Suzan de Jonge

Midportion Achilles Tendinopathy: Incidence, Imaging and Treatment

MIDPORTION ACHILLES TENDINOPATHY: INCIDENCE, IMAGING AND TREATMENT

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Midportion Achilles Tendinopathy: Incidence, Imaging and Treatment

Midortion Achilles tendinopathie: incidentie, beeldvorming en behandeling

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TABLE OF CONTENTS

Chapter 1 General introduction

ANATOMY

The Achilles tendon inserts proximally to the gastrocnemius and soleus muscles and distally it attaches to the tuber calcanei. Unlike other tendons in the leg, the Achilles tendon lacks a synovial sheath, but is surrounded by a peritendinous sheet called the paratenon which functions as an elastic sleeve to reduce friction.[1]

AETIOLOGY

Overuse injury of the Achilles tendon was firstly described by Albert in 1893.[2] Patients present with pain in the tendon after loading activities, and when the condition become chronic the pain also exists during loading activities and in daily activities. In 1998, Khan argued that the combination of pain, swelling, and impaired performance should be labelled tendinopathy.[3] The pathogenesis pathways of Achilles tendinopathy is highly heterogeneous. Many risk factors have been identified, for example: age, circulating and local cytokine levels, gender, biomechanics and body composition.[4]

Histopathology of symptomatic tendons shows a degenerative non-inflammatory process with a disorganized collagen structure in most cases. However, these abnormalities are also found in 34% of asymptomatic tendons.[5] This finding supposes that the intratendinous degenerative changes may not be directly the cause of pain.

Different hypothesis are described in literature about the origin of pain in tendinopathy. One hypothesis is that painful tendons are only the tip of the iceberg after a continuum from physiology to overt clinical presentation. The neurogenic hypothesis is based on stimulation of neuropeptides like substance P resulting in tissue breakdown and release of inflammatory mediators.[6] It has frequently been hypothesized that neovascularization and the accompanying nerves are the source of pain in chronic midportion Achilles tendinopathy.[7] Recently an additional theory was described about the stiffer plantaris longus tendon forming adhesions to the Achilles tendon as a source of pain.[8,9]

EPIDEMIOLOGY

Tendinopathy is common in athletes. Especially in runners high incidence rates (incidence rate 9.1-10.9%) are reported.[10] Incidence rates in general population are lacking. With the high prevalence in athletes, overuse seems to be an important risk factor for developing Achilles tendinopathy. Interestingly degenerative changes in Achilles tendons are also observed in wild animals kept in cavity.[1] While the incidence was related to age, the major cause for the tendon degeneration was decreased activity from being caged.[11]

CLINICAL PRESENTATION

As noticed above, midportion Achilles tendinopathy is a clinical diagnosis that can be made in presence of a painful swelling of the Achilles tendon 2-8 cm from the calcaneal insertion which impede loaded activities.[12]

OUTCOME SCORES

A validated outcome measure to assess the clinical severity of decreased activity and symptoms in Achilles tendinopathy is the Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire.[13,14] The VISA-A questionnaire (0–100) consists of eight questions and includes the three domains of pain, function in daily living and sporting activity.

IMAGING

Tendons can be imaged by ultrasound and magnetic resonance imaging (MRI). Fiber disorganisation, tendon swelling, fluid accumulation or fatty degeneration can be discriminated with MRI.[15] The superficial position of the Achilles tendon under the skin makes it highly suitable for ultrasound examination. With regular ultrasound, thickness of the tendon, degenerative areas, calcifications and abnormalities of the peritendinous space can be visualised . With ultrasound Doppler the ingrowth of new blood vessels into tendinopathic areas can be detected.[16] New imaging technique like sonoelastography and ultrasonographic tissue characterisation (UTC) were developed last years.[17,18]

THERAPY

Initially it was thought that symptoms of tendinopathy might improve without intervention after approximately one year.[19] However, prognostic studies on a wait-and-see regime are scarce. Two studies reported inferior results of a wait and see policy compared to eccentric exercise and shock wave treatment.[20] Eccentric exercises are best studied of all treatment options in Achilles tendinopathy. The eccentric exercise starts with a heel lift, after that the eccentric drop is performed with the injured leg. During 12 weeks patients are instructed to perform 180 repetitions daily, despite the presence of pain.[21] Different systematic reviews show beneficial effects of a 12-week eccentric exercise protocol.[22,23]

While corticosteroid injections are still used for the treatment of tendinopathy, there is emerging evidence that those cause significant long-term harms to tendon tissue and cells.[24] Sclerosing injections are a popular technique targeting the neovascularization of the tendon. However large randomized trials are lacking and therefore no conclusion can be made on this therapy.[25] Injection of platelet-rich plasma (PRP) to release growth factors into degenerative tendon areas, is increasingly used in the field of sports medicine. However different systematic reviews shows a lack of benefit over placebo treatments.[26,27] The use of cell based therapies is under active investigation for sports injuries. Lui reported in their systematic review on cell therapy nine pre-clinical and two clinical studies. They found improvement of tendon architecture in histology and in sonographic/MRI examination, and increase in functional and biomechanical performance. However the available data is insufficient to result in hard conclusion.[28]

The literature on the use of orthotics in Achilles tendinopathy is scarce. A recent review showed weak evidence that foot orthotics are equivalent to physical therapy. The effectiveness of heel raises for Achilles tendinopathy is unknown.[29]

Extracorporeal shockwave therapy (ESWT), a physical therapy modality that uses pressure waves to treat tendinopathy. While in vitro studies often show the effects of ESWT on tendon tissue, results of clinical studies are inconsistent.[30]

Low Level Laser Therapy (LLLT) is thought to decrease inflammation, increase fibroblast activity leading to improved collagen production. A systematic review reported conflicting evidence of the effectiveness of LLLT in the treatment of tendinopathy.[31]

All investigated operative methods were demonstrated to improve patients s conditions, though success rates varied between operative techniques. The complication rate differs between used techniques. Minimal invasive operative techniques seem to be related with fewer complications but open techniques report on higher success rates. Results vary between subjects according to sex and activity level.[32]

AIMS AND OUTLINE OF THIS THESIS

This thesis aims at elucidating the effect of different treatment options in midportion Achilles tendinopathy, with optimizing current diagnostic methods. A better understanding will have positive consequences for the patients.

First we tried to outline the size of the problem, by determining the incidence of mid-portion Achilles tendinopathy in the general practitioner population in the Netherlands (**chapter 2**). To evaluate the effect of different post injection protocols after intratendinous injections on the spread of the injected substance, a cadaveric study was performed and described in **chapter 3**. The clinical relevance of neovascularization measured with Doppler ultrasound was evaluated in a prospective cohort study

(**chapter 4**). As degenerative tendon injuries are prevalent in people with diabetes, we conducted a case-control study to determine whether diabetic patients have poorer ultrasonographic structure in their Achilles tendons compared to age-matched controls (**chapter 5**). In chapter 5 we also investigated if age, BMI, and sports activity were associated with Achilles tendon structure. Mid- and long term effects of the eccentric exercise protocol were evaluated in **chapter 6.1 and 6.2**. The one year follow-up of a doubled blinded randomised controlled trial on platelet rich plasma therapy is described in **chapter 7**.

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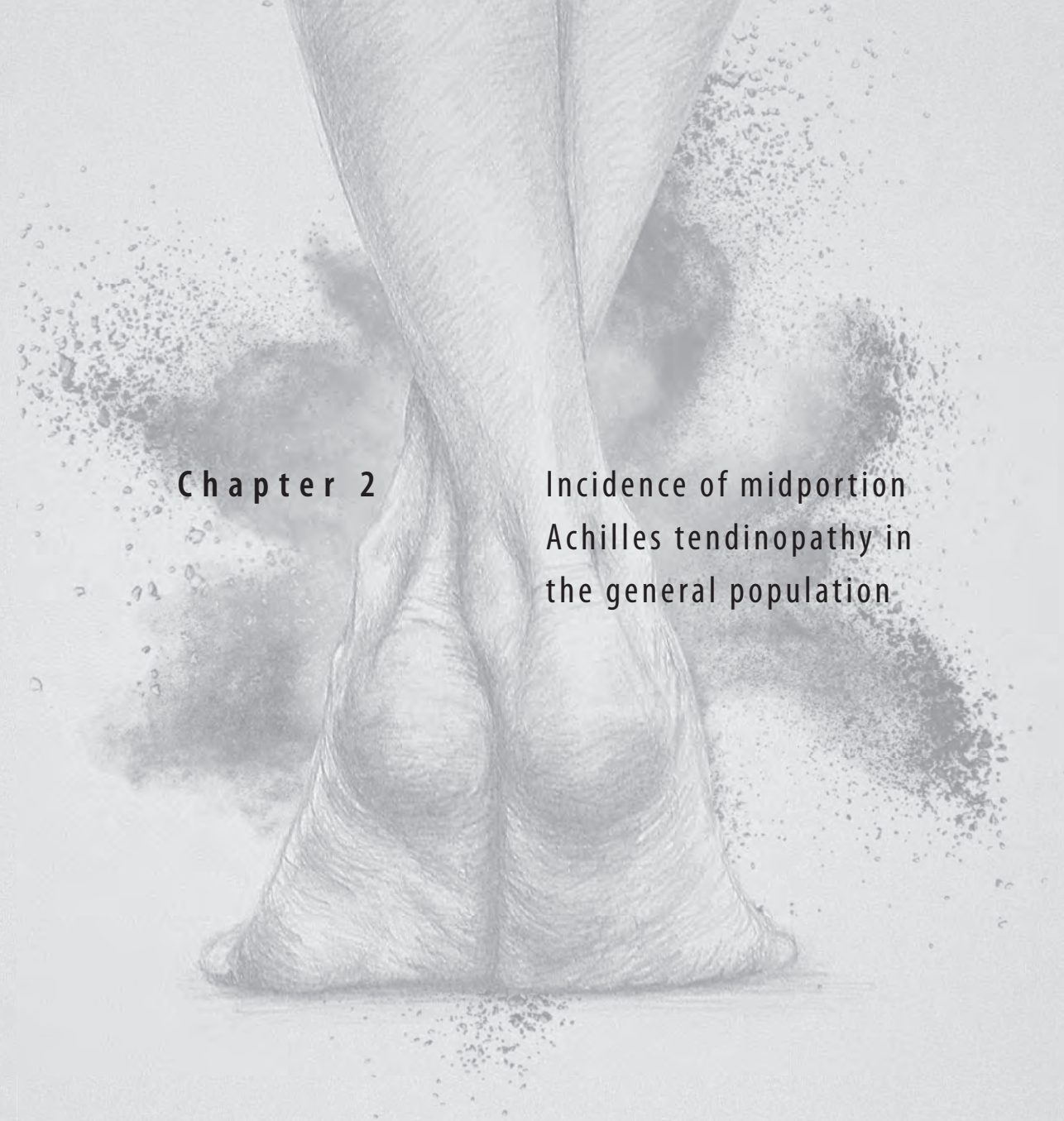

Chapter 2

Incidence of midportion Achilles tendinopathy in the general population

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ABSTRACT

Background: Achilles tendon disorders, like Achilles tendinopathy, are very common among athletes. In the general population, however, knowledge about the incidence of Achilles tendinopathy is lacking.

Design: Cross-sectional study.

Methods: In a cohort of 57.725 persons registered in primary care, the number of patients visiting the general practitioner (GP) with diagnosis of mid-portion Achilles tendon problems was counted using computerized registration networks of GPs in 2009. Subsequently, the authors assessed associations of these rates with demographic characteristics.

Results: The incidence rate of Achilles tendinopathy is 1.85 per 1,000 Dutch GP registered patients. In the adult population (21–60 years), the incidence rate is 2.35 per 1,000. In 35% of the cases, a relationship with sports activity was recorded.

Conclusion: This is the first report on incidence rates of mid-portion Achilles tendinopathy in general practice. With an incidence of 1.85 per 1,000 registered persons, Achilles tendinopathy is frequently seen by GPs. The actual incidence might even be higher due to study limitations. More research on the frequency of this injury is required.

INTRODUCTION

Achilles tendon problems frequently occur in athletes and are supposed to be common as well in the general population. The frequency of Achilles tendinopathy in athletes has been reported in several studies. Elite long-distance runners have a lifetime risk of 52%, and the lifetime incidence of 416 participants of Finnish conscription was 5.9%.[1] Others reported annual incidence rates of Achilles tendon disorders of 7% and 9%, respectively, in top-level runners.[2 3] Among the military population, an incidence of 2.98 per 1,000 person years was found.[4] A cohort study of 725 male marathon runners reported an incidence of 7.4% in the month before the Rotterdam marathon.[5] While these frequency rates were recorded in the sporting population, Achilles tendinopathy is not always associated with excessive physical activity; it is also seen in patients who do not participate in sports.[6–8] To our knowledge, there are no studies on the incidence of Achilles tendinopathy in the general population. Incidence rates are useful for studying trends in occurrence of diseases, future intervention studies, and for burden of disease estimates. To obtain this incidence rate, a cross-sectional study within the Dutch general practice setting was performed. In the Netherlands, every non-institutionalised inhabitant is registered with a general practitioner. In case of a health problem, the general practice is intended to be a gatekeeper to specialist care. The primary aim of this study was to ascertain the frequency of mid-portion Achilles tendinopathy seen in the general practitioner (GP) setting.

METHODS

In this cross-sectional study, data were obtained from computerised registration systems of Dutch GPs. General practices were approached for participation by mail and telephone. After permission, the researcher visited the practices. During this visit, all electronic patient files for consultations in 2009 were systematically searched under supervision of the GP. GPs in the Netherlands use International Classification of Primary Care (ICPC)[9] codes to register the reason for the visit. These codes include disease-specific codes as well as complaint specific codes. There is, however, no specific code for Achilles tendinopathy. Another sensitive way of searching for certain diagnosis is to use diagnosis specific words in the free text of the records. We searched for the term *achil* to find as many records describing the diagnosis of Achilles tendinopathy (eg, terms as *Achillodynia* could also be found). Medical files of the found records were read by a single researcher (CvdB) to assess whether they met the inclusion criteria. For the diagnosis of Achilles tendinopathy, a description of pain in the Achilles tendon above the insertion was required. Lack of this description resulted in exclusion. When the first contact with the GP for complaints was in the year 2009 without a previous visit in 2008, the patient was scored as an incident case.

In addition, age, gender, date of presentation and sports activity (related to complaints) were recorded if these had been recorded in the medical record. The medical record was also screened for diabetes mellitus (DM) type 1 and 2. Statistical analysis was performed using SPSS (version 17). Incidence rates were calculated separately for age group and sex.

RESULTS

Between February 2011 and April 2011, 128 general practices were approached. Fourteen practitioners did not answer repeated phone calls and 94 GPs refused to participate. Twenty GPs at different geographic locations responded positively to the invitation and were visited by the researcher. The 20 participating practices contained 57.725 registered persons, with an average of 2,886 persons in each practice (range 1,757–6,486). The research strategy "Achil" in the free text resulted in 277 cases in 2009. After screening the medical files, 116 cases of mid-portion Achilles tendinopathy could be recorded. Frequently reported other Achilles tendon disorders were insertional disorder, lash and bursitis. The prevalence rate of Achilles tendinopathy is 2.01 per 1,000 registered patients. Of these 116 prevalent cases, 9 patients had visited the general practitioner in 2008 for the same reason, resulting in 107 incident cases in 2009. The incidence rate for mid-portion Achilles tendinopathy is 1.85 per 1,000 registered patients. The 107 incident cases contained 56 females (52.3%) and 51 males (47.7%). Age- and sex-specific incidence rates are given in table 1. The overall incidence rate in the adult population between 21 and 60 years is 2.35 per 1,000. The mean age at time of presentation within the cases was 43.4 years (range 7–85 years). Mid-portion Achilles tendinopathy equally affects women and men. Mean duration of symptoms at presentation (reported in 39 cases) was 11.3 weeks (range 1–52). In 37 cases (34.6%), a relationship with sports activity was recorded. Ten patients (9.3%) were known to have DM—two patients with type 1 DM and eight patients with type 2 DM. Table 2 shows the patient characteristics of the case group compared with the study population and the Dutch population.

Table 1: Age and sex specific incidence rates for Achilles tendinopathy in 20 general practices.

	Age at time of diagnosis														
	< 20 years			21-40 years			41-60 years			> 60 years			Total		
	n	Persons	IR	n	Persons	IR	n	Persons	IR	n	Persons	IR	n	Persons	IR
Male	7	6371	1.1	13	7289	1.8	24	8459	2.8	7	5642	1.2	51	27761	1.8
Female	6	6342	0.9	21	7584	2.8	18	8996	2.0	11	7042	1.6	56	29964	1.9
Total	13	12713	1.0	34	14873	2.3	42	17455	2.4	18	12684	1.4	107	57725	1.9

n = number of persons with Achilles tendinopathy. Persons = number of registered persons. IR, incidence rate = number cases per 1000 registered persons.

Table 2: Patient characteristics in the cases with Achilles tendinopathy, in the total study population, and in the Dutch population (as recorded by CBS, Statistics Netherlands http://www.cbs.nl 2009).

	Patients with Achilles tendinopathy (95% confidence interval) n=107	Study population n=57.725	Dutch population in year 2009 n=16.485.787
Gender			
male	47.7% (95% CI, 38.0-57.3)	48.1%	49.5%
female	52.3% (95% CI, 42.7-62.0)	51.9%	50.5%
Diabetes Mellitus	9.3% (95% CI, 3.7-15.0)		4.1%
Type 1	1.8% (95% CI, 0-4.5)		0.8%
Type 2	7.5% (95% CI, 2.4-12.5)		3.3%
Age groups			
<20 years	12.1% (95% CI, 5.9-18.4)	22.0%	23.9%
21-40 years	31.8% (95% CI, 22.8-40.7)	25.8%	25.7%
41-60 years	39.3% (95% CI, 29.8-48.7)	30.2%	35.5%
>60 years	16.8% (95% CI, 9.6-24.0)	22.0%	15.0%

DISCUSSION

This is the first study presenting incidence rates of Achilles tendinopathy in the general practice. The overall incidence rate is 1.85 per 1,000 registered persons per year, and for the adult population it is 2.35. There are no other studies on the incidence rates of Achilles tendinopathy in the general population to compare these results with. The prevalence rate was higher than that for another tendinopathy like lateral epicondylitis of 1.3% (men) and 1.1% (women) in 9,696 persons registered at two general practitioners.[10] The incidence rates in our study are lower than the incidence of 2.98 found in the military population[4] and than the annual incidence 7% and 9% in top-level runners.[2 3] While it seems plausible that the incidence rate of Achilles tendon injuries is higher in athletes than within a more general population, only in 35% of the cases in our study was a relationship with sports activity described. Intrinsic risk factors such as body weight and insulin resistance might also play a role.[11] Although we could not assess information on body weight, the diagnosis of DM was available from the medical records. DM seemed more prevalent among the incident cases compared with the general Dutch population (table 2). However, more research is needed to draw any conclusions on a causative association The minor difference between the incidence and prevalence rate suggests that most patients only visit their GP once with their Achilles tendon problems. This might be because of a short duration of symptoms or that the patients go to a physiotherapist or sports physician afterwards. This cross-sectional study has some limitations, due to which the actual incidence of Achilles tendinopathy in the general population is probably higher than observed in this study. Firstly, not every person with a certain com-

plaint will visit a healthcare professional. In a cross-sectional population-based study, Picavet *et al.* reported that approximately 50% of the patients with musculoskeletal complaints visited a healthcare professional.[12] However, those with severe or persistent complaints will probably seek healthcare. Second, while most patients in the Dutch healthcare system will visit their GP before being referred to a therapist or specialist, since 2006 patients can visit a physiotherapist or sports physician without referral by a GP. It would be interesting to know the incidence rates of Achilles tendinopathy within the patient population of the Dutch physiotherapists and sports physicians as well, but since the denominators of these populations are unknown, no exact incidence rates could be obtained. Finally, because there is no specific registration code (ICPC) available for Achilles tendinopathy, GPs register this injury using other or more general codes. The search strategy "Achil" is considered to be highly sensitive for Achilles tendon problems; however, there is a possibility of missing some cases. Furthermore, the 13 patients less than 20 years old might have a growth-related disorder rather than mid-portion Achilles tendinopathy. In concordance with other studies,[4,13] most cases were encountered in the middle-aged population (age group 41–60 years). It is unclear why Achilles tendinopathy is more frequent within this age group. A possible explanation might be a higher incidence of degenerative tendons, susceptible to overuse, in the elderly.

CONCLUSION

In conclusion, this is the first study to report an incidence rate of Achilles tendinopathy in the general population. With an incidence of 1.85 per 1,000 registered patients, and of 2.35 in the adult population, more research on pathophysiology and therapy is warranted.

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Chapter 3

Comparison of postinjection protocols after intratendinous Achilles platelet-rich plasma injections: A cadaveric study

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J.A.N. Verhaar and C.N. van Dijk

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ABSTRACT

The purpose of the present investigation was to evaluate the distribution of intratendinous injected platelet-rich plasma (PRP) after 15 minutes of prone resting versus immediate manipulation simulating weightbearing. Ten cadaveric lower limbs were injected under ultrasound guidance with PRP dyed with India blue ink. The dyed PRP was injected into the mid-portion of the Achilles tendon, after which 5 specimens were placed in the prone position for 15 minutes (simulating rest) and the remaining 5 specimens were manipulated through100 cycles of ankle dorsiflexion and plantar flexion (simulating walking). Thereafter, the specimens were dissected, and the distribution of the India blue dye was ascertained. In the simulated rest group, every specimen showed dyed PRP in the Achilles tendon and in the space between the paratenon and tendon. The median craniocaudal spread of the PRP was 140 (range 125 to 190) mm. In 4 of the simulated rest tendons (80%), the distribution of PRP extended across the entire transverse plane width of the tendon. In the simulated motion group, every specimen showed dyed PRP extending across the entire transverse planewidth of the tendon and in the space between the paratenon and tendon. The median craniocaudal spread was 135 (range 115 to 117) mm. No statistically significant difference was found in the amount of craniocaudal spread between the simulated motion and rest groups. In conclusion, it does not appear to matter whether the ankle has been moved through its range of motion or maintained stationary during the first 15 minutes after PRP injection into the mid-portion of the Achilles tendon. The precise meaning of this information in the clinical realm remains to be discerned.

INTRODUCTION

The possible healing effect of platelet-rich plasma (PRP) on Achilles tendinopathy depends on the influence of the platelets on the damaged tenocytes and adequate delivery of the PRP at the lesion site.[1–5] A previous study has confirmed that PRP reaches the designated anatomic location after ultrasound-guided injection into and around the Achilles tendon (AT).[6] In addition to the role of the specific injection location, the postinjection protocol could be of importance.[6] Little is known about the distribution of the fluid after injection into the AT.[6] The PRP, injected at the desired location, might gradually disperse to other locations under the influence of gravity or ankle movement after injection. Different postinjection protocols have been described in clinical studies reporting on the effects of PRP in tendinopathy.[7–12] One postinjection protocol advocated immediate weightbearing. In contrast, others[7] have advised maintaining a prone position for at least 10 to 15 minutes after injection.[11,12] Finally, partial weightbearing for the first few days after the injection has also been recommended.[8-10] These considerable differences could cause variation in the clinical outcomes after PRP therapy for Achilles tendinopathy.[1,12] The primary purpose of the present study was to evaluate the effect of 2 different postinjection protocols after intratendinous, mid-portion AT PRP injection on the spread of PRP in and around the AT. We measured the spread of the PRP after simulated ankle motion and compared it with the spread after a 15-minute postinjection period of rest in a cadaveric model. Our secondary aim was to compare the results of our investigation with those described in a previously published report.[6]

MATERIALS AND METHODS

In the present cadaveric study, 10 lower limbs were injected with India blue-dyed PRP. The PRP was injected into the AT. The duration of each injection was timed, with the time starting as the radiologist (M.J.) received the syringe with dyed PRP and ending as the radiologist signaled the injection had finished. After injection, 5 limbs (50%) were placed in the prone position for 15 minutes. The other 5 (50%) were manipulated manually for 5 minutes through 100 cycles of ankle dorsiflexion and plantar flexion in an effort to simulate the motion associated with immediate weightbearing ambulation in the clinical setting. The specimens were randomly assigned in equal size groups using a computerized randomization program to either the simulated motion or rest group. Specifically, the postinjection cadaveric ankle was maximally dorsiflexed from the neutral position (foot at 90° to the leg) and maximally plantar flexed to the soft tissue end range of motion in each direction, with each excursion from the neutral position to maximum dorsiflexion and then to maximum plantar flexion and back to the neutral

position, accounting for 1 cycle. Thereafter, an orthopedic surgeon (G.K., C.D.) carefully dissected each specimen, and the presence of the dyed PRP was documented in regard to its gross anatomic distribution in and about the AT. Also, the extent of the spread from the site of the injection in the mid-portion of the AT was measured.

