



**Karolinska
Institutet**

Karolinska Institutet

<http://openarchive.ki.se>

This is a Peer Reviewed Accepted version of the following article, accepted for publication in *The Bone & Joint Journal*.

2019-03-14

Ageing, deep vein thrombosis and male gender predict poor outcome after acute Achilles tendon rupture

Domeij-Arverud, Erica; Anundsson, Per; Hardell, Eva; Barreng, Gunilla; Edman, Gunnar; Latifi, Ali; Labruto, Fausto; Ackermann, Paul W

Bone Joint J. 2016 Dec;98-B(12):1635-1641.

British Editorial Society of Bone & Joint Surgery

<http://doi.org/10.1302/0301-620X.98B12.BJJ-2016-0008.R1>

<http://hdl.handle.net/10616/46682>

If not otherwise stated by the Publisher's Terms and conditions, the manuscript is deposited under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.

Aging, Deep Venous Thrombosis and Male Gender Predict Poor Outcome after Acute Achilles Tendon Rupture.

Arverud E¹, Anundsson P¹, Hardell E², Barreng G², Edman G³, Latifi A⁴, Labruto F⁴, Ackermann PW¹

¹Department of Orthopaedics, Institution of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

²Department of Physical Therapy, Institution of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

³Department of Psychiatry, Tiohundra AB, Norrtälje, Sweden

⁴Section of Diagnostic Imaging, Institution of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

Abstract

Background: Patients with acute Achilles tendon rupture (ATR) exhibit prolonged healing, high incidence of deep venous thrombosis (DVT) and a wide variation of functional outcome. This extensive discrepancy in outcome may be explained by a lack of knowledge of detrimental factors, and subsequent shortage of adequate interventions.

Methods: A total of 111 patients (84 men, 16 women; mean age 40.3 ± 8.4) with acute total ATR were prospectively assessed. At one year post-operatively a uniform outcome score, Achilles Combined Outcome Score (ACOS), was obtained by combining three validated, independent, outcome measures: Achilles tendon Total Rupture Score, heel-rise height test, and limb symmetry heel-rise height. Candidate predictors of ACOS included; treatment, sex, age, smoking, body mass index (BMI), time to surgery, physical activity level pre- and post-injury, symptoms, quality of life and DVT-incidence.

Results: Three independent variables correlated significantly with the dichotomized outcome score ACOS, while the other factors demonstrated no correlation. Low age (40 or less=0; above 40=1) was the strongest independent predictor of developing a good outcome at one year after ATR (OR= 0.20, 95 % C.I. 0.08 – 0.51), followed by female gender (Man= 1; Woman= 2) (OR= 4.18, 95 % C.I. 1.01 – 17.24). Notably, patients without a DVT (No=0, Yes=1) during post-operative immobilization experienced a better outcome (OR= 0.31, 95 % C.I. 0.12 – 0.80).

Conclusion: DVT during leg immobilization, aging and male gender are independent negative predictors of outcome in patients with acute ATR. Age and gender should be further studied as to pinpoint the underlying causes leading to poor outcome. To enhance the outcome after ATR the first clinical focus should be on DVT-prevention

during immobilization, possibly by usage of mechanical compression therapy and early weight bearing and mobilization.

Introduction

Repair after acute Achilles tendon rupture (ATR) is a prolonged process, associated with major functional deficits and an unknown wide variation of outcome between patients (1-5).

Current meta-analyses of the outcome after ATR have mainly focused on operative versus non-operative treatment, lately demonstrating no superiority of one over the other when early mobilization is applied. However, when it comes to other factors and variables affecting outcome of ATR there is currently a lack of knowledge.

Recently one study investigated how patient characteristics affected outcome in male ATR patients (6). It was found that increased age was a strong predictor of reduced function (6). In an earlier paper a substantial impaired function at one year postoperatively ATR was demonstrated (7). Gender, pain, and physical functioning during rehabilitation seemed to be important factors for functional outcome. However, the under-representation of female ATR patients has made it difficult to investigate the importance of gender on outcome (7).

The reason for the variability in outcome at least one year after ATR, however, is still unknown. Recently, a very high rate of deep venous thrombosis (DVT) 36-50%, irrespective of operative or non-operative treatment, has been demonstrated after ATR (8-10). Yet, whether common complications with DVT are associated with impaired outcome of ATR patients remains unclear.

In the present study we hypothesized that DVT and gender as well as multiple variables including age, BMI, treatment, physical activity score and smoking would influence the outcome of ATR. The aim of this observational cohort study was to

assess intrinsic and extrinsic factors that could predict the combined objective and subjective outcome as assessed with validated scores of lower limb function and patient-related outcome at one year after ATR.

