance the healing potential of the tendon (75). Plantar flexion exercises increase blood flow in the Achilles peritendinous region (76), and exercise has also been linked to increased collagen synthesis in the peritendinous tissue in the AT (77) with the microdialysis technique. In the healing AT, metabolites were increased in the peritendinous tissue, and patients treated with early mobilization demonstrated greater levels of glutamate that were correlated to increased collagen synthesis compared to immobilization (78).

Mechanical loading plays an important role in tendon healing (27,76,79–82). Weightbearing after ATR is suggested to provide advantageous mechanical stimuli of the AT (28,29) through activation of the triceps surae and the passive tension generated in the muscle-tendon unit (34,83–85).

With surgical treatment, tendon ends are sutured, and apposition of tendon ends is achieved (86). This treatment may allow for a more accelerated rehabilitation regimen. However, the postoperative treatment regimen is not consistent over studies, and the start of weightbearing and ankle motion varies, with start within two weeks in most studies (87,88).

Early functional mobilization (EFM), i.e. early weightbearing and ankle motion, has a tendency towards producing less symptoms, greater improvements in function, higher patient satisfaction and faster return to work in surgically treated groups, compared to immobilization (60,89–91). Although early motion, per se, does not seem to prevent muscle atrophy or strength deficits (89,92), one study has shown better strength in the long term (93). EFM, including both weightbearing and ankle motion, has been recommended due to superior functional results (87,91).

The definition of EFM varies across studies (87,88), and few studies have used a combination of weightbearing and ankle motion immediately post-surgery (6,94). Whether this accelerated rehabilitation regimen enhances functional recovery is unknown.

1.5 COMPLICATIONS

1.5.1 Re-rupture

The re-rupture rate after ATR has been frequently investigated in systematic reviews and meta-analyses over the past decades (52,53,55–60,95). When casting was used for a prolonged period following injury, the re-rupture rate was higher. Surgical treatment was then considered the treatment of choice to minimize the risk of re-rupture. Functional rehabilitation using early weightbearing or/and ankle motion has become more commonplace lately and has not resulted in an increased risk of re-rupture (91,96,97).

Pooled results of re-rupture rate in meta-analyses range from 2.3% – 5% with surgical treatment to 3.9% – 13% with non-surgical treatment (52,54,56,95).

1.5.2 Surgery-induced complications

Wound infections and scar tissue formation are complications related to the surgery. AT repairs are generally associated with a low risk of both infection and re-rupture (98).

The overall superficial wound infection rate is low – around 2−3% – but smokers, even former smokers, have an increased incidence of superficial surgical site infections (98). The risk of surgery-induced complications is suggested to be increased in high-risk patients, i.e. patients who are obese (BMI>30), have a history of diabetes, or have a history of smoking (99).

Nevertheless, the annual incidence of deep infections has increased (100). Around 1−2% report deep infections (98,100). Deep infections are more common in patients with risk factors such as older age, obesity, diabetes, corticosteroids use and smoking (100). A deep infection postoperatively is a rare complication, but devastating for the patient (100).

1.5.3 Venous thromboembolism

Immobilization of the lower limb is a risk factor for venous thromboembolism (VTE) in adults. Additional risk factors are individual factors, trauma, and surgery-related factors. Examples of individual factors include age over 40, history of venous thrombosis, obesity, thrombophilia, and cardiac or respiratory failure (101).

Regardless of treatment, ATR is associated with a high prevalence (around 35−50%) of deep venous thrombosis (DVT) (9,10,102–104) when screened with ultrasound. The prevalence of DVT is higher in ATR patients than in other isolated foot and ankle surgeries (102). However, most of the DVTs are asymptomatic and not diagnosed in the clinic, thereby increasing the risk of pulmonary embolism (PE) (105). The incidence of PE in ATR patients is low, around 0.2–3.2% (106), but fatal cases has been reported (106,107).

Thromboprophylaxis with low molecular weight heparin (LMWH) has been shown to be non-effective in the prevention of DVT in ATR patients (102,104). There are several risks associated with administering LWMH, such as postoperative bleeding, bruising and hematomas, wound healing problems and infections (102). The guidelines of the American College of Chest Physicians do not recommend pharmacological thromboprophylaxis in patients with isolated, immobilized lower limb injuries (108). However, high-risk patients should be assessed individually (102,109–111).

Ankle dorsiflexion exercises during limb immobilization increase the blood flow in the popliteal vein (112). Moreover, leg immobilization with the ankle fixed in plantar flexion was associated with a significant reduction in venous blood flow as compared to the ankle being in a neutral position (113). For this reason, it may be plausible there is a risk of increased venous stasis and, subsequently, an increased risk of blood clot formation when the ankle is fixed in the equinus position, as after ATR.

The soleus muscle acts as a peripheral vascular pump (18). A way to counteract the negative effects of immobilization is therefore to gradually allow for early motion during immobilization. Those micro motions may activate the “muscle pump”, enhance the venous return, and hypothetically reduce the risk of blood clots. Active toe- and isometric ankle movements in plaster cast have been shown to increase blood flow (114). However, it has not been shown whether EFM can lower the risk of venous thromboembolism.

1.5.4 Tendon elongation

Excessive tendon elongation is a complication following ATR injury, affecting function and strength. Elongation has been measured using different methods. Shifts in range of motion of the ankle (i.e. increased dorsiflexion and decreased plantar flexion) or solely increased dorsiflexion was previously used as a marker for tendon elongation (12,92,115). A new clinical measure is the Achilles tendon resting angle (ATRA). It is defined as the angle

between the long axis of fibula, the tip of the fibula to the line of the fifth metatarsal head, and is measured using a goniometer with the patient in prone position with knee flexed 90 degrees. The measure has demonstrated a high level of reliability and may be an indirect clinical measure of tendon elongation (116,117).

Methods of more direct measurement are US imaging or radiographic measures (118,119). To evaluate tendon elongation with ultrasound imaging, the AT length is measured between the insertion on calcaneus (OTJ) to the myotendinous junction (MTJ) of the gastrocnemius, with the use of extended field-of-view (EFOV) images (Figure 6). This measurement has been found to be valid and reliable when using the contralateral limb as comparison (120).

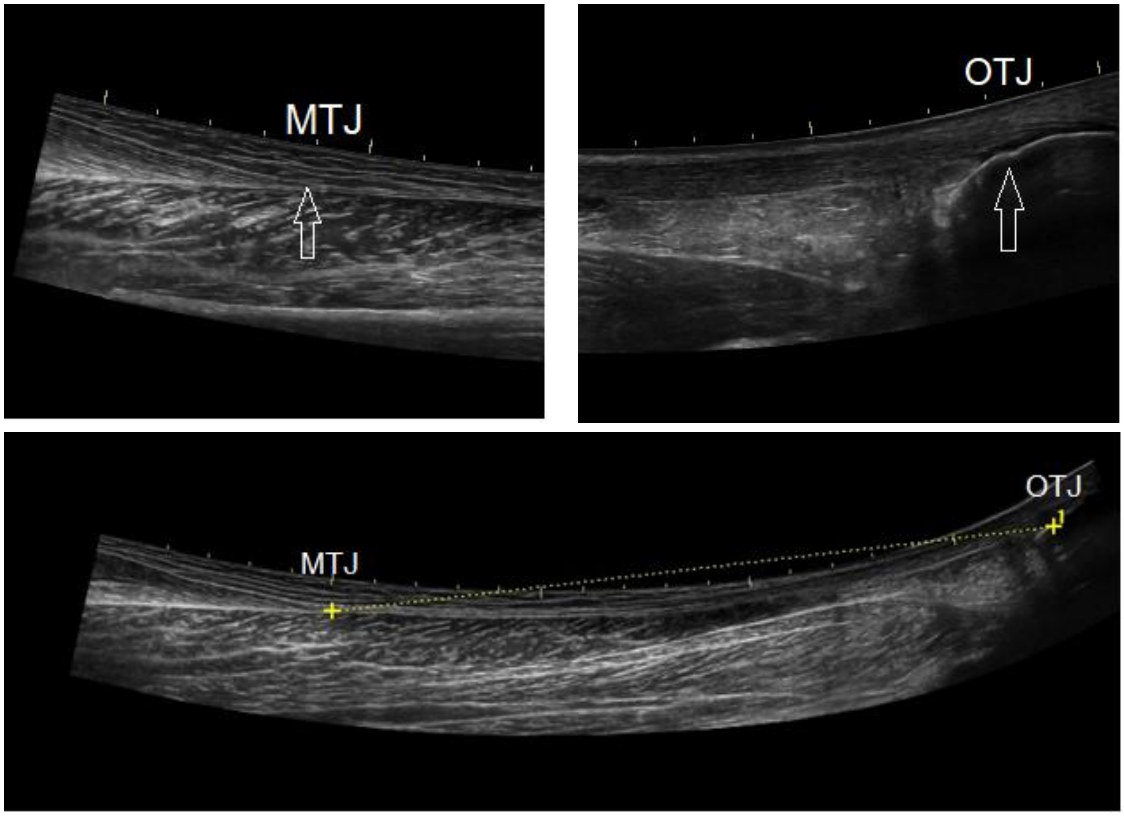

Figure 6. Tendon length measurement with US EFOV imaging.

Elongation has been shown to impact both gait pattern and function (14,118,119). Tendon elongation was correlated to poorer heel-rise height one-year post-ATR repair, and correlated to more patient-reported symptoms at six months (121). The deficits in heel-rise height post-surgery has been proposed as a result of the tendon healing in an elongated position coupled with muscle weakness (121).

Muscle activation of the triceps surae has been shown to be greater in the affected side with an elongated AT after rupture (118). The additional length of the tendon may require more activation from the muscle to be able to create force due to the altered position on the force-length curve, and the force produced at peak contraction may also be weaker (118). Tendon elongation is suggested to cause end-range plantar flexion weakness (122,123) because the

muscle is already in a shortened position and therefore below the angle for optimal force production (118).

Early motion has been shown to result in less tendon elongation compared to immobilization (119). Changes in tendon length appear in the first three months postinjury (82,92,119), and the separation between tendon ends is similar regardless of whether surgery is performed or not (124,125). However, tendon elongation following non-surgical treatment has been shown in the long term, resulting in soleus atrophy and reduced strength (123,126). Whether EFM following surgical repair is beneficial for minimizing tendon elongation over time is not known.

1.5.5 Muscle atrophy

Muscle atrophy after ATR may occur from disuse of the calf muscles during immobilization and from changes in the muscle-tendon unit due to an elongated tendon. Studies have shown that the medial gastrocnemius (MG) undergoes remodeling early after ATR to restore tendon resting length. When the tendon is elongated, the fascicle length of the MG is shorter and muscle thickness or cross-sectional area (CSA) is reduced, which in turn leads to persisting strength impairment (127–132). Ultrasound imaging has been used to quantify muscle thickness and/or CSA changes in clinical studies after ATR. With the exception of changes in the structure of the MG, the soleus muscle has shown irreversible atrophy after ATR (126,131–133). The soleus muscle is susceptible to atrophy when immobilized due to the high amount of type I muscle fibers (134). To minimize atrophy, the muscle-tendon unit needs tension during immobilization (17,134). Muscle atrophy may impair the patient's performance in sports and daily activities due to a reduction in muscle strength and endurance. It is unclear whether EFM after ATR repair can minimize muscle loss.

1.6 OUTCOME

1.6.1 Patient-reported outcome

Patient-reported outcome measures (PROM) are used to assess patients' subjective recovery. The use of PROMs has increased in clinical research in recent decades. Both generic questionnaires and injury-specific questionnaires are used to capture the multidimensional facets of recovery (135). PROMs in orthopedic research have been divided into three different categories: overall health (generic), joint or anatomic region, and condition-specific (135). Generic questionnaires are general assessments of factors such as health-related quality of life or activity level, while condition-specific questionnaires are constructed and validated for a specific injury/condition.

The Achilles tendon Total Rupture Score (ATRS) (136) is the only injury-specific, validated tool for assessing patients' perceived limitations in function, symptoms, and activity after

ATR. This questionnaire has been widely adapted cross-culturally and psychometrically tested in different languages, making it a useful outcome measure in clinical research.

There is a large heterogeneity of outcome measures used in research studies post-ATR, making comparisons across studies more difficult.

1.6.2 Functional outcome

Functional deficits and decreased strength after ATR injury is common in both surgically and non-surgically treated patients (6–8,12,13,61,67,137). Decreased strength in the end-range of plantar flexion (122) and decreased eccentric plantar flexion strength have also been found, which affect gait postinjury (14). In the long term, plantar flexion strength deficits have been shown during more demanding activities, such as running and jumping, which leads to compensatory strategies and altered biomechanics (138–142).

Functional recovery and calf muscle endurance strength is often evaluated using a heel-rise test. The heel-rise test has been shown to be reliable and valid for evaluating muscular endurance of the calf muscles. It is easy to perform and useful in both research and clinical settings (143). The heel-rise test has also been shown to correlate to plantar flexion function during gait (144). Other strength measurements, such as isokinetic dynamometer torque measurements, may be used for additional strength measurements (61,67,119,137). However, this test is performed in a non-weightbearing position, which may not be representative of calf muscle function.

Different jump tests are used to evaluate various aspects of long-term calf muscle function. Examples of jump tests used in the literature are countermovement jump (CMJ), hopping, and single-legged hop for distance (6,13,145).

Test batteries including different jump tests, strength and endurance measurements are recommended for a more complete picture of functional recovery (145). Silbernagel et al. (145) have constructed a valid and reliable test battery consisting of 2 jump tests (drop CMJ and hopping), 2 strength tests (concentric heel-rise, eccentric-concentric heel-rise) and a muscular endurance test. This test battery has been used for evaluation of calf muscle function in patients with ATR (6,7,143,145).

1.6.3 Gait pattern

Most of the previous research on gait patterns following ATR has been cohort studies investigating side-to-side differences during gait in ATR patients. However, there has been no investigation as to whether early mobilization can facilitate early return to normal gait pattern compared to standard treatment.

Plantar flexion weakness can be measured with 3D gait analysis as reduced internal plantar flexion moment (144). Previous studies have found that the work of the plantar flexors after injury is decreased in both the short and long term (14,16,146,147). Weakness and inhibition of the plantar flexors after ATR may result in an abnormal gait pattern that increases the load on both the tendon and the knee joint (14,139,142).

An increased dorsiflexion of the ankle during mid-stance might occur if the soleus muscle is weak. The weakness of soleus also affects terminal stance, which requires twice as much muscular effort as the mid-stance. Knee hyperextension, decreased walking speed, and reduced step length decrease the load on the plantar flexors (39).

A shift in range of motion, i.e. increased dorsiflexion and decreased plantar flexion, of the ankle during gait has been reported (14,16) (Figure 7). Increased ankle dorsiflexion and decreased plantar flexion moment during gait may be a sign of tendon elongation (16). Another proposed explanation for the increased peak dorsiflexion is the persistent deficits in eccentric calf muscle strength that have been observed during gait (14,146).