Specimen Demographics

The present study included 10 fresh frozen cadaveric lower limbs (4 [40%] male and 6 [60%] female specimens). The median age of the specimens was 74 (range 58 to 83) years. None of the specimens displayed evidence of previous surgery on any part of the extremity, and we did not have any information regarding any specific AT pathologic features. To be included in the present study, inspection of the cadaveric specimen had to reveal the absence of any apparent scarring in the AT region.

PRP Production, Coloring, and Injection Technique

For meaningful comparison with previous studies[6,13], we chose to use a PRP production, coloring (dyeing), and injection technique that has been previously described.[6] The PRP was prepared at the clinical chemistry laboratory of the Academic Medical Center (Amsterdam, The Netherlands). The process involved the use of 210 mL of donor citrate blood (0.0109 M), which was used to make 50 mL of PRP. The blood was retrieved using an open system without storing the whole blood, after which the blood was centrifuged at 180g for 15 minutes at 20 C (Rotina 46 RS Hettich Zentrifugen, Tuttlingen, Germany). After centrifuging, the PRP was removed using a pipette, and 1.25 mL of India blue dye was added to the 50-mL aliquot of PRP, binding directly with the plasma, enabling a thorough detection of PRP with the bound dye in the tissues after injection. The ankles were placed in the prone position (Fig. 1). The designated injection location was recorded before the injection. A medial approach to the mid-portion of the AT was used, because this is commonly used in clinical practice to avoid damage to the sural nerve. A Philips iU22 ultrasound machine with a 17.5-mHz transducer (Philips Healthcare, Philips Medical Systems, Eindhoven, The Netherlands), tuned to the musculoskeletal presetting, was used to visualize the tendon for accurate placement of the injection into the substance of the AT and to determine whether any of the specimens displayed a defect identifiable by ultrasonography. Each of the cadavers was injected intratendinously at the mid-portion level (2 to 6 cm proximal to the AT insertion into the calcaneus).[14] The injections were not specifically directed toward a tendon lesion, because hypoechogenicity (irregular or few internal echo patterns) of the AT was not found in any of the specimens. The total injection, consisting of 5 mL of dyed PRP, was administered in 3 separate portions of approximately 1.5 mL, placed approximately 1.5 cm apart using a peppering technique, as previously described for the in vivo treatment of Achilles tendinopathy.[7] The same 16-gauge needle and 5-mL syringe were used for each of the 3 injections, and the ul-

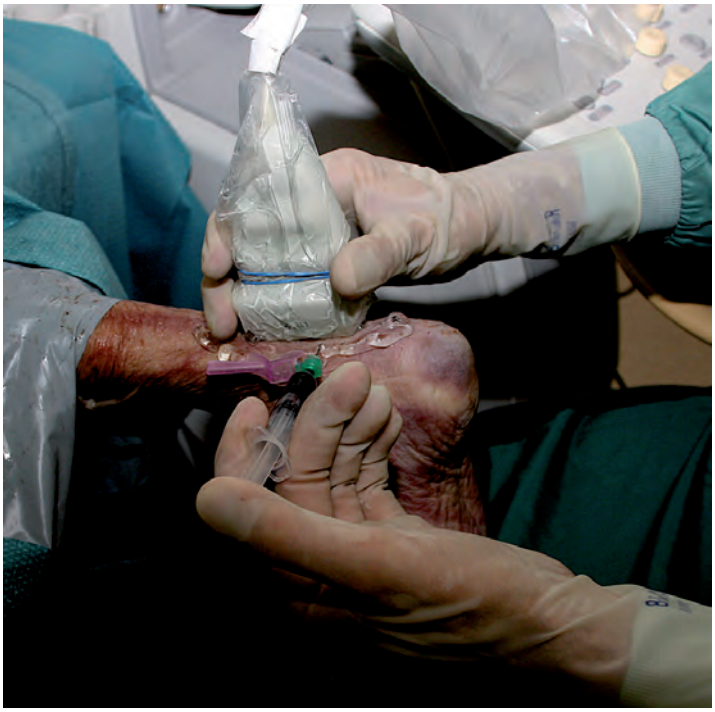

Figure 1: Placement of cadaveric ankles for injection procedure and location of ultrasound-guided injections.

trasound transducer was used to guide the transverse plane injection of the dyed PRP. After positioning the tip of the needle in the desired intratendinous location, the dyed PRP was injected. Thereafter, the specimen was either manipulated to simulate motion or allowed to rest in the prone position, similar to the clinical setting,[7] for 15 minutes.

Anatomic Dissection

Just as with the PRP production and injection technique, the anatomic dissection of the specimens was performed using a previously described technique.[6] The technique preserves the anatomic relationship among the paratenon, AT, and surrounding tissues during dissection (Fig. 2). The dissection entailed a longitudinal skin incision that extended from the distal margin of the gastrocnemius muscle to the calcaneal insertion of the AT (Fig. 3). The most proximal and most distal grossly visible extent was measured from the point of injection of the dyed PRP using a ruler and confirmed by 2 observers. To fully appreciate the spread of the dyed PRP, the AT was transected proximally, distally, and at the level of the injection point (Fig. 4).

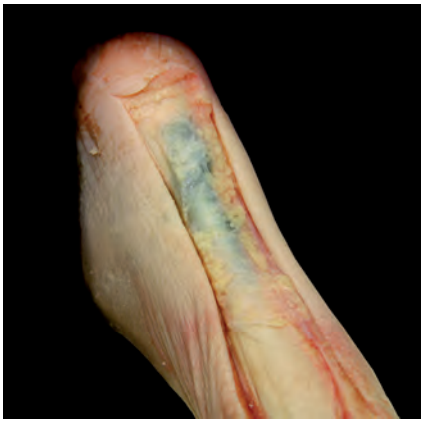

Figure 2: Anatomic dissection of the cadaveric lower leg showing infiltration of the Achilles tendon with India blue-dyed platelet-rich plasma.

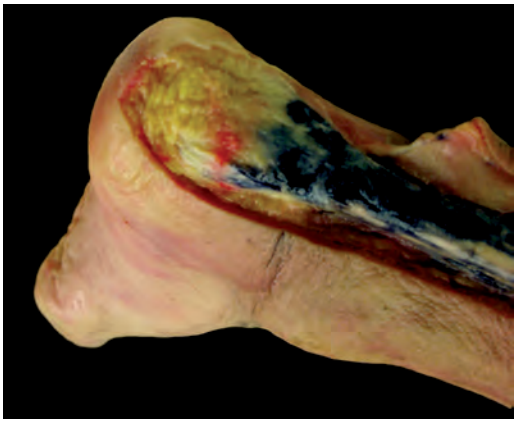

Figure 3: Anatomic dissection of the cadaveric lower leg showing infiltration of the Achilles tendon with India blue-dyed platelet-rich plasma spreading up to the insertion of the Achilles tendon onto the calcaneus.

RESULTS

A statistical description of the results is presented in Table 1. In the simulated rest group, the median duration of the injection of the dyed PRP was 111 (range 99 to 164) seconds. Moreover, in the rest group, the median craniocaudal gross visible spread of the dyed PRP after 15 minutes in the prone position was 140 (range 125 to 190) mm. All the specimens displayed dyed PRP in the AT at the tendon's insertion into the calcaneus and proximal to the mid-portion injection site and in the area between the paratenon and AT (Fig. 3). In 4 (80%) of the 5 tendons, the dyed PRP was distributed throughout the entire coronal plane of the AT (Fig. 4). Three of the tendons (60%) showed grossly visible traces of the dyed PRP in the pre-Achilles fat pad, and none of the tendons in the rest group showed infiltration of the dyed PRP into the plantaris tendon. In the simulated motion group, the median duration of the injection of the dyed PRP was 124 (range 99 to 131) seconds. Moreover, in the simulated motion group, the median craniocaudal gross visible spread of the dyed PRP after 100 cycles of dorsiflexion and plantar flexion motion was 135 (range 115 to 170) mm. In all 5 of these tendons, the dyed PRP was distributed throughout the entire coronal plane of the AT and in the area between the paratenon and AT. Four of the simulated motion tendons (80%) showed grossly visible traces of the dyed PRP in the pre-Achilles fat pad (Fig. 5), and none showed infiltration of the dyed PRP into the plantaris tendon.

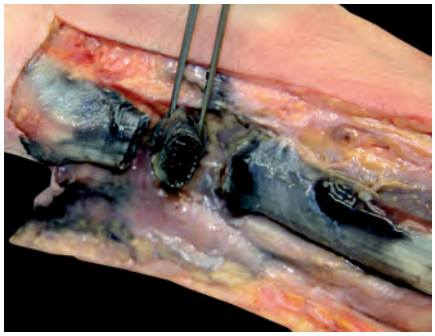

Figure 4: Anatomic dissection of the cadaveric lower leg showing infiltration of India blue-dyed platelet-rich plasma throughout the transverse plane of the Achilles tendon.

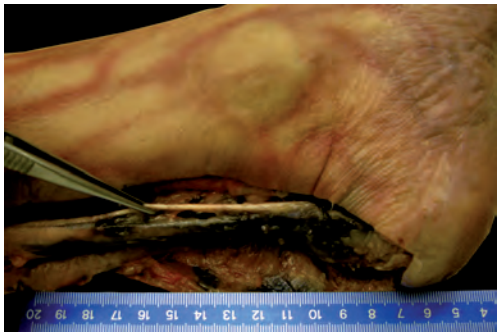

Figure 5: Anatomic dissection of the cadaveric lower leg showing infiltration of India blue-dyed platelet-rich plasma throughout the Achilles tendon. The plantaris tendon was not infiltrated with platelet-rich plasma because it has a separate tendon sheath. Note how the platelet-rich plasma spreads throughout the insertion of the Achilles tendon onto the calcaneus.

Table 1: Comparison of the results from simulated rest and manipulation groups after injection with India blue-dyed platelet-rich plasma (n = 10 cadaveric lower extremities).

Variable	Rest (n = 5)	Manipulation (n = 5)	Overall
Craniocaudal spread (cm)			
Median	140	135	145
Range	125 to 190	115 to 170	115 to 190
Dyed PRP between paratenon and AT	5 (100)	5 (100)	10 (100)
Dyed PRP evident in AT	5 (100)	5 (100)	10 (100)
Dyed PRP in plantaris tendon	0 (0)	0 (0)	0 (0)
Dyed PRP in pre-Achilles fat space	3 (60)	4 (80)	7 (70)
Duration of injection (s)			
Median	111	124	115
Range	99 to 164	99 to 131	99 to 164

Abbreviations: AT, Achilles tendon; PRP, platelet-rich plasma.

DISCUSSION

The present study evaluated the effect of 2 different postinjection protocols after injection of PRP, dyed with India ink, into the mid-portion of cadaveric ATs. In 1 group of ATs, motion was simulated using ankle 100 cycles of dorsiflexion and plantar flexion; in the other group, the specimen was maintained stationary in the prone position for 15 minutes before dissection and identification of the spread of the dyed PRP. Previous studies have evaluated the feasibility of fluid injections into and around different ankle

ligament and the feasibility and accuracy of PRP injections into and around the AT.[6,13] To our knowledge, this is the first study comparing postinjection protocols on the spread of PRP after intratendinous injection. As a consequence of this absence, the postinjection protocols have differed widely among therapeutic studies on the effect of PRP.[7,12] With the varying results from these studies and the accuracy of the injections in mind, the postinjection protocol could have significant influence on the outcomes of these studies.[4,7–9,12,15–19] Because most intratendinous injection methods are currently comparable, it would be interesting to examine the influence of the postinjection protocols on the outcomes of PRP injection. From the results of the present study, no relation seems to be present between a specific postinjection protocol and the spread of PRP. Hence, when extrapolating the results of our study to clinical scenarios, no benefit seems to exist for 1 compared with the other postinjection protocol. The clinical use of different postinjection protocols therefore remains debatable. Compared with direct dissection, a substantially more expanded spread of PRP was found with any postinjection protocol.[6] The direct dissection injections were placed identical to the injections used in the present study, with only the postinjection method as the variable. The different results are obvious. Wiegerinck *et al*.[6] published a craniocaudal spread of 95 mm directly after injection.[6] Compared with the current median of 135 mm in the simulated rest group and 140 mm in the simulated movement group, substantially expanded spread was noted. Although it might seem irrelevant and prone to bias to compare the spread of PRP directly after dissection (this was not a clinical situation), with any postinjection protocol, the findings were highly interesting. Also, from this comparison, one can conclude that PRP will spread further than was observed directly after the injection.[6] Hence, it might not be necessary to locate the PRP exactly at the location of the pathologic lesion, knowing the PRP will spread substantially throughout the entire AT (and its near surrounding tissue). One of the obvious limitations of the present study was the cadaveric setting in which our study was performed. Logically, the effect of blood flow, microcirculation, muscle pumps, and diffusion at the cellular level was not possible to test in the present study.[17,18] However, the results of our study have shown a large spread of PRP after injection. The spread seen in the present study would easily reach over the preferred designated location of the PRP to treat Achilles tendinopathy. When taking the possible beneficial effects of blood flow and muscle pumps into account, one can hypothesize that the in vitro spread would be even larger than that in the cadaveric setting.[17,18] We realize that our conclusions could be threatened by a number of methodologic shortcomings. As previously stated, we were not informed about any AT-related pathologic features of the limbs. However, the fresh frozen limbs were selected to not have any macroscopic scarring in the AT region, and no hypoechoic zones were observed during the ultrasound-guided injection. Another possible limitation with the use of any fresh frozen cadaveric specimens is contracture, specimen age, and method

of freezing and defrosting. This was countered by using the hospital's standard fresh frozen limb freezing and prolonged defrosting protocol. After dissection, we did not perform any histologic testing of the state of the AT. As mentioned, the results might be different in a noncadaveric setting. Also, the total group (power) of the present study was low (n ¼ 5 in each group). No proper statistical analyses could be performed with such a small group owing to the presence of a type 2 statistical error. A full analysis would suggest the proper power of the study, creating an unjustifiable suggestion that the results, regardless of their outcome, were based on proper power. The postinjection protocols used were chosen in accordance with results from previous clinical studies; however, postinjection placement in the patients differed substantially among the studies. Some have advised supine placement, which was not evaluated in our study; others have advised a prolonged prone position. The results of the present cadaveric study should not be used to represent these postinjection protocols. Furthermore, because these protocols have differed slightly or substantially, the effect of gravity should not be underestimated; this was not evaluated in the present study. Finally, the comparison with the previous study in this field was prone to bias because methodologic differences and interpretation could easily occur.[6] Additional evaluation of the spread of PRP could be of interest, because all current studies regarding this matter have been cadaveric. Future studies should thus focus on the evaluation of the spread of PRP in vivo. In conclusion, we found every AT to have been gradually infiltrated with PRP after mid-portion AT injection. No difference was found in the craniocaudal spread between 15 minutes of rest after injection and 100 manipulations after injection. The plantaris tendon was never infiltrated with PRP in either subgroup. Our findings showed no relation between the spread of PRP (both intratendinously and peritendinously) and a specific postinjection protocol after mid-portion AT PRP injection.

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Chapter 4

Relationship between neovascularization and clinical severity in Achilles tendinopathy in 556 paired measurements

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ABSTRACT

Neovascularization is frequently observed in tendinopathy. Previous studies have focused on the role of neovascularization in Achilles tendinopathy, but have been conducted in small series. It is still unclear whether the degree of neovascularization is related to severity of symptoms. The purpose was to study the relationship between ultrasonographic neovascularization and clinical severity in patients with Achilles tendinopathy. In this prospective cohort study, data on 127 patients (141 tendons) were assembled from databases of three clinical trials. All patients followed an eccentric exercise program. The Öhberg neovascularization score (0–4+) and Victorian Institute of Sports Assessment-Achilles (VISA-A) score (split into domains: pain, function and activity) were collected during baseline and follow-up. The relationship between neovascularization and VISA-A score was calculated. At baseline, 107 tendons (76%) showed some degree of neovascularization. In 556 coupled measurements, neovascularization was weakly related to the VISA-A score [Exp (B) 1.017, 95% confidence interval (CI), 1.007–1.026]. No significant relationship was found between neovascularization and the pain domain (P = 0.277) and the activity domain (P = 0.283), but there was between neovascularization and the function domain of the VISA-A score [Exp (B) = 1.067, 95% CI 1.018–1.119]. In conclusion, neovascularization in Achilles tendinopathy is weakly related to clinical severity, mainly based on the function domain of the VISA-A score.

INTRODUCTION

Although chronic Achilles tendinopathy is common in athletes and the sedentary, the exact pathologic mechanism is still unknown. Some suggest a disbalance in loading is important, other hypotheses are focused on excessive vessel and nerve ingrowth as a cause of the pain. Irrespective of the unknown etiology, Achilles tendinopathy is a clear clinical diagnosis based on a combination of pain, swelling, and impaired performance.[1]

A commonly used method to evaluate the severity of Achilles tendinopathy is the Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire. This patient-reported questionnaire provides a valid and reliable index of the clinical severity.[2] Like other validated questionnaires for musculoskeletal injuries, it covers three domains: pain, function, and activity.

The ingrowth of new blood vessels into tendinopathic areas of a tendon can often be seen on ultrasound. The assessment of the severity of neovascularization can be done reliably using the modified Öhberg scoring system.[3,4] Neovascularization, detected on the ultrasonographic images using power Doppler or color Doppler, is frequently thought to indicate the severity of Achilles tendinopathy.[3] It has frequently been hypothesized that neovascularization and the accompanying nerves are the source of pain in chronic midportion Achilles tendinopathy.[5] However, the results are conflicting and not all studies on the role of neovascularization have found this relationship. Some studies found neovascularization in only 47–88% of the symptomatic cases,[6-9] while others found neovascularization in all symptomatic tendons.[3,10-12]

Only a few studies have examined the relationship between neovascularization and pain or function in Achilles tendinopathy. Reiter *et al.* found a positive relationship between the presence of neovascularization and pain and restricted function in 20 patients,[8] but de Vos *et al.* found no relationship between degree of neovascularization and pain or VISA-A score.[9] Because of low patient numbers and variation between study protocols, the exact role of neovascularization is still unknown.[13]

This study had two aims. The first was to investigate the relationship between neovascularization and clinical severity parameter (VISA-A score) in a large database of three clinical trials. The second was to find out if baseline characteristics available in the databases used for this study, such as age and duration of symptoms influence the presence of neovascularization at baseline.

MATERIAL AND METHODS

Patients

In this cross-sectional study, data from three different clinical trials was used: two randomized controlled trials (RCT) and one observational prospective clinical trial.[9,14-19] All patients in these studies were clinically diagnosed with Achilles tendinopathy based on a painful swelling 2–7 cm proximal to the distal insertion (see Table 1). They were all treated with an eccentric training program, as described by Alfredson *et al.*[5] In two trials, an additional therapy was studied, the use of a night splint, which provides passive dorsal flexion or platelet-rich plasma injection.[14-18] The inclusion criteria were similar for all of the three studies and are listed in Table 1. Age, gender, height, weight, sports participation, and duration of symptoms were collected at baseline in all studies. At baseline and all follow-up moments the patients were asked to fill in the VISA-A questionnaire with minimal researcher assistance. The researcher was present when completing the questionnaire and the patient may possibly asked a question, but the researcher did not influence the patient. Besides, ultrasound Doppler was performed and evaluated

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Clinical diagnosis "chronic midportion Achilles tendinopathy": Painful swelling 2–7 cm proximal to the distal insertion	Clinical suspicion of other musculoskeletal injuries (insertional disorders or ruptures)
Age 18–70 years	Systemic illness
	Already performed heavy load eccentric exercises or inability to perform the exercises

during the examination by a blinded observer at baseline and all follow-up moments. One study had two follow-up moments: at 12 and 52 weeks.[14,15] The other studies[16-19] measured both outcomes at five different times: 6, 12, 24, and 52 weeks, and 2, 8, 16, and 24 weeks after baseline. All study protocols were approved by regional Medical Ethics Committee (MEC05-21, MEC08-041, and MEC05-100).

VISA-A score

The VISA-A questionnaire (0–100) consists of eight questions and provides a standardized measure of severity. The validation and reliability has been tested by Robinson *et al.*[2] After a literature research and interviews with patients and experts in the area of Achilles tendinopathy, a focus group stated that the questionnaire should include the three domains of pain, function in daily living and sporting activity. The pain domain (questions1–3), the function domain (questions 4–6) and the activity domain (questions 7 and 8) contribute equally to the total score. The worst possible score is 0 and the best

possible score is 30 for pain and function domain and 40 for the activity domain. The VISA-A questionnaire has a good test–retest reliability (r = 0.93).[2]

Ultrasonographic examination

Neovascularization was determined by Doppler ultrasonography of the Achilles tendon in both transversal and longitudinal planes and scored according to Öhberg[3] ranged from 0 to 4+. The examinations were performed by a musculoskeletal radiologist and two trained observers (R. D. V. and S. D. J.). On investigation, the neovascularization score was evaluated as 0 (no vessels visible), 1+ (one vessel mostly in the anterior part), 2+ (one or two vessels throughout the tendon), 3+ (three vessels through- out the tendon), and 4+ (more than three large vessels throughout the tendon). In one study,[14,15] ultrasound measurements at the first two appointments were obtained using a linear high-frequency 8–13-MHz transducer with a pulse repetition frequency of 868 Hz (Elegra; Siemens Medical Systems, Erlangen, Germany). At the latest follow-up a linear high-frequency 12–15-MHz transducer with a pulse repetition frequency of 500–1000 Hz (MyLab30) was used. Exactly the same device was used in the other two studies.[16-18]

Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 17.0 statistical software (SPSS Science Inc., Chicago, IL, USA) was used for the statistical analysis. Associations between different baseline parameters and presence of neovascularization at baseline were measured using a binary logistic regression model. To determine relationship between the presence of neovascularization and VISA-A scores and different domains of VISA-A scores a binary logistic regression model was also used. Adjustments were made for the variables that influenced the outcome with $P < 0.10$. Odds ratios [Exp(B)] were obtained. According to the Cohen's effect size criteria, an odds ratio of less than 1.50 was considered to be weak, an odds ratio of 1.50–4.30 was considered to be moderate, and an odds ratio above 4.30 was called strong. To compare different parameters, such as increase/decrease in neovascularization on improvement in VISA-A score over a short time period, changes in neovascularization and VISA-A score between baseline and the first follow-up directly after the 12–16 weeks eccentric exercise program were calculated. For the long-term period, changes in neovascularization and VISA-A score between baseline and the 1-year follow-up moment of the study were calculated. To calculate the prognostic value of all parameters in the short and longer terms, a repeated measurement general linear model was used. Statistical significance was assumed when P-values were less than 0.05.