Patients and Methods

Patients: The patients were included from a cohort of 150 patients with acute Achilles tendon rupture included in a prospective, randomized controlled trial (RCT) study (www.clinicaltrials.gov; trial number NCT01317160). The results on DVT incidence of the RCT have been previously described (11). A total number of 111 patients were assessed at the one-year follow-up (Table 1).

The inclusion criteria were (i): acute unilateral Achilles tendon rupture, operated on within 96 hours, (ii) age between 18 and 75 years. The exclusion criteria were identical as described in earlier published material (11). Two patients were withdrawn, one because of an ongoing thrombosis and the other because of being too young. Of the included patients, three sustained a re-rupture during the initial study and were also withdrawn from the one-year follow-up.

Eight patients ceased to participate and dropped out before two week follow-up (Fig. 1), owing either to unwillingness to continue with the research project (n = 4), violations of the research protocol (n = 2) or difficulty in tolerating the IPC device (n = 2). Twenty-six patients did not attend their scheduled appointment to the one-year follow-up control. Hence a total number of 111 patients were analyzed after the one-year follow-up and functional evaluation (Figure 1).

All eligible subjects received standardized verbal and written information about the trial, and gave written informed consent to participate in the study. The study was

conducted with approval by the Regional Ethical Review Committee in Stockholm, Sweden.

Treatment protocol

The surgical procedure and treatment protocol is described elsewhere (11). After completion of surgery study patients were randomized to receive either conventional post-operative plaster cast immobilization or adjuvant intermittent pneumatic compression in an orthosis during the first two post-operative weeks. At two weeks all patients returned for follow-up with assessment of DVT. After the two weeks visit all patients were mobilised with an orthosis (Don-Joy Walker; DJO, Vista, California) and were instructed to start full weight-bearing. At the six weeks visit the brace was removed.

Assessment of deep venous thrombosis (DVT)

All patients were screened for DVT in the operated leg by unilateral color duplex sonography (CDS) at 2 weeks post operatively, described in detail in previous report (11). Two experienced ultrasonographers, blinded to the treatment regimens, performed all the screening for DVTs using a Philips CX 50 (Philips Medical Systems, Andover, MA, USA). The standard procedure included evaluation of all deep proximal and distal veins, including muscle veins. 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 diagnostic procedure and the criteria for DVT diagnosis have been described in detail elsewhere (12, 13). Briefly, 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. Data

collection on symptomatic and asymptomatic DVTs was performed but due to uncertain data quality statistical analysis was not possible. The study protocol stated that the patients with diagnosed DVTs should receive LMWH, dalteparine, in therapeutic dose based on the patient's weight, and according to the protocol of the coagulation unit of our hospital. Hence, patients with a diagnosed DVT received subcutaneous injection of dalteparine (Fragmin®, Pfizer) 15 000 U or 18 000 U once daily for 8-12 weeks.

Patient-reported outcome and physical activity

The patients' symptoms and physical activity levels were assessed using four reliable and valid scores; the Achilles tendon Total Rupture Score (ATRS) (14) Physical Activity scale (PAS) (15) Foot and Ankle Outcome Score (FAOS)(16) and EuroQol Group's questionnaire (EQ-5D) (17). The ATRS ranges from 0 to 100; a lower score indicates more symptoms and greater limitation of physical activity. For the PAS, a score of 1 equals no physical activity, whereas a score of 6 equals heavy physical exercise several times per week. An EQ-5D score of 0 is considered to be the worst imaginable health state and a score of 1.00 the best imaginable health state.

Functional evaluation

One year after injury all patients returned for assessment of functional outcome. The functional evaluation consisted of muscular endurance tests and was performed as previously described in the literature (18, 19)(Figure 2). The tests have been shown to be reliable and valid (20, 21) and have frequently been used in evaluating outcome after Achilles tendon rupture (3, 6, 19, 22, 23). All evaluations were performed by two independent physical therapists. The patients' height and weight were measured and

documented. The tests were always performed in the same order, and the uninjured side was always tested first. All subjects were given standardized instructions and the tests were demonstrated by the examiner. Verbal encouragement was used and athletic footwear was standardized. Prior to testing, the patients warmed up on a stationary bicycle for 5 min followed by one set of 10 two-legged heel-rises. MuscleLab (Ergotest Technology, Oslo, Norway) measurement system was used for the evaluations.

The heel-rise test for endurance was performed on one leg at a time with the participant standing on a box with an incline of 10 degrees. The participants were allowed to place the fingertips, at shoulder height, against the wall, for balance. A metronome was used to keep a heel-rise frequency of 30 per minute. The participant was instructed to go as high as possible on each heel-rise and then lower the heel to the starting position, and to perform as many heel-rises as possible. The test was terminated when the patient stopped, could not maintain the frequency, or did not perform a proper heel-rise. The numbers of heel-rises, the time and height of each heel-rise, the total work (the body weight x total distance) in joules and the power (work / time) were used for data analysis.

