REGULATION IN VASCULARITY AFTER EXTRACORPOREAL SHOCK WAVE THERAPY IN INDIVIDUALS WITH PROXIMAL PLANTAR FASCIITIS

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CERTIFICATE OF ORIGINALITY

The idea of the present investigation originated from Dr Amy Fu. The design of the study, the planning of the experiment and data interpretation resulted from discussions and multiple trials between the author and Dr Amy Fu.

I hereby declare that this thesis, to the best of my knowledge and belief, reproduces no material previously published or written, nor material that has been accepted for the award of any other degree or diploma, except where due acknowledgement has been made in the text.

________________ (Signed)

HONGYING CHEN (Name of student)

ABSTRACT

Plantar fasciitis is one of the most common causes of heel pain, but its etiology and pathogenesis are unclear. Vascular disturbance with consequent metabolic impairment is thought to play an important role. Vascular changes have been observed in patients with plantar fasciitis and modulation in vascularity is detected in individuals with tendinopathy after extracorporeal shock wave therapy (ESWT). ESWT has been approved by the Food and Drug Administration (FDA) of the Unites States in 2000 for treating patients with plantar fasciitis and gives evident pain reduction when the treatment was delivered at low to medium intensity at weekly basis for multi-sessions. If treatment should be prescribed based on the stage of the disease, vascularization could be one of the determining factors in delineating a treatment protocol. In order to have a better understanding of the treatment's efficacy, biological effects studies need to be assessed in the short and long term after treatment. Such information would enhance our understanding of the ESWT-induced biological changes in vascularization and form a scientific basis for ESWT's clinical application.

This project consisted of 5 inter-related studies. The first study (Chapter 2) aimed to establish a reliable measure to quantify the vascularity of the plantar fascia as well as delineate the minimum detectable changes and cut-off point for

identifying individuals with and without unusual vascularization. Study 2 (Chapter 3) explored vascularization and fascia thickness in patients diagnosed with plantar fasciitis and able-bodied controls. The study also explored relationships between the duration of the disorder with vascularity and fascia thickness. In study 3 (Chapter 4), regulation in vascularity was assessed in patients with plantar fasciitis after 3 or 6 sessions of ESWT and compared with patients with no intervention. The influence of pre-intervention vascularization on treatment planning was explored in study 4 (Chapter 5). Patients with duration of symptoms less than 12 months were followed up 3 and 6 months after the application of ESWT. Factors affecting treatment success were investigated and reported in study 5(Chapter 6). Aside from vascularization and fascia thickness, the outcome measures included self-perceived pain and foot function.

Based on Power Doppler Ultrasonography, a quantitative vascularity index (VI) was defined which correlated well with Newman's grading scale. It provided a minimum detectable difference of 0.68% in vascularity. In addition, vascular index of 2.60% was shown to differentiate patients with and without morderate to severe vascularization. Vascularization and thickened plantar fascia were evident in the patient group. In patients with symptoms lasting less than 12 months, vascularity index was shown to be positively correlated with pain and foot function. Minimal vascularity was observed in subjects with symptoms lasting beyond 12 months. The plantar fascia in these patients had similar thickness as those with symptoms less than 12 months. Immediate after ESWT, regulation in vascularity was observed in 60% of the patients studied. The direction of change was shown to depend on the treatment dosage and baseline vascularization. Down-regulation in vascularity was observed in vascularized patients (with VI >2.6%) after 6 sessions of ESWT. Vascularity was up-regulated in non-vascularized patients after receiving either 3 or 6 sessions of ESWT. A VI score >1.55% at baseline was a strong predictor of unsuccessful recovery with only 3 sessions of ESWT, but 62.50% of patients with a baseline VI score <3.25% recovered successfully after 6 sessions of ESWT. No patients could be treated successfully if their pre-intervention VIs were beyond 3.25%. Regression of vascularity was continued to 6 months post intervention, and 91.67% patients with excellent treatment results had normal vascularity. Fascia thinning was evident after 3 months, and about 50% of the patients had regained normal fascia thickness by 6 months post intervention. Our findings thus indicate that 6 sessions of treatment were more effective for patients with greater vascularization.