RESULTS

Patients

Patients were included in the clinical trials between March 2005 and February 2009. One hundred forty-one tendons of 127 patients (57% female) were included. Mean age was 47.1 years [standard deviation (SD) 8.7] and mean body mass index (BMI) was 25.8 kg/m^2 (SD 3.6). 91% of the patients were active in sports, 41 patients (32%) at competitive level and 87 patients (68%) at recreational level. Mean VISA-A score was 49.0 (SD 18.5) and the median of the duration of symptoms was 38 weeks (interquartile range 24–88). The seven follow-up moments were at different time points ranging from 2 to 52 weeks after the baseline measurements (see Table 2). Eight VISA-A scores were missing because two patients were lost to follow-up (n = 7) and one patient failed to attend a follow-up moment (n = 1). Twenty-five neovascularization scores were lacking because of the two patients who were lost to follow-up (n = 7), repair of the sonographic machine (n = 5), and patients failing to attend the follow-up moment (n = 12). A total of 556 cases in which both VISA-A and modified Öhberg score were measured were collected in the database. In nine patients, the VISA-A questionnaire was not able to split the score into the different domains, because the hard copy questionnaires were not available.

Table 2: Overview of number of patients and tendons for each time point

	Time points (weeks)							
	0	**2**	**6**	**8**	**12**	**16**	**24**	**52**
Patients	127	25	53	25	102	25	78	102
Tendons	141	25	54	25	116	25	79	116
VISA-A questionnaires	141	24	54	23	116	22	77	116
Doppler analysis	141	23	54	23	111	22	77	105

VISA-A, Victorian Institute of Sports Assessment-Achilles.

Neovascularization at baseline

At baseline, 107 tendons (76%) showed some degree of neovascularization, whereas in 34 tendons (24%) no vascularization was found on Doppler ultrasonography. In a binary logistic regression model no significant associations were found between presence of neovascularization at baseline and age (P = 0.600), gender (P = 0.958), BMI (P = 0.123), sports participation (P = 0.708), and duration of symptoms (P = 0.622). Study type was considered as predictor for the primary outcome (P = 0.035), therefore adjustments were made for this parameter in all analyses.

Relationship between neovascularization and clinical outcome

All 556 coupled measurements are shown in Figure 1. Tendons without neovessels had a mean corresponding VISA-A score of 68.9 (SD 27.3) and tendons with neovessels had a corresponding VISA-A score of 59.1 (SD 23.0). With an Exp(B) of 1.017 (95% CI, 1.007–1.026) a statistically significant, but weak relationship between presence of neovascularization and VISA-A score was found in a binary logistic regression model ($P < 0.001$). Figure 2 shows the mean scores of the different domains (pain, function, and activity) in patients with and without neovascularization. A significant relationship was found between the functional domain of the VISA-A score and neovascularization score ($P = 0.007$). However, the regression coefficient Exp(B) of 1.067 (95% CI 1.018–1.119) indicates that the relationship is weak. No statistically significant relationships were found between the VISA-A pain domain and neovascularization score ($P = 0.277$) or between the activity domain of the VISA-A score and neovascularization score ($P = 0.283$).

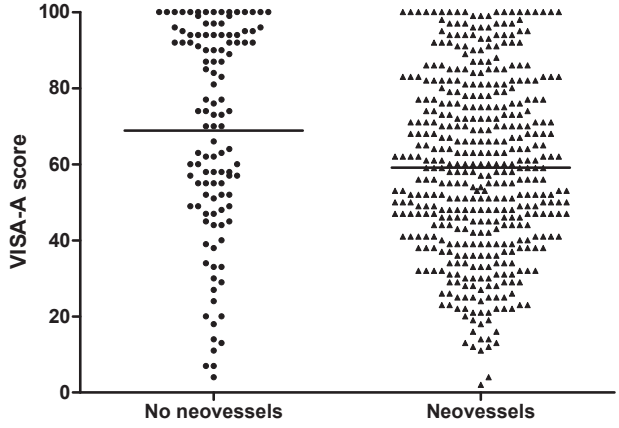

Figure 1: Individual Victorian Institute of Sports Assessment-Achilles (VISA-A) scores in patients with and without neovessels at different time points during the studies. The lines indicate the mean VISA-A scores of the groups. Patients without neovessels had a mean VISA-A score of 68.9 and patients with neovessels had a mean VISA-A score of 59.1.

Prognostic value of neovascularization

Short- (12–16-week follow-up) and long-term (1-year follow-up) improvements in VISA-A score within groups with (grades 1–4) and without neovascularization (grade 0) at baseline are shown in Figure 3. In a general linear model, only the baseline VISA-A score significantly influenced the short- and long-term improvement in VISA-A score ($P < 0.001$). A higher VISA-A score at baseline resulted in less improvement in VISA-A score. A longer duration of symptoms resulted in less improvement of the VISA-A score in the longer term, this influence was significant ($P = 0.037$).

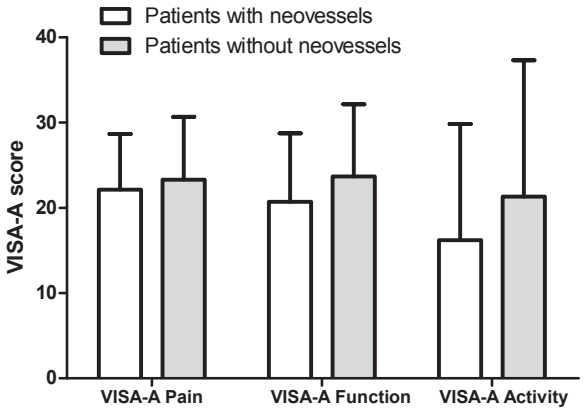

Figure 2: Mean Victorian Institute of Sports Assessment-Achilles (VISA-A) scores in patients with some degree of neovascularization (white bars) compared with patients without neovascularization (grey bars) for the three different VISA-A domains of pain, function, and activity. Error bars denote standard deviation (SD). The functional domain differed significantly between patients with and without neovessels ($P = 0.007$). No statistically significant differences were found for the pain domain and the activity domain of the VISA-A score.

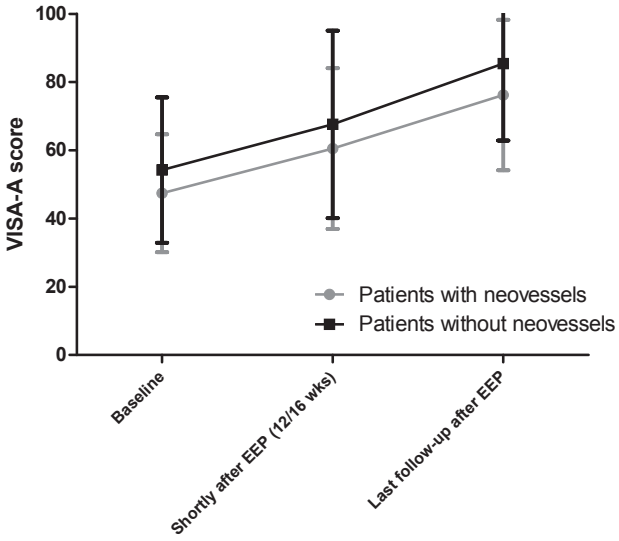

Figure 3: Short- and long-term changes in Victorian Institute of Sports Assessment-Achilles (VISA-A) score in patients with and without neovessels at baseline. Presence of neovascularization at baseline did not influence the short-term improvement significantly ($P = 0.337$) neither the long-term improvement ($P = 0.865$). The last follow-up after eccentric exercise program (EEP) ranged from 24 weeks to 1 year.

DISCUSSION

This is the first study analyzing the clinical significance of neovascularization in Achilles tendinopathy in more than 500 paired measurements. Approximately, a quarter of the symptomatic patients showed no degree of neovascularization. A weak relationship between the neovascularization score and VISA-A score was found. A relationship between the VISA-A domain of function could be identified, but not with the VISA-A domains of pain and activity. The fact that no relationship with the pain domain (first three questions) could be found, seems to contradict with the frequently cited hypothesis that the source of pain in chronic midportion Achilles tendinosis is related to the ingrowth of neovessels and accompanying nerves.[20] Many studies have been done on the presence of neovascularization in tendinopathy, but unfortunately with inadequate numbers of patients. Whereas some research groups have reported neovascularization in all symptomatic patients ,[3,10-12] other study groups have shown that only 47–88% of the symptomatic patients had some degree of neovascularization.[6-9] For the presence of neovascularization in other types of tendinopathy, like patellar tendinopathy and plantar fasciitis, even less evidence is available.[21-23] A possible reason for the deviations in results is the positive effect of activity prior to the measurement on the Doppler flow[24] who showed that neovascularization may be a physical response to activity. However, Mahieu *et al.*[25] could not demonstrate this relation in their study, and in another study a decrease in neovascularization was found after short activity.[26] In the present study the patients were not instructed to do or avoid exercises prior to the ultrasound measurement and all measurements were performed at physical rest. It is hypothesized that healthy tendons contain physiologically slow blood flow that cannot be detected with Power Doppler or Color Doppler techniques, but the threshold for detectable flow in tendons is still unknown.[23,27] Zanetti *et al.*[7] studied the relationship between clinical severity and neovascularization in 40 patients with Achilles tendinopathy and found no significant difference in VAS pain score between patients with and without neovascularization. Reiter *et al.*[8] concluded that patients with detected blood flow had a significantly lower VISA-A score than those without blood flow. This is in accordance with our finding that the VISA-A score was higher in patients without neovessels, although the relationship between VISA-A score and neovascularization score was only weak in our study. This weak relationship was mainly based on the relationship between the functional domain of the VISA-A score and neovascularization score. No significant relationships were found for the pain domain or activity domain of the VISA-A score. Although the questionnaire was designed based on these three domains, one may wonder to what extent the domains influence each other. In the present study, a decrease in neovascularization did not result in an increase in VISA-A score on either short- and long-term outcomes after the treatment. Comparable results have been published by others.[7,9]

Whereas some therapies destroy the neovessels with irritant solutions it is also known from the literature that neovascularization is a critical phase in physiological tendon healing after trauma.[28,29] Power Doppler ultrasonography is unable to distinguish between the pathological neovascularization and neovessels necessary in the healing response. The strength of this study was the large pooled database, but there were also some limitations. Although the inclusion criteria in the three studies we combined were more or less the same (see Table 1), there may have been some small differences between the study populations. The most important difference may be the fact that the patients do not have the same amount of sporting activities. Besides, the additional therapies next to the eccentric exercise program differed between the studies. In our analyses we therefore corrected for type of study. Additional analyses with adjustments for parameters that influenced the primary outcome with $P < 0.20$ (BMI) did not change the conclusions of our study. The study might have lost power by dichotomizing the primary outcome (neovascularization); however, because of ordinal scale, it was judged that this was a more valid choice than assessing using linear techniques. The methods used to examine neovascularization in the studies were either color Doppler ultrasound or power Doppler ultrasound, both of which have been shown to be equally effective in detecting neovascularization.[8] Although different observers scored the degree of neovascularization during the studies, Sengkerij *et al.*[4] reported that the technique used, the modified Öhberg scoring system (intraclass correlation coefficient 0.85), has an excellent interobserver reliability for scoring neovascularization in patients with midportion Achilles tendinopathy.[4]

PERSPECTIVES

The absence of either a positive or a negative role of neovascularization in tendinopathy implies there is a discrepancy between imaging and the clinical picture. Although neovascularization can be scored very reliably,[4] the interpretation of this outcome with respect to patient-related outcomes is lacking. This may explain the recently published inferior results of sclerosing neovessels[22,30] compared with earlier trials.[11,12] Our results are in line with the current concept that neovessels should not be the only target for treatment of Achilles tendinopathy.[32,33]

CONCLUSION

This study showed that neovascularization was not present in 24% of chronic symptomatic Achilles tendons. A longer duration of symptoms was not related to presence

of neovascularization. The weak relationship between neovascularization and clinical outcome (VISA-A score) is based on the relationship with the function domain of the questionnaire. For the other domains, pain and activity of the VISA-A questionnaire, no relationship between neovascularization and the domain was found. A decrease in neovascularization over time during the study was not related with a better improvement in the VISA-A score. Based on this study, with over 500 paired measurements, there is no relation- ship between the amount of pain and degree of neovascularization. A longer duration of symptoms at baseline was associated with less improvement of complaints after the treatment.

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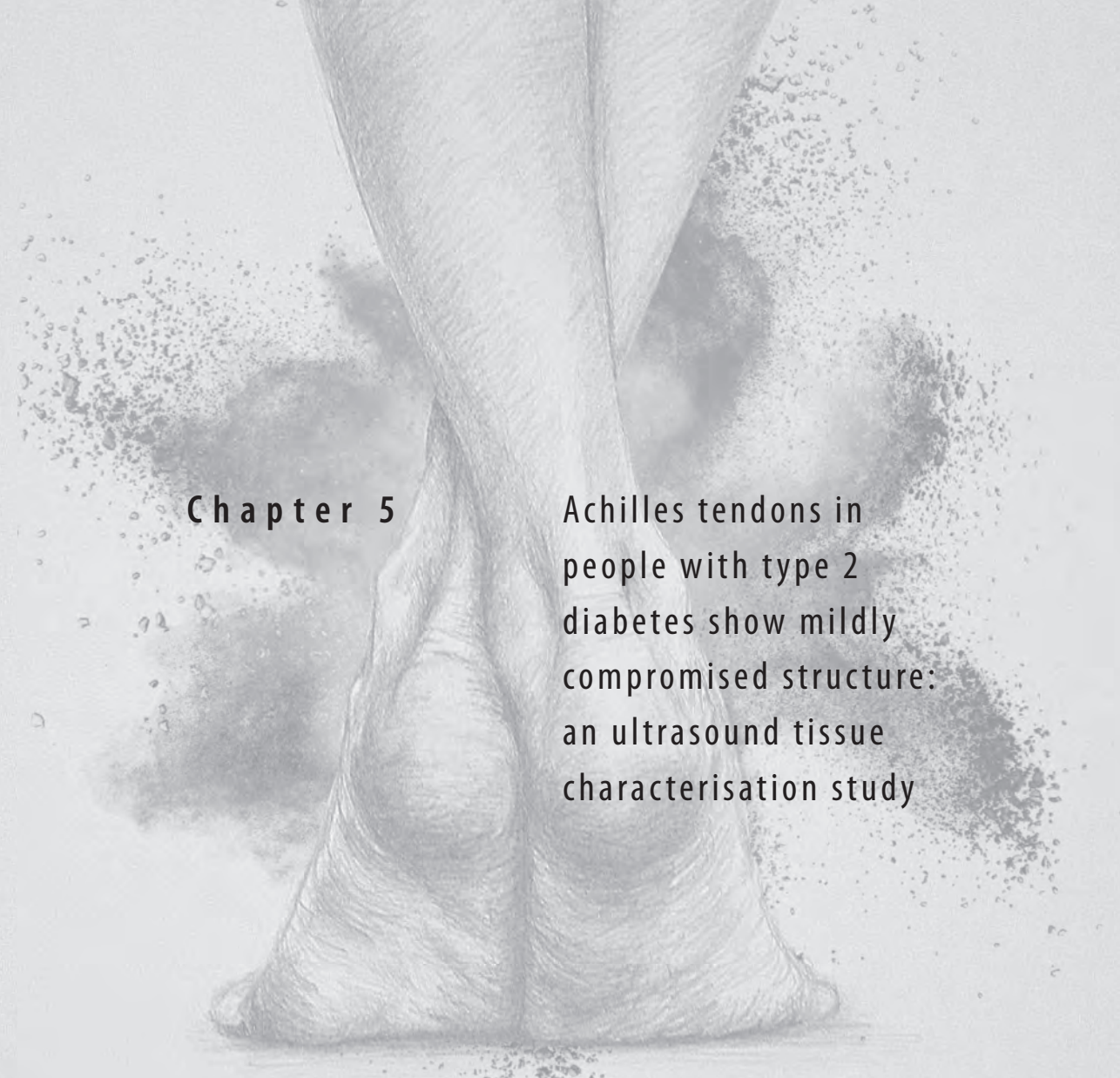

Chapter 5

Achilles tendons in people with type 2 diabetes show mildly compromised structure: an ultrasound tissue characterisation study

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ABSTRACT

Background: Musculotendinous overuse injuries are prevalent in people with type 2 diabetes. Non-enzymatic glycosylation of collagen resulting in tendon stiffening may play a role. In this case–control study we determined whether patients with diabetes had poorer ultrasonographic structure in their Achilles tendons compared to age-matched controls.

Methods: People with type 1 diabetes or type 2 diabetes, and age-matched controls, had computerised ultrasound tissue characterisation of both Achilles tendons. In contiguous ultrasonographic images of the tendon, echopatterns were quantified and categorised into four echo-types. Tendon abnormality was quantified as sum of echo-types III+IV. Furthermore, skin autofluorescence (AF) of the forearm (AF-value) was gathered.

Results: Twenty four type 2 diabetes patients, 24 controls, 24 type 1 diabetes patients and 20 controls were included. AF-value was higher in type 1 diabetes (1.55±0.17) than in their controls (1.39±0.18, $p<0.001$) and in type 2 diabetes (2.28±0.38) compared to their controls (1.84±0.32, $p<0.001$) Achilles tendons of type 2 diabetes patients contained more echo-types III+IV (14.1±7.9%) than matched controls (8.0±5.4%, $p<0.001$). There was a trend towards a difference in echo-types III+IV between type 1 diabetes patients (9.5±5.3%) and their controls (6.5±3.7%, $p=0.055$). In a stepwise linear regression analysis, body mass index (BMI) was moderately associated with tendon abnormality in patients with diabetes and controls ($\beta=0.393$, $p<0.001$).

Conclusions: Type 2, and possibly type 1, diabetes patients showed poorer ultrasonographic Achilles tendon structure that may be a risk factor for tendinopathy. Although markers for accumulation of advanced glycation end products were elevated in both diabetes populations, only BMI was associated with these abnormalities.

Trial registration number NTR2209.

INTRODUCTION

Exercise is a cornerstone in the treatment of type 2 diabetes mellitus. However, patients with diabetes are vulnerable to overuse injuries.[1-4] Although not significant, diabetes seemed more prevalent in people with Achilles tendinopathy than in asymptomatic people.[5] These injuries may be due to overload because of obesity or altered moving patterns due to motor-sensory neuropathy, but tendons might also be directly affected by hyperglycaemia.[6] Previous research shows that people with type 2 diabetes have thicker tendons[7–9] and an increased level of ultrasonographic tendon disorganisation.[10–12] Craig *et al.*[13] reported an association between plantar fascia thickness and complications in type 1 diabetes. Unfortunately, these studies were hampered by the fact that standard two-dimensional ultrasonography does not quantify tendon structure. Although Movinetal[14] showed that hypoechoic areas seen on ultrasonography corresponded to histological collagen degeneration, a recent rodent study indicated that experimental induced diabetes resulted in structural, inflammatory and vascular changes in the Achilles tendon.[15] Hyperglycaemia itself may also increase expression of matrix metalloproteinase-9 and metalloproteinase-13 in tendon cells and impair collagen synthesis.[16] Nevertheless, the pathomechanics behind tendon degeneration in either type 1 or type 2 diabetes is most likely multifactorial and still largely unknown.[12,17] It can be hypothesised that the accumulation of non-enzymatic advanced glycation end products (AGEs) in the connective tissues cause tendon overuse injuries and increased matrix disorganisation.[18] AGEs are the result of non-enzymatic glycosylation of proteins, induced by diabetes-related hyperglycaemia and hyperlipidaemia. AGEs create cross-links with short and long-lived proteins, and the formation of AGEs is one of the pathophysiological mechanisms that links hyperglycaemia and hyperlipidaemia to microvascular and macrovascular pathology. Since AGEs also form cross-links with collagen they might explain the predisposition to tendinopathy in people with diabetes.[19] An autopsy study showed significantly higher levels of non-enzymatically bound glucose in tendons and other tissues of patients with type 2 diabetes.[20] A validated non-invasive technique to estimate the level of glycated collagen in the skin is autofluorescence (AF).[21] AGE levels based on skin biopsies[22] and the skin AF measurement have been shown to be independent predictors for both the severity of long-term hyperglycaemia as well as the development of microvascular[23] and macrovascular[22] complications and cardiac death in type 1 diabetes and type 2 diabetes.[24] Ultrasound tissue characterisation (UTC) was developed in equine tendons to detect and quantify more subtle tendon structural changes.[25,26] In contiguous ultrasonographic images, dedicated algorithms quantified three-dimensional (3D)-stability of echo-patterns. Four echo-types can be discriminated: (I) intact and aligned tendon bundles; (II) discontinuous or waving tendon bundles; (III) fibrillar tissue; (IV) amorphous tissue with mainly cellular components and fluid. Greater

levels of echo-types III+IV suggest poorer tendon structure. In previous human research symptomatic tendons showed significantly more echo-types III+IV than asymptomatic tendons.[27] The primary aim of this study was to compare Achilles tendon structure in type 1 diabetes and type 2 diabetes patients with healthy age-matched controls. The secondary study aim was to correlate skin AF as a general indicator of AGEs with Achilles tendon structure. Furthermore, we investigated if age, body mass index (BMI), duration of diabetes, sports activity and glycated haemoglobin (HbA1c) levels were associated with Achilles tendon structure.

METHODS

Patients

Patients and age-matched control participants were recruited in outpatient departments at the Erasmus MC University Medical Center in Rotterdam, The Netherlands, and a national expert centre for diabetes care (Diabeter, Rotterdam, the Netherlands). Inclusion criteria for the case group were type 1 diabetes (aged between 18 and 30 years) or type 2 diabetes (aged 35–60 years) diagnosed according to the WHO criteria. People with Achilles tendon pain and participants whose ultrasound scan was of poor quality were excluded. A written informed consent was obtained from all participants before participation in the study, approved by the ethical committee of the Erasmus University Medical Center in Rotterdam and listed in the Dutch Trial Register (number NTR2209).

Study measurements

Weight and height were measured to calculate the BMI. All participants recorded current sports and exercise activities (hours/week). Fasting venous blood samples were collected in a sodium fluoride tube and EDTA tube to, respectively, measure fasting glucose by a clinical chemistry analyser (Modular P Module, Roche Diagnostics, Almere, the Netherlands) and blood HbA1c content through high-performance liquid chromatography (ADAMS A1c HA-8160 analyser, Arkray Europe B.V., Amstelveen, the Netherlands).

Activity monitor

The participants received a preprogrammed accelerometer (GT1M; ActiGraph, LLC, Pensacola, Florida, USA) and wore it on the right hip for seven consecutive days while awake and not in the water. The activity levels assessed by the accelerometer are presented as mean counts per day.

Skin AF

Forearm skin AF was measured using the AGE-Reader (DiagnOptics Technologies BV, Groningen, the Netherlands). The AGE-Reader is a desktop device that uses the characteristic fluorescent properties of glycated collagen to estimate the level of AGE accumulation in the skin.[24] The measurement is automated and obtained by placing the forearm on the device. Three measurements were taken and the mean AF-score of the three measurements was used in the analyses.

Ultrasound tissue characterisation

Tendon integrity was evaluated quantitatively by one of two experienced examiners (HTMvS and SdJ) with the use of UTC (UTC2000, UTC imaging, Stein, the Netherlands). Participants were laying prone on an examination table with their feet hanging over the edge and with the ankle in approximately 5–10° dorsiflexion, to slightly pretension the Achilles tendon. A 10MHz linear-array transducer (Smartprobe 10L5, Terason 2000, Teratech, USA) was moved automatically along and perpendicular to the Achilles tendon's long axis by means of a motor-drive. Transverse images were collected at regular distances of 0.2 mm and a 3D data block was reconstructed. The following UTC setting was used; Window Size=9. The stability of the echo pattern over contiguous images was analysed by means of custom-designed algorithms (UTC 2010 UTC imaging, http://www.utcimaging.com) resulting in discrimination of four echo-types. Previous research has shown that these echotypes are highly correlated to histomorphology of tendon tissue at various stages of integrity. Echotypes I and II represent more or less organised (secondary) tendon bundles. Echotypes III represent smaller, disorganised and more fibrillar tissue. Echotypes IV represent amorphous tissue.[27] By one blinded researcher (SdJ), a point 4 cm from calcaneal insertion was determined in the sagittal plane. The tendon border was outlined at five equally spaced points from 3 to 5 cm proximal to the calcaneal insertion. The five outlines were interpolated to create a tendon volume of 2 cm length, making the region of interest for analysis. Proportions of the four echo-types were calculated within this volume. The sum of echo-types III and IV, representing poorer tendon structure, was used for statistical analyses. The interobserver reliability of this method appeared to be excellent with an intraclass correlation coefficient (ICC) of 0.89 and a mean difference of 0.9% in the sum of echo-types III+IV.[28]

Statistical analysis

Statistical analyses were performed using statistical software (PASW V.19.0). Values are presented as mean±SD for normally distributed parameters. For non-parametric parameters median and IQR are given. Differences in echo-types III+IV, AGE value and non-parametric baseline characteristics between the groups were tested using the Mann-Whitney U test. For differences in parametric baseline characteristics the unpaired

t test was used. To calculate the association between the parameters age, BMI, AF-score, duration of diabetes, hours of sports participation, blood HbA1c level and tendon structure, a stepwise linear regression analysis was used. Standardised regression coefficients (β) were given. A $p<0.05$ level was chosen to indicate statistical significance.