Achilles Combined Outcome Score (ACOS)

In order to obtain one uniform outcome score for ATR patients, three validated outcome measures were combined to yield the Achilles Combined Outcome Score (ACOS). Based on previous studies (7, 24, 25), indirect tendon length (Heel-rise height and Limb Symmetry Index-height) and ATRS are the most validated variables/methods for assessment of tendon function. The correlations between these three outcome measures were very weak, i.e. below 0.30 (the highest

correlation was found between maximum heel rise and the symmetry index ($r= 0.28$, $p= 0.001$) indicating that they are independent measures of the outcome.

The uniform outcome measure, ACOS, was therefore established from the three variables ATRS, maximum height of heel-rise (injured side), and limb symmetry index (height). These three measures were first dichotomized at the median value. If the value was above the median, the patient received a score of 1.0, or below a zero value. The three values were then added to a total unweighted score that ranged from 0 (minimum outcome) to 3 (maximum outcome). Fifteen (14 %) patients received a total score of zero, 37 (33 %) patients a total score of 1.0, 36 (32 %) patients a total score of 2.0, and 23 (21 %) patients a total score of 3.0. This outcome score was, finally, dichotomized according to the median (2.0).

Demographic and clinical data

Several variables were documented for each patient, including age, gender, Body Mass Index (BMI) smoking habits, and the duration of daily intermittent pneumatic compression.

Statistical analysis

The descriptive statistics and statistical analyses were conducted with SPSS, version 22.0. All variables were summarized with standard descriptive statistics such as frequencies, means and standard deviations. The Limb symmetry index (LSI) was defined as the ratio between the involved limb and the uninvolved limb expressed as a percentage ($\text{involved/uninvolved} \times 100 = \text{LSI}$). Provided that the distribution of a variable was not severely skewed differences between groups were analyzed with oneway analysis of variance (ANOVA) or Student's t-test (for two-groups

comparisons). If a variable was severely skewed, i.e. the skewness statistics was greater than 1.5, Mann-Whitney U test was applied for the two-groups comparison.

The significance level in all analyses was 5 percent (two-tailed).

The dichotomized outcome measure, ACOS, was entered into a logistic regression analysis (stepwise forward with an inclusion level of 5 %) as the dependent variable with six independent variables or predictors: gender (man= 1 and woman= 2) age (age \leq 40 was set to 0, and age $>$ 40 to 1) smoker (nonsmoker= 0, and current smoker= 1) BMI (BMI \leq 26.0 was set to 0, and BMI $>$ 26.0 to 1) DVT (no DVT= 0, and a DVT= 1) and, finally, pre-injury level of activity (exercise up to 1-2 hours/week= 0, and above= 1). For age, BMI, and pre-injury level of activity the median was used as an unbiased cut-off. The relationships between the dependent and independent variables were expressed as odds ratios (OR) with 95 percent confidence intervals (C.I.). Since the regression analysis was a stepwise forward, only significant contributions to the prediction were entered in the regression equation.

Results

Multiple Linear Regression Analysis

A multiple logistic regression analysis was performed based on the dichotomized ACOS (dACOS) assigned 1, good outcome (n=59) or 0, poor outcome (n=50) (please see materials and methods for a description of ACOS). The analysis examined the unique contribution of: age, gender, BMI, treatment, smoking, physical activity score (PAS) as well as deep venous thrombosis (DVT).

The multiple logistic regression analysis demonstrated that three independent variables correlated significantly and independently with dACOS at one year; age,

gender and deep venous thrombosis after two weeks. Thus, higher age, age ≥ 40 years, was the strongest independent predictor of developing a poor outcome (dACOS=1) at one year after ATR (Table 2). Male gender was the second most important factor for obtaining a poor outcome. Notably, exhibiting a DVT during the post-operative immobilization was also an important independent predictor for a poor outcome after ATR (dACOS=0). BMI, PAS treatment and smoking did not significantly predict the outcome after ATR as assessed with dACOS.

Age

The strongest predictor of functional outcome and symptoms at one year was age. Patients aged over 40 years demonstrated a LSI of total concentric work of 58% compared to patients aged below 40 that reached 71% ($p < 0.001$). Maximum heel-rise height was 9.73 cm in the older patient group and 11.51 cm in the younger patients ($p < 0.001$). PAS differed significantly between the two age groups before injury ($p = 0.047$), while the difference was not significant after injury ($p = 0.157$). BMI as well as patient-reported outcome, ATRS and EQ-5D, however, did not differ between the two age groups (Table 3).