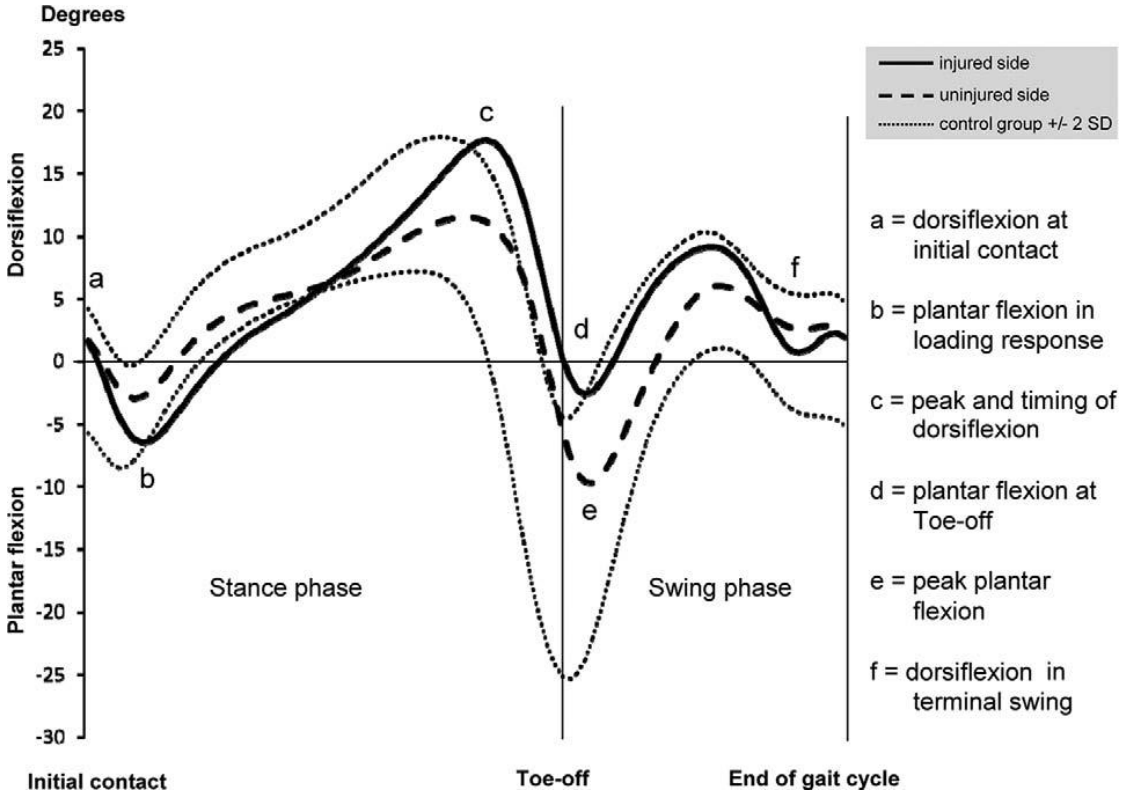

Figure 7. Sagittal plane ankle kinematics, 2–5 years after ATR injury *(from Tengman & Riad (16), reprinted with permission from SAGE publications).*

Increased load on the knee joint during more demanding activities like jogging and jumping has been reported in the long term (>5 years) (139–142). The deficits in the muscle-tendon complex result in compensatory strategies with altered knee joint kinematics, which could place individuals with ATR at risk of knee injuries during sports activities involving running and jumping (138,140–142).

1.6.4 Return to sports

Return to preinjury activity level after ATR can be challenging. Persistent functional deficits and fear of reinjury are possible causes for recreational athletes not being able to return to preinjury activities (148). The mean amount of time to return to sports/activity was six months (149). Return to play criteria is not clearly defined for ATR (150). The mean return to play rate was 80%, but again, it is difficult to pool data from studies with different outcome measures and definitions (149).

For professional athletes in the National Football League (NFL), around 70% were able to return to competition after ATR, but most often at a lower level than their preinjury level (150). In the National Basketball Association (NBA) only around 60% of ATR-injured players were able to return to competition. However, when athletes can continue as a professional the second year after injury, activity levels were back at preinjury levels (151). In a study on male professional soccer players, almost all players returned to training and competition within 9 months of surgery. However, 82% of the players performed at their preinjury levels at two seasons post-ATR (152).

For recreational sport practitioners and more sedentary people, fewer are returning to preinjury sporting activity, possibly due to fear of re-rupture (94). Two studies have reported that the mean time for returning to some kind of sports activity was around six months (133,153). But at one year, Eliasson et al. (133) reported that only 24% had returned to preinjury sporting level, while Barfod et al. (153) reported less than 10% had returned to the same level. In two studies using the same outcome measure, the PAS questionnaire, Olsson et al. (6) did not find any significant differences in physical activity level preinjury or at six and 12 months postinjury, while Nilsson-Helander et al. (7) found significant differences between preinjury and postinjury activity levels, with lower levels at both six months and one year compared to preinjury. In the study by Olsson et al. (6) participants were allowed full weightbearing immediately after injury and/or surgery, which could possibly account for the difference and should be investigated further.

1.6.5 Predictors of outcome

There are only a few studies on predictors for outcome after ATR. Being male, with pain in the AT during rest at three months, having lower physical functioning and calf muscle endurance at six months seem to result in delayed recovery of calf muscle endurance at one year (12). Pain in the AT three months post-surgery has been suggested as a possible early marker of poor prognosis and therefore an important factor to take into consideration during rehabilitation (12).

On the other hand, being female has been found to be a predictor of inferior outcome in both surgically (154) and non-surgically treated patients (155). Age over 40 and having a DVT are additional predictors of negative outcome at 1-year post-surgery (156). High BMI and a higher preinjury physical activity level were found to be predictors of a greater number of symptoms (157), while older age is a predictor of decreased function (157,158). At three months postinjury, the Achilles tendon Total Rupture Score (ATRS) may predict patients' ability to return to sports after one year (159).

1.6.6 Sex differences

In general, females are more susceptible to sustaining soft tissue injuries than males (160), but males are more likely to sustain an ATR than females. This could be due to higher levels of tendon force, stress and stiffness compared to females (161). However, the mechanical properties of the tendons responded equally in both sexes after repetitive loading (161). In healthy individuals, tendon collagen synthesis seems to be lower in females than males. A lower rate of tissue repair seen in females after exercise could be due to female sex hormones. Males have an elevated collagen synthesis response to exercise for a longer time period than females (162). In addition to higher collagen metabolism in males, tendon collagen fascicles from males have higher mechanical strength.

It is hard to make comparisons of outcome after ATR because of the small number of females sustaining ATR compared to males, with around 20–25% being female (1,3,4). However, there are a few studies that report sex differences in outcome. One year after ATR, males had higher LSI (limb symmetry index) heel-rise height during the heel-rise test compared to females (154). Females who had received surgical repair had more self-reported symptoms than males at both six and 12 months postoperatively. In the non-surgical group, males had higher LSI heel-rise height than females at one year (154). In addition, females tended to have more self-reported symptoms than males three months and one year after injury, assessed using the ATRS (159).

1.7 RATIONALE

With surgery, a more accelerated rehabilitation has been considered safe and recommended. However, as studies have used different postoperative protocols and different time points for loading and range of motion exercises, it is difficult to make comparisons between studies.

When pooling data from studies with different mobilization regimens and heterogenous outcome measures, it is difficult to draw any conclusions and make decisions about the different components of early mobilization and rehabilitation. Due to these constraints, there is still no consensus regarding the optimal rehabilitation protocol.

We know that mechanical loading is important to tendon healing and that immobilization is negative for tissue repair. But the magnitude and timing of loading to enhance tendon healing and restore muscle function are still unknown. Earlier studies have shown beneficial effects of early mobilization on minimizing tendon elongation and loss of strength. Immobilization is also a risk factor for sustaining DVT postoperatively. Early functional mobilization (EFM) could be one way to reduce the risk of DVT.

Clinical questions that remain unanswered:

- Is it possible to reduce the risk of DVT with EFM?
- What are the functional consequences of a DVT?
- How much are patients loading in the orthosis postoperatively?
- Can EFM minimize the risk of excessive tendon elongation and muscle atrophy?
- Does EFM result in faster return to a normal gait pattern?
- Is EFM beneficial for long-term patient-reported and functional outcome?

There is a need to perform studies with homogenous and validated outcome measures to be able to make comparisons between studies. But we also need to combine methods of different aspects of function to provide a complete picture of patients' limitations and loss of function. More in-depth knowledge in this area, i.e. knowledge that spans the gap between the basic science of tendon healing and later rehabilitation, is needed to optimize treatment post-surgery and subsequent rehabilitation protocols.

2 AIMS OF THE THESIS

The overall aim of this thesis was to investigate whether early functional mobilization (EFM), including immediate postoperative weightbearing and ankle motion, could reduce the risk of complications and improve functional recovery in individuals after surgical treatment of an acute Achilles tendon rupture (ATR) compared to standard treatment (ST), i.e. two weeks of plaster cast followed by four weeks' orthosis immobilization.

The specific aims of the included studies in this thesis were:

Study I

To assess the efficacy of EFM in reducing the incidence of deep venous thrombosis (DVT) at two and six weeks postoperatively, compared to ST. The secondary aim was to evaluate the effect of patient extrinsic factors (amount of weightbearing, number of daily steps) as well as patient intrinsic factors (age, sex, BMI) on the risk of sustaining a DVT.

Study II

To assess the number of steps and the amount of loading in a weightbearing orthosis during the first six weeks of EFM and to investigate whether there were correlations between the amount of loading and fear of movement and/or pain.

Study III

To describe and analyze differences over time in relation to tendon elongation, tendon cross-sectional area (CSA) and muscle atrophy between two groups treated with either EFM or ST.

Study IV

To compare recovery of gait, including ankle and knee kinematics and kinetics, in patients treated with either EFM or ST.

Study V

To assess the efficacy of EFM, compared to ST, in relation to patient-reported and functional outcome in ATR patients following acute operative repair. The secondary aim was to explore whether the occurrence of DVT during the two postoperative treatments affected the 6- and 12-months patient-reported and functional outcome.

3 SUBJECTS

Demographics for patients included in the different studies are presented in Table 1. All patients were included in a randomized controlled trial based on the following criteria:

Inclusion criteria: Patients age 18–75 with acute unilateral Achilles tendon rupture and surgery within one week of injury.

Exclusion criteria: Inability to provide informed consent, current anticoagulation treatment, known kidney failure, heart failure with pitting edema, thrombophlebitis, thromboembolic event within the previous three months, known malignancy, hemophilia, pregnancy, other surgery within the previous month, inability to follow instructions and planned follow-up at another hospital.

Study I

Between December 2013 and February 2018, 311 patients with Achilles tendon rupture were screened for eligibility at Karolinska University Hospital, Danderyds Hospital and Södersjukhuset. Of these, 150 patients (114 men and 36 women) were enrolled and randomized postoperatively. Due to one incorrect inclusion, a total of 149 patients, with a mean age (SD) of 39.6 (8.1), were included. All patients underwent standardized open surgery performed at Karolinska University Hospital, Stockholm (Figure 8).

Study II

Only patients randomized to EFM were included. Between September 2016 and January 2018, a total of 34 patients were consecutively included in this study. The inclusion for this study started after the original RCT, therefore only a subgroup of patients was evaluated. An additional inclusion criterion was that the pair of insoles for force measurements needed to fit in the patient's own shoes. Two patients could not be included due to technical errors with the equipment.

Study III

A subgroup of patients from Study I were included in Study III. Between October 2016 and February 2019, a total of 86 patients were evaluated with ultrasound imaging. The US imaging evaluation was initiated after the original RCT started, therefore, not all patients included in the RCT are part of this study (Figure 8).

Study IV

Study IV was made up of a subgroup of patients included in Study I. Between June 2015 and June 2018, a total of 47 patients, 18 randomized to ST and 29 to EFM, were included. For this study, a contralateral injury was an exclusion criterion so that the uninjured limb could be used as a healthy comparison.

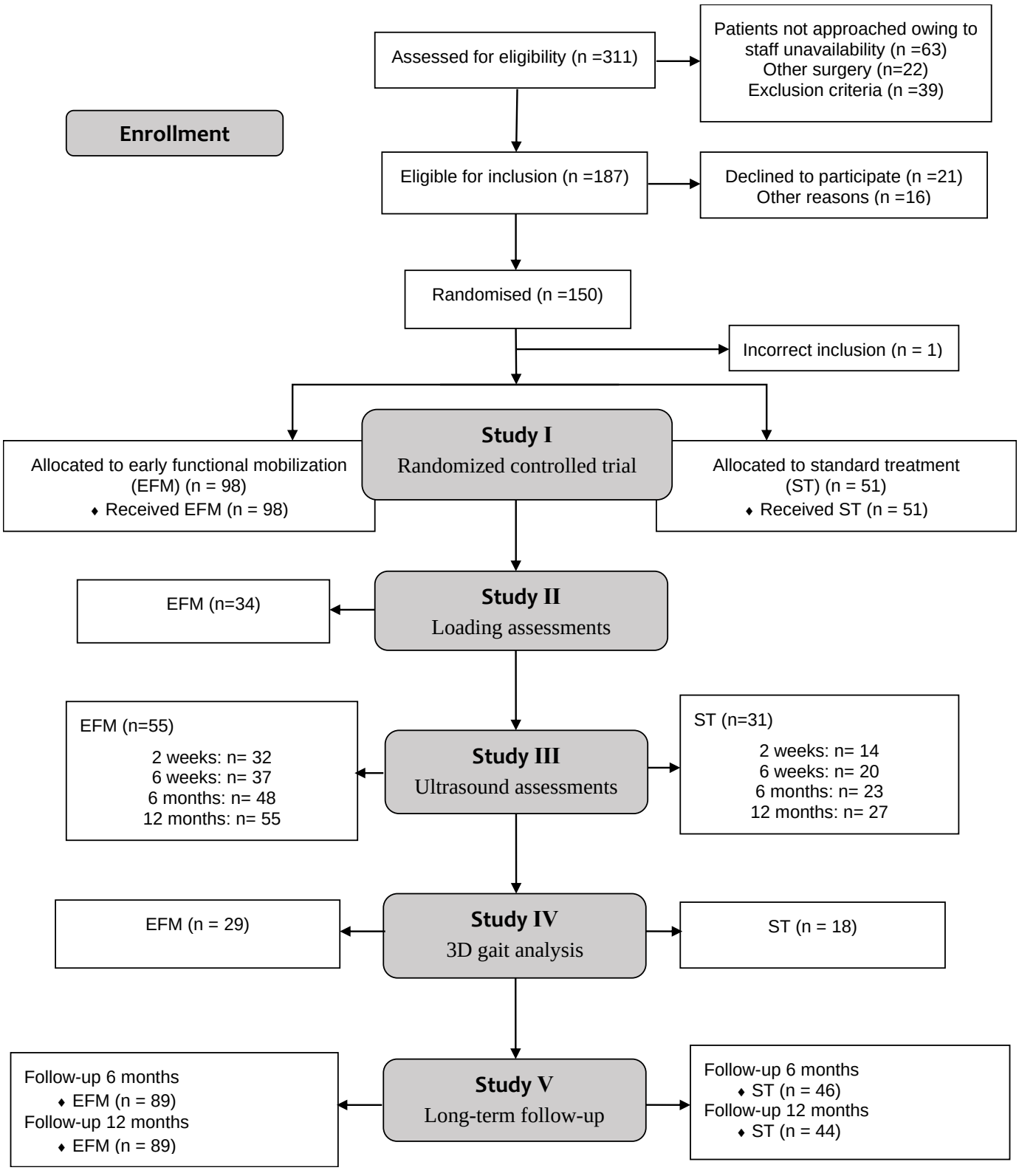

Figure 8. Flow chart over included subjects in the studies in this thesis.

Study V

The patient cohort is the same as in Study I. A total of 135 patients who obtained long-term outcome were included and evaluated in this study (Figure 8). Fourteen patients were not available for follow-up: 3 patients declined to participate, 4 patients discontinued intervention due to complications and 7 patients had an earlier contralateral ATR injury. Two patients were excluded from the one-year follow-up due to a contralateral injury during the study period.

Table 1. Demographic data for patients in Study I–V

Study	Patients included (n)	Age M (SD) Min-max	Male/female n (%)	BMI M (SD)	Nicotine n (%)	Injured side Left n (%)
I	149	39.6 (8.1) 23 – 64	114/35 (77/23)	25.2 (2.8)	30 (20)	78 (52)
II	34	38.8 (8.7) 23 – 64	28/6 (82/18)	25.6 (2.7)	8 (24)	17 (50)
III	86	39.3 (8.2) 23 – 64	66/20 (77/23)	25.0 (2.7)	19 (22)	45 (52)
IV	47	38.7 (7.3) 23 – 53	35/12 (75/25)	25.0 (2.7)	10 (21)	26 (55)
V	135	39.5 (8.0) 23 – 64	102/33 (76/24)	25.0 (2.6)	25 (19)	71 (53)

M=mean, SD= standard deviation, BMI=Body Mass Index, Nicotine included both smoking and snuff

4 METHODS

4.1 ETHICAL APPROVAL

Ethical approval for the study was obtained from the Regional Ethical Review Committee in Stockholm (Dnr 2013/1791-31/3). The study was conducted in accordance with the Declaration of Helsinki and all patients received written and verbal information about the study and provided written informed consent prior to participation. The study was also registered at clinicaltrials.gov (trial number NCT02318472).