RESULTS

Sixty two people with diabetes and 58 age-matched controls were screened for eligibility and resulted in 102 participants who met the inclusion criteria (figure 1). Ten people were excluded because of abnormal blood results (n=3), presence of Achilles tendon pain (n=3) or technical failure of ultrasound (n=4). Those with type 2 diabetes had a significantly higher BMI than their controls (table 1). Fewer people with type 1 diabetes were active in sports (75%), compared to their controls (95%). The self-reported hours of sport participation was significantly higher in the controls compared to the patients with diabetes.

Table 1: Baseline characteristics

	Type 1 diabetes	Controls		Type 2 diabetes	Controls	
	n=24	n=20	p Value	n=24	n=24	p Value
Age (years) mean (SD)	23.3 (3.2)	24.2 (2.7)	0.386	49.6 (7.9)	46.6 (6.0)	0.114
Gender (% male)	37.5	45.0	0.760	62.5	54.2	0.770
Duration of diabetes (years) median (IQR)	12 (18)	NA		6.8 (7.5)	NA	
BMI (kg/m^2) mean (SD)	24.6 (2.8)	23.3 (2.6)	0.124	31.7 (5.0)	26.4 (4.5)	<0.001
HbA1c (mmol/mol) median (IQR)	59.5 (11)	32.5 (2)	<0.001	50 (16)	35 (5)	<0.001
Hours sports/week* median (IQR)	2.5 (4)	5 (8)	0.018	1 (3)	3 (4)	0.029
PA ($\times 10^6$ counts/day)† median (IQR)	1.47 (0.84)	1.84 (0.99)	0.133	1.68 (1.47)	2.01 (1.52)	0.218
AF-score (AU)‡ mean (SD)	1.54 (0.16)	1.38 (0.19)	0.008	2.31 (0.40)	1.85 0.31)	<0.001

*Hours sports/week: self-reported estimate of weekly hours participating in sports activities. †PA: objectively determined physical activity level (in counts per day) based on seven-day activity monitoring. ‡AF-score: average skin autofluorescence score based on three AGE-reader measurements of forearm. AGE, advanced glycation end products; AF, autofluorescence; AU, arbitrary units; BMI, body mass index; HbA1c, glycated haemoglobin; PA, physical activity.

Skin AF measurement

Mean AF-score for the type 1 diabetes group was 1.54 (0.16), which is 111% (12.0) of the predicted value for equally aged healthy individuals using the Koetsier *et al.*[21] regression model. The control group for type 1 diabetes had a mean AF-score of 1.38 (0.19): 98% (13.8) of predicted value. This was significantly lower than the patients with type 1

diabetes (p=0.008). The AF score of the type 2 diabetes patients was 2.31 (0.40), 114% (16.8) of the predicted value for healthy individuals. Their controls had significant lower value of 1.85 (0.31), which is 95% (16.1) of predicted value, p<0.001).

Ultrasound tissue characterisation

Tendons of people with type 1 diabetes contained 9.5% (5.3) echo-types III+IV (table 2). The tendons of matched controls contained 6.5% (3.7) echo-types III+IV (p=0.055). People with type 2 diabetes and matched controls had, respectively, 14.1% (7.9) and 8.0% (5.4) echo-types III+IV (p<0.001). In a stepwise multiple regression analysis BMI (β=0.393, p<0.001) and presence of diabetes (β=0.234, p=0.024) was associated with poorer tendon structure (echo-types III+IV). HbA1c (β=0.095, p=0.549), age (β=0.070, p=0.516), hours of sports participation (β=0.047, p=0.653) and AF score (β=0.003, p=0.978) did not contribute significantly to the model. In a subanalysis on the predictive value of diabetes-associated parameters in the patients with diabetes, only BMI was associated with Achilles tendon structure. Duration of diabetes (β=−0.013, p=0.933), HbA1c (β=−0.055, p=0.715) and AF score (β=0.075, p=0.683) did not contribute to the regression model.

Table 2: Mean proportions of four echo-types measured with UTC

	Type 1 diabetes	Controls		Type 2 diabetes	Controls	
	n=24	n=20	p Value	n=24	n=24	p Value
Echo-type I	65.0 (6.9)	68.9 (5.4)	0.032	64.0 (6.4)	76.4 (7.8)	0.018
Echo-type II	25.6 (3.3)	24.8 (3.1)	0.408	22.1 (4.0)	24.6 (4.2)	0.081
Echo-type III	6.1 (3.7)	4.1 (2.3)	0.058	7.0 (3.6)	4.9 (3.9)	0.012
Echo-type IV	3.4 (1.7)	2.4 (1.6)	0.058	7.1 (4.6)	3.0 (1.8)	0.001
Echo-types III+IV*	9.5 (5.3)	6.5 (3.7)	0.055	14.1 (7.9)	8.0 (5.4)	<0.001

*Echotypes III and IV represent poorer tendon structure. UTC, ultrasound tissue characterisation.

DISCUSSION

This study shows that asymptomatic Achilles tendons of people with type 2 diabetes had worse structure than age-matched controls. The observed difference in tendon disorganisation between type 1 diabetes patients and healthy matched controls did not reach statistical significance and requires replication. Nevertheless, it is an interesting finding that can be regarded as a hint that the hyperglycaemic state in young, but otherwise healthy, type 1 diabetes patients may lead to an impaired Achilles tendon structure. These ultrasonographic tendon structure irregularities suggest tendon disintegration, which may lead to clinical symptoms of tendinopathy.[25-27] This finding might explain previous study results showing tendinomuscular overuse injury as a frequent

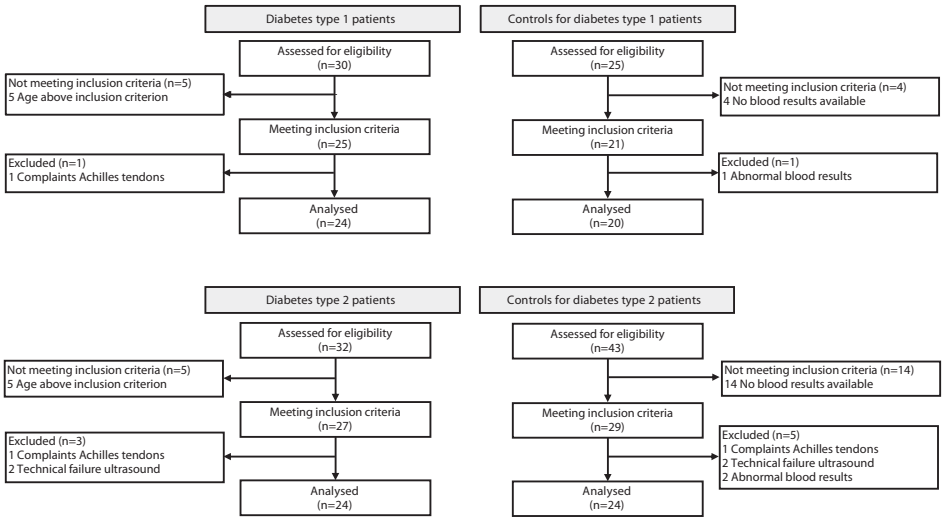

Figure 1: Flow chart.

cause for early termination of exercise programmes in type 2 diabetes.[29,30] In accordance, our study results extend on a recent qualitative ultrasound study by Abate *et al.*[12] and are consistent with epidemiological data providing a hint that diabetes mellitus is more prevalent in patients with Achilles tendinopathy than in asymptomatic persons.[5] We are not sure whether the ultrasonographic differences between diabetes and control groups are caused by measurement errors. Nevertheless, our cross-sectional comparison suggests that overweight and obese patients with diabetes participating in weightbearing exercise, should be controlled regularly on Achilles tendon pain or stiffness to avoid premature drop-out due to Achilles tendinopathy. Since we only measured asymptomatic people, we can only speculate at which level of echo-type III and IV asymptomatic people with type 1 or type 2 diabetes may develop or experience tendon pain or stiffness. Furthermore, the observed difference in echo-types III+IV between people with type 1 diabetes and their aged-matched controls was only borderline significant. Owing to limited power, a type 2 statistical error cannot be excluded. Therefore, our findings in people with type 1 diabetes should be taken cautiously and warrant further investigations.

At this stage, we can only speculate on the underlying causal relation between diabetes and the observed ultrasonographic tendon irregularities in our asymptomatic populations. In the present study, BMI shows the strongest association with poorer ultrasonographic tendon structure (echo-types III+IV). The group with patients with type 1 diabetes had a mean BMI in the healthy 20–25 kg/m^2 range. This may partly explain the borderline association with an increased percentage of ultrasonographic tendon abnormalities, as BMI has been shown to be an important risk factor for tendinopathy in

previous research.[31] However, its association with ultrasonographic tendon disintegration was not examined previously. The deleterious effect of BMI on tendon disintegration could be mediated by increased mechanical loading, suggesting that not only body weight, but also increased physical activity might be associated with ultrasonographic tendon abnormalities. However, our results could not confirm an association or interaction between objectively determined physical activity level, body weight and ultrasonographic tendon structure irregularities. In a previous publication, Gaida *et al.*[32] have suggested that cytokines released by visceral fat may play a role in the pathogenesis of tendinopathy. In addition, they noted that a large proportion of their tendinopathy population have signs of metabolic obesity with a normal weight.[32] Since we excluded participants with clinical tendinopathy, the present study design is not well suited to study the long-term effects of metabolic syndrome on Achilles tendon complaints. Nevertheless, our results do support the notion that biomarkers for hyperlipidaemia, insulin resistance and visceral fat deposition should be integrated in future studies on diabetes and tendinopathy risk.[31]

Although presence of diabetes was associated with poorer tendon structure on ultrasound, diabetes associated parameters, like duration of diabetes, HbA1c and skin AF, lack to clarify an association with percentage of ultrasonographic tendon abnormalities. Hyperglycaemia could be a determinant for ultrasonographic tendon structure abnormalities, but our study does not support the hypothesis that skin AF predicts tendon disintegration.[33,34] The lack of a significant association does not exclude a role of AGEs in tendon pathology, since skin AF has not been validated as a predictor of AGE accumulation in the tendon. Skin AF is an indicator of general glycation products and known to predict the severity of long-term hyperglycaemia in diabetes. [22,23] The higher levels of non-enzymatically bound glucose found in tendons of patients with diabetes in an autopsy study[20] suggest there is a missing link between skin measured AGEs and AGEs in tendons. Different ex vivo studies demonstrated that elevated glycation caused increased tendon stiffness.[35,36] Possibly this is caused by supraphysiological concentrations of AGE forming metabolites such as methylglyoxal and ribose. Also, other factors like pentosidine concentration or altered gait might play a role. Abate *et al.*[17] concluded in their review that many complex pathogenetic mechanisms are involved in rheumatological manifestations of diabetes.

One limitation to this study was that, in terms of BMI, our diabetes patients were not perfectly matched with the controls. It was particularly difficult to find controls for type 2 diabetes patients with an equal BMI. Possibly the metabolic syndrome is a risk factor on itself and should not be split up. Type 1 diabetes patients were recruited from a national expert centre for diabetes care and can be considered a random sample. We cannot be certain that the type 2 diabetes patients represent a random sample. Although patients were referred by general practitioners and medical specialists and presence of diabetes

related diseases was comparable with the prevalence in diabetes type 2 patients in the Netherlands, patients were not specifically tested for diabetic polyneuropathy. Nevertheless, clinical polyneuropathy was documented in none of the available medical files and was also not reported by the patients.

This study noticed that people with type 2 diabetes have poorer tendon structure measured with ultrasound which may make them vulnerable for tendon overuse injuries. For a good outcome of exercise programmes it is necessary to reduce the risk of myotendinous overuse injuries in patients with type 2 diabetes. It might be advisable to implement an adapted exercise protocol for the patients at risk for tendinopathy.[29] However, more research is needed to identify these risk factors.

CONCLUSION

This study showed that people with type 2, and potentially also type 1 diabetes, have compromised structure of the mid-portion of the Achilles tendon. Although diabetes patients have elevated AGE skin AF scores compared with their controls, the difference in ultrasonographic tendon disintegration seems to be based mainly on the BMI.

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Chapter 6.1

One-year follow-up of a randomised controlled trial on added splinting to eccentric exercises in chronic midportion Achilles tendinopathy

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ABSTRACT

Objective: The study examined whether the addition of a night splint to eccentric exercises is beneficial for functional outcome in chronic midportion Achilles tendinopathy.

Design: One-year follow-up of a randomised controlled single blinded clinical trial.

Setting: Sports medicine department in a general hospital.

Patients: 58 patients (70 tendons) were included.

Interventions: All patients completed a 12-week heavy load eccentric training programme. One group received a night splint in addition to eccentric exercises.

Main outcome measurements: Outcome scores were: Victorian Institute of Sport Assessment-Achilles (VISA- A) score, subjective patient satisfaction and neovascularisation score measured with power Doppler ultrasonography (PDU).

Results: For both groups the VISA-A score increased significantly (from 50 to 76 ($p<0.01$) in the eccentric group and from 49 to 78 ($p<0.01$) in the night splint group). No significant differences in the VISA-A score were found between the groups from baseline to one year ($p = 0.32$). The presence of neovessels at baseline did not predict a change in the VISA-A score after one year in the whole group ($p = 0.71$).

Conclusion: Eccentric exercises with or without a night splint improved functional outcome at one year follow-up. At follow-up there was no significant difference in clinical outcome when a night splint was used in addition to an eccentric exercise programme. Between 3 months and one year follow-up, a continuing increase in the VISA-A score was found. Assessment of the neovascularisation score with PDU at baseline has no prognostic value on long-term clinical outcome.

INTRODUCTION

Achilles tendinopathy is the clinical term used when the triad of a painful, swollen tendon with impaired function is present.[1] Achilles tendinopathy remains a serious injury for athletes, especially in running sports.[1] Several Scandinavian studies have reported good results with eccentric exercises in the treatment of Achilles tendinopathy.[2-4] Subsequently other studies showed only moderate results.[5,6] More recently, a systematic review concluded that treatment with eccentric exercises possibly has no benefits compared with other forms of exercises.[7] Morning stiffness is a common complaint in athletes with Achilles tendinopathy.[8,9] It was hypothesised that a night splint would be effective in reducing morning stiffness. Functional status and return to sports activity were not reported in many previous studies. In a systematic review Kingma *et al.*[10] stated that, besides pain, the functional outcome should be scored. The authors proposed to use the Victorian Institute of Sports Assessment-Achilles (VISA-A) score, which measures two factors: pain and physical activity.[11] Several studies have used the VISA-A to assess outcome.[6,12-15] In Achilles tendinopathy, colour and power Doppler ultrasonography (PDU) shows an increased vascularity with an increased number of blood vessels, which is referred to as "neovascularisation" in the literature.[16] The pathophysiological mechanism of these neovessels is unknown.[17] Several authors studied the presence of neovascularisation as a prognostic factor for the outcome of treatment of tendinopathy.[18,19] The first aim of this single blinded prospective randomised trial was to compare the effects at one-year follow-up of a heavy load eccentric exercise programme compared with a heavy load eccentric programme in combination with the use of a night splint. The second aim was to evaluate the change in neovascularisation score at one year follow-up.

MATERIAL AND METHODS

This is a follow-up study of the randomised controlled trial that initially investigated the value of additional splinting to eccentric exercises with use of the VISA-A score and PDU.[5,18]

Patients

Patients were referred by a general practitioner, physical therapist or a medical specialist. Volunteers without referral were also allowed for inclusion. Inclusion and exclusion criteria are summarised in table 1. The diagnosis was established based upon clinical examination. When there was pain on palpation of the Achilles tendon, 2–7 cm proximal from the distal insertion, the diagnosis of midportion Achilles tendinopathy was made. If there was pain on palpation of the insertion, this was considered an insertional ten-

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age 18–70 years	Insertional disorder
>2 Months' duration of symptoms	Tendon ruptures
Active sport participation before onset	Systemic illness
Wish to return to original sports level	Heavy load training in the past
Swollen tendon, tender on palpation and during sports	Inability to perform exercises
Tendon thickening 2–7 cm proximal to insertion	

dinopathy and the patient was excluded. After informed consent was given all patients were included by a clinician and then examined by a single researcher. The study protocol was approved by the Medical Ethics Committee of the Hospital.

Standardised outcome measures were assessed: The VISA-A score was the primary outcome measurement to evaluate the results at follow-up. The VISA-A questionnaire was completed with minimal researcher assistance. The first question in VISA-A is related to morning stiffness (0 to 10). A higher score is associated with less duration of stiffness in the morning. Subjective patient satisfaction was scored as excellent, good, moderate or poor. PDU was performed and neovascularization was scored according to the modified Öhberg score.[18] A detailed exercise instruction was performed. Patients were randomly assigned into one of the treatment groups, using sealed envelopes. The researcher was blinded to this randomisation and patients were instructed not to inform the researcher. Patients who were randomly assigned to the night splint group received further instruction from their treating physician.

Both groups performed treatment for 12 weeks. The detailed description of the treatment has been described earlier.[5] Outcome was evaluated by a blinded researcher at baseline, 3 months and one year. When patients needed surgery, the outcome was considered as poor patient satisfaction, the presurgical VISA-A score was obtained and the value used for the final measurement.

Ultrasound examination

On the first appointment Doppler ultrasonography was performed using a linear high frequency 8–13 MHz transducer with a pulse repetition frequency of 868 Hz. (Elegra; Siemens Medical Systems, Erlangen, Germany). At the one-year follow- up a linear high frequency 12–15 MHz transducer with a pulse repetition frequency of 500–1000 Hz (MyLab30; Esaote Piemedical, Maastricht, The Netherlands) was used. Patients lay prone during the examination, with their feet hanging over the edge of the examination table. The symptomatic Achilles tendons were observed in the longitudinal and transverse plane. On investigation, the researcher and the radiologists scored the neovascularisation of both Achilles tendons. This score was evaluated as 0 (no vessels visible), 1+ (one

vessel mostly in the anterior part), 2+ (one or two vessels throughout the tendon), 3+ (three vessels throughout the tendon) and 4+ (more than three large vessels throughout the tendon).

Statistical analysis was performed using statistical package for the social sciences software (SPSS 12.0). To assess changes over time in the variables within groups the Wilcoxon signed rank test was used. The Mann–Whitney U test was used to detect changes over time between the two groups. The X^2 test was used to evaluate differences in subjective patient satisfaction between the groups. Statistical significance was assumed when p values were less than 0.05. We calculated that the number of subjects to treat was 26 for each group. This sample size accounted for a 10% loss to follow-up, a significance level of 0.05 and a power of 80%. The assumptions of a delta of 10 points on the VISA-A questionnaire and a standard deviation of 12 were based on the data of previous studies.[11,14]

RESULTS

Patients

At baseline, 70 tendons of 58 patients met the inclusion criteria. Seventy tendons were randomly assigned into two treatment groups: 34 in the eccentric group and 36 in the night splint group. The mean age was 44.6 years (26–59), the mean body mass index was 25.1 kg/m^2 (20.2–34.5). The mean duration of symptoms was 30.7 months (median 44, range 2–204). There were no significant differences in patient characteristics between the groups at baseline.

Fifty patients (63 tendons) could be included for follow-up at one year. One patient did not answer repeated phone calls and 10 patients were not able to visit our centre for PDU examination but did complete the VISA-A scores and patient satisfaction (fig 1).

Between 3 months and one year follow-up, six patients (seven tendons) did not respond to conservative treatment. All had a poor/moderate patient satisfaction score at 12 weeks follow-up. These patients underwent surgical treatment after a mean duration of 9 months (6–12). In these patients, the presurgical VISA-A scores were obtained.

Eccentric training

Some patients continued the eccentric exercises at a lower level after the 12 weeks exercise programme. Eleven patients (14 tendons; 22.6%) continued for 1–6 months (mean 2.5 months). Eight patients (nine tendons; 14.5%) were still doing the exercises at the one year follow-up.

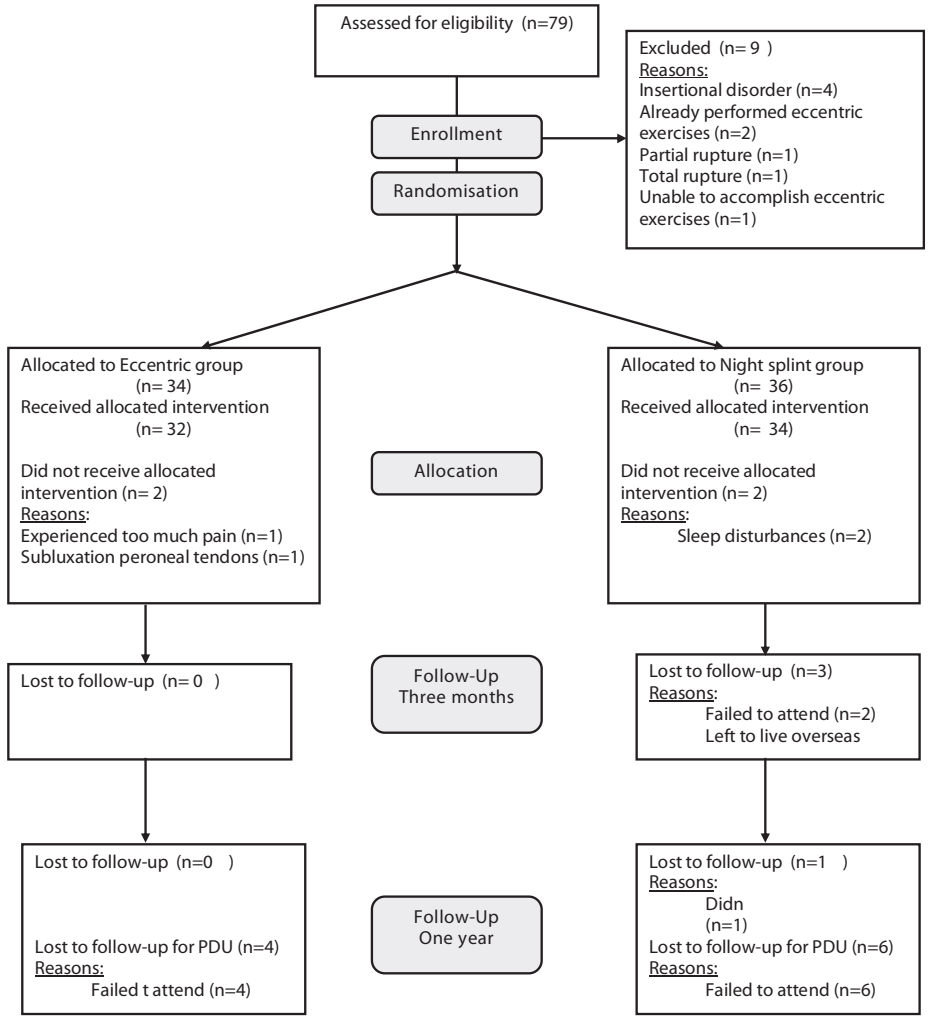

Figure 1: Flowchart of patients in the study.