DVT

Patients experiencing a DVT postoperatively exhibited a significantly lower maximum heel-rise height of 9.89 cm as compared to patients without a DVT that reached 11.14 cm ($p = 0.018$). LSI of heel-rise height was significantly different between patients without (84%) and patients with a DVT (75%) ($p = 0.008$). LSI of total concentric work did not reach the recommended levels of 85% in the DVT group (61%), nor the non-DVT group (67%), and the difference between the groups was not

significant ($p = 0.164$). ATRS was lower in the DVT group (73.21) than in the healthy group (79.16), but the difference did not reach significance ($p = 0.131$) (Table 4).

In the recently published RCT the effect of receiving IPC beneath orthosis compared to standard plaster cast following ATR was assessed (26). Screening with CDU at two weeks post-operatively demonstrated a DVT in 23% of patients ($n = 16/69$) in the ITT analysis and 21 % of patients ($n = 14/67$) in the PP analysis in the IPC group and in 37% of patients ($n = 26/71$) in the control group. The patients who were compliant with the IPC-treatment exhibited a significant reduction in the risk of DVT, after correction for age differences between groups (ITT analysis: OR = 2.11; 95% CI 0.97 to 4.62; $p = 0.061$ and PP analysis: OR = 2.60; 95% CI 1.15 to 5.91; $p = 0.022$). Patients with a diagnosed DVT received subcutaneous injection of dalteparine (Fragmin®, Pfizer) 15 000 U or 18 000 U once daily for 8-12 weeks. No adverse events related to the treatment were observed.

Formatted: English (US)

Gender

Male gender exhibited a tendency towards lower LSI of concentric power 81% compared to women who reached 91% ($p = 0.099$). Maximum heel-rise height was 10.6 cm among men and 11.5 cm among women ($p = 0.251$). However, since the BMI in men was higher than in women (27 versus 24) ($p < 0.001$) the LSI of total concentric work (65% versus 71%) did not differ significantly ($p = 0.265$). Interestingly, the difference in PAS between men and women (3.67 vs. 4.27) was larger post injury (16%) compared to preinjury (7%) (4.56 vs. 4.87) (Table 5).

Age, DVT and Gender Combined

To illustrate the difference in outcome of patients with combined good predictors versus patients with combined bad predictors, we extracted these two groups from the cohort (Table 6). Being a female aged less than 40 years and without experiencing a DVT during post-operative immobilization resulted in almost 50% better heel-rise height ($p=0.009$) and around 40% better LSI of height ($p=0.004$) as well as LSI of concentric power ($p=0.027$) compared to males over 40, who experienced a DVT.

Discussion

This study established three critical independent predictors of clinical outcome after acute Achilles tendon rupture; age, gender and DVT. The data herein corroborate age and sex as predictors for all ATR-patients, but also highlight a novel and possibly preventable factor for poor outcome, i.e. DVT.

Our findings of increasing age and male gender being independent negative predictors of outcome after ATR confirm the hypothesis of two earlier studies in this area (6, 22). Moreover, this patient cohort also included female patients, which were not included in one earlier study (6).

This study also included new and preventable factors such as DVT and smoking into the analysis of predictors. DVT incidence in ATR patients has recently been found very high, 36-50% as assessed with Doppler ultrasound, irrespective of operation or conservative treatment (8-10). Thus, the demonstrated independent negative predictive value of exhibiting a DVT suggests that measures of preventing the development of DVT may improve outcome after ATR.

Pharmacological DVT prophylaxis, however, has been demonstrated non-effective for preventing the development of DVT after ATR (8), possibly because of deficient blood flow in the immobilized leg. Conceivably, DVT prophylaxis, i.e. low molecular weight heparin (LMWH), may even be deleterious for tendon healing. Thus, earlier experimental studies on rat Achilles tendon repair during continuous administration of LMWH demonstrated impairment of tendon healing (28). In this study patients diagnosed with DVT received treatment with LMWH, dalteparine, in therapeutic dose, which theoretically may have affected the outcome. Whether dalteparin administered once daily in patients can affect the outcome after ATR is yet unknown. However, all these facts urge the establishment of alternative DVT-preventive measures, eg. mechanical DVT prophylaxis.

Deleted: The deleterious effect of heparin on tendon healing

Deleted: observed in

Deleted: healing

Deleted: ,

Another option to address the venous stasis during immobilization would be to use mechanical DVT prophylaxis applying intermittent pneumatic compression (IPC), an effective method of reducing the DVT rate during leg immobilization after ATR without any negative side effects (11). IPC has also been proven effective in an outpatient setting.