The above findings lead to 3 main conclusions. 1) Patients with plantar fasciitis for more than 3 months (9.21 ± 6.44 months) show increased vascularity in the affected fascia. ESWT can modify the vascularity in 60% of patients, but the direction of regulation depends on the baseline vascularization and the number of treatment sessions. 2) Individuals with increased vascularization could not reach a satisfactory result after only 3 sessions of ESWT; 6 sessions of ESWT could improve about 60% of vascularized patients at 1 month follow-up. 3) The regression of vascularity after ESWT continues to 6 months post-intervention. This could be related to natural history as well as treatment effects from the shock wave. Regression analysis indicated that patients' baseline vascularization together with treatment protocol are two factors that affect treatment effectiveness in terms of pain reduction.

RESEARCH OUTPUT ARISING FROM THE THESIS

PUBLICATIONS

- Hongying Chen, Hokming Ho, Michael Ying, Siu-Ngor Fu. Correlation between computerized and Newman's scaling on vascularity using Power Doppler Ultrasonography and its predictive value in patients with plantar fasciitis. Accepted by British Journal of Radiology, 2011.

CONFERENCE PRESENTATIONS

- Hongying Chen, Hok-ming Ho, Michael Ying, Siu-Ngor Fu. Poster presentation: Proximal plantar fascia microcirculation is modulated in patients with plantar fasciitis. Proceedings of the 16th international World confederation for Physical therapy congress, Amsterdam, Netherlands.
- Chen Hongying, Fu SN, Ho HM, Ying M. Changes in proximal plantar fascia microcirculation in patients with plantar fasciitis. Proceedings of the 30th annual congress of the Hong Kong Orthopaedic association, Hong Kong S.A.R., China
- Hongying CHEN, Siu-ngor FU, Hok-ming HO, Michael YING. Changes in proximal plantar fascia microcirculation in patients with plantar fasciitis. Proceedings of the 7th Pan-Pacific Conference on Rehabilitation, Hong Kong S.A.R., China
- Hongying Chen, Siu-Ngor Fu, Kevin Kwong, Michael Ying. Quantitatively Measuring Proximal Plantar fascia Microcirculation by Power Doppler Ultrasonography. Proceedings of the 12th world congress of the world Federation of ultrasound in medicine and biology. Sydney, Australia. Ultrasound in Medicine & Biology, Volume 35, Issue 8, Supplement 1, August 2009, Page S191.
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LIST OF ABBREVIATIONS

ANOVA	:	Analysis of variance
AROM	:	Active range of motion
AUC	:	Area under curve
BMI	:	Body mass index
C	:	Calcaneus
CI	:	Confidence interval
D_P	:	Dominant foot being affected
DVs	:	Dummy variables
EFD	:	Energy flux density
ESWT	:	Extracorporeal shock wave therapy
$ESWT_3$	:	3 sessions of ESWT
$ESWT_6$	:	Received 6 sessions of maximum intensity of ESWT
FFI	:	Foot function index
FFI_pain	:	Pain subscale of the foot function index
ICC	:	Intraclass correlation coefficient
mJ	:	Mega joule
mm^2	:	Millimeter square
MDD	:	Minimal detectable difference
MPa	:	Million pascal
MTP	:	Metatarsal-phalangeal joint
ND_P	:	Non-dominant foot affected
NO	:	Nitric oxide
ns	:	Nanoseconds
NSAIDs	:	Nonsteroidal anti-inflammatory drugs
O_2	:	Oxygen
OR	:	Odds ratio

p	:	Significant level
PDU	:	Power Doppler Ultrasonography
PF	:	Plantar fascia
PRF	:	Pulsed repetition frequency
PROM	:	Passive range of motion
ROC	:	Receiver operating characteristic curves
ROI	:	Region of interest
ROMs	:	Range of motions
SD	:	Standard deviation
SEM	:	Standard error measurement
VAS	:	Visual analogue scale
VEGF	:	Vascular endothelial growth factor
VI	:	Vascular index
VI_5	:	Vascularity index from averaging of all 5 images
VI_3	:	Vascularity index from first 3 images
VI_{Max}	:	Maximum vascularity index of all 5 images
%	:	Percentage
=	:	Equal
$<$	:	Less than
$\leq$	:	Less or equal to
$>$	:	More than
$\pm$	:	Plus and minus
$\surd$	:	Square root

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CHAPTER 1

INTRODUCTION

1.1 The plantar fascia

1.1.1 Functional anatomy of the plantar fascia

The plantar fascia is an investing fibrous sheet of connective tissue which arises predominantly from the medial process of the calcaneal tuberosity. It attaches distally to the medial and lateral intermuscular septa and the plantar aspect of the forefoot through several slips (Sarrafian 1983). The fascia forms a mechanical linkage between the calcaneus and the toes.