VISA-A score

The VISA-A score in the eccentric group increased significantly from 50.1 at baseline to 75.7 after one year (p,0.01). From 3 months to one year the VISA-A score also increased significantly from 68.8 to 75.7 in the eccentric group ($p = 0.02$). In the night splint group the VISA-A score increased from 49.2 at baseline to 78.2 at one year ($p<0.01$; fig 2). A significant increase was also seen from 3 months follow-up (65.9 points) to one year follow-up ($p<0.01$).

There was no significant difference found in increases in VISA-A scores between both groups from baseline to one year (p = 0.36) and from 3 months to one year (p = 0.24; fig 2)

The score for morning stiffness increased significantly in the eccentric group from 5.8 at baseline to 9.1 at one year follow-up (p<0.01). In the night splint group the score for morning stiffness increased significantly from 4.7 at baseline to 8.7 at one-year follow-up (p<0.01). There was no significant difference in morning stiffness between both groups at baseline (p = 0.19), 3 months follow-up (p = 0.09) and one year follow- up (p = 0.12).

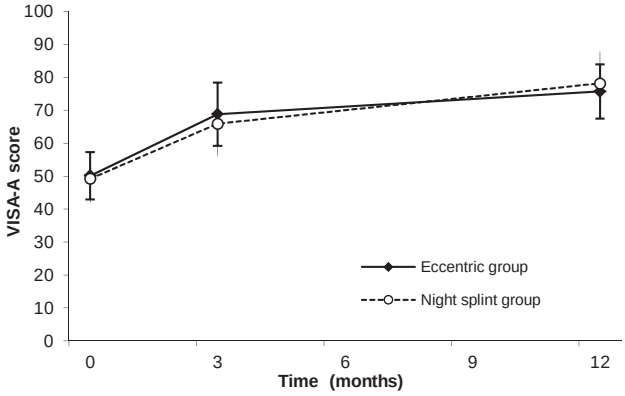

Figure 2: Changes in the Victorian Institute of Sports Assessment– Achilles (VISA-A) score in both treatment groups at baseline, 3 months follow-up and one year follow-up. No significant differences were found between the two treatment groups. A significant increase for the eccentric and night splint group between 3 months and one year follow-up was found.

Subjective patient satisfaction

As described in table 2, patient satisfaction at one year follow- up in the eccentric group was excellent or good in 17 (53.1%) tendons and moderate or poor in 15 (46.9%) tendons. After one year the patient satisfaction in the night splint group was excellent or good in 21 (70%) tendons and moderate or poor in nine (30%). No significant difference in patient satisfaction was found between the eccentric group and the night splint group (p = 0.20).

Table 2: Subjective patient satisfaction in both treatment groups at one year follow-up

	Patient satisfaction	
	Moderate or poor (%)	**Excellent or good (%)**
Eccentric group	15 (47)	17 (53)
Night splint group	9 (30)	21 (70)

The number of tendons is denoted (%). There was no significant difference in patient satisfaction between the eccentric group and the night splint group.

Ultrasonographic neovascularisation

At baseline 40 (65%) of the 62 tendons showed some degree of neovascularisation. At one year 37 of 52 (71%) showed some degree of neovascularisation. Patients with neovessels at baseline (grades 1–4) showed a mean increase in the VISA-A score of 25.7 from baseline to one year follow-up. Patients without neovessels (grade 0) at baseline showed a mean increase of 30.1 in the VISA-A score. There was no significant difference in outcome measured with the VISA-A between patients with or without neovessels at baseline (p = 0.71; fig 3)

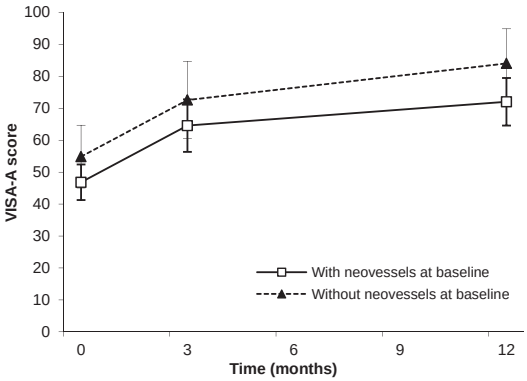

Figure 3: Changes in the Victorian Institute of Sports Assessment– Achilles (VISA-A) score at baseline, 3 months and one year follow-up in patients with neovessels (grades 1–4) at baseline and without neovessels at baseline (grade 0). There was no significant difference in improvement in the VISA-A score between these groups at 3 months and one year follow-up.

DISCUSSION

This randomised trial shows that at one year follow-up there was no difference in functional outcome between treatment with eccentric exercise only or a combination of eccentric exercises and the use of a night splint in chronic Achilles tendinopathy. The improvement in the VISA-A score continued after finishing the 12 weeks of therapy. The presence or absence of neovascularisation within or around the Achilles tendon could not predict outcome at long-term follow-up.

All studies that compared short-term versus middle and long- term outcomes, showed an improvement in the results between 6–12 weeks and one year.[9,12,20] It is questionable if the improvement after a period of 3 months eccentric training is caused by continuing the eccentric exercises after the prescribed 3-month period. In our population almost a quarter continued the eccentric exercises for 2.5 months on average after finishing

the therapy programme. At one year follow-up 15% were still performing the eccentric exercises. This phenomenon has not been reported in previous studies.

Another explanation is the "slow" natural healing process of the tendon. The effect of natural healing examined with a wait and see policy, was recently studied by Rompe *et al.*[14] They reported that an increase in the VISA-A score from 48 to 55 was found after 4 months without treatment. This improvement was not statistically significant. Another hypothesis is that eccentric exercises elicit longer term adaptations in extracellular matrix production. Tendons can adapt to enhanced loading conditions by changing tenocyte metabolism, leading to an alteration of structure and composition; however, the process of tissue degradation, and the synthesis and incorporation of new matrix components as well as the final crosslinking of the newly produced collagen network takes time. Altered biomechanical loading conditions can influence tendon cell (tenocyte) metabolic activities, altering the production and degradation of extracellular matrix components.[21] In humans it has been demonstrated using a microdialysis technique that collagen type I synthesis is increased after 12 weeks eccentric loading of initially injured human Achilles tendons.[22] From veterinary medicine we know that the tendon repair process in equine superficial digital flexors including the final remodelling phase takes many months.[23] Therefore, it is likely that the remodelling of the tendon tissue will continue for a longer period even after ceasing the eccentric loading regime. Ultimately this might lead to tendon structure adaptation and improved tendon function at long term.[24]

It may also be that patients might notice an initial relief and symptomatic recovery, which frequently precedes a functional recovery. It has been described that an initial symptomatic recovery reached shortly after the eccentric exercises does not automatically lead to a long-term functional recovery.[25] A postponed or extended period of restoration of tendon tissue structure and function might be responsible for the continuing increase in the VISA-A score after the eccentric exercises.

Few studies reported the functional results of more than one year follow-up. In a study in non-athletes with a mean follow- up of 15 months, Sayana and Maffulli[6] have shown the VISA-A scores of 34 patients after a 12-week heavy load eccentric exercise programme. In their population a significant increase in the VISA-A score from 39 to 50 was found, which was a smaller improvement than in this study. A possible explanation is the difference in the study population. In the study of Sayana and Maffulli[6] the patients were non-athletes, whereas in this study the included patients were all participating in sports. It could be postulated that active individuals do have a better compliance for the prescribed exercises. The VISA-A scores after one year in the study of Brown *et al.*[12] are more comparable with the present study. Those authors showed an improvement from 62 to 95 in 18 patients treated with eccentric exercises plus an injection of aprotinin or placebo. Other studies also showed an increase in VISA-A scores after finishing the eccentric programme.[5,14,15]

In contrast to the hypothesis that a night splint would reduce morning stiffness, the results in the present study did not show a significant benefit of using a night splint for the duration of stiffness in the morning.

There is conflicting evidence on the significance of neovascularisation in Achilles tendinopathy.[26] Peers *et al.*[27] found a correlation between neovascularisation and pain scores and Reiter *et al.*[28] reported a relationship between the presence of neovascularisation and a worse VISA-A score. However, these data were not supported by Zanetti *et al.*,[19] and de Vos *et al.*[18] found no relationship between the visual analogue scale score or the VISA-A score and the presence of neovascularisation.

In this study there was no relationship between neovascularisation at baseline and clinical outcome at one year. Zanetti *et al.*[19] and de Vos *et al.*[18] analysed the presence of neovessels at baseline related to outcome after 3 months of conservative treatment and reported similar results.

The use of a night splint in Achilles tendinopathy has been studied by Roos *et al.*[9] They reported a pain reduction of 35–42% at one year follow-up in all patients treated with eccentric exercises, a night splint or a combination of both. There was no significant difference in pain reduction between these groups after one year.

At one-year follow-up another PDU device was used. Although the pulse repetition frequency did not differ much, comparison between baseline and one-year follow-up could be unreliable. Another weakness of this study is the high number of patients who were not able to attend for PDU examination at one year follow-up. An intention-to-treat analysis was used for the patients who received conservative treatment to avoid bias. However, because some patients received surgical treatment they were not comparable with the group of patients treated conservatively. Therefore, these tendons were scored as poor patient satisfaction with the presurgical VISA-A score. A type II error may have occurred in the present study; however, with a total of 62 patients analysed at follow-up a high power was achieved.

CONCLUSION

Eccentric exercises, with or without a night splint, improved functional outcome after one year follow-up in patients with chronic Achilles tendinopathy. At follow-up there was no significant difference when a night splint was used in addition to an eccentric exercise programme. There was a continued improvement in functional outcome between 3 months and one year. Thirty-seven per cent of the patients treated with eccentric exercises continued to perform them after the 3 months prescribed duration. The presence of neovascularisation at baseline did not predict pain and functional outcome at

one year follow-up. Seventy-one per cent of the tendons still showed some degree of neovascularisation at follow-up.

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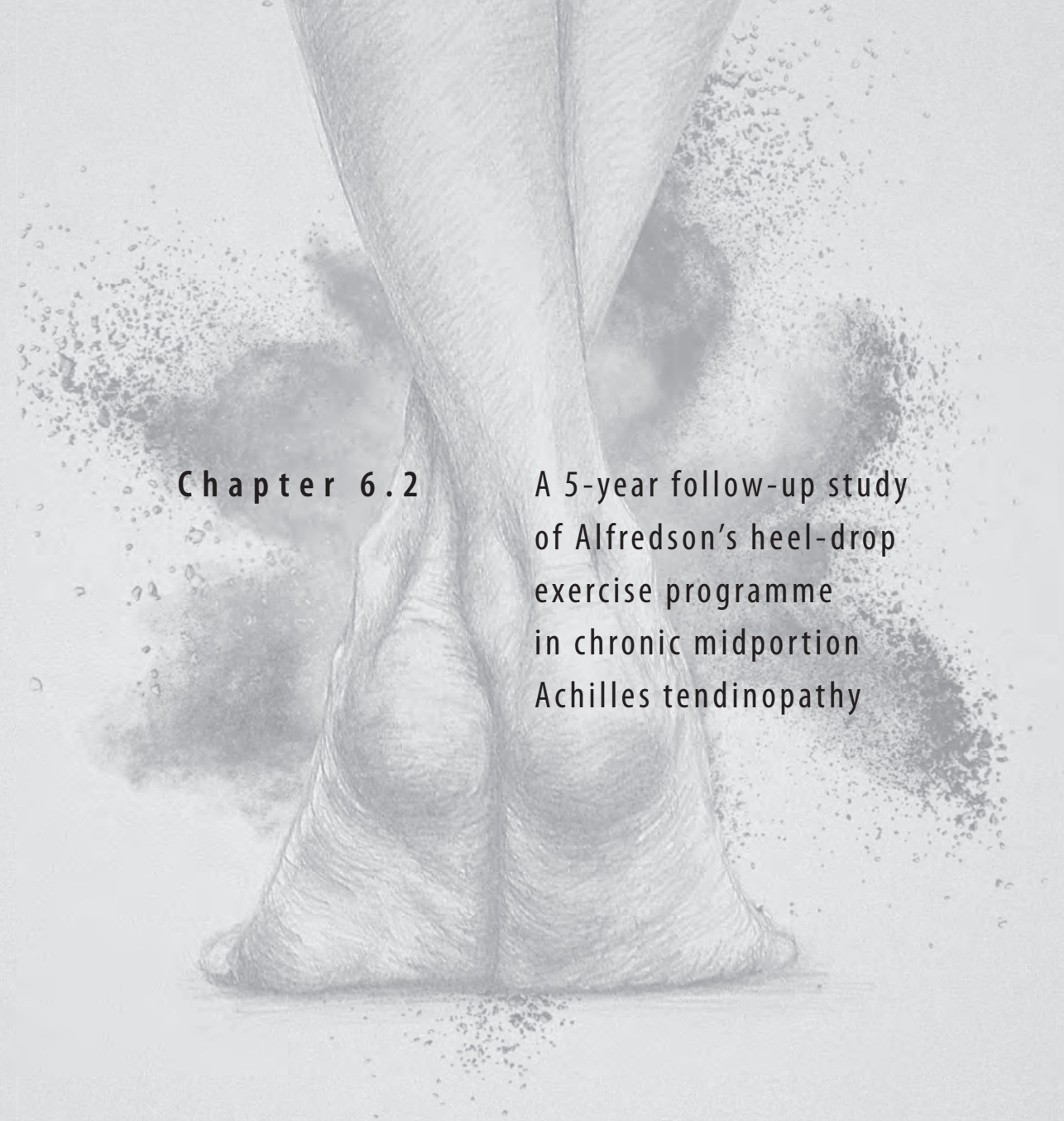

Chapter 6.2

A 5-year follow-up study of Alfredson's heel-drop exercise programme in chronic midportion Achilles tendinopathy

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ABSTRACT

Background: Eccentric exercises have the most evidence in conservative treatment of midportion Achilles tendinopathy. Although short-term studies show significant improvement, little is known of the long-term (>3 years) results.

Aim: To evaluate the 5-year outcome of patients with chronic midportion Achilles tendinopathy treated with the classical Alfredson's heel-drop exercise programme.

Study design: Part of a 5-year follow-up of a previously conducted randomised controlled trial.

Methods: 58 patients (70 tendons) were approached 5 years after the start of the heel-drop exercise programme according to Alfredson. At baseline and at 5-year follow-up, the validated Victorian Institute of Sports Assessment–Achilles (VISA-A) questionnaire score, pain status, alternative treatments received and ultrasonographic neovascularisation score were recorded.

Results: In 46 patients (58 tendons), the VISA-A score significantly increased from 49.2 at baseline to 83.6 after 5 years ($p<0.001$) and from the 1-year to 5-year follow-up from 75.0 to 83.4 ($p<0.01$). 39.7% of the patients were completely pain-free at follow-up and 48.3% had received one or more alternative treatments. The sagittal tendon thickness decreased from 8.05 mm (SD 2.1) at baseline to 7.50 mm (SD 1.6) at the 5-year follow-up ($p=0.051$).

Conclusion: At 5-year follow-up, a significant increase of VISA-A score can be expected. After the 3-month Alfredson's heel-drop exercise programme, almost half of the patients had received other therapies. Although improvement of symptoms can be expected at long term, mild pain may remain.

INTRODUCTION

There are many conservative treatment options for chronic Achilles tendinopathy. Systematic reviews showed that the heavy load eccentric exercise programme has the most evidence of effectiveness in the treatment of chronic midportion Achilles tendinopathy.[1-4] The reviews demonstrated promising results on pain. However, there is limited evidence to show that eccentric exercises are more effective than other treatments in the management of tendinopathies. The exact mechanism involved in the eccentric exercises is unclear and there is an ongoing debate on the optimal load, frequency and duration.[5,6] It is suggested that eccentric training might stimulate remodelling and tissue repair in tendons, the so-called therapeutic mechano transduction.[7] The classical heel-drop exercise programme first described by Alfredson *et al.*[8] is time-consuming (180 repetitions per day for 12 weeks). The majority of the published studies have a maximum follow-up of 1 year, and there is a lack of evidence about the long-term (>3 years) outcome.[9-13] Three studies evaluated the long-term (>3 years) results of the eccentric exercises in chronic midportion Achilles tendinopathy.[14-16] Only one study used the validated Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire, but in that study the exercise regimen differed from that described by Alfredson *et al.*[6] The VISA-A questionnaire is a validated score that measures pain and physical activity of the Achilles tendon.[17] The test is developed to create an index of severity of Achilles tendinopathy.

So far, no long-term VISA-A score results (>3 years) are known of the widely used heel-drop programme according to Alfredson. We evaluated the long-term clinical outcome of the heel-drop programme as described by Alfredson with the VISA-A score as the primary outcome measure. We also evaluated the ultrasonographic improvement 5 years after conservative therapy, alternative treatments received, pain status and patient satisfaction.

METHODS

This study is the 5-year follow-up of an earlier published randomised controlled trial (RCT).[13] The RCT evaluated the effect of the addition of a night splint to eccentric exercises in patients with chronic Achilles tendinopathy. At baseline, 58 patients (70 tendons) with chronic midportion Achilles tendinopathy were included. Inclusion criteria at baseline were the presence of symptoms for more than 2 months and participation in sporting activities. All patients in the trial preformed the heel-drop programme as described by Alfredson *et al.*[8] Half of the patients additionally received a night splint. The night splint had no significant influence on the VISA-A score at the 3-month and 1-year follow-up; all patients were therefore merged into one group for the 5-year follow-up.[13,18]

After completion of the heel-drop programme, patients were free to choose additional treatment(s); no instructions or recommendations were given to the patients.

The study protocol was approved by the Medical Ethics Committee of the Hospital (MEC05-21) and informed consent was given.

Follow-up

All patients were approached by telephone for the 5-year follow-up. At the outpatient clinic, each patient completed the VISA-A score questionnaire and received an ultrasound examination by a single researcher. The VISA-A score was completed with minimal researcher assistance. Secondary outcome scores were obtained using a standardised questionnaire: (1) pain status (pain-free, not pain-free), (2) condition of the uninvolved tendon (affected, not affected), (3) subjective patient satisfaction towards the current status (categorised in poor, moderate, good, excellent), (4) received alternative treatments after the heel-drop programme and, (5) continuation of the eccentric exercises (continued, stopped after the heel-drop programme).

Ultrasound examination

For ultrasound examination, patients were asked to lie prone with their feet hanging over the edge of the table. During the examination, both Achilles tendons were evaluated in the sagittal plane for thickness and neovascularisation according to the Öhberg scoring system. This score was evaluated as 0 (no vessels visible), 1+ (one vessel mostly in the anterior part), 2+ (one or two vessels throughout the tendon), 3+ (three vessels throughout the tendon) and 4+ (more than three large vessels throughout the tendon). Two different power Doppler machines were used to examine the tendons: the MyLab25Gold (Esaote Piemedical, Maastricht, The Netherlands) and the BK Pro Focus (BK Medical, Herlev, Denmark). Both power Doppler machines used a frequency of 12 MHz, 0.5 PRF (pulse repetition frequency). The colour gain setting was optimised for low flow; putting the setting just below that level produces random noise, varying from 66% to 79%.[19]

Statistical analysis

Differences in VISA-A score and tendon thickness between baseline and follow-up were evaluated using a sample t test. Differences between two categorical variables were evaluated using a χ^2 test. Dependency analysis of the VISA-A score was performed using a non-repetitive analysis of covariance test. Statistical Package for the Social Sciences software (SPSS 17.0) was used. A P value of less than 0.05 was considered to be statistically significant.

RESULTS

Attempts were made to contact all 58 patients (70 tendons). Six patients (six tendons) were not reachable for follow-up and five patients (five tendons) refused to participate (see figure 1). Three out of these five patients reported having no or minimal complaints of the Achilles tendon; unfortunately, further details are unknown. The VISA-A score and questionnaire results were obtained from 47 patients (59 tendons): 12 bilateral and 35 unilateral. One patient (one tendon) was excluded from analysis due to a direct trauma to the Achilles tendon 2 days before the follow-up appointment, making the outcome non-representative. For general statistical analysis, 46 patients (58 tendons) were used. Five patients (six tendons) were not able to visit the hospital (no time or living abroad) but filled out the general questionnaire and the VISA-A score (see figure 1 for details). The ultrasonographic data consisted of information from 41 patients (52 tendons).

At follow-up, the mean age was 50.9 years, with a mean body mass index of 25.4 kg/m^2 (see table 1 for details). Baseline specifics are described by de Vos *et al.*[13]

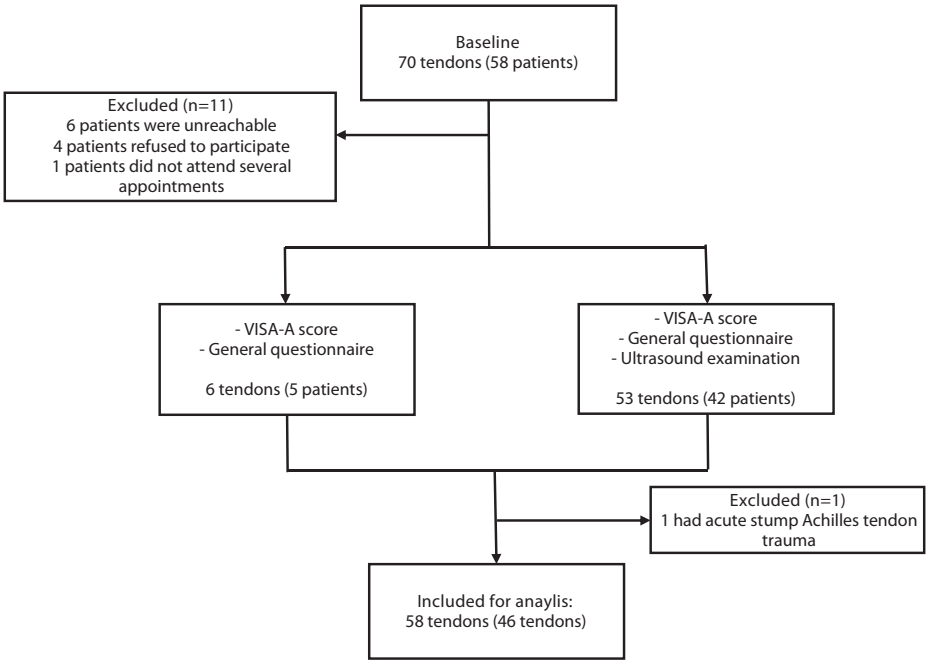

Figure 1: Flowchart of included patients.

Table 1: Patient characteristics at 5-year follow-up

	46 Patients (58 tendons)
Mean age (years (range))	50.9 (36–64)
Body mass index (kg/m^2 (range))	25.4 (19.9–33.5)
Unilateral/bilateral	34/12
No sports activity	4
Recreational sports	35
Competitive sports	7

Primary outcome: VISA-A score

The VISA-A score (n=58) improved significantly from 49.2 (SD 20.1) at baseline to 83.6 (SD 14.9) at the 5-year follow-up (p<0.001). The VISA-A score (n=55) improved significantly between the 1-year follow-up and the 5-year follow-up from 75.0 (SD 25.0) to 83.4 (SD 15.1) (p=0.006). See figure 2 for the trend line of the VISA-A score.

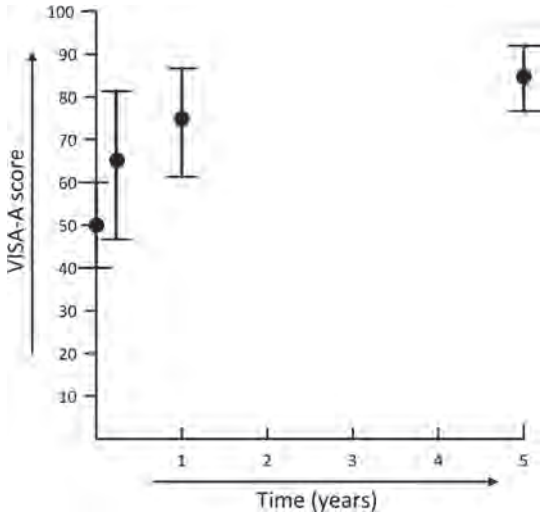

Figure 2: The VISA-A score in time.