Deleted: makes it even more urgent to establish alternative treatment regimes. In this study patients diagnosed with DVT received treatment with low molecular weight heparin (LMWH), dalteparine, in therapeutic dose, which theoretically may have affected the outcome. Whether dalteparin administered once daily in patients can affect the outcome after ATR is yet unknown.¶

The observed link between DVT and impaired outcome may also be due to a decreased arterial blood flow during immobilization. Mechanical compression may target this problem by increasing venous return, which in turn improves arterial flow (27). IPC can furthermore by cyclical tissue shear stress induce the production of chemical substances: antithrombotic and pro-fibrinolytic substances as well as substances that are known to enhance tissue repair (12, 21, 22). However, there is

still a need of more direct proof that mechanical compression therapy can increase the functional outcome after ATR.

The negative outcome associated with aging may be related to intrinsic or extrinsic factors, independent of the higher risk of DVT associated with aging. Intrinsic changes of aging may be related to reductions in tendon stiffness and resistance to loads (29), as well as metabolic interactions in tendon collagen production. Thus, high glucose (glycation) and diabetes can impair and lead to defective Achilles tendon healing (30, 31).

We noted in our study that patients aged over 40 exhibited reduced heel-rise height, repetitions and total work as compared to patients below 40. Thus, extrinsic alterations of aging may be related to decreased physical activity and less mobilization post-injury, which presumably could be counteracted by specific interventions (32). Specific rehabilitative interventions should be scientifically tested, specifically for the older ATR patients.

The gender differences found in ATR patients are intriguing, i.e. that male patients experience worse outcome. These results are consistent with data presented by Bostick et al (22), but differ from the results shown by Olsson et al (7). Such differences between cohorts may be due to dissimilarities in patient characteristics as well as physical rehabilitation.

One variable differing between genders was a higher BMI in male patients, suggesting that the male patients were overweight and thereby maybe also undertook less early mobilization. Our data at one year post-operatively indicated a tendency towards that female patients were more physically active than males. These parameters may be important underlying factors affecting gender differences.

Deleted:

Another factor which theoretically may affect outcome is that patients diagnosed with DVT received treatment with low molecular weight heparin (LMWH), dalteparine, in therapeutic dose. Earlier experimental studies on rat Achilles tendon healing during continuous administration of LMWH has demonstrated impairment on tendon repair (28). Whether dalteparin administrated once daily in patients can affect the outcome after ATR is yet unknown.

In fact, the study by Olsson et al. supports our hypothesis that BMI and physical activity may influence gender differences. Thus, they found that male patients with higher BMI exhibited worse patient-reported outcome but no major effect on function. Higher preoperative physical activity level was associated with worse patient-reported outcome, but had a small positive influence on functional outcome. In a cohort study by Silbernagel et al., female patients had a greater degree of deficit in heel-rise height as compared to males, irrespective of surgical- or non-surgical treatment (33). Since female ATR patients are <20% of all ATR patients, larger randomized clinical trials are needed to conclude on the associations between gender and outcome.

The observed reduction of functional outcome was not paralleled with the same extent of reduced patient-reported outcome as assessed by the ATRS questionnaire. This discrepancy is partly assumed to be an adaptation to the injury (2, 5). We therefore believe that the combination of the outcomes in a uniform score, Achilles Combined Outcome Score (ACOS), as used in this study, gives a broader view of the patient status at [one](#) year post Achilles tendon rupture.

Deleted: 1

Conclusion

This study provides predictors, which will lead the way towards a more individualized and evidence-based clinical decision-making of ATR patients. DVT during leg immobilization, aging and male gender are independent, negative predictive factors for outcome of patients at [one-year](#) post Achilles tendon rupture. This is the first manuscript to demonstrate that patients, who sustain a DVT post Achilles tendon rupture, exhibit impaired both patient-reported and functional outcome. The results

Deleted: one year

from this study suggest that patients should be informed about predictive risk factors. Further studies should address risk factors in a targeted manner, eg. by individualized treatment protocols with focus on early weight bearing and mechanical thromboprophylaxis, to improve outcome after Achilles tendon rupture.

References:

1. Horstmann T, Lukas C, Merk J, Brauner T, Mundermann A. Deficits 10-years after Achilles tendon repair. *International journal of sports medicine*. 2012;33(6):474-9.
2. Keating JF, Will EM. Operative versus non-operative treatment of acute rupture of tendo Achillis: a prospective randomised evaluation of functional outcome. *The Journal of bone and joint surgery British volume*. 2011;93(8):1071-8.
3. Nilsson-Helander K, Silbernagel KG, Thomee R, Faxen E, Olsson N, Eriksson BI, et al. Acute achilles tendon rupture: a randomized, controlled study comparing surgical and nonsurgical treatments using validated outcome measures. *The American journal of sports medicine*. 2010;38(11):2186-93.
4. Mullaney MJ, McHugh MP, Tyler TF, Nicholas SJ, Lee SJ. Weakness in end-range plantar flexion after Achilles tendon repair. *The American journal of sports medicine*. 2006;34(7):1120-5.
5. Willits K, Amendola A, Bryant D, Mohtadi NG, Giffin JR, Fowler P, et al. Operative versus Nonoperative Treatment of Acute Achilles Tendon Ruptures A Multicenter Randomized Trial Using Accelerated Functional Rehabilitation. *Journal of Bone and Joint Surgery-American Volume*. 2010;92A(17):2767-75.
6. Olsson N, Petzold M, Brorsson A, Karlsson J, Eriksson BI, Gravare Silbernagel K. Predictors of Clinical Outcome After Acute Achilles Tendon Ruptures. *The American journal of sports medicine*. 2014;42(6):1448-55.
7. Olsson N, Karlsson J, Eriksson BI, Brorsson A, Lundberg M, Silbernagel KG. Ability to perform a single heel-rise is significantly related to patient-reported outcome after Achilles tendon rupture. *Scandinavian Journal of Medicine & Science in Sports*. 2012;24(1):152-8.
8. Lapidus LJ, Rosfors S, Ponzer S, Levander C, Elvin A, Larfars G, et al. Prolonged thromboprophylaxis with dalteparin after surgical treatment of achilles tendon rupture: a randomized, placebo-controlled study. *Journal of orthopaedic trauma*. 2007;21(1):52-7.
9. Nilsson-Helander K, Thurin A, Karlsson J, Eriksson BI. High incidence of deep venous thrombosis after Achilles tendon rupture: a prospective study. *Knee Surgery, Sports Traumatology, Arthroscopy*. 2009;17(10):1234-8.
10. Domeij-Arverud E, Latifi A, Labruto F, Nilsson G, Ackermann PW. Can foot compression under a plaster cast prevent deep-vein thrombosis during lower limb immobilisation? *Bone Joint J* 2013 95(B(9)):1227-31.
11. Domeij-Arverud E, Latifi A, Labruto F, Nilsson G, Edman G, Ackermann PW. Intermittent pneumatic compression reduces the risk of deep vein thrombosis during post-operative lower limb immobilisation

- A prospective randomised trial of acute Achilles tendon ruptures. *Bone Joint J* 2015;Accepted for publication.
12. Lapidus L, de Bri E, Ponzer S, Elvin A, Noren A, Rosfors S. High sensitivity with color duplex sonography in thrombosis screening after ankle fracture surgery. *Journal of thrombosis and haemostasis : JTH.* 2006;4(4):807-12.
 13. Andrews EJ, Jr., Fleischer AC. Sonography for deep venous thrombosis: current and future applications. *Ultrasound quarterly.* 2005;21(4):213-25.
 14. Nilsson-Helander K, Thomee R, Silbernagel KG, Thomee P, Faxen E, Eriksson BI, et al. The Achilles tendon Total Rupture Score (ATRS): development and validation. *The American journal of sports medicine.* 2007;35(3):421-6.
 15. Grimby G. Physical activity and muscle training in the elderly. *Acta medica Scandinavica Supplementum.* 1986;711:233-7.
 16. Roos EM, Brandsson S, Karlsson J. Validation of the foot and ankle outcome score for ankle ligament reconstruction. *Foot & ankle international / American Orthopaedic Foot and Ankle Society [and] Swiss Foot and Ankle Society.* 2001;22(10):788-94.
 17. Brooks R. EuroQol: the current state of play. *Health policy (Amsterdam, Netherlands).* 1996;37(1):53-72.
 18. Silbernagel KG, Gustavsson A, Thomee R, Karlsson J. Evaluation of lower leg function in patients with Achilles tendinopathy. *Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA.* 2006;14(11):1207-17.
 19. Silbernagel KG, Nilsson-Helander K, Thomee R, Eriksson BI, Karlsson J. A new measurement of heel-rise endurance with the ability to detect functional deficits in patients with Achilles tendon rupture. *Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA.* 2010;18(2):258-64.
 20. Moller M, Lind K, Styf J, Karlsson J. The reliability of isokinetic testing of the ankle joint and a heel-raise test for endurance. *Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA.* 2005;13(1):60-71.
 21. Svantesson U, Carlsson U, Takahashi H, Thomee R, Grimby G. Comparison of muscle and tendon stiffness, jumping ability, muscle strength and fatigue in the plantar flexors. *Scand J Med Sci Sports.* 1998;8(5 Pt 1):252-6.
 22. Bostick GP, Jomha NM, Suchak AA, Beaupre LA. Factors associated with calf muscle endurance recovery 1 year after achilles tendon rupture repair. *The Journal of orthopaedic and sports physical therapy.* 2010;40(6):345-51.
 23. Silbernagel KG, Thomee R, Eriksson BI, Karlsson J. Continued sports activity, using a pain-monitoring model, during rehabilitation in patients with Achilles tendinopathy - A randomized controlled study. *American Journal of Sports Medicine.* 2007;35(6):897-906.
 24. Silbernagel KG, Steele R, Manal K. Deficits in heel-rise height and achilles tendon elongation occur in patients recovering from an Achilles tendon rupture. *The American journal of sports medicine.* 2012;40(7):1564-71.
 25. Kangas J, Pajala A, Ohtonen P, Leppilahti J. Achilles tendon elongation after rupture repair: a randomized comparison of 2 postoperative regimens. *The American journal of sports medicine.* 2007;35(1):59-64.
 26. Domeij-Arverud E, Labruto F, Latifi A, Nilsson G, Edman G, Ackermann PW. Intermittent pneumatic compression reduces the risk of deep vein thrombosis during post-operative lower limb immobilisation: a prospective randomised trial of acute ruptures of the Achilles tendon. *The bone & joint journal.* 2015;97-b(5):675-80.