The plantar fascia has a thicker central part which forms the strong plantar aponeurosis, and weaker medial and lateral parts (Hedrick 1996). The central aponeurotic band, which is often considered the major component of the plantar fascia, is dense and tough (Wearing et al. 2006). This central part can be viewed as a continuation of either the triceps surae or the plantaris tendon (Viel and Esnault 1989; Waller and Maddalo 1986). However, human ontogenetic studies have shown that the central part develops independently (Dylevsky 1988).

Biomechanically, the elastic plantar fascia acts as a tie-bar connecting the rigid calcaneus and the metatarsal bones. It forms part of a passive mechanism which modulates the stiffness of the arch in relation to the applied load (Vogler and Bojsen-Moller 2000) and is important in supporting the medial longitudinal arch during static stance (Wearing et al. 2006). The plantar fascia also plays an important role in increasing the stability of the arch in preparation for the swing phase of the gait cycle (Bojsen-Møller 1979; Rush et al.2000). In 1954, Hicks described this as a “windlass” mechanism (Hicks 1954). He explained that during metatarsal-phalangeal joint dorsiflexion, the effective length of the fascia is shortened and the tension within the fascia is increased proportionally. Such changes would result in increased stability of the arch. The plantar fascia also serves as a dynamic shock absorber for the foot during walking and running (Cornwall and McPoil 1999; Roxas 2005).

1.1.2 Vascularity of the plantar fascia

Like other connective tissues, the plantar fascia is a relatively hypovascular structure (Wearing et al. 2006). Blood supply to the plantar fascia is mainly from the lateral plantar artery, which is a tributary of the posterior tibial artery (Moore et al. 2010). A group led by Morel has studied the plantar fascia insertions of 10 healthy volunteers using contrast-enhanced ultrasonography and an intravenous bolus injection. Inferior branches of the lateral plantar artery were observed running toward the calcaneal tuberosity, near the insertion of the plantar fascia (Morel et al. 2005). These results suggest some vascularization in the immediate vicinity of the insertion of the plantar fascia.

1.2 Plantar fasciitis

Plantar fasciitis is suggested to have an inflammatory response at acute stage due to the mechanical overload (Kaya 2002; Warren 1984), and resulting in chronic inflammation followed by degeneration (Healey and Chen 2010; League 2008; Lemelle et al. 1990). Plantar fasciitis is a localized inflammation and degeneration of the proximal plantar fascia (League 2008).

1.2.1 Diagnosis

The diagnosis of plantar fasciitis is mainly based on clinical presentation with no specific objective or reliable diagnostic test (Neufeld and Cerrato 2008). The typical presentation from patients with plantar fasciitis is pain and palpable tenderness in the area of the medial tubercle of the calcaneus at the heel. The inferior heel is especially painful in the first few steps in the morning or when getting up to walk after prolonged sitting, and it may lessen after further ambulation but increases after continued weight bearing activity (Cole et al. 2005; Cornwall and McPoil 1999; Cullen and Singh 2006; Neufeld and Cerrato 2008). The pain may be exacerbated by walking barefoot, on the toes, or up stairs (League 2008). In radiological examination, about 50% to 75% of patients with heel pain were also found to have heel spurs (Davis et al. 1994; Williams et al. 1987), compared with 15% to 25% of asymptomatic individuals (Young et al. 2001). This indicates that osteophytes can occur with plantar fasciitis but may not be the cause of the pain (Glzaer 2009; Neufeld and Cerrato 2008). Ultrasound measurement of plantar fascia thickness has been used as one of the diagnostic criteria for plantar fasciitis (Healey and Chen 2010). An individual is considered as having plantar fasciitis if the thickness of the plantar fascia is 4mm or more (Akfirat et al. 2003; Gibbon and Long 1999; Karabay et al. 2007; Wall et al. 1993).