Pain status

Of the patients, 39.7% reported being completely pain-free at the 5-year follow-up (mean VISA-A score 92.8, SD 8.8). The remaining 60.3% experienced some degree of pain, varying from only during extensive exercise to permanent pain (mean VISA-A score 77.5, SD 15.1). From the 34 patients with unilateral Achilles tendinopathy, 43.3% developed some degree of pain in the contralateral Achilles tendon.

Patient satisfaction

Patient subjective satisfaction towards the current status was excellent in 8.6% (mean VISA-A score 89.0, SD 8.0), good in 41.4% (mean VISA-A score 84.6, SD 16.3), moderate in 31.0% (mean VISA-A score 84.4, SD 15.2) and poor in 19.0% (mean VISA-A score 77.6, SD 13.5).

Alternative treatments

In total, 48.3% (22 patients) had received one or more alternative treatments, non-custom-made inlays (11 patients), surgery (6 patients), physiotherapy/massage/friction (6 patients), shockwave therapy (2 patients), immobilisation cast (2 patients), Polidocanol injection (1 patient), platelet-rich plasma injection (1 patient), glyceryl trinitrate patches (1 patient), acupuncture (1 patient), non-steroidal anti-inflammatory drugs (1 patient) and rest for 2 years (1 patient). Of the group of patients treated with an alternative treatment, 21.4% was completely pain-free. In the group of patients who did not receive an alternative treatment, 56.7% was completely pain-free. After completing the 3 months heel-drop programme in the original study, 67.2% (31 patients) never performed the eccentric exercises again. No correlation in pain status was found between patients who continued the eccentric exercises and those who did not (p=0.15).

Ultrasonographic examination

The sagittal thickness decreased from 8.1 mm (SD 2.1) at baseline to 7.5 mm (SD 1.6) at the 5-year follow-up (n=50, p=0.051). At baseline, 58.8% had some degree of neovascularisation (Öhberg score 1 to 4+). After 5 years, 47% showed neovascularisation during the ultrasonographic examination (n=51). There was no difference in increase in VISA-A score between the patients with neovessels at baseline (increase of 32.1 points, SD 22.1) and patients without neovessels at baseline (increase of 32.1 points, SD 23.7).

Fifty-four per cent of the patients without pain at follow-up had some degree of neovascularisation. No significant difference was found in tendon thickness at 5-year follow-up between the patients with and without symptoms (p=0.59).

Factors influencing the VISA-A score

The VISA-A score at 5-year follow-up and the ΔVISA-A (= difference between baseline and the 5-year follow-up) score were not influenced by age (p=0.61 resp. p=0.18), sex (p=0.50 resp. p=0.39), body mass index (p=0.83 resp. p=0.50), duration of symptoms at baseline (p=0.11 resp. p=0.27), degree of neovascularisation at baseline (p=0.53 resp. p=0.81) and sagittal tendon thickness at baseline (p=0.43 resp. p=0.39).

DISCUSSION

This is the first study evaluating the 5-years results of the Alfredson heel-drop programme with the validated VISA-A score. The VISA-A score increased significantly from 49.2 at baseline to 83.6 at the 5-year follow-up and from the 1-year follow-up to 5-year follow-up from 75.0 to 83.4 ($p<0.01$).

Until now the VISA-A score has only been used in one long-term follow-up study on eccentric exercises in Achilles tendinopathy.[16] Silbernagel *et al.* reported a VISA-A score of 90.5 at 5-year follow-up, 65% of symptom-free patients and approximately 6% receiving alternative treatments. In their study, the training programme lasted from 12 weeks to 6 months and was performed under the supervision of a physiotherapist. Patients in the current study received very accurate instruction for the heel-drop programme and were instructed to do the exercises with pain. The compliance for the exercises was good/excellent in the majority of the patients (>70%).[13] The basic population of Silbernagel *et al.* showed many similarities with our population, however, no competitive athletes were included in the study of Silbernagel *et al.* Maffulli *et al.*[20] suggested there could be a difference in response to eccentric training in the Scandinavian population. Several Scandinavian studies have demonstrated good/excellent short-term results from the eccentric exercises in the treatment of chronic Achilles tendinopathy.[9-12] In recent years, differing results have been found by non-Scandinavian studies showing only moderate short-term results.[13,21,22] The long-term Scandinavian studies evaluating eccentric exercises in chronic Achilles tendinopathy suggest a good long-term prognosis.[14–16] Further studies will be needed to reveal if there is a genetic explanation for this difference.[23]

Two other studies have reported long-term effects of the heel-drop programme used in this study in patients with Achilles tendinopathy.[14,15] However, neither of them used the validated VISA-A score. Ohberg *et al.* showed that 22 of 25 (88%) patients were satisfied with the treatment at a mean follow-up of 3.8 years (range 1.6–7.75). The second long-term follow-up study reported that 65% of the patients had no or mild pain after 4.2 years (range 29–58 months).[14] In our study, 39.7% of the study population was completely pain-free at the 5-year follow-up. Almost half of our patients had received one or more alternative treatments. These secondary subjective outcomes suggest a discrepancy with the significant increase of the primary outcome score. For advise to patients it implies that a quantified improvement can be expected, but mild remaining pain symptoms may be present at long term.

Ultrasonographic evaluation demonstrated a comparable decrease in tendon thickness from 8.8 mm before the heel-drop programme to 7.6 mm at follow-up. However, the clinical relevance of this minor decrease is questionable. In recent years, a debate has arisen about the meaning and the significance of neovascularisation in Achilles tendons. Some studies have found a correlation between the patient's symptoms and the degree

of neovascularisation,[24-26] and others found that the presence of neovascularisation did not per se indicate a disease state.[27-31] Also the circumstances during the examination, for example, activity just before the measurement, was not controlled and is unknown. This study found that the VISA-A score was not related to the degree of neovascularisation. Further research is needed to understand the relevance of neovascularisation in Achilles tendons.

This study has some limitations. The 11 dropouts might have influenced the outcome. In a best case scenario analysis where the dropouts have the best outcome score, 50% of the patients would be pain-free. However, the value of this non-validated subjective outcome measurement is questionable. Patients had to answer questions concerning the last 5 years, which may have given recall bias. The long-term outcome could be influenced by the alternative treatments that the patients received after completion of the heel-drop programme. However, of the patients who did not receive alternative treatments, 56.7% were completely pain-free after 5 years. Robinson *et al.*[17] recommended to use the VISA-A score in a homogenous group of athletes. Especially at long-term follow-up, the VISA-A score questionnaire can be subject to other influences than solely the symptoms of the Achilles tendinopathy. Factors like general ageing and new comorbidity may have influenced the outcome in this study. Finally, the ultrasonographic examinations at baseline and at follow-up were performed by different observers. However, in an earlier study, an excellent interobserver reliability of grading the neovascularisation was found.[32]

CONCLUSION

This is the first study evaluating the 5-year results of the widely used heel-drop exercise programme as described by Alfredson *et al.* with the validated VISA-A score. At 5-year follow-up, the VISA-A score increased significantly. After the 3-month eccentric training programme, almost half of the patients had received other therapies. Although improvement of symptoms can be expected at long term, mild pain may remain.

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Chapter 7

One-Year Follow-up of Platelet-Rich Plasma Treatment in Chronic Achilles Tendinopathy A Double-Blind Randomized Placebo-Controlled Trial

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ABSTRACT

Background: Achilles tendinopathy is a common disease among both athletes and in the general population in which the use of platelet-rich plasma has recently been increasing. Good evidence for the use of this autologous product in tendinopathy is limited, and data on longer-term results are lacking.

Purpose: To study the effects of a platelet-rich plasma injection in patients with chronic midportion Achilles tendinopathy at 1-year follow-up.

Study Design: Randomized controlled trial; Level of evidence, 1.

Methods: Fifty-four patients, aged 18 to 70 years, with chronic tendinopathy 2 to 7 cm proximal to the Achilles tendon insertion were randomized to receive either a blinded injection containing platelet-rich plasma or saline (placebo group) in addition to an eccentric training program. The main outcome was the validated Victorian Institute of Sports Assessment–Achilles score. Patient satisfaction was recorded and ultrasound examination performed at baseline and follow-up.

Results: The mean Victorian Institute of Sports Assessment–Achilles score improved in both the platelet-rich plasma group and the placebo group after 1 year. There was no significant difference in increase between both groups (adjusted between-group difference, 5.5; 95% confidence interval, –4.9 to 15.8, P = .292). In both groups, 59% of the patients were satisfied with the received treatment. Ultrasonographic tendon structure improved significantly in both groups but was not significantly different between groups (adjusted between-group difference, 1.2%; 95% confidence interval, –4.1 to 6.6, P = .647).

Conclusion: This randomized controlled trial showed no clinical and ultrasonographic superiority of platelet-rich plasma injection over a placebo injection in chronic Achilles tendinopathy at 1 year combined with an eccentric training program.

INTRODUCTION

Chronic tendinopathy is frequent in both athletes and the general population.[25] The poor regenerative capability of tendons seems to play a major role in this chronic disease. Tendinosis, which is characterized by degeneration and disorganization of collagen fibers, increased vascularization, and irregular cellularity, is commonly found on histological examination in tendinopathy. Classic inflammation is minimal or absent in this condition.[1,6,14,22,28] Because of this finding, the initially used term tendinitis has been replaced by tendinopathy. The Achilles tendon is one of the most vulnerable tendons.[26,37] The diagnosis of Achilles tendinopathy can be made in the presence of a painful swollen tendon with impaired function.[26]

Regenerative medicine is being studied more intensively in the field of tendinopathy. It is assumed that growth factors and/or (stem) cells are able to reverse the degenerative process.[4] Platelet-rich plasma (PRP) is a popular application form for growth factor release. With the increase of platelet concentration in this product, the amounts of several growth factors are also increased.[18] Growth factors act on different aspects of tendon repair, including angiogenesis, chemotaxis, and cell proliferation by activating intracellular signal-transduction pathways.[5,13]

Sports orthopaedic physicians have increasingly been using PRP as treatment for tendinopathy. A recent systematic review showed that high-quality randomized clinical trials and midterm and long-term follow-up results are lacking.[15] Of the few studies reporting high success rates for PRP treatment in tendinopathy,[19,24,27,32] only 1 trial had an adequate control group with 1-year follow-up.[32] None of these publications included a standardized ultrasonographic evaluation of tendon structure. The short-term results of the current study were reported earlier. No additional effects of PRP injection to eccentric exercises were found after 6 months.[17] However, biologic agents could bring forth a response that becomes pronounced over time. In a recent randomized controlled trial on the effects of PRP in lateral epicondylitis, there was no difference in outcome between PRP injections and corticosteroid injections at 3 months, whereas at 1 year the PRP group did significantly better.[32]

Ultrasonography can be used for the evaluation of therapy in tendinopathy.[7] Recently, ultrasonographic tissue characterization (UTC) was introduced as a reliable method for quantification of tendon structure.[41] The method calculates the 3-dimensional stability of the echo pattern over continuous cross-sectional images of the tendon and was extensively evaluated in equine studies using histology as the reference. This new technique, with a high interobserver and intraobserver reliability, can discriminate between symptomatic and asymptomatic human tendons.[43]

Neovascularization score alters during treatment of Achilles tendinopathy. Although the interpretation of neovascularization remains unclear, different trials used neovascularization as an objective parameter in their results.[12,30,47]

In further follow-up of the 6-month clinical results,[17] the aim of the current study is to evaluate both the clinical and the ultrasonographic tissue effects of a PRP injection versus placebo in patients with chronic Achilles tendinopathy after 1 year.

MATERIALS AND METHODS

This is a 1-year follow-up study of a randomized controlled trial.[17] Materials and methods were as extensively described in the article by de Vos *et al.*[17] and reported in the study protocol registered at clinicaltrials.gov (Identifier: NCT00761423).

Patients

Patients were recruited in a large district hospital at the department of sports medicine. Inclusion criteria were patients with the clinical diagnosis of Achilles tendinopathy with a minimal duration of symptoms of 2 months. Patients were excluded if they already had performed a full eccentric exercise program or already received a PRP injection in the Achilles tendon. Other exclusion criteria were known presence of a systemic illness, presence of other musculoskeletal injury (such as insertional disorder or tendon rupture), use of fluoroquinolones, and presence of pregnancy.

Procedures

Both the PRP injection (4 mL) and a saline injection (4 mL) were prepared for each patient. For the PRP injection, 54 mL of whole blood was collected from the cubital vein; 6 mL of citrate was added to prevent clotting. The collected blood was centrifuged for 15 minutes using the Recover Platelet Separation Kit (type Gravitational Platelet Separation III), and 0.3 mL of 8.4% sodium bicarbonate buffer was added.[18] No calcium chloride or thrombin was added to activate the platelets before injecting because we assumed that platelets are also activated by collagen.[20]

Randomization

A block randomization was performed with a block size of 12 participants. The patients were randomized into 1 of the treatment groups by choosing a blank sealed envelope. The content of this envelope was only visible for 1 unblinded independent sports medicine physician (A.W.) who selected the randomized injection and blinded it with a covering sleeve.

Intervention

First, the skin and subcutaneous tissue were anesthetized with 2 mL of 0.5% Marcaine. The injection was performed under ultrasonographic guidance by an experienced sports physician who was also blinded to the allocated treatment. At 3 different needle locations, 5 little aliquots were injected (with a total amount of 4 mL). After the injection, patients had to avoid sports activities for 4 weeks; in the second week, they performed a stretching program. After this, all patients started an eccentric exercise program for 12 weeks.[3]

Follow-up

Recruitment, inclusion, and follow-up contacts at 6, 12, and 24 weeks after injection were performed by one researcher (R.J.d.V.). One-year follow-up was performed by another researcher (S.d.J.) who was also blinded for the allocated intervention. Both clinical and ultrasonographic outcomes were assessed at all time points. Patients remained blinded until 1-year follow-up.

Clinical Outcome Measures

The primary outcome was the Victorian Institute of Sports Assessment–Achilles (VISA-A) score (validated questionnaire for outcome in Achilles tendinopathy). Other outcome measures were subjective patient satisfaction (scored as moderate, poor, good, or excellent) and return to sports activity (scored as not active in sports, no return to sports, returning to sport but not in desired sport, returning to desired sport but not at the preinjury level, or returning to preinjury level in the desired sport). For analysis of patient satisfaction, patients reporting good or excellent satisfaction were reported as satisfied. For return to sports activity, cutoff was made for return to desired sport on preinjury level.

Sonographic Evaluation

Tendon structure was evaluated quantitatively by means of UTC (UTCimaging, Stein, the Netherlands). With the ankle joint in 15° of dorsal flexion, a 10-MHz linear-array transducer (Smartprobe 10L5, Terason 2000, TeraTech, Rockville, Maryland) was moved automatically along and perpendicular to the Achilles tendon's long axis over a distance of 9.6 cm. The transverse images collected at regular distances of 0.2 mm were used to reconstruct a 3-dimensional data block. The stability of the echo pattern over contiguous images was analyzed by means of custom-designed algorithms (UTCimaging) and results in discrimination of 4 echo types: Echo types I and II represent more or less organized (secondary) tendon bundles; echo types III and IV represent smaller, disorganized, and more amorphous or fibrillar structures.[42] In transverse and sagittal planes of view, the maximum anterior-posterior diameter was determined and measured. At 5

points around this thickest part, from 1.5 cm proximal to 1.5 cm distal to the maximum anterior-posterior diameter, the border of the tendon was marked and intermediate borders interpolated, creating a volume with an overall length of 3 cm. Proportions of the 4 echo types were measured within this volume. The sum of echo types I and II, representing more or less organized secondary tendon bundles, was used for statistical analysis. Ultrasound examination at the 1-year follow-up was performed by another researcher (S.d.J.). The interobserver reliability between the 2 examiners (R.J.d.V. and S.d.J.) was tested in 17 tendons at 2 different time points within 1 week. The reliability appeared to be excellent, with an intraclass correlation coefficient of 0.89 and a mean difference of 0.9%.

Neovascularization

Neovascularization was scored using the modified Öhberg scoring system.[23,38] In this scoring system, scores were determined as 0 (no vessels), 1+ (1 vessel, mostly anterior to the tendon), 2+ (1 or 2 vessels throughout the tendon), 3+ (3 vessels throughout the tendon), or 4+ (more than 3 vessels throughout the tendon). The degree of neovascularization can be measured with an excellent interobserver reliability (intraclass correlation, 0.85).[38] This color Doppler ultrasonography examination was performed with a linear high-frequency 12- to 15-MHz transducer (MyLab30, Esaote Piemedical, Maastricht, the Netherlands) with Doppler gain at 79% and Doppler frequency at 6.6 MHz. Patients were laying prone on the examination table with their feet hanging over the edge. The neovascularization of the tendon was scored in longitudinal and transverse planes.[12,16]

Statistics

The sample size calculation showed that with a power of 80% (2-sided testing at a significance level of .05) and compensating for 10% loss to follow-up, a sample size of 27 participants in each group was needed to show a difference of 12 points on the VISA score (SD, 15). Statistical analyses were performed using social sciences software (SPSS 16.0, SPSS Inc, an IBM Company, Chicago, Illinois). Between-group differences at long-term follow-up in the VISA-A score and ultrasonographic outcome measurements were estimated using a repeated-measurement general linear model including all measurement time points. Adjustments were made for variables that influenced the outcome measurement with $P < .10$. For between-group differences in nominal outcomes, a generalized estimating equations model was used. Positive values in between-group differences favor the PRP group. A difference of $P < .05$ was considered to be statistically significant. Patients were analyzed on an intention-to-treat basis.

RESULTS

Patients

At baseline, 54 of the 99 eligible patients were willing to participate, met the inclusion criteria, and were randomized into the 2 treatment groups. The mean age was 49.7 years (range, 26-70 years), mean body mass index (weight in kg/height [m]^2) was 26.5 (range, 20.2-35.3), and the mean duration of symptoms was 62.6 weeks (median, 32 weeks; range, 8-520 weeks). There were no significant differences in baseline characteristics between the 2 groups.

No patients were lost to follow-up (Figure 1). One patient was not able to visit the center for ultrasonographic examination but did complete the clinical outcome measures by mail. After 24 weeks, 4 patients in the PRP group decided to undergo another treatment because of failure to improve. These treatments included orthotics (n = 1), extracorporeal shockwave therapy (n = 3), and glyceryl trinitrate patches (n = 1). In the placebo group, 1 patient received glyceryl trinitrate patches. No complications were reported between 24-week and 1-year follow-up.

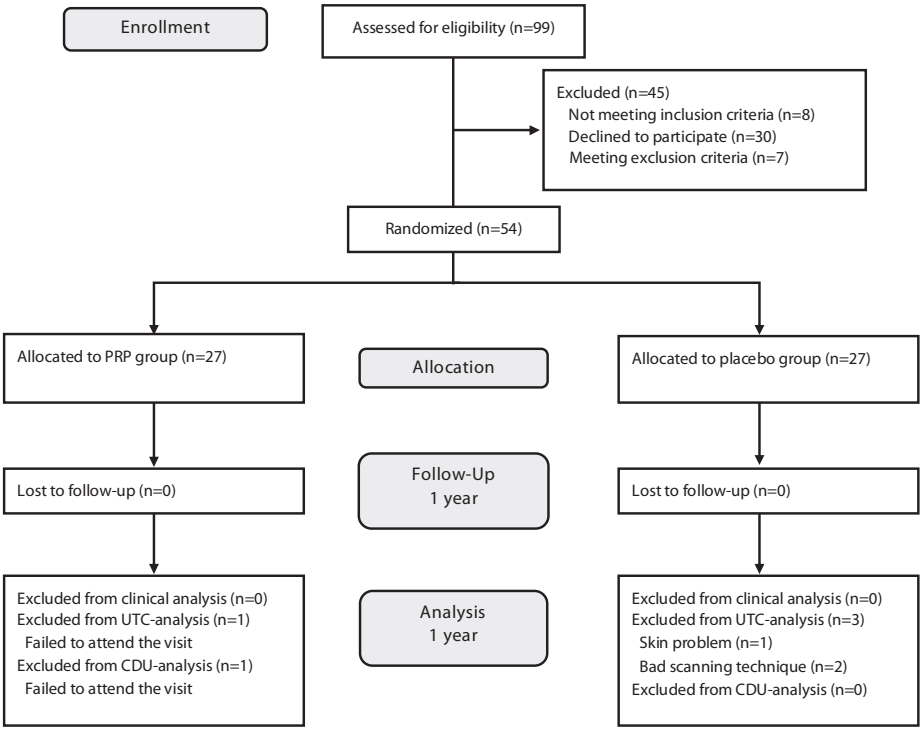

Figure 1: Flowchart of patients in the study. CDU, color Doppler ultrasonography; PRP, platelet-rich plasma; UTC, ultrasonographic tissue characterization.

Clinical Outcome

At 1-year follow-up, the VISA-A score improved significantly by 31.6 points (95% confidence interval [CI], 22.2-40.9) from 46.7 (95% CI, 40.3-53.1) at baseline to 78.2 (95% CI, 68.0-88.5) in the PRP group and by 25.0 (95% CI, 18.0-32.0) points from 52.6 (95% CI, 54.1-60.2) to 77.6 (95% CI, 70.8-84.4) in the placebo group. In the general linear model, adjustments were made for baseline VISA-A score (P = .023) and duration of symptoms (P = .023). The adjusted between-group difference at 1-year follow-up was not significant (5.5 points on VISA-A score; 95% CI, −4.9 to 15.8). The VISA-A scores at all follow-up moments for both groups are shown in Figure 2.

After 1 year in both groups, 16 patients (59.3%) were satisfied with their allocated treatment. Adjusted between-group difference for subjective patient satisfaction after 1 year was −2.7% (95% CI, −23.5 to 18.1; P = .801).

In the PRP group, 56.5% of the patients returned to their previous sports levels in the desired sport, compared with 41.7% in the placebo group. The adjusted between-group difference for return to sports at 1-year follow-up was 1.8% (95% CI, −24.5 to 28.1; P = .894).

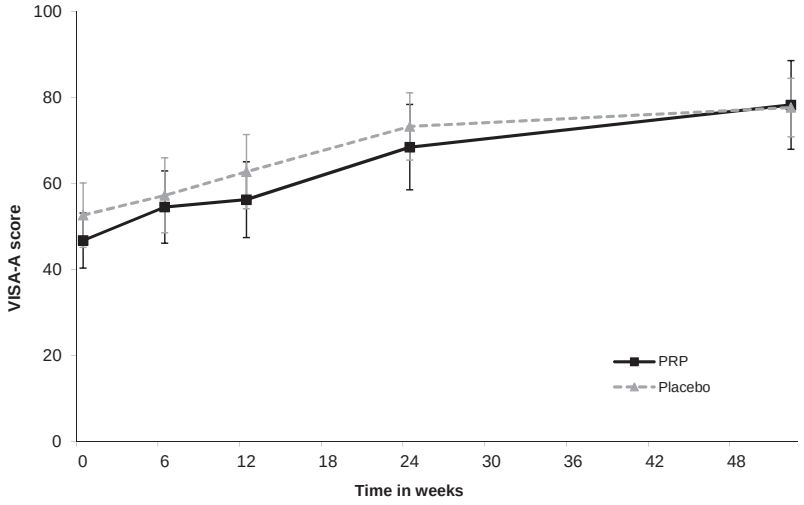

Figure 2: Changes in mean Victorian Institute of Sports Assessment–Achilles (VISA-A) score for both groups. There was improvement in VISA-A score within both groups but no significant difference between the groups.