27. Domeij-Arverud E, Azevedo J, Labruto F, Ackermann PW. Adjuvant compression therapy in orthopedic surgery - an evidence based review. *European Orthopaedics and Traumatology*. 2013;4:49-57.
28. Virchenko O, Aspenberg P, Lindahl TL. Low molecular weight heparin impairs tendon repair. *The Journal of bone and joint surgery British volume*. 2008;90(3):388-92.
29. Magnusson SP, Narici MV, Maganaris CN, Kjaer M. Human tendon behaviour and adaptation, in vivo. *The Journal of physiology*. 2008;586(1):71-81.
30. Ahmed AS, Ahmed M, Li J, Gu HF, Bakalkin G, Stark A, et al. Proteasome inhibitor MG132 modulates inflammatory pain by central mechanisms in adjuvant arthritis. *International journal of rheumatic diseases*. 2014.
31. Ahmed AS, Schizas N, Li J, Ahmed M, Ostenson CG, Salo P, et al. Type 2 diabetes impairs tendon repair after injury in a rat model. *Journal of applied physiology* (Bethesda, Md : 1985). 2012;113(11):1784-91.
32. Kragstrup TW, Kjaer M, Mackey AL. Structural, biochemical, cellular, and functional changes in skeletal muscle extracellular matrix with aging. *Scand J Med Sci Sports*. 2011;21(6):749-57.
33. Silbernagel KG. Sex differences in outcome after an acute Achilles tendon rupture 2015.

Table 1. Patient Demographics

<i>Variable</i>	<i>(n = 111)</i>
Age ± SD	40.8±9.0
Gender (%)	
Male	95 (87)
Female	15 (13)
Smoker (%)	3/111 (3)
Post-operative Treatment (%)	
Orthosis with IPC	52 (47)
Plaster cast	59 (53)
Deep Venous Thrombosis (%)	34/111 (31)
Body Mass Index ± SD	26.8 ±3.3
Time to Surgery (h) ± SD	54.5 ±30.8
Time in Surgery (min) ± SD	35 ±11

Data are given as the mean and standard deviation (SD). n = number of patients.

Table 2. Relationship between gender, age, deep venous thrombosis, and outcome

<i>Independent variable</i>	<i>B</i>	<i>S.E.</i>	<i>df</i>	<i>p</i>	<i>OR²</i>	<i>95% C. I.¹ for OR²</i>	
						<i>Lower</i>	<i>Upper</i>
Gender (Man= 1; Woman= 2)	1.43	0.724	1	0.048	4.18	1.01	17.24
Age (40 or less= 0; above 40= 1)	-1.59	0.462	1	0.001	0.20	0.08	0.51
Deep venous thrombosis after two weeks? (No= 0, Yes= 1)	-1.19	0.491	1	0.016	0.31	0.12	0.80

Constant -0.36 0.784

¹ C.I. = Confidence Interval

² OR = Odds Ratio

Table 3. Outcome at one year post-operatively treated Achilles tendon rupture in younger (aged≤40 years) compared with older patients (aged>40 years).