4.2 STUDY PROCEDURE

4.2.1 Study location

This study was performed at the Karolinska University Hospital, Stockholm. Patients were screened for eligibility at three hospitals in Stockholm (including Danderyds Hospital and Södersjukhuset). Surgery was performed on an outpatient basis by multiple orthopedic surgeons at Karolinska University Hospital, Stockholm. Between December 2013 and February 2019, 149 patients with an acute unilateral ATR were included and evaluated. Follow-up evaluations were performed at 2 and 6 weeks and at 6 and 12 months postoperatively, and a cohort included in Study IV completed an additional follow-up at 8 weeks (Figure 9).

4.2.2 Randomization

Patients were randomized postoperatively using consecutively numbered sealed envelopes produced by a biostatistician and opened after surgery by a study nurse. Non-stratified block randomization was used to assign the patient to either the intervention group, receiving immediate postoperative EFM, or to ST, including immobilization and non-weightbearing postoperatively. A computer program was used to generate random numbers in permuted blocks of six, and patients were allocated in a ratio 2:1. The 2:1 allocation ratio was chosen based on recommendations by the ethical review committee.

4.2.3 Surgery

All patients underwent a standardized open surgical procedure, using the modified Kessler suture technique, performed according to a prespecified protocol. The surgery was performed on an outpatient basis and under local anesthesia. Patients were operated on in the prone position without the use of a tourniquet. Postoperatively, patients were prescribed painkillers, but no pharmacological anti-inflammatory or thromboprophylactic drugs were administered.

4.2.4 Postoperative treatment

4.2.4.1 Intervention group (EFM)

After surgery, on the postoperative ward, patients were randomized into one of two groups. The intervention group received EFM in a dynamic orthosis (VACO®ped, OPED) with adjustable range of motion of the ankle joint (Figure 10). The orthosis was initially set with a range of motion of 15–30 degrees of plantar flexion with a rocker sole, and patients could bear weight as tolerated immediately. At two weeks, the range of motion in the orthosis was increased to 5–30 degrees of plantar flexion for the subsequent four weeks, and the patients could weight bear fully. After three weeks, patients switched the rocker sole to a flat sole at home. Patients were encouraged to perform unloaded plantar flexion exercises immediately postoperatively, from neutral and free plantar flexion, for a total of one hour daily the first two weeks.

Figure 10. The VACO®ped, OPED orthosis used for EFM treatment.

4.2.4.2 Control group (ST)

The control group received the standard treatment (ST) performed at Karolinska University Hospital at that time, which included immobilization in a below-knee plaster cast for two weeks and non-weightbearing with crutches (Figure 11). After removal of the cast at two weeks postoperatively, the patients received an ankle-stable orthosis (Aircast®Air Select™ Elite, DJO, USA) (Figure 11). The orthosis was provided with three heel wedges that were gradually removed during the subsequent four weeks. Full weightbearing was allowed with the orthosis.

Figure 11. Below-knee plaster cast in gravity equinus (left), Aircast®Air Select™ Elite walker, DJO (right).

4.2.4.3 Rehabilitation

From two weeks and onward, both groups followed the same home exercise program with active plantar flexion exercises. Patients were allowed to exercise on a stationary bike with the orthosis. At six weeks, the orthoses treatment ended in both groups and the patients were recommended to wear their normal shoes with a heel wedge on the injured side for another month. The home exercise program included seated active heel rises, plantar flexion exercises with an elastic band, and balance exercises. These were gradually increased (Appendix 1). Patients were recommended to contact a physiotherapist in primary care for supervised rehabilitation.

4.3 FOLLOW-UP EVALUATIONS

4.3.1.1 Follow-up visits at the orthopedic clinic

The first follow-up visit was at two weeks postoperatively, in the orthopedic clinic. All patients were screened for DVT in the injured limb using compression duplex ultrasound (CDU). When DVT was present, patients received LMWH according to guidelines from the Department of Hematology at Karolinska University Hospital. The wound was controlled, and the sutures were removed.

The second and final follow-up visit at the clinic was made at six weeks postoperatively. DVT screening was performed, and the tendon function was assessed using the Thompsons test.

4.3.1.2 Follow-up visits at the research lab

Follow-ups according to the research protocol were performed at the physiotherapy department and at the Motion Analysis Laboratory at Karolinska University Hospital. Those evaluations are not included in the clinical routine. Gait analysis was performed at eight weeks and six months postoperatively by two physiotherapists (PT). Clinical and functional evaluations were performed by the same research PT at all time points postoperatively.

4.4 OUTCOME MEASURES

An overview of the outcome measures, and the studies and timepoint when used are presented in in Table 2 and Figure 9.

Table 2. Overview of outcome measures used in the studies

	Study I	Study II	Study III	Study IV	Study V
Patient-reported outcome					
Self-reported diary	●	●			
Physical Activity Scale (PAS)	●	●			●
Tampa Scale of Kinesiophobia (TSK-SV)		●			●
Achilles tendon Total rupture Score (ATRS)			●		●
Foot and Ankle Outcome Score (FAOS)					●
RAND-36					●
Clinical outcome					
DVT screening	●				●
Ankle dorsiflexion*					
Calf circumference*					
Functional outcome					
Insoles (plantar pressure)		●			
Pedometer (steps/day)	●	●			
US imaging			●		
Heel-rise test			●		●
Jump tests					●
3D gait analysis				●	

*Ankle dorsiflexion and calf circumference measurements are not reported in the studies, but are presented as additional results in the thesis

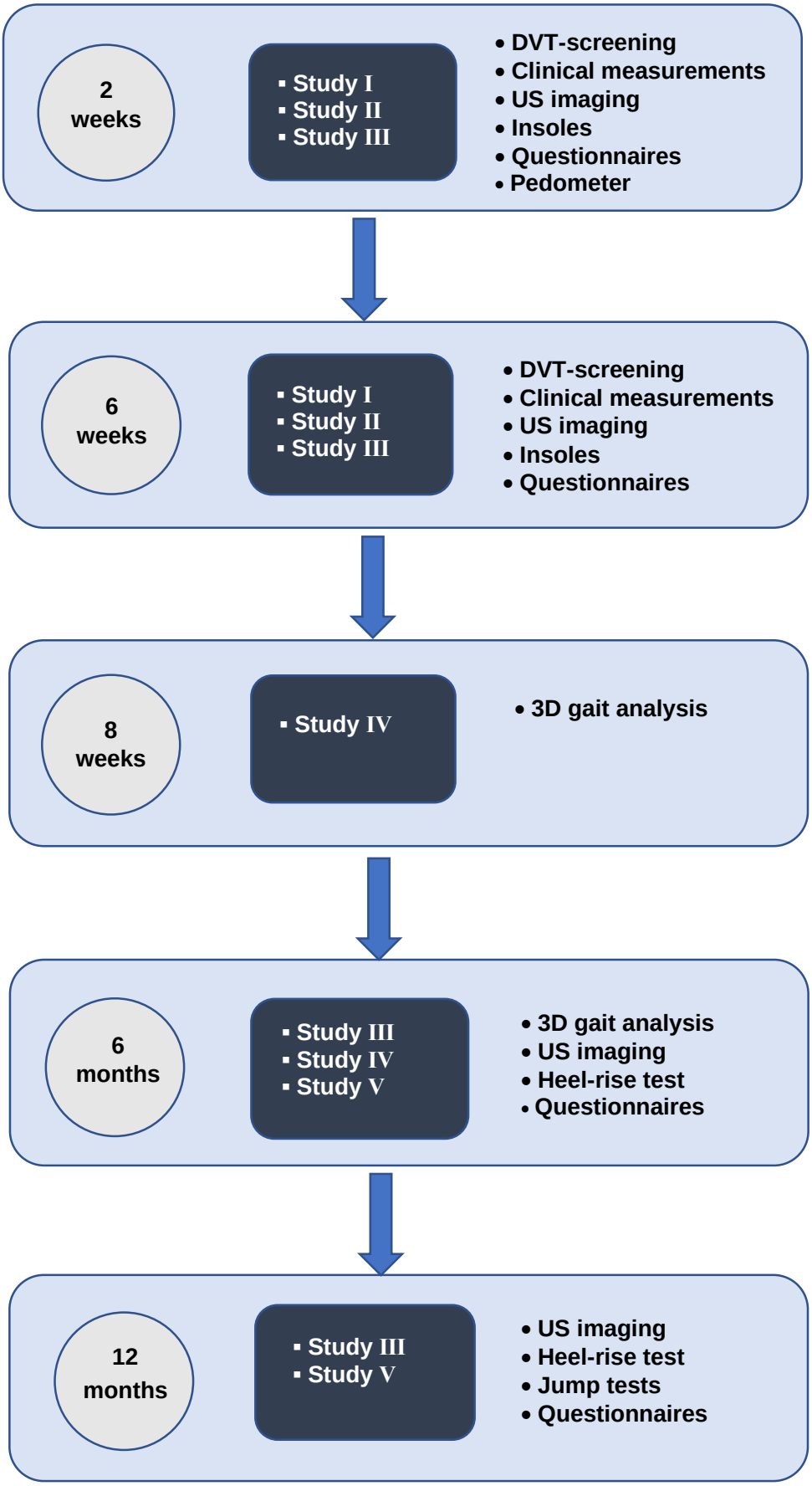

Figure 9. Flowchart over follow-up occasions and methods used for the different studies included in this thesis.

4.4.1 Patient-reported outcome measures (PROM)

All questionnaires are provided in Appendix 2 at the end of the thesis.

4.4.1.1 Self-reported diary

A self-reported diary was used to collect data on loading, steps/day and pain during the first two postoperative weeks at home. On a daily basis, patients in the EFM group filled out their estimation of loading on a VAS scale ranging from 0 "unloading" to 100 "full weightbearing" in the diary from day one after surgery until the first follow-up visit at two weeks postoperatively. Steps/day were registered and for both groups, pain rating on a VAS scale ranging from 0 (no pain) to 100 (worst imaginable pain) during the first postoperative week was estimated during activity and at rest. The diary has not been validated and was made specifically for this study.

4.4.1.2 The Achilles tendon Total Rupture Score

The Achilles tendon Total Rupture Score (ATRS) (136) is an injury-specific questionnaire consisting of 10 items. The items are scored from 0 ("Very limited") to 10 ("Not at all limited") and a total score out of 100 is computed. A low score indicates more symptoms and greater limitation in physical activity after ATR. The score has demonstrated good construct validity (r_s=0.60 – 0.84), high reliability (ICC=0.98; Cronbach's alpha 0.96) and responsiveness. The effect size for follow-up at 6 to 12 months was 0.87 (136).

4.4.1.3 The Physical Activity Scale

The Physical Activity Scale (PAS) (163,164) was developed to evaluate physical activity level in middle-aged former athletes (163). The scale was originally a four-point scale but has been further developed to six points to better match activity level for elderly people. The six-point version is scored from 1 (no physical activity) to 6 (heavy physical exercise several times/week) (164). The PAS can be used to evaluate physical activity before and after injury. The PAS has been used as an outcome measure for ATR patients in several studies (6–8,13,141,156,165,166), but has not been psychometrically tested in an ATR population. However, the scale is widely used in Scandinavian countries for evaluating physical activity among different populations (167,168).

4.4.1.4 The Tampa scale of kinesiophobia, Swedish version

The Tampa scale of kinesiophobia, Swedish version (TSK-SV) (169) is made up of 17 items and is scored on a 4-point Likert scale with alternatives ranging from 1 (''strongly disagree'') to 4 (''strongly agree''). A total sum of the 17 items is calculated and the total score ranges from 17 to 68. A high score (>37) is defined as kinesiophobia (fear of movement/pain). The score has demonstrated good reliability in a population with chronic low back pain. ICC was 0.91, and internal consistency as measured with Cronbach's alpha was 0.81 (169). The score has not been psychometrically evaluated in the ATR population.

4.4.1.5 The Foot and Ankle Outcome Score

The Foot and Ankle Outcome Score (FAOS) (170) evaluate foot- and ankle-related symptoms and pain, function in activities of daily living (ADL), function in sports and recreation (Sports/rec) and quality of life in relation to foot problems (QoL). The questionnaire consists of 42 items and is divided into five subscales. Each item is scored on a four-point Likert scale, and the total score for each subscale ranges from 0 ("Worst") to 100 ("Best"). The reliability measured as internal consistency for the five subscales using Cronbach's alpha ranges from 0.88 to 0.97. Test-retest r_s=0.85–0.96, and ICC was 0.70–0.92. For construct validity, correlation coefficients ranged from 0.58 to 0.67 in a population with ankle ligament injuries (170). The FAOS has not been psychometrically tested in an ATR population.

4.4.1.6 The RAND-36

The RAND-36 (171,172) is a generic health-related quality of life questionnaire that consists of 36 items on physical and psychosocial health. It is divided into eight subscales and scored using a verbal rating scale with different scoring alternatives. The eight health concepts are physical functioning, role limitations (physical problems), role limitations (emotional problems), social functioning, mental health (emotional well-being), vitality (energy/fatigue), bodily pain and general health perceptions (172). A higher subscale score indicates better health status. The RAND-36 and SF-36 (173) consist of the same items, but with different scoring methods. The RAND-36 has shown a correlation to SF-36 of r=0.99. (171). The SF-36 is commercially copyrighted and the RAND-36 is license-free, public domain (174).

4.4.2 DVT screening

At two and six weeks postoperatively, all patients were screened for DVT in the injured leg using unilateral compression duplex ultrasound (CDU) following a standardized procedure. All CDU scans were performed by a trained nurse or experienced ultrasonographer using a Philips CX 50 ultrasound machine (Philips Medical Systems, Andover, Massachusetts). The evaluation included all deep proximal and distal veins, including muscle veins, as well as vena saphena magna. Proximal DVT was defined as a thrombosis that involved the popliteal vein or any more proximal veins, with or without involvement of the calf veins. The DVT diagnosis was based on a transversal ultrasound compression test of the blood vessel, and assessment of blood flow in the veins by color Doppler flow. CDUs have been shown to have a 96% sensitivity and a negative predictive value of 99% for asymptomatic DVTs (175).

4.4.3 Clinical evaluation

Calf circumference was measured at the thickest part of the lower limb using a tape measure with the patient in sitting with thighs supported and lower legs hanging free. Ankle dorsiflexion was assessed while the patient was sitting with feet in full contact on the ground, sliding the foot backwards as far as tolerated without lifting the heel off the floor (Figure 12). A goniometer parallel to the floor and parallel to the fibula was used to record the amount of maximal ankle dorsiflexion range of motion. Both ankles were examined separately, with the healthy side tested first. The average of three measurements was used for analysis.

Figure 12. Measurements of calf circumference (left) and ankle dorsiflexion (right).

4.4.4 Plantar pressure

Plantar pressure was measured with a mobile force sensor, the Loadsol® insoles (Novel GmbH, Munich, Germany) (Figure 13). The insoles were connected through Bluetooth to an iPod touch device and were calibrated to body weight before use. The measurement was performed with the insoles in the patient's normal shoe on the healthy side and in the orthosis on the injured side. Since the orthosis is provided with a wedged sole externally, the insole lies flat in the orthosis. The patients were instructed to walk in a corridor at a self-selected speed for three minutes, with crutches allowed if needed. The insoles have been tested for validity and reliability in healthy individuals during walking, running, and hopping. The ICC for ground reaction forces was between 0.88 and 0.96 for all three modalities (176).

Figure 13. Mobile force sensors (Loadsol® Novel).

4.4.5 Pedometer

Patients received a pedometer (Yamax SW 200/LS2000, Yamax Corporation, Japan) to register the number of steps/day (Figure 14). The pedometer was worn at the hip. The Yamax SW-200 has been used as a gold standard pedometer in earlier validation studies (177) and has been shown to maintain good validity (ICC=0.88) in a healthy population (178,179).

Figure 14. Pedometer (Yamax SW200), Japan.