Sonographic Outcome

The percentages of the more or less organized echo types I and II increased 7.2% (95% CI, 3.4-11.0) in the PRP group from 76.9% (95% CI, 72.6-81.1) at baseline to 83.7% (95% CI, 79.6-87.9) at 1-year follow-up. In the placebo group, these echo types increased

8.4% (95% CI, 3.1-13.6) from 72.1% (95% CI, 67.7-76.5) to 81.3% (95% CI, 77.3-85.3). In the general linear model, adjustments were made for baseline value echo type I and II ($P < .001$). Between-group difference at 1-year follow-up was 1.2% (95% CI, −4.1 to 6.6; $P = .647$). Alterations in all echo types in the PRP group (Figure 3A) and control group (Figure 3B) are plotted in Figure 3.

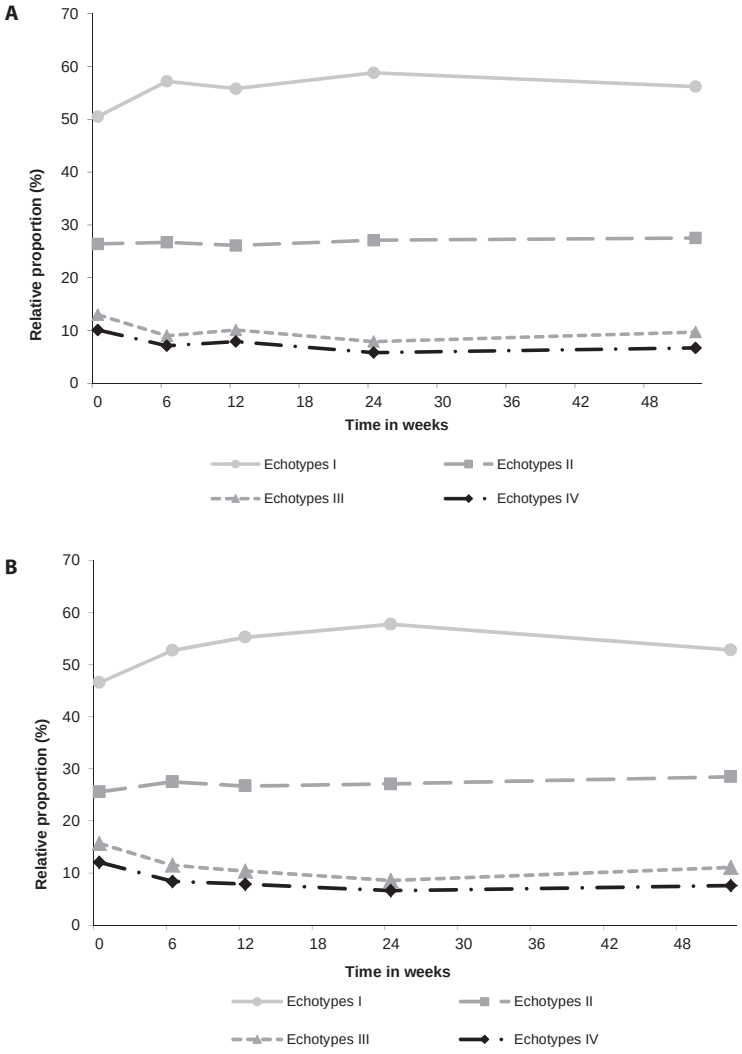

Figure 3: A, changes in UTC echo types in PRP group. Echo type I increased over time, whereas echo type II remained stable. Echo types III and IV decreased slightly. B, changes in UTC echo types in placebo group. Echo type I increased over time, whereas echo type II remained stable. Echo types III and IV decreased slightly.

Maximum anterior-posterior diameter of the Achilles tendon decreased in the PRP group from 9.8 mm (95% CI, 9.1-10.5) at baseline to 9.0 mm (95% CI, 8.2-9.8) at 1-year follow-up. This was not significantly different from the decrease in the placebo group from 9.8 mm (95% CI, 8.6-11.1) at baseline to 8.6 mm (95% CI, 7.6-9.5) after 1 year. Between-group difference was 0.4 mm (95% CI, −0.8 to 1.7; P = .457).

Mean neovascularization score increased in the PRP group in the first 12 weeks from 2.3 (95% CI, 1.8-2.7) to 3.0 (95% CI, 2.6-3.5) and in the placebo group from 2.2 (95% CI, 1.6-2.7) to 2.5 (95% CI, 2.1-2.9). From 12 weeks to 1-year follow-up, a decrease was found in both groups, to 1.4 (95% CI, 0.8-2.0) in the PRP group and 1.2 (95% CI, 0.7-1.7) in the placebo group. Between-group difference at 1-year follow-up was 0.1 point (95% CI, −0.6 to 0.9; P = .714). Mean neovascularization scores for both groups are shown in Figure 4.

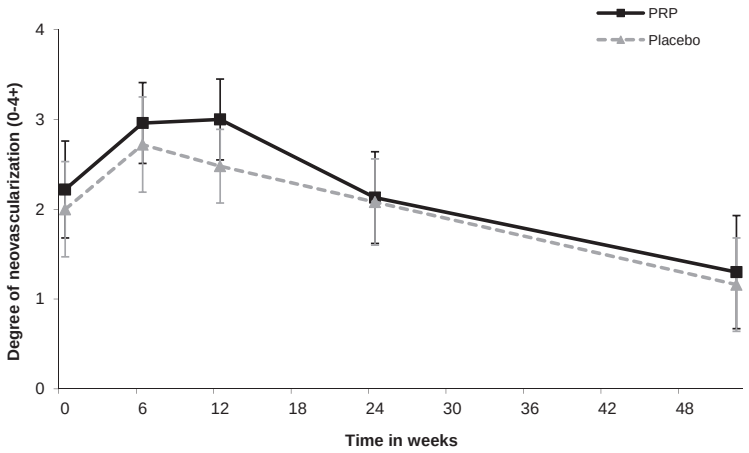

Figure 4: The alterations of the mean neovascularization score within both groups. In both groups, the neovascularization score continued decreasing after the increase at the 12-week follow-up.

DISCUSSION

In this double-blind randomized placebo-controlled clinical trial with 1-year follow-up, no clinical or sonographic benefit of a PRP injection was found. These results are in line with the findings after 6 months.[17] This is the first trial using standardized sonography in 1-year clinical results of PRP therapy in Achilles tendinopathy.

In different types of tendinopathy, promising results for PRP therapy have been published recently.[19,24,27,31] Two pilot studies reported high patient satisfaction and pain reduction after PRP therapy[24,27]; the group sizes of these studies, however, were small,

and a control group was lacking. Filardo *et al.*[19] selected a control group with patients with moderate patellar tendinopathy receiving a regular physical therapy program versus patients with nonresponding patellar tendinopathy receiving multiple PRP injections. They found equal clinical improvements after 6 months in both groups. In a recent publication, Gaweda *et al.*[21] studied the effect of PRP in 14 patients with Achilles tendinopathy without the use of a control group and found significant improvement in VISA-A score after 18 months.

The only other randomized controlled trial on PRP therapy in tendinopathy showed a significant benefit of PRP injection in wrist extensor tendinopathy compared with corticosteroid injection after 1 year.[32] Comparing the pattern of visual analog scale score with the VISA-A score in our study, the deviating course in the control group of Peerbooms *et al.*[32] is remarkable. Unlike our study, the control group received a corticosteroid injection instead of a placebo injection, which very well may have negatively affected the outcome in the control group.[40] In addition, there may be differences in the natural healing response between load-bearing tendons, such as the Achilles tendon, and non–load-bearing tendons, such as the wrist extensors. Although a tennis elbow is a self-limiting injury,[34] Achilles tendinopathy seems not to be.[35]

It is possible that the needling during the injection could influence the outcome in both groups. Brown *et al.*[8] compared aprotinin injections and eccentric exercises with a saline injection and eccentric exercises. They found similar improvement in both the aprotinin and placebo groups. A healing response can be initiated by needle trauma or local bleeding.[33] Another hypothesis for the positive effects in both groups is the increase in peritendinous volume, thereby destroying the vascular and neural growth that is thought to be the source of pain.[10] The increase of neovessels after the injection contradicts this theory. It is not certain that the injected volume stays intratendinous for a sustained period or leaks, for example, to the peritendinous space. Using an injection procedure similar to the procedure in this study, Wiegerinck *et al.*[46] showed an equal distribution of intratendinously injected volumes in the Achilles tendons of human cadavers. The assumption that PRP only has great potency in traumatic lesions is invalidated by Schepull *et al.*[36] They found no benefit of PRP in treatment of Achilles tendon rupture. Cell therapy has recently been proposed as the most promising therapy for degenerated tendons,[48] but further research in this field is required.

The sample size of this study was calculated to detect a minimal clinically relevant difference of 12 points on VISA-A score. After 1 year, this difference lies within the 95% CI of the adjusted between-group difference (–4.9 to 15.8). Although we cannot exclude a clinically relevant effect of PRP, which was the case at 6 months of follow-up, the chance of such an effect at long term with this CI seems unlikely.

Furthermore, no beneficial effect of PRP on ultrasonographic tendon structure and neovascularization was found in our study. Both the PRP group and placebo group im-

proved tendon structure, but no significant differences between the groups were found. These results are in line with the ultrasonographic changes after 6 months.[16] In equine studies, a correlation between UTC and histologic findings was reported.[41,42] In humans, UTC can differentiate between symptomatic and asymptomatic tendons[43]; however, a clear correlation between tendon structure measured with UTC and clinical outcome after 6 months cannot be found (de Vos *et al.*, unpublished data). In both groups, neovascularization continued decreasing after the increase at the 12-week follow-up. The same pattern was described by Alfredson and Öhberg,[2] reporting neovascularization after sclerosing injections for Achilles tendinopathy. In a previous study on splinting in addition to eccentric exercises, such a pattern was not shown,[12] suggesting that the fluctuations in vascularization may be a direct response to needle trauma.

A limitation of this study is that the exact composition of the PRP is unknown. The platelet separation system used in this trial has been examined in other studies that reported sufficient platelet counts.[27] However, there are a variety of methods for preparing PRP and various forms in which it can be administered. The value of altering variables like platelet count, injected volume, number of injections, preactivation, and presence of leukocytes could not be determined in this study due to the design. More research will be needed to assess the effects of altering these variables on the clinical outcome. At this point in time, there are 7 level 1B studies on PRP in acute and chronic tendon or ligament injuries.[9,17,29,32,36,39,44] In all these studies, very differing preparation and administration techniques were used. None of these high-quality studies showed a statistically significant superior effect compared with placebo.

Some researchers believe PRP should only be reserved for use in severe cases.[11] In the field of tendinopathy research, there is, however, no validated classification for the severity of complaints. Our study population had a mean duration of symptoms of 16 months (range, 2-130 months). In our analysis, the duration of symptoms and baseline VISA-A score were found to be important predictors for VISA-A improvement. For this reason, adjustments were made for these values in the analysis. It is questionable whether PRP treatment can only play a role in patients with resistant tendinopathy that fails to respond to eccentric loading or that the eccentric exercise program dominates the effect of PRP. An animal study revealed that PRP needs to be combined with mechanical stimulation to achieve tendon healing.[45] Furthermore, all published studies on PRP treatment in tendinopathy combined it with strengthening programs.[15]

Based on the current results, no benefit of an injection with PRP, in addition to eccentric exercises in patients with chronic midportion Achilles tendinopathy, was shown at 1-year follow-up.

CONCLUSION

A PRP injection in addition to eccentric exercises did not result in clinical improvement and/or improved structural reorganization on ultrasound after 1 year in chronic midportion Achilles tendinopathy, compared with a placebo injection.

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Chapter 9 General discussion

EPIDEMIOLOGY

The optimal management of a health disorder starts with an accurate description of the problem. We are the first reporting a prevalence of 2.01 per 1000 person years for Achilles tendinopathy in the general population (chapter 2). This prevalence was reproduced by Albers and colleagues, who found a prevalence rate of 2.35 per 1000 person years.[1] The 35% sports-related origin in our prevalence study might be an underestimation. From literature we know that approximately 30% of Achilles tendinopathy patients are sedentary.[2] This confirms the idea that overload is not the only pathomechanism of tendinopathy. Moreover, previous animal studies showed that unloading has an important detrimental effect on mechanical properties tendons.[3,4]

AETIOLOGY

Scott and colleagues debate the role of adiposity and hyperlipidemia in tendinopathy.[5] They suggest that both systemic hyperlipidemia as higher mechanical load contribute to the development of tendon pathology (tendinopathy, ruptures or ultrasound abnormalities. We only measured baseline BMI in our clinical studies and did not find an association between BMI and primary outcome of the study (VISA-A score). We did not measure BMI at the follow-up moments, to evaluate the influence of weight loss on the outcome. In chapter 5 we found a strong association of BMI with poorer ultrasonographic tendon structure in both diabetes type 1 and diabetes type 2 patients. After correction for BMI, diabetes type 2 patients had still poorer tendon structure than controls. This is in accordance with the review of Abate *et al.* who describe the combination of diabetes and obesity as a potential cause of tendon damage.[6]

CONSERVATIVE TREATMENT

In our clinical trials (chapter 6.1, 6.2 and 7) we combined the interventions with an eccentric exercise programme of Alfredson.[7] There is strong evidence for the prescription of an eccentric exercise programmes of 12 weeks in cases with chronic Achilles tendinopathy and this evidence has not changed over the last ten year.[8-10] In a five year follow-up of patients treated with eccentric exercises, we found disappointing patient satisfaction, despite of a continuing increase in VISA-A score (chapter 6.2). The VISA-A is a robust tool that can be used extensively for initial assessment of and following treatment for Achilles tendinopathy. However, as 40% of the questions are about activity, there is a great variety in outcome between athletes and sedentary patients.[11] For the

related questionnaire in patellar tendinopathy (VISA-P) a minimum clinically important difference of 13 points was defined.[12] In our studies (described in chapter 6.1 and 7) we found an improvement of more than 13 points after three months. While there is no clear minimum score for return to sports, success rates of a therapy can not only be based on VISA-A score.

INJECTION TREATMENT

The study on injection treatment with platelet-rich plasma (chapter 7) in this thesis lacks to show effect over placebo injections. One can question whether the investigated injections arrived at the exact site of injury. The injection was ultrasound guided. A cadaveric study (chapter 3) described good distribution of intratendinous injected substance into the Achilles tendon as well as peritendinously independent from post injection ankle movements.

ULTRASONOGRAPHY

Ultrasonographic tissue characterisation was used to monitor tendon structure in chapter 5 and 7. In chapter 4 we lack to show a relationship between the amount of pain and degree of neovascularization. Many imaging studies indicate that abnormalities can exist in asymptomatic tendons.[13-15] Clearly, there is a missing link between the amount of pain and the degree of tendon structural disorganisation on ultrasound.

This is similar to radiologic imaging in patients with knee osteoarthritis, where a discordance is present between pain levels and radiographic signs of osteoarthritis.[16] Another typical similarity between tendinopathy and osteoarthritis is morning stiffness, however one large difference is the fact that pain osteoarthritis continues with ageing, while painful tendons seem to disappear in the very elderly.

CONTINUUM OF TENDON PATHOLOGY

A comparison between tendinopathy and osteoarthritis was also made by Cook and Purdam.[17] They introduced a model about the 'continuum of tendon pathology' based on a continuum from a reversible stage through to advanced osteoarthritis.[18] In their model they describe three distinct stages: (1) reactive tendinopathy,(2) tendon disrepair (failed healing) and (3) degenerative tendinopathy. This interesting model is mainly based on disbalance in loading and the cause of pain cannot explained by it.

PAIN IN TENDINOPATHY

Rio and colleagues described the role of pain in tendinopathy.[19] Physiologic (or nociceptive) pain is a helpful warning sign in case of impending tissue damage or inflammation. Pain in chronic tendinopathy seems to be based on this nociceptive pathway, but also central pain mechanisms might play a role. Van Wilgen *et al.* found some evidence for central sensitization in patellar tendinopathy.[20,21] Because classical inflammation and innervation pattern seem not contributing to the pain in tendinopathy, Rio *et al.* suggest that changes in matrix and cell function are potential sources of nociception in tendons.

We did not measure whether our therapies, altered the matrix and cell function in the patients, but there was no benefit on clinical outcome compared Possibly a combined therapy on pain sensitization would result in a better outcome.

FUTURE PROSPECTS

Future research should focus on the etiology and the role of pain in chronic tendinopathy. For example the role of adiposity in tendinopathy should be further investigated. Therefore, clinical trials should include BMI, fat percentage and blood lipid measurement at start of the study and during follow-up moments.

However, patients who lack to respond to the eccentric exercise can possibly not wait for this holy grail and need an evidence based treatment. Therefore, high quality randomized clinical trials on new treatment options for patients with Achilles tendinopathy who do not respond to an eccentric exercise programme should be conducted in the future. In order to evaluate the effect of treatments in tendinopathy a minimum clinically important change (MCIC) for the VISA-A questionnaire must be determined.

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Chapter 10.1 Summary

SUMMARY

Chronic Achilles tendon pathology is a big problem in sports involving running and jumping. However, it is not always related to excessive physical activity. Recalcitrant Achilles tendons may cause pain for years and are often resistant to any form of treatment. In the end, chronic Achilles tendon complaints may be self-limiting. The aim of this thesis was to elucidate the effect of different treatment options in midportion Achilles tendinopathy, with optimizing current diagnostic methods. For this purpose we conducted two randomised controlled trials, a case control study, a cadaveric study, and a cross sectional study.

The aim of the cross sectional study in **chapter 2** was to ascertain the frequency of midportion Achilles tendinopathy seen in the general practitioner (GP) setting. We were the first to report an incidence rate of Achilles tendinopathy of 1.85 per 1000 registered patients, and of 2.35 in the adult population.

In **chapter 3** we evaluated the effect of two post injection protocols after intratendinous platelet-rich plasma injection on the spread in and around the Achilles tendon. We measured the spread after simulated ankle motion and after a 15 minutes rest post injection in a cadaveric model. We found all ten Achilles tendons to have been gradually infiltrated with platelet-rich plasma after mid-portion injection. No difference was found in intratendinously and peritendinously spread between the two post-injection protocol.

The prospective cohort study in **chapter 4** used a large database of three clinical trials, with over 500 paired measurements, there is no relationship between the amount of pain and degree of ultrasonographically measured neovascularization in symptomatic tendons. Neovascularisation was not present in 24% of chronic symptomatic Achilles tendons. A longer duration of symptoms was not related to presence of neovascularization. A decrease in neovascularization over time during the study was not related with a better improvement in the VISA-A score.

The primary aim of the case-control study in **chapter 5** was to compare Achilles tendon structure in type 1 diabetes and type 2 diabetes patients with healthy age-matched controls. Secondary aim was to correlate skin autofluorescence (AF) as a general indicator of advanced glycation end products (AGEs) with Achilles tendon structure. Furthermore, we investigated prognostic baseline characteristics for Achilles tendon structure. This study showed that people with type 2, and potentially also type 1 diabetes, have compromised structure of the mid-portion of the Achilles tendon. Although patients

with diabetes mellitus have elevated skin AF scores compared with their controls, the difference in ultrasonographic tendon disintegration seems to be based mainly on body mass index (BMI).

Chapter 6.1 and 6.2 contain the one year and five year follow-up of a prospective randomised trial on the effects of a heavy load eccentric exercise programme compared with a heavy load eccentric programme in combination with the use of a night splint in patients with chronic Achilles tendinopathy. Eccentric exercises, with or without a night splint, improved functional outcome after one year follow-up. At follow-up there was no significant benefit of using a night splint in addition to the eccentric exercise programme. There was a continued improvement in functional outcome (VISA-A score) between one year and five year follow-up. Between finishing the 3-month eccentric training programme and the five year follow-up, almost half of the patients had received other therapies. Only 40% of the patients reported being completely pain-free at the 5-year follow-up.

The aim of the follow-up study of a double blinded randomised controlled trial, described in **chapter 7**, was to evaluate both the clinical and the ultrasonographic tissue effects of a PRP injection versus placebo in patients with chronic Achilles tendinopathy after 1 year. A PRP injection in addition to eccentric exercises did not result in clinical improvement or improved structural reorganization on ultrasound, compared with a placebo injection.

Chapter 10.2 Samenvatting

SAMENVATTING

Chronische achillespees aandoeningen vormen een groot probleem voor sporters met hardloop- en sprong belastingen. Het is echter niet altijd gerelateerd aan fysieke overbelasting. De pijn bij recalcitrante Achillespees tendinopathie kan jaren aanhouden zonder te reageren op behandeling. Uiteindelijk lijkt de aandoening wel self-limiting te zijn. Het doel van dit proefschrift was om verschillende behandelopties van midportion Achilles tendinopathie te onderzoeken met betrouwbare diagnostische methoden. Hiervoor voerden we twee gerandomiseerde klinische studies, een case-control studie, een kadaver studie en een cross-sectionele studie uit.

Het doel van de cross-sectionele studie in **hoofdstuk 2** was het vaststellen van het voorkomen van mid-portion Achilles tendinopathie in de huisartsenpraktijk. Dit was de eerste studie die voor achilles tendinopathie een incidentie van 1.85 per 1000 geregistreerde patiënten laat zien en een incidentie van 2.35/1000 in de volwassen populatie.

In **hoofdstuk 3** onderzochten we het effect van twee post-injectie protocollen op de verspreiding van geïnjecteerd plaatjes-rijk plasma (PRP) in het midden van de Achilles pees. We maten de verspreiding van de geïnjecteerde vloeistof na 100 enkel manipulaties en na 15 minuten rust post-injectie in een kadaver studie. In alle tien de Achilles pezen werd een geleidelijke verspreiding van geïnjecteerd PRP gezien. Er was geen verschil in intratendineuze (in de pees) en peritendineuze (rond de pees) verspreiding tussen de twee post-injectie protocollen.

In de prospectieve cohort studie in **hoofdstuk 4** werd gebruik gemaakt van een grote database van drie klinische studies, met meer dan 500 gekoppelde metingen. Er werd geen relatie gevonden tussen de hoeveelheid pijn en met echografie gemeten neovascularisatie in symptomatische pezen. Neovascularisatie was helemaal niet aanwezig in 24% van de pijnlijke achillespezen. Langere duur van de klachten was niet gerelateerd aan meer neovascularisatie. Afname van neovascularisatie gedurende de follow-up periode tot een jaar, was niet gerelateerd aan een betere klinische uitkomst (verbetering VISA-A score).

Het eerste doel van de case-control studie in **hoofdstuk 5** was om echografische gemeten structuur van de achillespezen van type 1 en typ 2 diabetes patiënten te vergelijken met gezonde leeftijds-gematchte controles. Tweede doel was om een huid autofluorescentie (AF) meting (wat de mate van versuikering van de huid aangeeft) te correleren aan de echografische achillespees. De studie liet zien dat patiënten met type 2 diabetes, en mogelijk ook patiënten met type 1 diabetes, een licht verminderde achillespees

structuur hebben dan de gezonde controles van dezelfde leeftijd. Hoewel patiënten met diabetes mellitus verhoogde AF-scores hadden vergeleken met hun controles, was het verschil in echostructuur hier niet door te verklaren. Groote voorspellende waarde voor echografische peesstructuur bleek de body-mass index (BMI).

Hoofdstuk 6.1 en 6.2 bevatten de één-jaars- en vijf-jaars follow-up van een prospectieve gerandomiseerde studie naar het effect van excentrische oefentherapie vergeleken met dezelfde excentrische oefentherapie in combinatie met het dragen van een nachtspalk bij patiënten met mid-portion achilles tendinopathie. Excentrische oefentherapie, mét en zonder nachtspalk, verbeterde de functionele uitkomst na één jaar. Er was geen significant effect van het gebruik van een nachtspalk naast de excentrische oefeningen. Tussen de één-jaars follow-up en de vijf-jaars follow-up was er een continuerende verbetering van de functionele uitkomst (verbetering van de VISA-A score) Tussen het afronden van het excentrische oefenprogramma na drie maanden en de vijf-jaars follow-up, had bijna de helft van de patiënten andere therapieën ondergaan. Slechte 40% van de patiënten gaf aan volledig pijnvrij te zijn bij de vijf-jaars follow-up.