Variable	Age					
	≤ 40 (n=63)		> 40 (n=48)		p-value	% Difference
	Mean	SD	Mean	SD		
Heel-rise concentric work (LSI)	71%	17.2	58%	22.4	<0.001	22%
Heel-rise height injured side (cm)	11,51	2.2	9,73	2.6	<0.001	18%
Heel-rise height (LSI)	86%	14.3	74%	14.9	<0.001	16%
Heel-rise concentric power (LSI)	87%	19.0	76%	22.6	0.006	14%
PAS postinjury	3.90	1.2	3.56	1.2	0.157	10%
Heel-rise Repetitions (LSI)	84%	18.1	77%	19.9	0.061	9%
PAS preinjury	4.75	0.9	4.43	0.8	0.047	7%
ATRS	77,55	19.0	77,02	18.9	0.885	1%
BMI	26.9	3.5	26.6	2.9	0.570	1%
EQ-5D	0.917	0.11	0.911	0.10	0.772	1%

LSI=Limb symmetry index; PAS=Physical Activity Scale; ATRS=Achilles tendon Total Rupture Score; EQ-5D=EuroQol Group's questionnaire; BMI=Body Mass Index; SD=Standard deviation; n=number of patients.

Table 4. Outcome at one year post-operatively treated Achilles tendon rupture in patients with a DVT compared with patients without a DVT.

Variable	DVT	
	Mean	SD

	No (n=77)		Yes (n=34)		<i>p-value</i>	% Difference
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>		
Heel-rise height injured side (cm)	11.14	2.4	9.89	2.7	0.018	13%
Heel-rise height (LSI)	84%	15.3	75%	15.2	0.008	12%
Heel-rise concentric work (LSI)	67%	17.6	61%	25.6	0.164	10%
ATRS	79.16	18.7	73.21	18.9	0.131	8%
PAS postinjury	3.84	1	3.58	1.1	0.32	7%
Heel-rise concentric power (LSI)	82%	19.7	78%	24.1	0.105	5%
Heel-rise repetitions (LSI)	82%	17.7	78%	22.1	0.356	5%
EQ-5D	0.918	0.1	0.906	0.1	0.604	1%
BMI	26.8	3.4	26.6	2.9	0.778	1%
PAS preinjury	4.6	0.9	4.63	0.8	0.877	-1%

LSI=Limb symmetry index; PAS=Physical Activity Scale; ATRS=Achilles tendon Total Rupture Score; EQ-5D=EuroQol Group's questionnaire; BMI=Body Mass Index; SD=Standard deviation; n=number of patients.

Table 5. Outcome at one year post-operatively treated Achilles tendon rupture in female patients compared with male patients.

Variable	Gender					
	Female (n=15)		Male (n=96)		<i>p-value</i>	% Difference
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>		
PAS postinjury	4.27	1	3.67	1.3	0.085	16%
Heel-rise concentric power (LSI)	91%	30%	81%	20%	0.099	12%
Heel-rise concentric work (LSI)	71%	27%	65%	19%	0.298	9%
Heel-rise height injured side (cm)	11.46	3.04	10.64	2.49	0.251	8%
PAS preinjury	4.87	0.8	4.56	0.8	0.195	7%
Heel-rise height (LSI)	84%	16%	81%	16%	0.402	4%
ATRS	79.2	16.28	77.02	19.33	0.68	3%
Heel-rise repetitions (LSI)	81%	20%	81%	19%	0.988	0%
EQ-5D	0.867	0.1	0.922	0.1	0.063	-6%
BMI	23.8	2.9	27.2	3.1	<0.001	-13%

LSI=Limb symmetry index; PAS=Physical Activity Scale; ATRS=Achilles tendon Total Rupture Score; EQ-5D=EuroQol Group's questionnaire; BMI=Body Mass Index; SD=Standard deviation; n=number of patients.

Table 6. Outcome at one year post-operatively treated Achilles tendon rupture in patients with or without predicting factors of poor outcome.

Variable	Female <40	Male >40
-----------------	----------------------	--------------------

	<i>without DVT (n=6)</i>		<i>with DVT (n=15)</i>		<i>p-value</i>	<i>% Difference</i>
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>		
Heel-rise height injured side (cm)	13.1	3.1	8.9	3.0	0.009	47%
PAS postinjury	4.3	1.0	3.1	1.1	0.025	39%
Heel-rise concentric power (LSI)	96%	24%	70%	22%	0.027	37%
Heel-rise concentric work (LSI)	74%	19%	54%	23%	0.071	37%
Heel-rise height (LSI)	96%	14%	71%	16%	0.004	35%
PAS preinjury	5.2	0.8	4.4	0.6	0.023	18%
Heel-rise repetitions (LSI)	85%	22%	76%	25%	0.457	12%
ATRS	75.3	18.4	71.0	21.1	0.666	6%
EQ-5D	0.853	0.1	0.901	0.1	0.393	-5%
BMI	21.7	1.5	26.8	3.0	0.001	-19%

LSI=Limb symmetry index; PAS=Physical Activity Scale; ATRS=Achilles tendon Total Rupture Score; EQ-5D=EuroQol Group's questionnaire; BMI=Body Mass Index; SD=Standard deviation; n=number of patients.