1.2.2 The prevalence of plantar fasciitis

Plantar fasciitis is one of the most common painful foot conditions. It affects both active and sedentary adults, with a peak incidence between 40 and 60 years of age (Cole et al. 2005; Davis et al.1994; Gill and Kiebzak 1996; Neufeld and Cerrato 2008). Each year, about two million individuals suffer from this condition in the United States (Riddle and Schappert 2004). About 10 to 20% of athletes are affected by this painful disorder (Taunton et al. 2002; Rome et al. 2001). Even though most of these sufferers recovered after conservative interventions within 6 to 18 months (Davis et al. 1994; Martin et al. 1998), about 5 to 10% of recalcitrant cases progress to surgery (O'Malley et al. 2000).

1.2.3 Etiology

The etiology of plantar fasciitis is still not well understood (Schepsis et al. 1991; Wang et al. 2006; Wearing et al. 2006). Biomechanics has been thought to play an important role in developing plantar fasciitis (Cornwall and McPoil 1999;

Cullen and Singh 2006; Riddle et al. 2003; Wearing et al. 2006). Any factors which increase loading and lower the medial longitudinal arch induce tension in the fascia which can lead to the development of plantar fasciitis (McGonagle et al. 2002; Wearing et al. 2006). Individuals with high body weight (Cullen and Singh 2006; Wearing et al. 2006), those spending most of the day on their feet (Cullen and Singh 2006; Riddle et al. 2003), and runners (Dyck and Boyajian-O'Neill 2004) are the high risk groups.

According to Hick's windlass effect, any increase in the arch as a result of increased digital dorsiflexion (extension) and limited ankle dorsiflexion can induce greater stress in the plantar fascia, but this is difficult to confirm experimentally. Rome et al. (2001) reported no differences in ankle dorsiflexion range in athletes with and without plantar fasciitis. Among five similar studies, 2 have reported increased range of ankle dorsiflexion among plantar fasciitis sufferers (Irving et al. 2007; Pohl et al. 2009) and 3 others found decreases (Kibler et al. 1991; Riddle et al. 2003; Warren 1984) compared with healthy individuals. It is worth noting that Pohl et al (2009) was testing a group of runners who were pain-free at the time of the assessment, and Irving et al. (2007) used a dorsiflexion lunge test to measure the range indirectly. Aside from reporting a decrease in the ankle dorsiflexion range in the patient group, Riddle et al. (2003) also suggested that a reduction of 1 to 5 degrees in ankle dorsiflexion would increase the possibility of developing plantar fasciitis eight-fold. Increased digital dorsiflexion was first reported by Creighton and Olson in 1987. Many years later, Allen and Gross (2003) found comparable passive range of motions (ROMs) of the first metatarsal-phalangeal joint (MTP) in affected and unaffected feet.

1.2.4 Pathogenesis

Aside from its unknown etiology, the pathogenesis of this common foot disorder is also not clear. It has been suggested that mechanical overload and excessive strain induce microscopic tears within the fascia that subsequently evoke an inflammatory repair process (Kaya 1996; League 2008). However, there are studies reporting that degenerative features such as collagen degeneration (Lemont et al. 2003; Tountas and Fornasier, 1996), increased mucoid ground substances (Lemont et al. 2003), and calcification (Lemont et al. 2003; Schepsis et al. 1991), rather than inflammation, are the predominant histological findings in patients with plantar fasciitis. These features have been found to be more profound in chronic sufferers (pain lasting for more than 6 months) and sedentary patients (Lemont et al. 2003; Wearing et al. 2006). The change in this condition is more like what is currently accepted for tendinopathy, that is, degenerative not inflammatory (Wearing et al. 2006). Plantar fasciopathy might, in fact, be a more appropriate term to describe this condition (Rompe 2009), but plantar fasciitis is still the term commonly being used (Healey and

Chen 2010; Toomey 2009).

Fibrovascular hyperplasia and proliferation are also reported frequently, and these indicate increased vascularity (Lemont et al. 2003; LeMelle et al. 1990; Tountas and Fornasier 1996; Snider et al. 1983). Increased vascularity is evident at the proximal plantar fascia (Walther et al. 2004), especially among those having had the problem for less than 12 months.