4.4.6 Ultrasound imaging

US images were recorded with B-mode ultrasound, a wide-band linear array probe (5.0–12.0 MHz) at 10 MHz, to assess tendon structure and muscle morphology. Patients were positioned in prone, lying with their feet hanging over the edge of the examination table (Figure 15). The extended field of view (EFOV) settings (GE Logiq e, GE Healthcare, Chicago, IL) were used to measure tendon length (120,180). The panoramic US enables imaging of structure that cannot be covered by conventional US (181). The EFOV images have demonstrated excellent inter-rater and test-retest reliability (ICC 0.94 – 0.99) and are excellent for between limb comparisons (120). The minimal detectable change (MDC) was

1.23 and 1.83 cm for AT length on an individual level (120,180) and 0.43 cm on a group level (120).

A mark was placed on the skin between the MG and LG muscle bellies to line up the probe for the tendon length measurements. The cross-sectional area (CSA) of the tendon was measured in transverse at the rupture site on the injured side and, where possible, at the corresponding site on the opposite leg or just below the soleus muscle (165,182). Skin marks were made at 25% of tibial length, distal to the medial tibial plateau, for measurements of the medial and lateral gastrocnemius CSA using EFOV settings, with the probe positioned transversely (183). Soleus thickness was assessed in the longitudinal view at 30% of tibial length proximal to the medial malleolus (182). US settings (i.e. gain, depth, and focus point) were optimized for the image quality of each image. Three images were taken for each measurement. The mean of the three images was used for calculations.

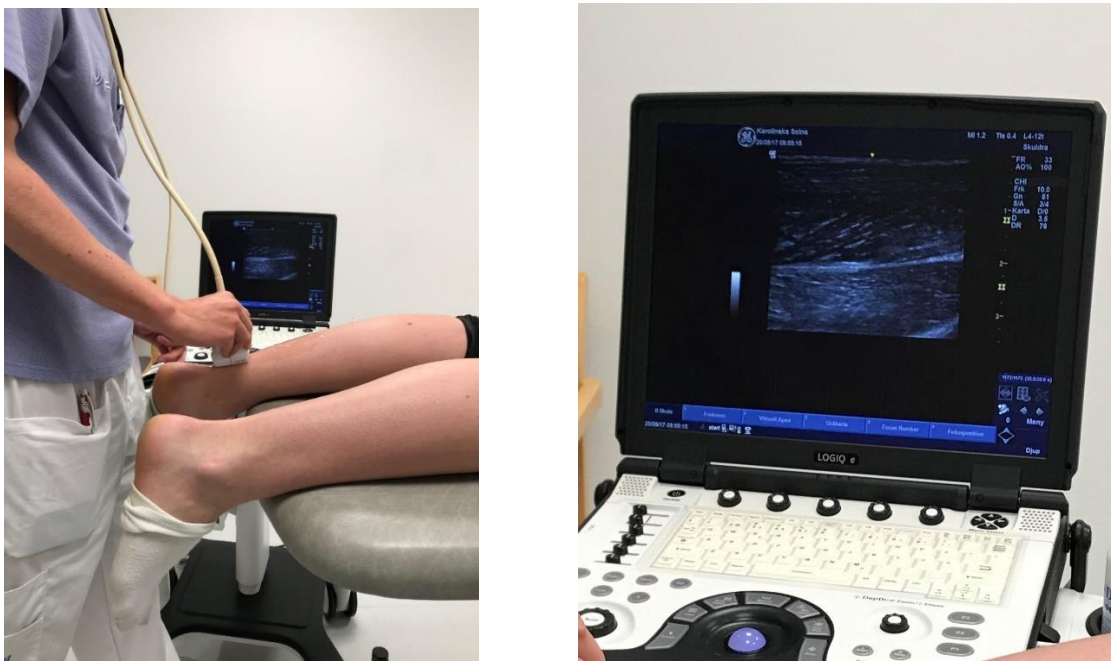

Figure 15. Ultrasound imaging (left) and GE Logiq e Ultrasound machine (right).

4.4.7 Functional evaluation

4.4.7.1 Heel-rise test

To evaluate the function of the triceps surae MTU, use of the heel-rise test is supported in the literature (184). The standing heel-rise test has been widely used to evaluate recovery of calf muscle function (6,7,9,67). The test was performed as described earlier (143) and, in this study, was used for functional evaluation at six and 12 months postoperatively. The Muscle lab® (Ergotest Technology, Oslo, Norway) system was used for data collection. Standardized footwear was used, with a small hook fixed in the shoe. Patients warmed up on a stationary

bike for five minutes followed by 10 repetitions of two-legged heel rises before testing. The uninjured side was always tested first. For testing, patients stood on one leg on a box with an incline of 10 degrees and used their fingertips against the wall at shoulder height for balance support (Figure 16). Standardized instructions and verbal encouragement were used during the heel-rise test. The patient was instructed to go as high as possible on each heel rise with a straight knee. A metronome was used for a standardized frequency of 30 heel rises per minute. The test ended when the patient stopped or could not maintain frequency or height above 2 cm. A linear encoder unit connected to the Muscle lab® was used for measurement. A spring-loaded string is attached to a sensor inside the linear encoder. During the heel-rise test, the string is pulled, and the sensor register a series of pulses, proportional of the distance carried (Figure 16). The number of heel rises, the maximum height of the heel rises and the total work (body weight x total distance) in Joules were used for data analysis. The heel-rise test has demonstrated a good ICC (0.78 – 0.84) for test-retest reliability (185).

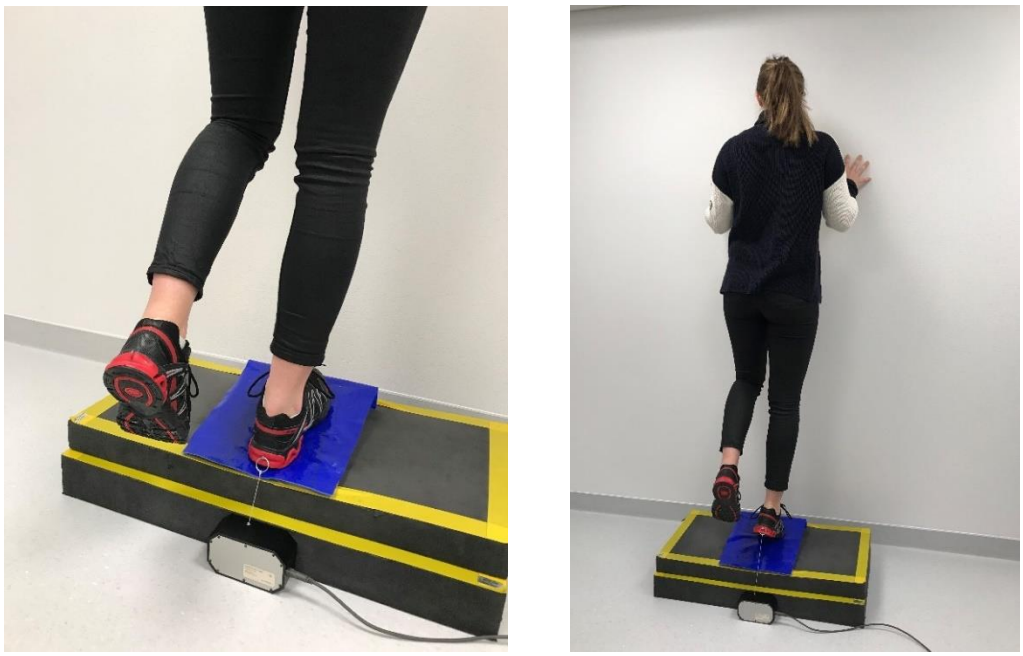

Figure 16. Heel-rise test for endurance on an incline board with standardized footwear.

4.4.7.2 Jump tests

Two jump tests were added to the functional assessment at 12 months. A vertical jump test, the Sargent jump test (SJT), was used as a measure of explosive strength in lower extremity (186). Patients stood next to a wall on one leg, making a mark on the wall with chalk. They were then instructed to jump as high as possible and put another mark on the wall at the highest point they could reach. They could flex their knee and use their arms during the jump. The jump height was the difference between the two marks on the wall. The best result of three attempts on each leg was recorded.

Immediately after the test, patients used a VAS scale to rate their perceived fear, pain and discomfort when jumping on the injured limb from 0 to 10 and perceived effort (force) on the injured side compared to the uninjured side from 0 to 100 (in %).

The second jump test was the side hop test, where the patient performs 10 jumps sideways on one leg and is timed (187). For the side hop test, only one trial was performed, but patients could do some jumps before to get to know the distance between the two lines. For both jump tests, the uninjured limb was tested first, and the tests were performed after the heel-rise test.

4.4.8 Three-dimensional gait analysis

3D gait analysis was performed at eight weeks and six months postoperatively. All gait analyses were performed in the Motion Analysis Laboratory, Karolinska University Hospital, and took around 45 minutes per recording. Each test session began with a physical examination to measure passive range of motion in the lower extremity joints (with the patient lying on an examination table), and collection of anthropometric data. Body weight and height were measured. After the physical examination, 23 retroreflective markers were placed according to the biomechanical model Plug-In-Gait (37) (Table 3 and Figure 17). From this model, joint kinematics, reaction forces, internal joint moments and joint power were computed. The Plug-In-Gait model is a widely used biomechanical model and has demonstrated good intra-subject repeatability (188).

Patients were instructed to walk barefoot at a self-selected speed along a 10-meter pathway. An 8-camera motion system (Vicon Motion Systems Ltd, Oxford, UK) and two force plates (Kistler, Winterthur, Switzerland) collected kinematic, kinetic, and spatiotemporal parameters. Patients walked back and forth until at least three gait trials with clean force plate strikes, consistent walking speed, and good marker visibility were collected.

Table 3. Marker placement used for gait analysis according to the Plug-In-Gait model

7th cervical vertebra	Left/right PSIS
Left/right shoulder	Left/right thigh
Clavicle (on sternum)	Left/right knee (lat. epicondyles)
Right back	Left/right tibia (shank)
10th thoracic vertebra	Left/right ankle (lat. malleolus)
Sternum (xiphoid process)	Left/right heel
Left/right ASIS	Left/right toe (2^{nd}/3^{rd} metatarsal base)

ASIS=Anterior superior iliac spine, PSIS=posterior superior iliac spine

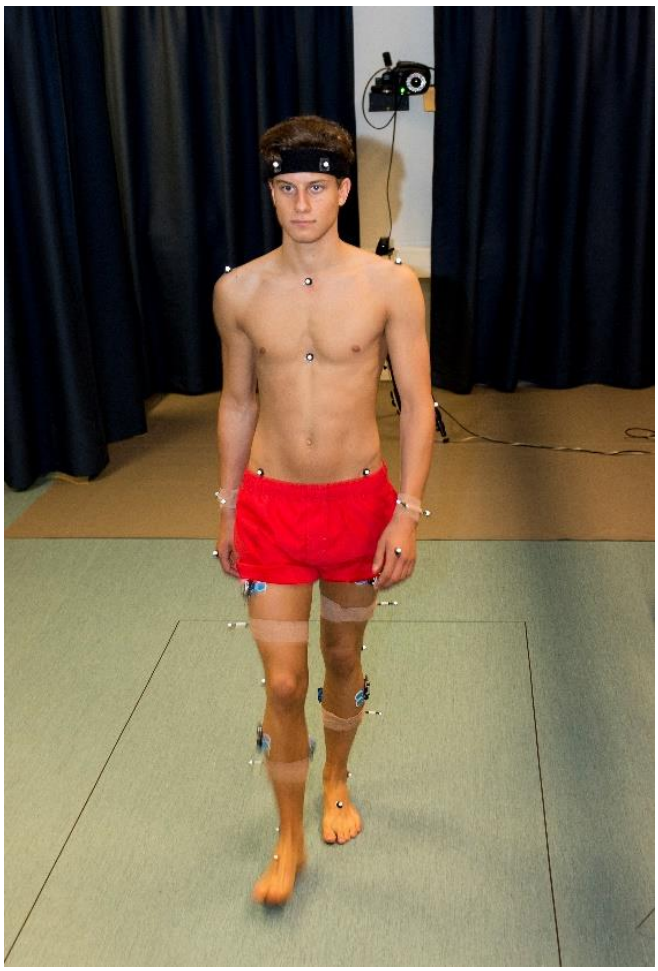

Figure 17. Marker placement for gait analysis.
Markers for head, elbow, wrists, and hands were not used in this study.

5 STATISTICAL METHODS

SPSS version 25 (IBM SPSS, Armonk, NY, USA) was used for all data analyses. Standard descriptive statistics were used, such as mean with standard deviation, median with interquartile range (IQR) or range, and frequency. The normal distribution was assessed with the Shapiro-Wilk's test and the variables were also checked by visual inspection of histograms and Q-Q plots. The Limb symmetry index (LSI) was defined as the ratio between the injured limb and the uninjured limb, expressed as a percentage (LSI, injured/uninjured x100). The statistical significance level was set as $p \leq 0.05$ for all analyses.

Study I

The power calculation was based on data from a previous study, reporting a 50% rate of CDU-verified DVT after ATR repair (9). With an estimation that EFM could result in a 50% risk reduction (189), 63 patients in each group were required to detect a difference of 25% in the DVT incidence (two-sided type I error rate = 5%; power = 80%). We decided to include 150 patients to counteract dropouts. An allocation ratio of 2:1 was chosen based on recommendations from the ethical review committee, since our hypothesis was that the EFM group would perform better.

All analyses were based on intention-to-treat. Categorical variables, including differences between the EFM and ST group, were analyzed using Pearson's χ^2-test. Differences between groups in the continuous variables were analyzed with a parametric Student's t-test. Nonparametric statistics were used for ordinal data, including questionnaires, and for data that were not normally distributed, as for the pedometer data.

The relationships between the independent variables (sex, age, BMI, nicotine, and loading) and the dependent variable (DVT) were expressed as correlation coefficients. A logistic regression enter analysis was used in the risk factor analysis, and only variables that had a significant correlation to the dependent variable were included in the logistic regression analysis independent of treatment group. Relationships were expressed as odds ratios (OR) with 95% confidence intervals (CI).

Study II

For analysis of force data, the maximum force (peak force) in Newtons, the average peak force over three minutes walking in Newtons, stance phase (single and double support) in % of the total gait cycle and cadence (step frequency) were recorded and used for analysis. Data were processed in the Loadpad Analysis® software and Microsoft Excel.

The LSI was used to compare differences between groups in loading parameters between the follow-up occasions. Correlation analyses were performed to assess whether the outcome data (self-reported loading, pedometer data, TSK-SV, PAS, plantar force loading) were correlated to patient characteristics (age, sex, BMI, nicotine usage). Nonparametric statistics were used for analyses of ordinal data and data that were not normally distributed. The

Wilcoxon signed ranked test was used to compare differences between injured and uninjured sides and for differences between follow-up occasions. Spearman's rank correlation was used to analyze the correlation between patient-reported outcomes and gait parameters as well as to understand the correlation between self-reported subjective load and plantar force measurement.

Study III

Tendon elongation was defined as the difference in tendon length between the injured and uninjured side in centimeters (cm). Muscle atrophy was defined as the difference between the uninjured and injured side. To assess muscle atrophy, the difference in thickness in cm was used for soleus, and the difference in muscle CSA in cm^2 was used for the medial (MG) and lateral (LG) gastrocnemius. Tendon CSA was measured as the circumference of the injured tendon (absolute value) in cm^2.

The LSI was used to compare functional outcome between groups. Differences between groups in relation to the continuous variables were analyzed with a parametric Student's t-test. Comparisons for categorical variables between groups were performed with Pearson's χ^2-test.

Repeated measure mixed ANOVAs (Group*Time) were performed to analyze whether there were any significant effects of time or differences between outcome of the treatment groups for tendon elongation, tendon cross-sectional area or muscle atrophy over time. Where an interaction effect was found, an analysis of simple effects was performed. When Mauchly's test of sphericity was violated, the Greenhouse-Geisser correction was used.

Study IV

Gait analysis data were processed using the software Nexus 2.9.1 (Vicon Motion Systems Ltd, Oxford, UK). Three gait trials were analyzed for each patient at each test session. All calculations of motion analysis data were performed using MATLAB® software R2016b (The MathWorks, Inc, Natick, MA).

Gait data were compared between (EFM vs. ST) and within groups (injured vs. uninjured side), respectively. To facilitate valuation of ATR impact on gait, the biomechanics, ankle kinematics and kinetics of the two studied groups (EFM and ST) were graphically illustrated alongside a healthy reference group (n=59). The reference group consisted of pathology-free individuals from the control database at the Motion Analysis Lab of Karolinska University Hospital.