Het doel van de follow-up studie van een dubbelblind gestratificeerde gerandomiseerde gecontroleerde studie, beschreven in **hoofdstuk 7**, was om het klinische en echografische effect van plaatjes-rijk plasma injectie versus placebo-injectie na één jaar te evalueren in patiënten met chronische midportion achilles tendinopathie. Een injectie met plaatjes-rijk plasma als toevoeging op excentrische oefentherapie resulteerde niet in een betere klinische uitkomstmaat of echo structuur, vergeleken met een placebo injectie.

Dankwoord

DANKWOORD

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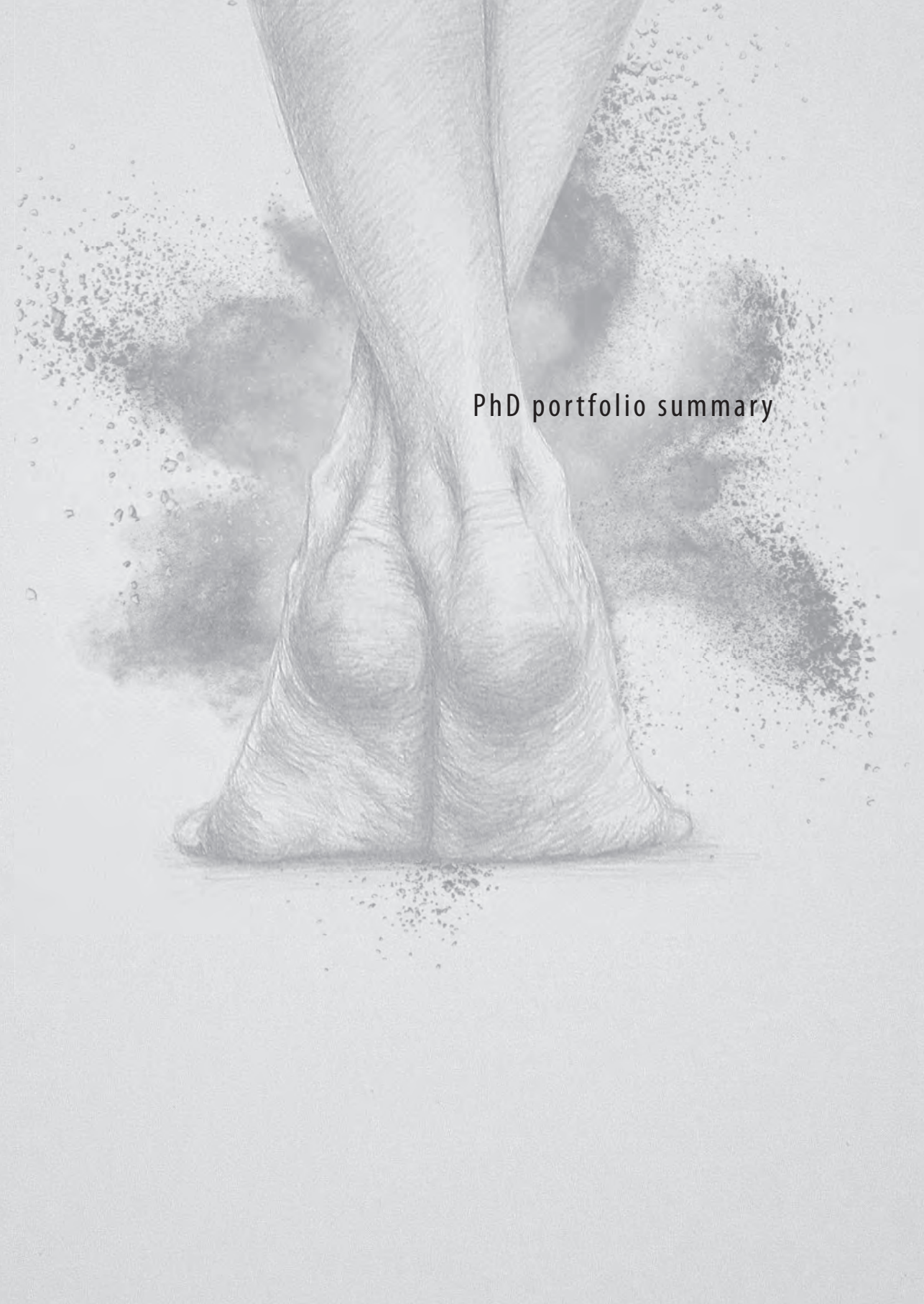
Curriculum vitae

CURRICULUM VITAE

Suzan de Jonge werd geboren op 3 januari 1984 te Oost-Souburg, gemeente Vlissingen. Van 1996 tot en met 2002 doorliep zij het atheneum aan het Erasmus College in Zoetermeer. Hierna startte zij de studie geneeskunde aan de Universiteit van Leiden, waar zij in 2003 haar propedeuse behaalde. Voor haar afstudeeronderzoek heeft zij 3 maanden stage gelopen op de afdeling Sportgeneeskunde in het Medisch Centrum Haaglanden te Leidschendam onder begeleiding van dr. Hans Tol, waarna in februari 2007 het doctoraal werd verkregen. Het artsexamen legde zij in maart 2009 af.

Vanaf juni 2009 werd zij door Prof. dr. Jan Verhaar en Prof. dr. ir. Harrie Weinans aangesteld als promovendus op het reeds bestaande peesproject in het Erasmus Medisch Centrum te Rotterdam. Dit promotietraject gecombineerd met de opleiding Sportgeneeskunde heeft geleid tot de totstandkoming van dit proefschrift. In mei 2014 volgde zij een travelling fellowship van The European College of Sport and Exercise Physicians (ECOSEP) in vijf Europese steden.

Suzan de Jonge woont sinds oktober 2009 samen met Arjen Joosse in Leiden. Momenteel is zij werkzaam als arts-assistent Sportgeneeskunde in het Medisch Centrum Haaglanden, locatie Antoniushove te Leidschendam onder hoofdopleider drs. Robert van Oosterom.



PhD portfolio summary

PHD PORTFOLIO

Summary of PhD training and teaching activities
Name PhD student: S. de Jonge
Erasmus MC Department: Orthopaedic Research Laboratory
PhD period: 2009-2015
Promotors: Prof.dr.ir. H. Weinans, Prof.dr. J.A.N. Verhaar
Supervisors: dr. J.L. Tol

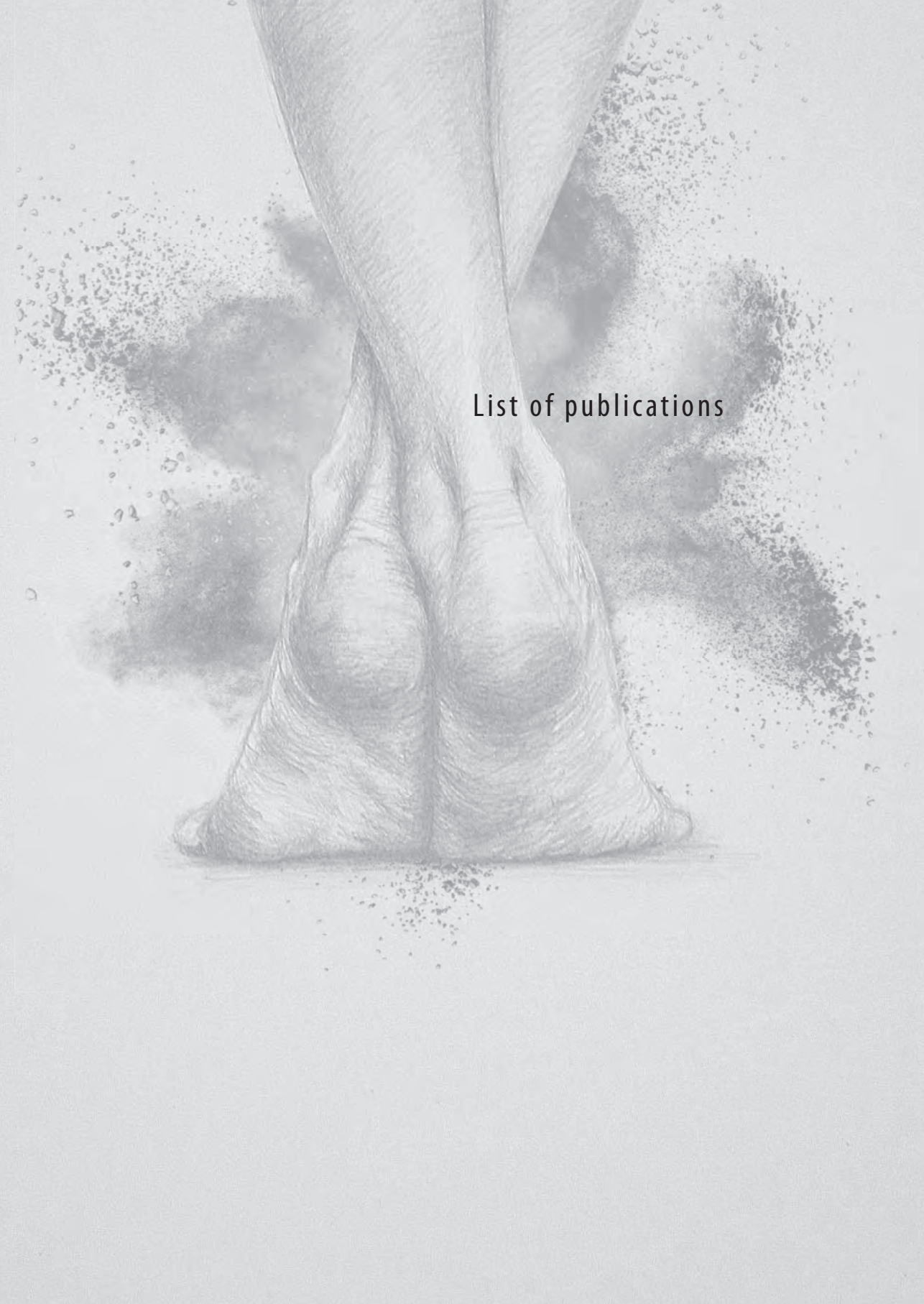
	Year	ECTS
1. PhD training		
In-depth courses		
Introduction to data-analysis (NIHES)	2010	5.7
Biomedical English Writing and Communication (EUR)	2011	4.0
Basiscursus Regelgeving & Organisatie voor Klinisch onderzoekers (BROK)	2011	4.0
Masterclass Medical Business	2013	0.3
(Inter)national Conferences: invited lectures		
Het effect van een Plaatjes-Rijk Plasma injectie in chronische midportion Achilles Tendinopathie. Een dubbelblind gerandomiseerd placebo-gecontroleerd klinisch onderzoek met 1-jaars follow-up. ZWOT bijeenkomst, 1 maart 2010, Rotterdam	2010	1.0
Platelet-Rich Plasma as a treatment for tendon injuries. FA Elite Football Medicine Conference, 12 October 2010, London, Great Britain	2010	1.0
PRP and tendinopathies: Cons 15th ESSKA Congress, 03 May 2012, Geneva, Switzerland	2012	1.0
Imaging and (injection) treatment in midportion Achilles tendinopathy 16th Annual Scientific Conference in SEM QMUL CSEM in association with European College of Sport and Exercise Physicians , 4 September 2014, London, Great Britain	2014	0.5
(Inter)national Conferences: podium presentations		
The additional value of splinting to eccentric exercises in chronic midportion Achilles Tendinopathy: a randomized controlled trial with one-year follow-up International Federation of Orthopaedic Manipulative Therapists (IFOMT), 13 June 2008, Rotterdam	2008	0.5
One-year follow-up of a randomised controlled trial on added splinting to Eccentric exercises in chronic midportion Achilles tendinopathy VSG congres "Sport, Bewegen & Gezondheid", 28 November 2008, Noordwijkerhout	2008	0.5
Inter- en intra observer betrouwbaarheid Ultrasonographic Tissue Characterisation (UTC) VSG congres "Sport, Bewegen & Gezondheid", 4 December 2009, Noordwijkerhout	2009	0.5

	Year	ECTS
Awarded 2nd best abstract price Stichting Sport & Orthopaedie		
The effect of Platelet-Rich Plasma injection in chronic midportion Achilles tendinopathy: A double-blinded randomized placebo-controlled clinical trial with 1-year follow-up NVA-VSG congress 'New Horizons in Arthroscopy', 27 May 2010, Noordwijk aan Zee, the Netherlands	2010	0.5
The effect of Platelet-Rich Plasma injection in chronic midportion Achilles tendinopathy. A double-blinded randomized placebo-controlled clinical trial with 1-year follow-up. 2nd Congress European College of Sport and Exercise Physicians 12th Annual Scientific Conference in SEM QMUL CSEM, 10 September 2010, London, Great Britain	2010	0.5
The effect of Platelet-Rich Plasma injection in chronic midportion Achilles Tendinopathy. A double-blinded randomised placebo-controlled clinical trial with 1-year follow-up. Dutch Tendon Meeting, 22 September 2010, Rotterdam, the Netherlands	2010	0.5
What about neovessels? Een database studie naar de correlatie tussen Neovascularisatie en kliniek. VSG congres "Sport, Bewegen & Gezondheid", 25 November 2010, Noordwijkerhout, the Netherlands	2010	1.0
Plaatjes-Rijk Plasma behandeling bij Achilles tendinopathie: een dubbelblind gerandomiseerde studie met één-jaars follow-up. VSG congres "Sport, Bewegen & Gezondheid", 25 November 2010, Noordwijkerhout, the Netherlands *Awarded best abstract price Stichting Sport & Orthopaedie*	2010	0.5
Plaatjes-Rijk Plasma behandeling bij Achilles tendinopathie: een dubbelblind gerandomiseerde studie met één-jaars follow-up. Landsteiner wetenschapsmiddag, 26 November 2010, Den Haag, the Netherlands	2010	0.5
Lange termijn follow-up van Achilles tendinopathie vijf jaar na excentrische oefentherapie VSG congres "Sport, Bewegen & Gezondheid", 02 December 2011, Kaatsheuvel, the Netherlands	2011	1.0
Type 2, But Not Type 1 Diabetes, Predisposes To Achilles Tendon Disintegration 59th Annual Meeting ACSM, 2 June 2012, San Fransisco, USA	2012	1.0
Determinants of early Achilles tendon degeneration in Diabetes patients VSG congres "Sport, Bewegen & Gezondheid", 29 December 2012, Ermelo, The Netherlands *Awarded 2nd best abstract price Stichting Sport & Orthopaedie*	2012	0.5

	Year	ECTS
(Inter)national Conferences: poster presentations		
The additional value of a night splint to eccentric exercises in chronic midportion Achilles tendinopathy: a randomized controlled trial Society for Tennis Medicine and Science World congress, February 2007, Antwerpen, Belgium	2007	1.0
The effect of Platelet-Rich Plasma injection in chronic midportion Achilles tendinopathy Tendinopathy Symposium, 30 September and 1 october, Umea, zweden	2010	1.0
Determinanten van vroege Achillespees-degeneratie bij Diabetes patiënten Landsteiner wetenschapsmiddag, 23 November 2012, Den Haag, the Netherlands	2012	0.5
Occasional Reviewer for		
Physical Medicine and Rehabilitation	2010	0.15
British Medical Journal	2011	0.20
Physical Therapy in sport	2011	0.20
British Journal of Sports Medicine	2012	0.15
Health Research Board (HRB) Ireland	2014	0.15
Sports Medicine	2014	0.15
Other		
ECOSEP/Bauerfind Travelling Fellowship (5 weeks)	2014	6.0
- Invited lecture: Sports Medicine in The Netherlands Sports Medicine Trainees meeting London , 3 September 2014, London, Great Britain		
- Invited lecture: ECOSEP-Bauerfeind travelling fellowship Sports Medicine Trainees meeting London , 4 September 2014, London, Great Britain		
2. Teaching activities	Year	ECTS
Lecturing		
Achilles tendinopathie college tweedejaars geneeskunde studenten 7 January 2010, Erasmus MC, Rotterdam, the Netherlands	2010	0.5
The effect of Platelet-Rich Plasma injection in chronic midportion Achilles tendinopathy onderwijs arts-assistenten Orthopaedie 14 July 2010, Erasmus MC, Rotterdam, the Netherlands	2010	0.5
Onderwijs Minor "Orthopaedische Sporttraumatologie" Pees en ligament 28 September 2010, Erasmus MC, Rotterdam, the Netherlands	2010	0.5
College tweedejaars geneeskunde studenten: Achilles tendinopathie 24 January 2011, Erasmus MC, Rotterdam, the Netherlands	2011	0.5
Intra-tendineuze afwijkingen; beeldvorming en aangrijpingspunten voor behandeling Wetenschappelijke Bijeenkomst VSG: Chronische Midportion tendinopathie van de Achillespees	2011	0.5

	Year	ECTS
1 February 2011, Cibit, Bilthoven, the Netherlands		
Intra-tendineuze afwijkingen; beeldvorming en aangrijpingspunten voor behandeling Onderwijs arts-assistenten Orthopaedie 2 February 2011, Erasmus MC, Rotterdam, the Netherlands	2011	0.5
Onderwijs Minor "Orthopaedische Sporttraumatologie" Pees onderwijs 19 September 2011, Erasmus MC, Rotterdam, the Netherlands	2011	0.5
Supervising practicals		
Begeleiding review tweedejaars geneeskunde studenten, EMC "Conservatieve behandeling van peesaandoeningen: effecten van autologe groeifactoren in tendinopathie?"	2009	0.5
Begeleiding review tweedejaars geneeskunde studenten, EMC "Het effect van geslacht op Achilles tendinopathie: een systematische review"	2009	0.5
Supervisie snuffelstage geneeskundestudent, AMC Correlatie neovascularisatie en klinische presentatie in Achilles tendinopathie	2010	0.5
Supervisie wetenschapsstage geneeskundestudent, Universiteit Leiden Incidence Achilles tendinopathy in the general population Jan 2011- Apr 2011	2011	0.5
Supervisie wetenschapsstage geneeskundestudent, Universiteit Leiden Ultrasonographic tissue characterisation of human Achilles tendons Feb 2012- Sep 2012	2012	1.0
Supervisie wetenschapsstage geneeskundestudent, Universiteit Leiden Clinical implications of the VISA-A score Sep 2012- Dec 2012	2012	0.5
Supervisie wetenschapsstage geneeskundestudent, Universiteit Leiden Dose reponse relation between eccentric exercises and clinical outcome Jul 2013-Dec 2013	2013	1.0
3. Other activities	Year	ECTS
Board positions		
Member of the board of registrars sports medicine (Juniorkamer VSG) - Guidelines & Science - Chairman	2011 2011-2013 2014-present	4.0
Member of the board of the Netherlands Association of Sports Medicine (VSG)	2014	3.0
Member workgroup "Coach, Cure & Care, healthcare in 2025" - Organisation Symposium Coach, Cure Care 08-10-2013 - Oral presentation and organisation: Coach, Cure, Care 2025 Discussion Meeting Dutch Association Sports Medicine: Healthcare in 2025, 27 November 2013, Ermelo, The Netherlands - Organisation Symposium Coaching, who cares 19-01-2015	2013-present 2013 2013 2015	4.0
National Conferences		

	Year	ECTS
Oral presentation: Anthropometric values as predictor for hamstring graft diameter in anterior cruciate ligament reconstruction NVA-VSG congress 'New Horizons in Arthroscopy', 27 May 2010, Noordwijk aan Zee, the Netherlands	2010	0.5
Invited lecture: Sportmedische screening bij dansers Dans & gezondheid-symposium KNOW MORE - DO BETTER, Codarts, University of the Arts 7 February, Rotterdam, The Netherlands	2015	0.5
Total		55.0



List of publications

LIST OF PUBLICATIONS

Weir A, Veger SA, Van de Sande HB, Bakker EW, de Jonge S, Tol HJ.
A manual therapy technique for chronic adductor related groin pain in athletes: a case series.
Scand J Med Sci Sports. 2009 Oct;19(5):616-20. Epub 2008 Aug 5.

de Jonge S, de Vos RJ, van Schie HT, Verhaar JA, Weir A, Tol JL.
One-year follow-up of a randomised controlled trial on added splinting to eccentric exercises in chronic midportion Achilles tendinopathy.
Br J Sports Med. 2010 Jul;44(9):673-7. Epub 2008 Oct 6.

van Schie HT, de Vos RJ, de Jonge S, Bakker EM, Heijboer MP, Verhaar JA, Tol JL, Weinans H.
Ultrasonographic tissue characterisation of human Achilles tendons: quantification of tendon structure through a novel non-invasive approach.
Br J Sports Med. 2010 Dec;44(16). Epub 2009 Aug 6.

de Jonge S.
Boekbespreking proefschrift R.J. de Vos: Imaging and Treatment of Chronic Midportion Achilles Tendinopathy.
Sport & Geneeskunde. Jaargang 43, nummer 4, oktober 2010.

de Jonge S, de Vos RJ, Weir A, van Schie HTM, Bierma-Zeinstra SMA, Verhaar JAN, Weinans H, Tol JL.
One-Year Follow-up of Platelet-Rich Plasma Treatment in Chronic Achilles Tendinopathy
A Double-Blind Randomized Placebo-Controlled Trial
Am J Sports Med. 2011 Aug;39(8):1623-9. Epub 2011 May 21.
Awarded best manuscript in 2011 TulipMed

de Jonge S, van den Berg C, de Vos RJ, van der Heide HJL, Weir A, Verhaar JAN, Bierma Zeinstra SMA, Tol JL.
Incidence of midportion Achilles tendinopathy in the general population.
Br J Sports Med. 2011 Oct;45(13):1026-8.

van der Plas A, de Jonge S, de Vos RJ, van der Heide HJ, Verhaar JA, Weir A, Tol JL.
A 5-year follow-up study of Alfredson's heel-drop exercise programme in chronic mid-portion Achilles tendinopathy.
Br J Sports Med. 2012 Mar;46(3):214-8. Epub 2011 Nov 10.

de Jonge S.
Congres verslag: 15th ESSKA Congress May 2012, Geneva, Switzerland
Sport & Geneeskunde. Jaargang 45, nummer 4, oktober 2012.

de Jonge S, Warnaars J, de Vos RJ, Weir A, van Schie HTM, Bierma Zeinstra SMA, Verhaar JAN, Tol JL.
Relationship between neovascularization and clinical severity in Achilles tendinopathy in 556 paired measurements
Scand J Med Sci Sports. 2014 Oct;24(5):773-8. Epub 2013 Apr 22

de Jonge S, van Dorssen E, Ottevanger C.
Verslag discussiebijeenkomst "Zorg 2025" December 2013, Ermelo, The Netherlands
Sport & Geneeskunde. Jaargang 47, nummer 1, februari 2014.

Wiegerinck JI, de Jonge S, de Jonge MC, Kerkhoffs GM, Verhaar J, van Dijk CN.
Comparison of Postinjection Protocols After Intratendinous Achilles Platelet-rich Plasma Injections: A Cadaveric Study.
J Foot Ankle Surg. Epub 2014 Aug 13

West L, Malliaropoulos N, de Jonge S
Editorial: ECOSEP – Bringing the European SEM family together.
Br J Sports Med. 2014;48:1585

de Jonge S, Joosse A
Verslag symposium Sports Medicine Meets Oncology: Oncologische revalidatie: noodzaak of luxe?
Sport & Geneeskunde. Jaargang 47, nummer 5, november2014

de Jonge S, Rozenberg R, Vieyra B, Stam HJ, Aanstoot HJ, Weinans H, van Schie HTM, Praet SFE
Achilles tendons in people with type 2 diabetes show mildly compromised structure: an ultrasound tissue characterisation study.
Br J Sports Med. Epub 2015 Jan 13

de Jonge S, Tol JL, Weir A, Waarsing JH, Verhaar JAN, de Vos RJ
Tendon structure returns to asymptomatic values in conservatively treated Achilles tendinopathy, but is not associated with symptoms: a prospective study.
Accepted in Am J Sports Med.