Plantar fasciitis is often, though not always, similar to tendonitis (Wright and Rennels 1964). Similar vascularization has also been observed in patients with Achilles tendinopathy (Ohberg and Alfredson 2004) and patellar tendinopathy (Alfredson and Ohberg 2005). Alfredson (2004) proposed vascularization in diseased tendons as one of the potential mediators of pain in cases of tendinopathy. He proposed that nerve ingrowth associated with new vessels causes the pain in these patients. Further studies have confirmed that the intensity of pain with chronic tendinopathy is greater in vascularized patients compared with those not newly vascularized (Cook et al. 2004; Zanetti et al. 2003). In vascularized plantar fasciitis, a higher Newman's grading has been associated with greater intensity of pain (Walther et al. 2004), and this has also been seen with patellar and Achilles tendinopathy (Alfredson et al. 2003, 2005). Information from these studies highlights a possible association between vascularization and plantar fasciitis.

Cook and Purdam (2009) proposed a continuum model for tendinopathy.

It involves three continuous stages: reactive tendinopathy, tendon disrepair and degenerative tendinopathy. The intensity of vascularity is one criterion in classifying tendinopathy. Generally swollen tendons, mildly hypoechoic with no or minimal vascular changes, indicate the early reactive stage. The presence of multiple vessels in the affected tendon indicates the degenerative stage. The authors proposed that ideal interventions should be tailored for the different pathological phases.

The results from all of these studies indicate that neither the etiology nor the pathogenesis of plantar fasciitis is very clear. Increased vascularity is observed in some but not all patients with chronic plantar fasciitis. How closely increased vascularity relates to function remains unknown, and it is still unclear whether classification based on vascularization can help prescribe ideal interventions for patients with plantar fasciitis.

1.3 Extracorporeal shock wave therapy for plantar fasciitis

1.3.1 Conventional conservative treatments for chronic plantar fasciitis

The conservative treatments commonly applied to treat chronic plantar fasciitis include stretching, orthotic devices, medication, manual therapy and electrical therapy. Most of them have generated only limited scientific evidence of their efficacy (Crawford and Thomson 2003; League 2008). Extracorporeal shock wave therapy (ESWT) is a relatively new physical treatment modality approved by the U.S. Food and Drug Administration only since 2000 (Ogden et al. 2001).

Stretching programmes are frequently prescribed to alleviate plantar fasciitis symptoms (DiGiovanni et al. 2006; Davis et al. 1994; Martin et al. 1998). Protocols have varied from Achilles tendon stretching (Martin et al. 1998; Wolgin et al. 1994) to plantar fascia-specific stretching (DiGiovanni et al. 2006). The exercises aim to stretch and increase the flexibility of the plantar fascia, recreating the windlass mechanism so that tissue tension is optimized. Ankle stretching combined with other non-operative treatments such as anti-inflammatory medication, relative rest, heel cushions and injections on some occasions alleviate the pain of almost 90% of patients within 11 months (Davis et al. 1994). It is not clear, however, whether the therapeutic effects are related to the ankle stretching exercises or the other interventions. Martin et al. (1998) treated patients using a standardized protocol consisting of Achilles and plantar fascia stretching, a night splint and a heel cup. 51% of the patients reported complete symptomatic relief. The authors suggested that the stretching, night splints and heel pads were equally important components of the treatment programme. On the other hand, DiGiovanni et al. (2006) observed that 52% of patients improved after 8 weeks with just a fascia-specific stretching programme, while only 22% improved with an Achilles tendon stretching programme, but there was no difference between the two groups at a 2-year follow-up. A night splint keeps the ankle neutral or in slight dorsiflexion, so it is a kind of prolonged stretch. This technique promotes stretching of the Achilles tendon and prevents contracture of the plantar fascia while resting at night. However, results from a prospective randomized study showed comparable pain reduction using a night splint or stretching the Achilles (Probe et al. 1999). The efficacy of immobilization using a night splint is not yet conclusive (Neufeld and Cerrato 2008).

Orthoses such as a heel pad or arch support decrease excessive pronation and optimize the biomechanical loading of the foot (Neufeld and Cerrato 2008). The cushioning provided by orthoses made of softer materials has been found to reduce shock in walking by 42% (DeMaio et al. 1993). An 80% success rate has been reported using orthotics, compared with 33% using nonsteroidal anti-inflammatory drugs (NSAIDs) and 30% with steroid injections (Lynch et al. 1998). But evidence of the effectiveness of orthoses in treating patients with plantar fasciitis is still insufficient (Cole et al. 2005). Collins et al. (2007) performed a systematic review and meta-analysis based on 22 papers which are on the foot orthoses in lower limb overuse conditions. Nine out of the 22 papers are on using orthoses to treat patients with plantar fasciitis: six are compared with other types of orthoses; one is compared with stretching; one is compared with injection and 1 is compared with stretching and other type of orthoses.