Differences between groups in terms of continuous gait variables were analyzed with a parametric Student's t-test. Side-to-side differences were analyzed with a parametric paired t-test.

Study V

Differences between groups in terms of the continuous variables were analyzed with a parametric Student's t-test. A paired Student's t-test was used for comparisons of the heel-rise variables between the 6-month and 12-month follow-ups and for side-to-side differences. The nonparametric Mann-Whitney U-test was used to compare differences between groups in term of ordinal data such as the outcome questionnaires and the Wilcoxon signed ranked test for comparing paired ordinal data. Comparisons between groups for categorical variables were performed with Pearson's χ^2-test.

A two-way ANOVA was conducted to examine whether there was an effect of treatment and the occurrence of DVT on the outcome variables from the heel-rise test and ATRS. The LSI was used to compare the groups in the heel-rise test.

6 RESULTS AND DISCUSSION

This chapter summarizes the main findings of the studies included in this thesis. A detailed description of the results of each study is given in the publications and manuscript at the end of this thesis.

6.1 EARLY FUNCTIONAL MOBILIZATION (EFM)

6.1.1.1 Validation of the EFM-protocol

The first question that arose was whether we know how much patients are actually loading when instructed to bear weight in the orthosis. The purpose of the orthosis treatment is to protect the healing tendon while allowing for loading. Measurement of the load in the orthosis was previously done using insoles, i.e. mobile force sensors (64,71).

We sought to investigate the actual magnitude of load in the orthosis the first six weeks following ATR surgery and, to examine factors that might inhibit desirable loading *(Study II)*. In this study, only patients randomized to EFM postoperatively were included and evaluated at two and six weeks after surgery. Patients increased both loading and steps taken per day during the first two postoperative weeks. Plantar pressure was measured at two and six weeks using mobile force sensors (insoles). Patients increased their loading significantly, as measured as LSI average peak force, from two to six weeks (Figure 18).

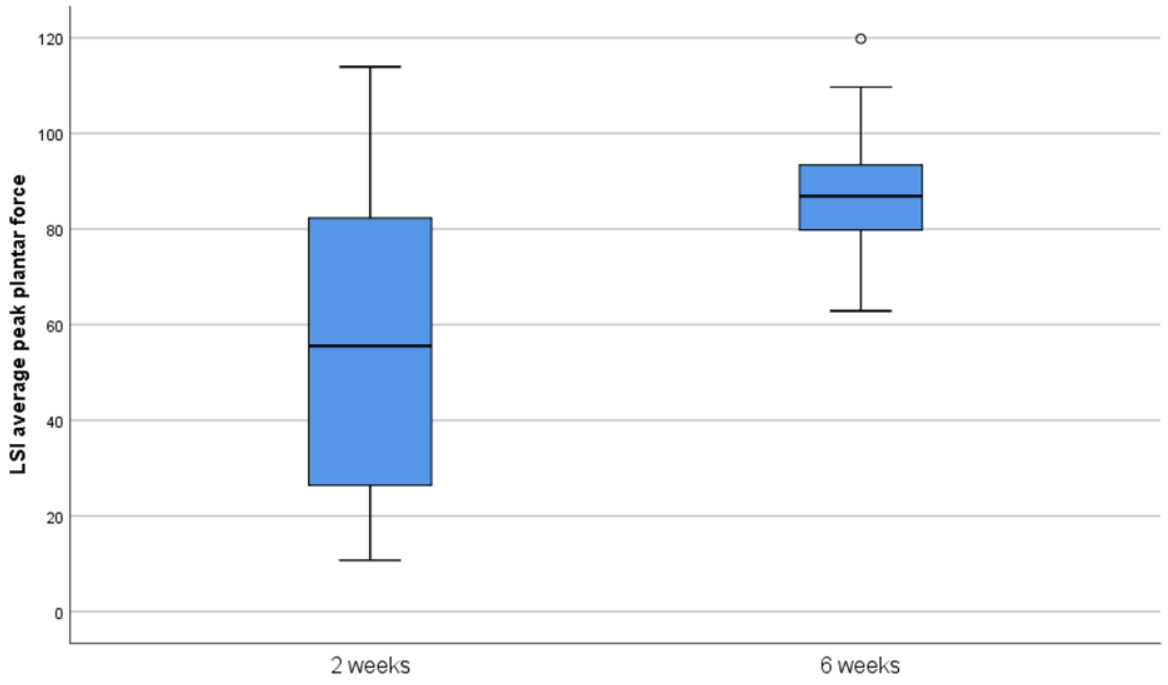

Figure 18. Boxplot of LSI average plantar pressure peak force measured with insoles at 2 and 6 weeks postoperatively. LSI= Limb symmetry index, injured/uninjured x100.

Self-reported loading was found to correlate to objective measured loading at two weeks (r_s=0.72, p<0.001). This means that self-reported loading is a feasible method for assessing loading early after ATR injury. This study also found that less pain during activity was associated with higher subjective load and more steps/day the first week after surgery, indicating that pain control is of importance if increased loading is the goal. For patients that were allowed weightbearing immediately after surgery, fear of movement as measured with the TSK-SV was not correlated to pedometer data, subjective loading data, pain, or force data. To our knowledge, this was the first study describing the timeline aspect of weightbearing and pedometer data in an early mobilization protocol.

In summary, the patients were loading in the orthosis at an average LSI peak force of 53% at 2 weeks, which increased to 88% at 6 weeks. Patient-reported loading can be used as a surrogate to load sensors to assess the degree of loading in an orthosis after ATR. Pain affects the degree of loading, and pain control may be an important factor if increased loading is the goal after surgery.

6.2 MAIN OUTCOME FROM THE RCT

In the RCT, a total of 149 patients were included in an intention to treat analysis (*Study I*). All patients had undergone standardized open surgical repair and were postoperatively randomized to either EFM or ST. The RCT was purposefully designed to examine differences in DVT frequency between groups and to explore the risk factors for DVT.

6.2.1 Deep venous thrombosis

6.2.1.1 Incidence of deep venous thrombosis (DVT)

The total incidence of DVT at two or six weeks was 37%, of which 38% were found in the EFM group and 35% in the ST group. This difference between groups was not significant. This result does not support our hypothesis that EFM would reduce the risk of DVT during immobilization after ATR repair compared to ST.

The DVT rate in this study is consistent with earlier studies using DVT screening in the study protocol (102,104,190). In non-surgically treated ATR-patients, even higher rates, up to 50%, have been reported recently (191). However, the reported DVT incidence was lower, between 1.4 and 8.6% (102,192–195) when not screening for DVT but only recording symptomatic DVTs. Nevertheless, it has not been demonstrated that symptomatic DVTs pose a greater danger to patients compared to non-symptomatic DVTs (196).

ATR patients have only minimal calf muscle activation when walking in an orthosis the first weeks postoperatively (71). This could be one reason why EFM was not enough to enhance the "muscle pump," promote venous return, and thereby reduce the risk of DVT. Another reason may be the low amount of loading, as demonstrated above, which may be connected to poor activation of the muscle pump.

This study did not use LMWH as prophylaxis. This was instead only used as treatment when a DVT was diagnosed. There is little to no evidence supporting the use of thromboprophylactic medication for lower limb immobilized patients (102,108,109,197,198). Other means of thromboprophylactic treatment include mechanical intermittent pneumatic compression (IPC) therapy. IPC treatment has been shown to decrease the risk of DVT post-ATR repair (9).

6.2.1.2 Risk factors for DVT

When examining the associations between patient characteristics (age, sex, BMI, time to surgery, nicotine usage), clinical outcome (dorsiflexion, calf circumference, pain, and fear of movement) and DVT, only a BMI over 26 (r= 0.21, p= 0.013) and older age (r= 0.25, p= 0.003) were significantly associated with an increased risk of experiencing a DVT at two weeks, independent of treatment group. Age and BMI were found to be two independent risk factors of sustaining a DVT, with 2.3 times higher odds in patients with a BMI of more than 26, and 1.07 times higher odds per each additional year of age.

When adding the number of steps and self-reported loading in a separate analysis of DVT risk factors in the EFM group, this analysis demonstrated that an average daily load of 50% or less at day seven (r= 0.22, p= 0.035) was significantly associated with an increased risk of experiencing a DVT. Also, in this subgroup, older age (r= 0.22, p=0.029) and a BMI>26 (r= 0.26, p= 0.010) were associated with a higher risk of DVT. So, in addition to older age and BMI>26, loading ≤ 50% at the end of week one was an independent risk factor associated with 4.3 times higher odds of sustaining a DVT.

Age over 40 has previously been found to be a risk factor for DVT after ATR (9,199). Older age and high BMI (> 30) are generally considered risk factors for VTE in combination with surgery and lower limb immobilization (197). It has, therefore, been proposed that early mobilization would reduce the risk of DVT (113,193). However, previous studies have shown that when weightbearing and controlled ankle motion were initiated at two weeks after injury, 34–52% of the patients still sustained a DVT (7,9,191).

The finding of higher loading associated with less risk of developing a DVT is novel and implies that means should be taken to promote early loading of more than 50% as early as one week post-surgery. Combining these results with the data showing that pain control is important for a higher degree of loading suggests that improved pain information and therapies should be delivered postoperatively to patients.

6.2.1.3 Clinical outcome following DVT

A subgroup analysis of patients included in Study I, showed that patients that exhibited a DVT (n=53) during immobilization were significantly older than those without DVT (n=91). Mean (SD) age without DVT was 38.1 (7.8) years, versus 42.5 (8.2) with DVT, p=0.002.

There were no significant differences in ankle dorsiflexion (DF) between patients with or without DVT at two or six weeks. At two weeks, the difference (i.e. uninjured−injured) in calf circumference was significantly less in patients with DVT, mean (SD) 0.7 (1.0) cm, versus without DVT, 1.5 (1.0) cm ($p<0.001$). At six weeks, the difference was no longer significant (mean difference 0.36 cm, $p= 0.057$). None of the patients with DVT at two weeks exhibited a difference in calf circumference that exceeded 3 cm, which is one criterion on the Wells score for clinical detection of a DVT. However, all patients were immobilized and had undergone surgery, leaving them with 2 points on the Wells score.

The Wells score is a scoring system used in clinical practice to evaluate signs of DVT (200,201). Calf swelling and cast immobilization are risk factors of DVT in this score, and more than 3 points indicates high probability of DVT (200,201). There is also a dichotomized version, where a score of ≥ 2 indicates that DVT is likely and that the patient should undergo a diagnostic ultrasound scan (202). Calf atrophy is expected after an ATR and subsequent immobilization. Side-to-side differences in calf circumference measurement would therefore be expected. In this study, patients with a DVT had less side-to-side difference in calf circumference measurement. This suggests that such patients might have calf swelling, but it presents as having a lesser degree of "atrophy" rather than a larger circumference measurement.

6.2.1.4 Patient-reported outcome following DVT

When comparing patient-reported outcome by DVT (S*tudy V*), patients who had experienced a DVT reported significantly lower self-reported outcome than patients without DVT both at six and 12 months. In a study by Barfod et al. (191), in non-surgically treated ATR patients, almost half of the patients sustained a DVT during immobilization. The study compared early controlled motion with immobilization and weightbearing starting at two weeks in both groups (191). Although they did not find inferior patient-reported outcome (ATRS) for patients with DVT compared to no DVT, the scores for both groups were lower than previously reported in non-surgically treated ATR patients (6,7). In addition, Arverud et al. (156) compared ATRS scores for patients with and without DVT. Patients without DVT showed better scores, but the difference between groups was small and did not reach statistical significance. Our finding that DVT following ATR was associated with poorer patient-reported outcome has been further corroborated in a recent study analyzing 250 patients. The study included a proportion of the patients from this study (203).

6.2.1.5 Functional outcome following DVT

There were no significant differences in functional outcome between the patients with and without DVT postoperatively (S*tudy V*). This finding is again in line with the study by Barfod et al. (191), who did not found any differences in LSI heel-rise work for patients with and without DVT. However, the results for both groups were lower compared to previous studies (6,7). In contrast to our study, Arverud et al. (156), found lower LSI heel-rise height in patients with DVT compared to those without DVT.

In summary, EFM immediately postoperatively of ATR repair does not decrease the risk of DVT as compared to ST. Rather, it is the degree of loading during the first week postoperatively that seems to be an essential factor for reducing the risk of DVT. Sustaining a DVT postoperatively results in inferior patient-reported outcome up to at least a year after surgery.

6.2.2 Secondary complications

6.2.2.1 Re-rupture

We demonstrated that EFM following ATR repair does not increase the risk of re-rupture. In this study, the re-rupture rate was 0.7% (1/149) (*Study I)*. This one patient sustained a partial re-rupture at three weeks postoperatively due to slipping when not wearing the orthosis. The re-rupture rate in this study is consistent and even lower than previous studies on operative repair (6,7,61,66,82,98,133). Surgery has been found to reduce re-rupture rates compared to non-surgical treatment (52,53,55–57,95). When using functional rehabilitation with a removable orthosis, one important factor to consider is having a compliant patient, who follows recommendations on wearing the orthosis.

6.2.2.2 Infections

The rate of superficial wound infections following open surgery and EFM in this RCT was low, 0.7% (1/149) at two weeks and 1.3% (2/149) at six weeks (*Study I)*. One patient in the EFM group had a superficial infection at two weeks and one patient from each group had a superficial infection at six weeks. Furthermore, one patient in the EFM group was diagnosed with a deep infection at three weeks. The infection rate in this study was comparable or lower than previously published studies (6,7,9,94,98,148,204,205). Infection rates and scar problems are post-surgical complications that do not occur following non-surgical treatment. In addition, orthosis treatment has been speculated to increase movement of the incision (6), which may add a risk of delayed healing. Our data, however, do not indicate incisional healing problems due to EFM. Superficial infections are commonly treated with oral antibiotics. Deep infections, however, often require multiple surgical debridement with

subsequent tendon transfer, soft-tissue coverage and skin-grafting with variable results (100,206).

In summary, EFM does not increase the risk of re-ruptures and infections compared to ST following ATR repair.

6.3 SECONDARY OUTCOMES FROM THE RCT

6.3.1 Structural outcome

6.3.1.1 Tendon elongation over time

Tendon elongation and subsequent muscle atrophy have been shown to impact functional outcome (123,132). In *Study III*, the purpose was to examine how the muscle-tendon complex changes over time after ATR repair and how EFM affected those changes.

Tendon elongation (i.e. difference injured – uninjured tendon length in cm) was significantly greater in the EFM group at two weeks compared to the ST group (Figure 19). There was a significant interaction effect (group*time) between the groups, meaning that the pattern of elongation differed between the groups.

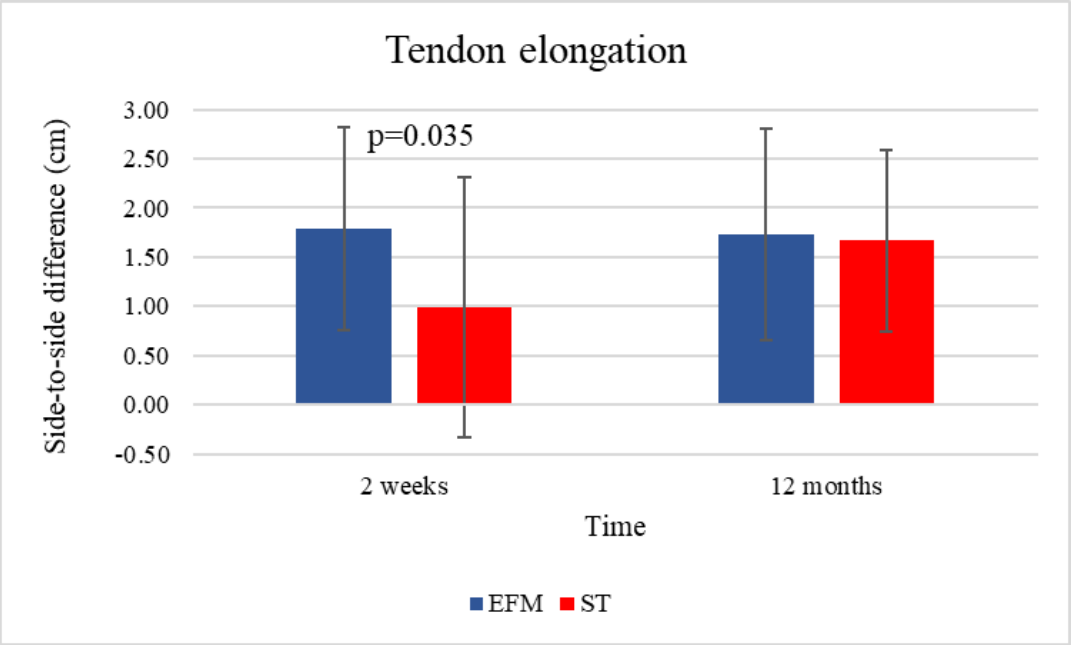

Figure 19. Difference in tendon elongation at 2 weeks (n=45) and 12 months (n=82). EFM=early functional mobilization, ST=standard treatment.

In this study, the increase in tendon length started with commencement of loading, i.e. elongation occurred before two weeks in the EFM group, when patients could weight bear immediate postoperatively while elongation started after week two in the ST group, when patients started loading. At six months and one year, there were no significant differences in tendon elongation between the groups. Thus, our hypothesis was not confirmed. EFM was not superior to ST in minimizing tendon elongation postoperatively.

In the EFM group, tendon elongation decreased from six weeks to one year. This finding is in line with a study by Kangas et al. (119) reporting decreased elongation with early motion between six months and one year. The degree of elongation has been shown to impact the functional outcome of the heel-rise test (82,207). In the present study, at one year, 13.4% (11/82) patients, almost equally distributed in each group, exhibited elongation of more than 3 cm on the injured compared to the uninjured side, resulting in inferior outcome in the heel-rise test. Moreover, the average patient reported ATRS score was lower in the elongated group, but the difference did not reach statistical significance (Table 4). These findings suggest that minimizing excessive tendon elongation is of importance in order to improve patient outcome.

Table 4. Impact of tendon elongation on patient outcome at 1 year

Outcome, mean (SD)	TE < 3cm (n=71)	TE > 3 cm (n=11)	p-value
Diff max height, cm	2.4 (2.0)	4.2 (1.3)	**0.006**
LSI max height, %	83.2 (15.0)	71.2 (8.6)	**0.011**
LSI total work, %	79.5 (20.2)	60.8 (17.9)	**0.005**
ATRS	80.3 (15.7)	71.8 (19.3)	0.12

TE= Tendon elongation, Diff = difference uninjured–injured in cm,
LSI= limb symmetry index, ATRS= Achilles tendon total rupture score

Previous studies have shown that tendon elongation occurs mostly during the first three months after injury (92,119,121,124). Studies evaluating tendon elongation with different loading protocols have not found any differences between early and late weightbearing. Okoroha et al. (208) found that tendon elongation was the greatest between two and six weeks even if patients were non-weightbearing, and then decreased between six and 12 weeks, while Eliasson et al. (133) found that elongation increased during the first 12 weeks and then continued for six months. Notably, neither of these studies used immediate full weightbearing postoperatively for the early mobilization group. Both studies used tantalum beads sutured in the tendon and then performed radiographic assessments of the distance between the beads as measurement of elongation, without comparison with the uninjured side. A potential benefit of minimizing tendon elongation comes with surgical repair, and the possibility of adding some tension between tendon ends (6,158).

In summary, tendon elongation occurs with start of loading. EFM was not superior to ST in minimizing tendon elongation postoperatively. An elongation of more than 3 cm results in inferior functional outcome.

6.3.1.2 Muscle atrophy over time

The atrophy of both the medial (MG) and lateral gastrocnemius (LG) increased rapidly and peaked at six weeks of postoperative leg immobilization. MG atrophy subsided slightly after six weeks, but remained atrophied at six months and one year at the same level as at two weeks. The LG atrophy, however, continued to subside below the levels seen at two weeks, and at one year there was only a small remaining atrophy as compared to the intact side. Soleus, conversely, did not exhibit significant muscle atrophy during the first six postoperative weeks. However, after the immobilization was discontinued, muscle atrophy of the soleus started to increase up to six months and remained persistent at the one-year assessment *(Study III)*.

When including the whole cohort, not only those cases measured at all four time points, the CSA of the MG was almost one centimeter larger in the EFM group (mean (SD) 1.55 (1.9) cm) compared to the ST group (mean (SD) 2.50 (1.2) cm), but this difference did not reach statistical significance (p=0.065). Soleus thickness was significantly greater in the EFM group at six months compared to the ST group (mean difference 0.16 cm, p=0.036) and almost remained the same at one year (mean difference 0.13 cm), but the difference was then no longer significant (p=0.088) (Figure 20).

It has been described that MG activity decreases with increased height of wedging, i.e. increased plantar flexion (70), whereas the soleus muscle activity decreases irrespective of the height of wedging in the orthosis. These findings could explain why the atrophy of the soleus muscle continues to increase over time. In our study, patients were immobilized in a greater degree of plantar flexion in the first few weeks and the gastrocnemii muscles might have been activated to a higher degree when wedges were removed, while the reduced soleus muscle activity could remain over the total immobilization time.

The same pattern of atrophy of the gastrocnemii muscles has been demonstrated in the long term as well (131). The MG is larger and stronger than the LG and is responsible for around 70% of the strength of the gastrocnemius muscles, whereas the force generation of the soleus is doubled compared to the MG (43). Clinically, we often see persistent atrophy or different muscle contours of the MG in the long term. MG has been investigated in modeling studies, showing structural changes in fiber length and pennation angle. Together with tendon elongation, such changes have been shown to correlate to inferior functional outcome (127–130,132).

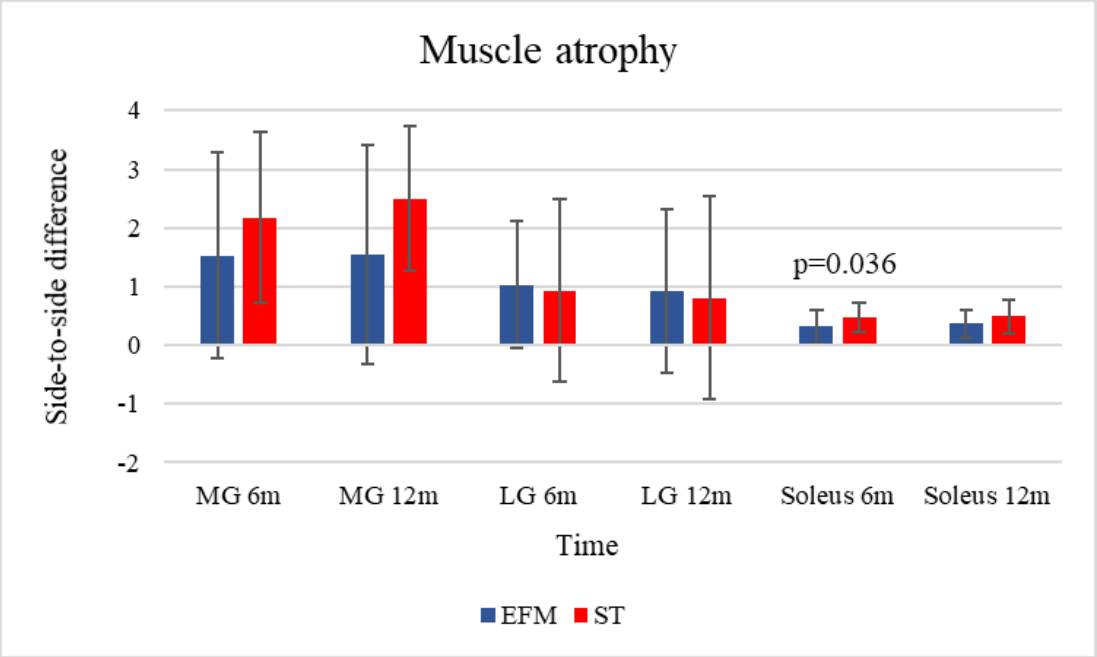

Figure 20. Muscle atrophy at 6 months (n=57) and 12 months (n=55).
MG=Medial Gastrocnemius in cm^2, LG=Lateral Gastrocnemius in cm^2, Soleus in cm, EFM=Early functional mobilization, ST=standard treatment.

The soleus muscle has shown persistent atrophy and fatty infiltration in the long term after ATR (126). A lack of strength in the end-range of plantar flexion has been associated with soleus atrophy (126,133). Type I fibers are more susceptible to atrophy (134), and this could be a reason for the marked soleus atrophy. Immobilization in the equinus position increases the atrophy of type I fibers (134). However, in this study, the soleus started to atrophy later than the gastrocnemius in both groups. Häggmark et al. (134) suggested already in 1979 that AT should be sutured and immobilized with some tension to minimize muscle atrophy. EFM following surgical repair does seem to reduce the soleus atrophy compared to immobilization in equinus position as with ST.

In summary, the largest atrophy of the MG was observed at 6 weeks but subsided over a year. The soleus atrophy peaked at 6 months and seemed to be persistent over time. Soleus muscle atrophy was significantly greater in the ST group compared to the EFM group at 6 months.

6.3.2 Clinical outcome

Ankle dorsiflexion (DF) at two weeks differed significantly between the groups on the injured side. The EFM group had a greater degree of DF compared to the ST group at two weeks ($p<0.001$), but not at six weeks ($p=0.22$) (Table 5). In a cadaver study, Costa et al. (115) found that the AT was the limiting factor of ankle DF and that a one-centimeter increase in tendon length corresponded to a 12-degree increase in DF. The authors suggested that ankle DF could be a surrogate measure of tendon length (115). In contrast, in a study by Rosso et al. (209), the authors did not advise use of ankle DF in vivo as a measure of tendon elongation due to poor correlations between tendon length and clinical ankle DF (209). In this present study, there was an increased ankle DF only at two weeks, which seems to be related to the patients having started weightbearing and performing active motion exercises of the ankle, leading to tendon lengthening. The findings of this present study agree with the results of Rosso et al. (209). However, we found a weak correlation between ankle DF and tendon length on the injured side at 2 weeks ($r=0.31$, $p=0.037$). There were no significant correlations between the injured side and tendon length at 6 weeks or between the uninjured side and tendon length at either occasion. Other measures, such as heel-rise height or the ATRA, therefore seem to be a better surrogate for measuring tendon elongation than ankle DF.

Table 5. Clinical measurements

Variable	*EFM (n=98)*	*ST (n=46)*	*p-value*
Ankle dorsiflexion (°) 2 w			
Injured/uninjured side	1.0 (6.9) /29.6 (5.5)	-6.7 (8.3) /30.5 (5.3)	**<0.001**
Ankle dorsiflexion (°) 6 w			
Injured/uninjured side	17.4 (6.6) /29.3 (4.6)	15.6 (9.0) /29.9 (5.5)	0.22
Calf circumference (cm) 2 w			
Injured/uninjured side	37.3 (2.9) /38.5 (2.7)	37.4 (2.2) /38.7 (2.2)	0.88
Calf circumference (cm) 6 w			
Injured/uninjured side	36.8 (2.9) /38.7 (2.7)	36.7 (2.3) /38.8 (2.2)	0.77

Values reported as mean and standard deviation, EFM=early functional mobilization, ST=standard treatment

Calf circumference measurements demonstrated no significant differences between the groups at two and six weeks (Table 5). Calf circumference measures have been shown to correlate to muscle CSA (209), and muscle CSA to muscle strength (210). Many patients do not recover from muscle atrophy over time, and calf circumference also remains smaller (67). Häggmark et al. (134) found that the muscle atrophy of the calf muscles was greater than the decrease in calf circumference due to an increase of subcutaneous tissue in the calf, resulting in the circumferential measure being considered an inaccurate marker of muscle loss (134). However, calf circumference measures are widely used as a measure of muscle atrophy, and

in our sample, we found high correlation coefficients (r=0.77–0.85) between calf circumference and gastrocnemius CSA over the first year.

In summary, EFM results in increased ankle dorsiflexion at 2 weeks compared to ST. No differences in calf circumference were found between the groups.

6.3.3 Patient-reported outcomes

6.3.3.1 Short-term PROM

In this thesis, fear of movement was assessed using the self-reported questionnaire, TSK-SV. It was demonstrated that 47% (24/44) of the patients in the ST group exhibited a higher degree of kinesiophobia (TSK-SV > 37p) at two weeks, mean (SD) 37.3 (7.0) compared to 37% (36/96) in the EFM group, mean (SD) 35.3 (6.4), p=0.058.

At six weeks, no significant difference in kinesiophobia was found between the groups. A high degree of kinesiophobia was present in 38% (18/47) of the patients in the ST group (mean (SD) 35.2 (7.6) and 36% (33/91) in the EFM group (mean (SD) 34.3 (6.9), p= 0.82. Within the EFM group, there were no significant differences in magnitude of loading between those with high versus low degree of kinesiophobia.

At two weeks, patients in the ST group were still non-weightbearing when filling out the TSK questionnaire. Most patients were feeling insecure when allowed to start bearing weight after injury. This could be a reason for the difference between groups at two weeks. The EFM group did not fill out the questionnaire before start of weightbearing. However, almost 1/3 of the patients in both groups still had a high degree of kinesiophobia at six weeks, which could reflect anxiety regarding reinjury. At 12 weeks postoperatively, Olsson et al. (211) found that patients with a higher degree of kinesiophobia had a lower activity level and more self-reported symptoms. The TSK-SV has been validated in chronic back pain patients (169). It has previously been used in studies of ATR patients (211). In this study, the questionnaire was difficult for some of the patients to fill out correctly. Most of the ATR patients did not report pain as a limiting factor, resulting in items in the questionnaire related to pain being omitted.

6.3.3.2 Long-term PROM

Long-term patient-reported outcome by treatment groups was evaluated in *Study V.* At six months, the EFM group scored higher on the quality of life questionnaire (RAND-36) subscales “General health (GH)” and “Vitality (VT)” compared to the ST group (Figure 21). Mean (median; min-max) GH: EFM 83.2 (85; 25–100), ST 74.8 (75; 20–100), p=0.012, VT: EFM 70.4 (75; 15–100), ST 61.0 (65; 20–100), p=0.022.

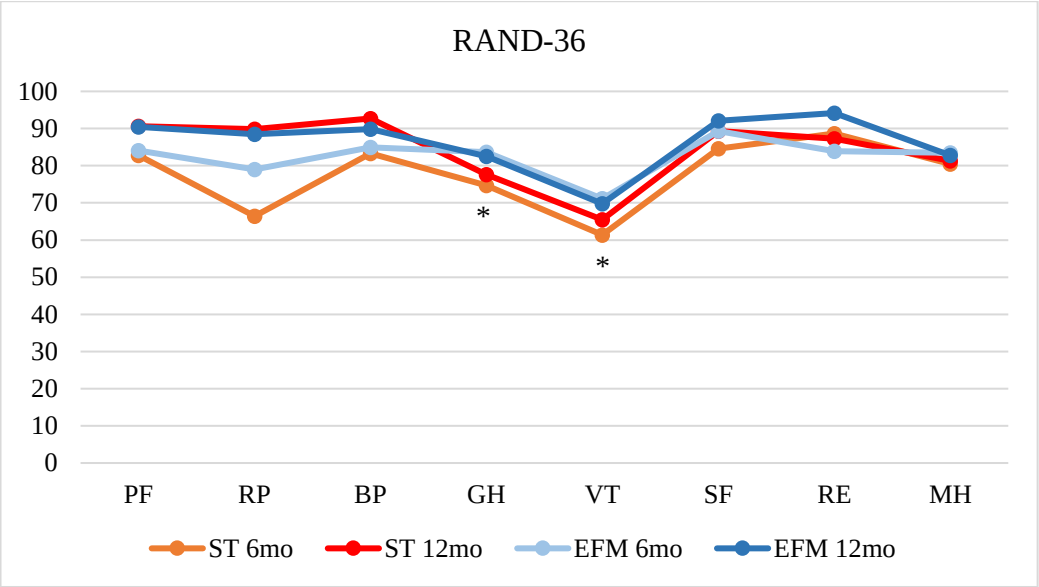

Figure 21. RAND-36 subscales mean values at 6 and 12 months.
PF=physical functioning, RP=role functioning/physical, BP=bodily pain, GH=general health, VT=vitality, SF=social functioning, RE=role functioning/emotional, MH=mental health, ST= standard treatment, EFM=early functional mobilization, *indicates significant difference ($p<0.05$).

Suchak et al. (212) found that patients treated with early weightbearing reported better outcome for physical and social functioning, vitality and role-emotional on RAND-36 at six weeks postoperatively compared to non-weightbearing, but only the subscale social functioning differed between groups at six months (212). Lantto et al. (61) used the RAND-36 at 18 months postinjury. Their results indicate the same pattern as in our study, where mental health, general health and vitality were scored lower than the more physical domains (61).

At six months, mean (median; min-max) ATRS was 65.1 (67; 16–98) in the EFM group and 59.1 (57.5; 18–97) in the ST group (p=0.13) and at 12 months 80.3 (85; 34–100) in the EFM group and 81.1 (86; 28–100) in the ST group (p=0.85). Both groups improved significantly between six and 12 months for the ATRS. Previous studies have reported a mean total score of 52–72 at six months and 74–88 at 12 months for surgically-treated ATR patients (6,7,133). Most of the improvement in ATRS takes place during the first year after ATR (8). At 12 months, no significant differences in any of the patient-reported outcome measures were seen between groups.

In summary, in the short term after ATR injury and surgery, patients may experience kinesiophobia, particularly when increasing activity. At 6 months, general health and vitality were the quality of life dimensions enhanced by EFM. ATRS did not differ significantly between the two groups during the first year.

6.3.4 Functional outcome

6.3.4.1 Functional outcome by treatment group

In *Study V*, no significant differences were observed between the EFM and ST group in the functional tests, at either six or 12 months postoperatively. Furthermore, there were large individual variations in both groups. The injured side improved significantly between the 6- and 12-month follow-up for all variables in the heel-rise test, but was still worse than the uninjured side. For the vertical jump test, no differences were found between groups but there was a significant deficit in jump height on the injured side in both groups (p<0.001) (Table 6).

Table 6. Jump tests at one year

Jump tests	***EFM*** *(n=80)*	***ST*** *(n=38)*	*p-value*
Vertical jump test *(cm)*			
injured side	24.3 (6.5)	23.6 (6.4)	0.58
uninjured side	27.5 (6.9)	27.3 (6.2)	0.88
p-value	**<0.001**	**<0.001**	
LSI (%)	89.2	86.9	0.43
Side hop test *(sec)*			
injured side	4.7 (1.5)	4.9 (1.6)	0.55
uninjured side	4.7 (1.5)	4.7 (1.7)	0.88
p-value	0.79	0.37	
LSI (%)	100.3	103.1	0.26
Patient perception scores during vertical jump			
Fear *(0 – 10)*	0.7 (1.4)	1.2 (1.9)	0.069
Discomfort *(0 – 10)*	0.9 (1.5)	1.2 (2.0)	0.58
Force *(0 – 100 %)*	96.8 (9.0)	93.2 (11.2)	**0.023**
Pain *(0 – 10)*	0.2 (0.7)	0.1 (0.4)	0.82

Values are reported as mean (SD), EFM=early functional mobilization, ST=standard treatment, LSI= limb symmetry index (injured/uninjured x100)

Patient perception when performing the vertical jump test was not significantly different between the groups. However, there was a significant difference between groups in perceived effort when jumping on the injured side compared to the uninjured side. However, this small difference was not considered clinically relevant.

Several earlier studies have shown that calf muscle endurance did not recover within 12 months, meaning a LSI of less than 85% compared to the uninjured side (6,7,133,156). At six months, patients exhibited a total work LSI of only 58.6% (range 0–104%) in this study, which aligns with other studies showing that the injured side was around 44–65% of the uninjured side in terms of total work capacity (6,7,133). At 12 months, the mean total work LSI was 75.4% (range 7–122%) and did not reach the desired recovery level of 85%.

Jumping is a modality causing larger deficits due to the greater load on the tendon-muscle complex. Decreased jump height and reduced ankle power during Drop CMJ were reported in the long term following ATR (140). Deficits in concentric ankle power were also demonstrated during jogging and the repetitive hopping test (141). In this study, there were no differences between groups in recovery of vertical jump height and both groups had recovered to a mean of 85% LSI at one year.

In summary, EFM was not superior to ST in enhancing functional recovery of calf muscle endurance after ATR repair.

6.3.5 Gait pattern

In *Study IV*, our aim was to quantify and describe gait parameters after EFM compared to ST following ATR repair. To date, only one additional study has examined gait pattern after ATR surgery in the short term, however the study included only a small study sample (n=13) (147). Our results were consistent with previous findings; specifically, no significant differences were found between different rehabilitation regimens, but there were significant differences between injured and uninjured side at eight weeks in terms of ankle kinematics, kinetics, and power (Figure 22) and for knee kinematics and kinetics (Figure 23).

At six months, we found group differences in ankle power generation and a trend towards higher ankle plantar flexion moment in favor of the ST group compared to EFM (Figure 22). However, knee extension moment during loading response (Figure 23) and internal knee valgus moment during stance phase were higher in the ST group, indicating a higher load on the knee joint. At six months, there were still side-to-side differences in ankle kinematics in both groups, but the only significant side-to side differences in kinetics were found in the EFM group (Figure 22).

Long-term studies (2–5 years of follow up) have reported side-to-side deficits in ankle kinematics, kinetics, and ankle power generation in ATR patients (16,146). In addition, in the study by Tengman & Riad (16), both the injured and uninjured sides differed from a healthy control group, indicating that also the uninjured side demonstrates an altered gait pattern. This should be kept in mind when using the uninjured limb as comparison. Therefore, we included a healthy reference group.

It has been reported that the soleus muscle is the primary contributor to knee stability throughout the stance phase (213), and it has been suggested that the quadriceps muscle activity is prolonged when the function of the soleus muscle is impaired (213). Prior studies have shown that, with reduced activity of the triceps surae, the work moves proximally (70), and that deficits in calf muscle function post ATR may, in the long term, predispose

individuals participating in high-demand sports activities to knee joint overload injuries (140,141).

Jandacka et al. (142) suggested two compensatory mechanisms for an elongated AT: either increased ankle dorsiflexion or decreased knee flexion during initial contact. In their study, ATR individuals showed a reduced knee flexion pattern compared to the healthy control. This compensatory mechanism could potentially increase the risk of knee injuries during sports (142).

In the present study, different compensatory strategies were observed among participants during gait in the early phase. Most patients walked with a reduced walking speed, which contributed to reduced force in the ankle joint and less load on the plantar flexors (39). Furthermore, greater external rotation of the ankle (in the transversal plane) was a compensatory strategy resulting in reduced plantarflexion at push-off. Moreover, to avoid increased dorsiflexion during mid-stance, hyperextension of the knee or walking with a stiff knee was observed. An increased dorsiflexion coupled with hyperextension in the knee was additionally seen and could possibly be related to tendon elongation. With the current data, we cannot know whether the strategies used differ between groups. At six months, most of the individual gait pattern deviations were recovered.

In summary, EFM was not superior to ST in reducing the negative effects of ATR and ATR repair on gait in both the early and late phases after ATR repair. At 8 weeks, both groups displayed significant side-to side differences that persisted for ankle kinematics in the ST group and for ankle kinetics in the EFM group.

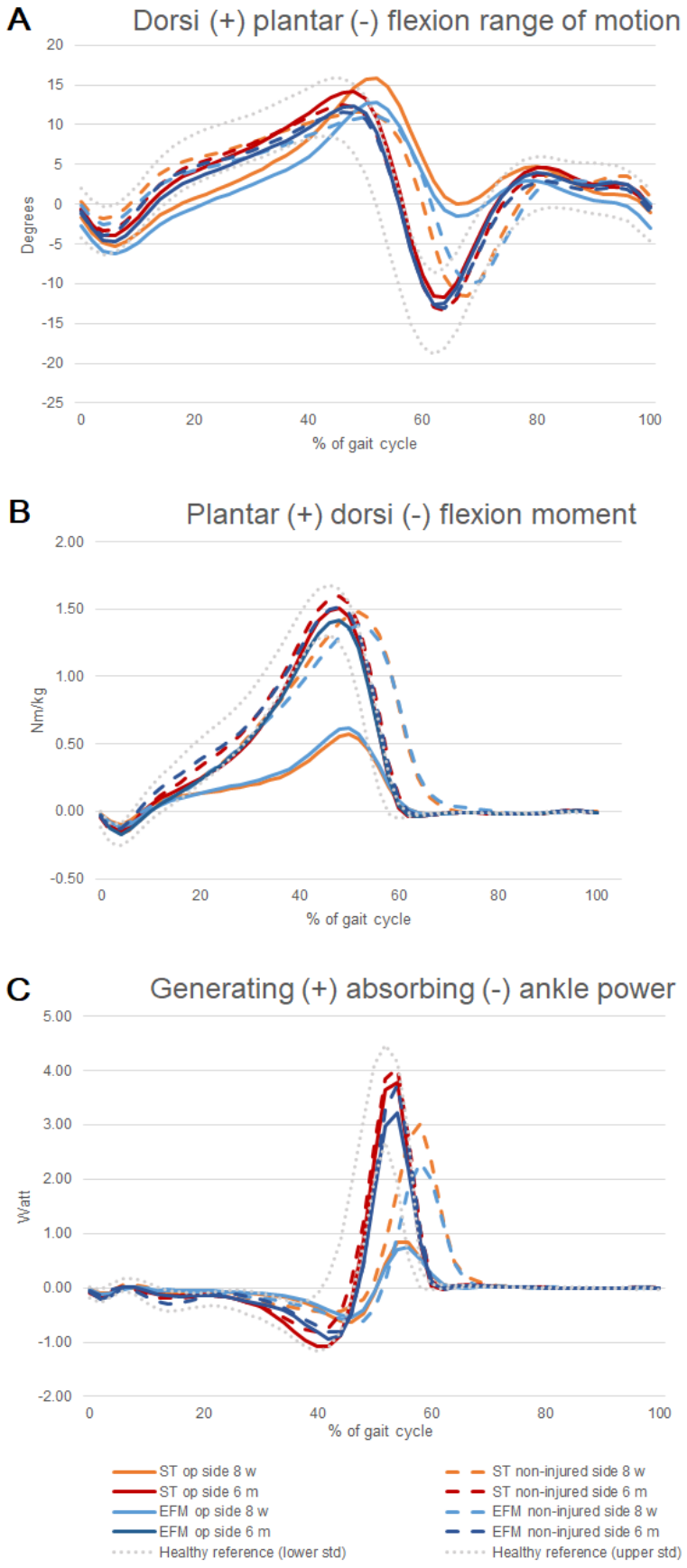

Figure 22. Sagittal plane ankle joint A) kinematics, B) kinetics, and C) power at 8 weeks and 6 months.

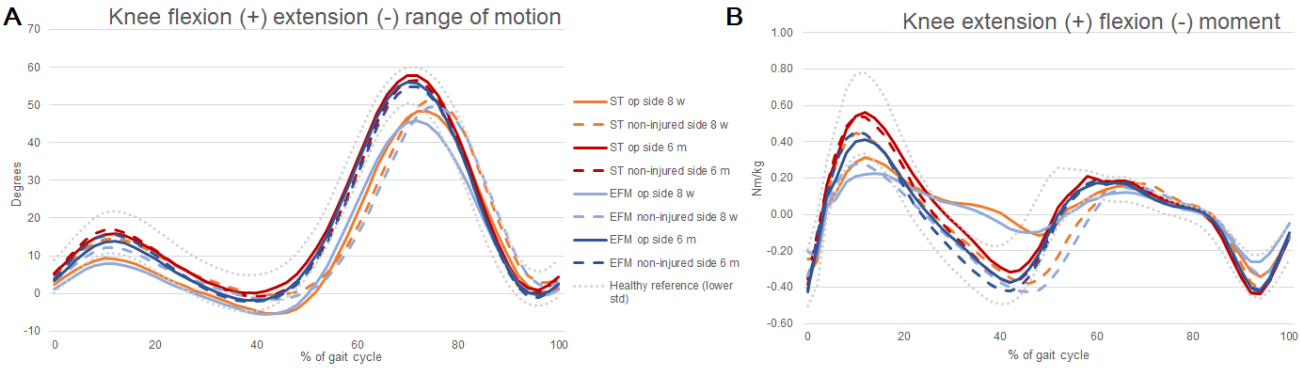

Figure 23. Sagittal plane knee joint A) kinematics, and B) kinetics at 8 weeks and 6 months.

6.4 PREDICTORS OF FUNCTIONAL OUTCOME

6.4.1.1 Correlations to functional outcome at six and 12 months

Additional results from Study III showed that less tendon elongation at six months significantly correlated to better LSI total work at six months and to LSI heel-rise height and total work at 12 months (Table 7). Increased tendon CSA on the injured side at six weeks was positively related to LSI total work at six and 12 months and to LSI maximal heel-rise height at one year. Patients with increased tendon CSA on the injured side at six months scored worse on the ATRS at 12 months (Table 7).

Soleus atrophy did not correlate to any of the functional outcome parameters. However, increased MG and LG atrophy correlated negatively to LSI total work and LSI maximal heel-rise height at both six and 12 months. There were no significant correlations between muscle atrophy and patient-reported outcome (ATRS) at six or 12 months (Table 7).

6.4.1.2 Predictors of functional outcome at six and 12 months

The US measurements at six weeks and six months were entered in stepwise multiple regression analyses of outcome at six and 12 months. The tendon CSA on the injured side at six weeks was a significant predictor of LSI total work at six months (*b*= 12.511 (5.762), β= 0.321, *p*=0.036, adj R^2 0.081) and LSI maximal heel-rise height at six months (*b*= 12.185 (4.231), β= 0.410, *p*=0.006, adj R^2 0.148). At six weeks, the degree of soleus atrophy predicted LSI total work at 12 months (*b*=28.644 (13.282), β= 0.319, *p*=0.037, adj R^2 0.08).

Tendon elongation at six months (*b*= -3.556 (1.393), β= - 0.313, *p*=0.014) and MG+LG atrophy (*b*= -2.160 (0.639), β= - 0.414, *p*=0.001, adj R^2 0.212) predicted maximum heel-rise height at one year. Atrophy of the MG+LG at six months predicted LSI total work at six months (*b*= -3,357 (0.988), β= -0.423, *p*=0.001, adj R^2 0.163) and LSI maximum height at six months (*b*= -2,499 (0.805), β= -0.392, *p*=0.003, adj R^2 0.138).

Table 7. Correlations between US measurements, functional and patient-reported outcome

Variable	Time point (wk)	Functional outcome 6 months			Functional outcome 12 months		
		LSI height	LSI work	ATRS	LSI height	LSI work	ATRS
AT elongation	2	r= − 0.158 p= 0.318 n= 42	r= − 0.122 p= 0.443 n= 42	r= 0.147 p= 0.373 n= 39	r= − 0.056 p= 0.723 n= 43	r= − 0.150 p= 0.339 n= 43	r= − 0.005 p= 0.975 n= 40
	6	r= 0.013 p= 0.925 n= 54	r= − 0.018 p= 0.895 n= 54	r= 0.240 p= 0.090 n= 51	r= − 0.118 p= 0.402 n= 53	r= − 0.080 p= 0.568 n= 53	r= − 0.067 p= 0.641 n= 51
	24	r= − 0.181 p= 0.132 n= 71	**r= − 0.251** **p= 0.035** **n= 71**	r= − 0.028 p= 0.823 n= 67	**r= − 0.258** **p= 0.033** **n= 68**	**r= − 0.292** **p= 0.016** **n= 68**	r= − 0.114 p= 0.363 n= 66
	52	N/A	N/A	N/A	**r= − 0.316** **p= 0.004** **n= 82**	**r= − 0.386** **p= 0.000** **n= 82**	r= − 0.133 p= 0.244 n= 79
AT CSA	2	N/A	N/A	N/A	N/A	N/A	N/A
	6	**r= 0.436** **p= 0.003** **n= 45**	**r= 0.354** **p= 0.017** **n= 45**	r= − 0.125 p= 0.425 n= 43	**r= 0.311** **p= 0.037** **n= 45**	r= 0.033 p= 0.827 n= 45	r= − 0.047 p= 0.769 n= 42
	24	r= − 0.024 p= 0.856 n= 60	r= − 0.039 p= 0.765 n= 60	r= 0.000 p= 0.988 n= 56	r= 0.050 p= 0.708 n= 58	r= − 0.238 p= 0.072 n= 58	**r= − 0.352** **p= 0.008** **n= 56**
	52	N/A	N/A	N/A	r= 0.038 p= 0.764 n= 65	r= − 0.022 p= 0.859 n= 65	r= − 0.113 p= 0.384 n= 62
Soleus thickness	2	r= 0.207 p= 0.189 n= 42	r= 0.071 p= 0.656 n= 42	r= 0.132 p= 0.423 n= 39	r= 0.242 p= 0.118 n= 43	r= 0.091 p= 0.561 n= 43	r= 0.091 p= 0.575 n= 40
	6	r= 0.042 p= 0.770 n= 50	r= 0.140 p= 0.331 n= 50	r= 0.160 p= 0.283 n= 47	r= 0.112 p= 0.437 n= 50	r= 0.215 p= 0.133 n= 50	r= − 0.002 p= 0.987 n= 47
	24	r= − 0.145 p= 0.286 n= 56	r= − 0.144 p= 0.289 n= 56	r= − 0.038 p= 0.787 n= 52	r= − 0.074 p= 0.594 n= 54	r= − 0.053 p= 0.705 n= 54	r= 0.033 p= 0.817 n= 51
	52	N/A	N/A	N/A	r= − 0.145 p= 0.297 n= 54	r= − 0.167 p= 0.226 n= 54	r= − 0.143 p= 0.317 n= 51
Gastrocnemius CSA (MG+LG)	2	r= − 0.100 p= 0.521 n= 43	r= − 0.140 p= 0.369 n= 43	r= − 0.093 p= 0.569 n= 40	r= − 0.145 p= 0.347 n= 44	r= − 0.056 p= 0.720 n= 44	r= − 0.207 p= 0.194 n= 41
	6	r= − 0.084 p= 0.560 n= 51	r= 0.023 p= 0.871 n= 51	r= 0.023 p= 0.874 n= 48	r= − 0.057 p= 0.693 n= 51	r= 0.039 p= 0.785 n= 51	r= − 0.099 p= 0.505 n= 48
	24	**r= − 0.429** **p= 0.001** **n= 57**	**r= − 0.449** **p= 0.000** **n= 57**	r= − 0.220 p= 0.113 n= 53	**r= − 0.470** **p= 0.000** **n= 55**	**r= − 0.327** **p= 0.015** **n= 55**	r= − 0.166 p= 0.240 n= 52
	52	N/A	N/A	N/A	**r= − 0.587** **p= 0.000** **n= 55**	**r= − 0.500** **p= 0.000** **n= 55**	r= − 0.263 p= 0.060 n= 52

LSI= Limb symmetry index, ATRS= Achilles tendon Total Rupture Score, N/A= not assessed, AT= Achilles tendon, CSA= cross-sectional area, MG= medial gastrocnemius, LG= lateral gastrocnemius

Few studies have reported associations between tendon structure and functional outcome. Zellers et al. (207) demonstrated that tendon CSA at 12 weeks was a strong predictor of LSI heel-rise height and total work at one year. In addition, intraoperative tightness of repair as measured with the ATRA has been shown to predict heel-rise height at one year (158).

In summary, measures of muscle- and tendon morphology in the early healing phase can predict functional outcome in the later phase. The tendon CSA on the injured side at 6 weeks was found to be a significant predictor of LSI total work and LSI maximal heel-rise height at 6 months, while the degree of soleus atrophy at 6 weeks predicted LSI total work at 12 months.

6.5 SEX DIFFERENCES

6.5.1.1 Demographic data

In the one-year cohort, 24% (33/102) were female and the male to female ratio was 3.1:1. There was no significant difference in age between sexes; the mean age was 39.7 (8.4) for the males and 38.9 (6.8) for the females. There was a significant difference in BMI between sexes (female 23.7 (2.7) and male 25.4 (2.4), p= 0.001). The degree of physical activity was in median 5 (2–6) for both sexes preinjury and 4 (1–6) at one-year postoperatively. The treatment groups had an equal distribution of sex, with 66% receiving EFM and 34% receiving ST. The incidence of DVT at two or six weeks was 37% in males and 31% in females (n.s). In this cohort, 58% of males injured their left side, while 64% of the females injured their right side.

There is a predominance of males sustaining an ATR. Previous studies have reported a male to female ratio of 1.7–6.9:1 (214). In Scandinavia, several RCTs over the past decade have shown that females only account for 8–20% of the ATR injuries (6,7,61,133,153,156). In the United States, the male to female ratio was found to be greater, 5.4:1 and the mean age was slightly higher for both sexes (214).

The DVT incidence in this study was higher in females compared to earlier studies reporting on DVT by sex. In a study by Nilsson-Helander et al. (10), only 5% of patients with DVT were female and Barfod et al. (191) had 15% females that sustained a DVT during immobilization post-ATR.

6.5.1.2 Functional and patient-reported outcome

There were no significant differences between males and females at six or 12 months for LSI total work or maximal height in the heel-rise test ($p > 0.05$).

For the patient-reported outcome, there were no significant differences between sexes at six or 12 months for ATRS or FAOS.

Males scored higher on the TSK-SV, indicating a higher degree of kinesiophobia, at all timepoints than females, but the differences were only significant at six weeks (35.3 vs 31.8, $p=0.018$) and six months (32.4 vs 28.8, $p=0.007$). However, the mean value did not reach the "cut-off" of high kinesiophobia defined as 37±3 points at six months.

Females scored higher on the subscale "general health" in the QoL questionnaire RAND-36 compared to males at six months (85.7 vs 78.4, $p=0.022$) and they also rated their health now compared to one year ago better than males at both six months (45.2 vs 35.7 $p=0.027$) and one year (66.7 vs 50.9, $p= 0.014$).

The results of our studies do not align with the results of Silbernagel et al. (154), who found that females treated with surgery reported more symptoms than males on the ATRS, and that males had a better heel-rise height than females on the heel-rise test (154). In addition, another study found that males scored significantly better on the ATRS compared to females one year after injury (159). In the current study, all patients had surgical treatment, which could explain the differences compared to the prior studies.

In summary, the male to female ratio was 3.1:1, and 24% of the subjects in this study were female. There were no differences in functional outcome between males and females. Females rated their general health better than males at 6 months.

6.6 LIMITATIONS

6.6.1.1 Study design and sample size

This thesis was based on a prospective RCT with an allocation ratio of 2:1, meaning more patients were randomized to the intervention group. This allocation ratio was chosen based on a recommendation by the ethical review committee because the EFM treatment seemed promising as a better alternative than ST in reducing the risk of DVT postoperatively. However, this randomization led to the two groups having different sample sizes, which could have jeopardized the power of the two prospective cohort studies in this thesis, where not all patients from the RCT were included, and with the 2:1 inclusion, the ST group was smaller.

Also, the main RCT could have been affected by low power (<0.8) which would increase the risk of type II error, because of a too small of a sample size in the control group. A type II error means that the null hypothesis (stating no differences between groups) is not rejected when in fact, it is false (215,216).

The main outcome variable for the RCT was DVT incidence, which could have resulted in the power being too low to detect significant differences in the secondary outcomes, such as patient-reported and functional outcomes. However, the study by Olsson et al. (6), using the patient reported ATRS as primary outcome variable, showed that 41 patients were required in each group to reach a power of 85%.

The external validity of this study, or the generalizability of the results, applies only to patients with open surgical repair of ATR and could not be transferable to non-surgical treatment.

As for internal validity, the study was primarily designed to evaluate the incidence and risk of DVT. The assessors of the DVT screening were blinded to group allocation. However, neither patients nor the PT performing the functional outcome assessments, were blinded to allocation group. Nevertheless, all outcome assessments were performed according to a predefined standardized protocol, identical for both treatment groups.

Another threat to the internal validity derives from the PROMs used, because only the ATRS is psychometrically tested for this specific population. Nonetheless, those outcome measures are frequently used in research studies to evaluate orthopedic lower limb injuries, including ATR.

6.6.1.2 Study I

One potential limitation could be that the patients were not encouraged enough to bear weight in the orthosis. Patients were instructed that weightbearing was safe and not harmful with the orthosis. Another limitation was related to the DVT screening, as the CDU scans do not give 100% correct diagnoses. Three patients with CDU-verified DVTs at two weeks were diagnosed as not having a DVT at six weeks. This may be explained by the CDU-verified

DVTs being misdiagnosed or the DVTs having been resolved. Because of the difficulties in distinguishing pain from different sources, it was not recorded whether a DVT was symptomatic or asymptomatic.

6.6.1.3 Study II

One limitation was that the measures of plantar pressure might not be directly translated into load on the Achilles tendon, and we do not know whether the patients were activating the triceps surae muscles. 3D gait analysis is the golden standard for objectively assessing forces during gait. However, this method is not suitable when wearing an orthosis due to the difficulty of marker placement on bony landmarks. Different types of insoles have demonstrated good reliability and validity in both healthy and patients, and wireless insoles may be a useful tool for evaluating plantar pressure forces during gait. The currently used insoles only measured the plantar pressure force as one force and did not divide it into different regions of pressure, such as forefoot, midfoot or heel.

Another limitation was the pedometer (Yamax SW-200) used. It has been suggested to be less accurate at slower gait speeds, which may cause a possible underestimation of steps during the first week, as patients are not walking at their normal gait speed with crutches. We did not assess gait speed. However, patients were walking more symmetrically and with a higher cadence at the 6-week follow-up than at two weeks.

6.6.1.4 Study III

The power to detect differences between the groups could have been reduced due to allocation ratio (2:1) in the RCT, as not all patients from the original RCT were assessed. Additionally, the repeated measures analysis induced decreased power due to missing data. Another limitation is related to the US measurements. The gastrocnemius muscle's CSA was measured at 25% of tibial length based on previous research and in order to standardize the measurement. This measurement did not correspond to the thickest part of the calf in all participants. However, the difference between uninjured and injured sides was used for measuring muscle atrophy instead of the absolute values.

An additional limitation was that this study used two different types of orthosis treatment. It has previously been demonstrated that different construction of orthoses, i.e. internal or external wedging or without support under the heel, result in a different angle of the ankle joint and/or load on the AT. The results might therefore have been influenced by the orthosis used, in addition to the other differences between the treatment groups.

6.6.1.5 Study IV

This study was also a cohort study and not all patients from the original RCT were included due to delayed accessibility of the motion analysis and logistical reasons. At the time of testing, barefoot walking was not yet encouraged and was challenging soon after completion

of the orthosis treatment. On the other hand, all patients had been loading fully for six weeks and were two weeks off orthosis prior to testing.

Since this study did not use electromyography (EMG), we are unable to make any inferences regarding calf muscle activity during gait.

6.6.1.6 Study V

The potential limitations were that there were several orthopedic surgeons involved in the surgical treatment of the patients, resulting in different degrees of tightness of the repair. The physical therapist performing the outcome tests was not blinded to treatment regimen. Another limitation of the study was that the rehabilitation protocol was not standardized after week six. These limitations may explain some of the variation in patient outcome, but may also make the results more generalizable in clinical practice.

Several questionnaires used for assessing patient-reported outcome were not validated for this specific population, but most of them are commonly used in research studies for ATR patients.

The treatment regimens may have been too similar to display greater differences between the two groups, and it may be that the early exercise was not optimized. Patients in the EFM group were encouraged to perform active plantar flexion exercises at home during the first two weeks postoperatively, but the training was not controlled or supervised.

6.7 CLINICAL IMPLICATIONS

Suffering from a DVT postoperatively resulted in inferior patient-reported outcome in the longer term. A higher degree of loading during the first week postoperatively was demonstrated to be an essential factor for reducing the risk of DVT. However, postoperative pain negatively impacted the degree of loading. Postoperative pain control may therefore be an important factor in increasing the load after surgery. Self-reported loading assessments could potentially assist in individual decisions about pain control to increase loading. Whether such means could reduce the rate of DVT to improve the patient-reported outcome after ATR warrants further investigations.

There are large variations in outcome after ATR, and this study proved to be no exception. Patient expectations for recovery do not always match the functional outcome. The results of this thesis indicate that it is of importance for recovery to avoid excessive tendon elongation, muscle atrophy and DVT during leg immobilization after ATR. Further research is needed to understand the underlying factors that influence variations of functional recovery. More knowledge about underlying influential factors may lead to more individualized patient treatments. The results indicate that we should treat and progress each patient based on their status instead of just following time-based standardized protocols.

Fear of re-injury and pain could be possible causes of the low loading seen in the early postoperative phase. Supervised rehabilitation during this early phase could be important for patients experiencing a higher degree of kinesiophobia. Moreover, EFM did not prevent an altered gait pattern, neither in the early nor the late phases following ATR repair. Physical therapy and gait training when weaning off the orthosis may be beneficial for all patients after ATR injury.

The EFM treatment was not found to be inferior to ST and was the treatment most appreciated by the patients. They were satisfied with being able to take the orthosis off for an hour a day during the first two weeks. EFM treatment also facilitated daily life activities and work compared to unloading. The findings from this study indicate that EFM is a feasible method for treatment following ATR repair. Patient education is of importance so that the patients follow guidelines and comply with treatment recommendations.

6.8 FUTURE PERSPECTIVES

The findings of this study demonstrated that patients suffering from a DVT during leg immobilization postoperative of ATR repair experienced inferior function and health compared to patients without DVT. Minimizing the risk of DVT during leg immobilization is therefore still a great concern. Furthermore, this study indicated that EFM, including both weightbearing and ankle motion exercises, was not enough stimulation to decrease the risk of DVT, possibly because of low loading due to postoperative pain. Future research is needed to explore whether improved pain control to increase loading and other methods, such as mechanical thromboprophylaxis treatment, could decrease the risk of DVT after ATR injury in order to improve outcome.

Tendon elongation and calf muscle atrophy should be carefully considered during rehabilitation. Tendon elongation occurs with the start of loading. If the elongation becomes excessive, this may result in persistent functional deficits. Further study is needed to determine how to avoid excessive tendon elongation during immobilization and subsequent rehabilitation. One means of counteracting immobilization-induced calf muscle atrophy could be the use of neuromuscular electrical stimulation.

Plantar pressure loading and 3D gait analysis were used to assess loading on the lower limb. However, no measurements were performed to assess muscle activity or strain on the tendon. Knowledge of the actual load and strain on the AT during functional mobilization are lacking and would be of interest to further understand how to improve treatments. Future ATR rehabilitation protocols should aim to optimize muscle activation and loading, while minimizing tendon elongation. If and how different orthosis with external or internal wedges can limit the degree of elongation are still unknown and warrants further research.

7 CONCLUSIONS

- EFM does not increase the risk of re-rupture and infections compared to ST following ATR repair. Nor does EFM decrease the risk of DVT as compared to ST. The degree of loading, however, during the first week postoperatively seems to be an essential factor for reducing the risk of DVT. Suffering from a DVT postoperatively results in inferior patient-reported outcome up to a year after surgery.

- EFM enhanced the quality of life dimensions general health and vitality at mid-term. However, EFM was not superior to ST in improving functional recovery after ATR repair.

- Patient-reported loading can be used as a surrogate to load sensors in assessing the degree of loading in an orthosis after ATR. Moreover, postoperative pain affects the degree of loading, and pain control may be an important factor if increased loading is the goal after surgery.

- Tendon elongation occurs with start of loading. EFM resulted in tendon elongation equal to that of ST at one year postoperatively. An elongation of more than 3 cm resulted in inferior functional outcome. Atrophy of the gastrocnemius was the greatest at six weeks but subsided over a year. The soleus atrophy peaked at six months and seemed to be persistent over time.

- Gait pattern alterations were observed during the early healing phase, but were mostly recovered at mid-term follow-up.

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10 APPENDICES

Appendix 1. *Home exercise program*

Appendix 2. *Patient-reported outcome measures*