Among these 9 articles, 1 showed Achilles and plantar fascia stretching have better pain reduction than orthoses, 5 showed no difference between groups, 3 showed low effect size. Another meta-analysis (Lee et al. 2008) analyzed 6 articles, which are on using orthoses in treating patients with plantar fasciitis. All the 6 articles are compared with different kind of orthoses, and the result from pooled data showed pain reduction is 37.04% at more than 11 weeks follow up. The author suggests adding a true control group to examine the effectiveness of orthoses intervention. One randomized clinical trial did by Landorf et al. (2006) compared customized orthosis, prefabricated orthosis and sham orthosis which means minimal structural support. At 3 months follow-up, both orthosis groups showed no significant pain reduction than sham orthosis group, but improved function in both orthosis groups observed than in sham orthosis group. At 12 months, there is no difference between groups for pain or foot function between two orthosis groups than sham orthosis group. Based on this study and a previous review article (Crawford and Thomson, 2003), a review article by Landorf and Menz (2008) concluded that custom-made insoles may improve function (but not pain) at 3 months in people with plantar heel pain compared with a sham orthosis, but they may be no better than prefabricated orthoses. Therefore, use of foot orthoses may have benefit in patients with plantar fasciitis (Landorf and Menz 2008; Lee et al. 2008), further studies to examine the effectiveness are needed.

Many local physical therapy modalities such as iontophoresis, ultrasound and low-intensity laser therapy are used for treating plantar fasciitis. Gudeman et al. (1997) compared iontophoresis of dexamethasone with a placebo group and reported pain relief after 2 weeks but no significant difference after 1 month. Other randomized clinical trials with small samples have failed to show the benefits of laser therapy (Basford et al. 1998) or therapeutic ultrasound (Crawford and Snaith, 1996) in treating patients with plantar fasciitis. The evidence supporting these electrical therapies in treating patients with plantar fasciitis remains limited (Crawford and Thomson, 2003).

Starting in the 1990s, extracorporeal shock waves have been used to treat patients with tendinopathies. Its efficacy in treating plantar fasciitis has been demonstrated (Rompe et al. 2002; Seil et al. 2006). However, the meta-analysis conducted by Thomson et al. (2005) based on 6 randomized control trials included a total of 897 patients suggested significant effects of ESWT for the treatment of proximal heel pain but the effect size was very small. A later review from Landorf and Menz (2007) had similar comment. However, Rompe (2007) pointed out that meta-analysis was not appropriate for evaluating the effects of ESWT in treating patients with plantar fasciitis. It was because the reported studies had considerable differences in treatment regiments, treatment intensity, patient selection, and definitions of treatment outcomes. Based on the 13 randomized control trials reported in English from 1996 to 2011 on patients with chronic plantar fasciitis, 10 out of these 13 randomized control trials reported better pain reducing in the treatment group when compared with the control. The studies with insignificant effects had patients with symptoms less than 3 months (Buchbind et al. 2002) or when ESWT was delivered at biweekly (Haake et al. 2003) or monthly (Speed et al. 2003) basis. Five of the 10 studies reported clinical insignificant findings (with Visual Analogue Scale<20mm) despite statistically significant difference were reported. Most of them used high intensity with nerve block (Kudo et al. 2006; Ogden et al. 2001; Porter et al. 2005; Theodore et al. 2004). For the studies with clinical (change in Visual Analogue Scale >20mm) and statically significant, the ESWT was delivered to patients with plantar fasciitis for more than 6 months with low to medium intensity at 1000-2000 impulse per session for 3 sessions (Gollwitzer et al. 2007; Ogden et al. 2004; Rompe et al. 2002, 2003) to 6 sessions (Cosentino et al. 2001). Based on review of papers in past 20 years, the efficacy of ESWT on chronic plantar fasciitis was found in studies with ESWT applied at low to medium intensity from 1000-2000 impulses on multi-session at weekly basis in patients with duration of symptom from 6 months.

1.3.2 Physical properties of extracorporeal shock waves

Shock waves are transient increases and decreases in pressure of high magnitude (often more than 100MPa) and short duration (often than 10ns). The rarefaction phase typically involves negative pressure values of -10MPa (Ogden et al. 2001) (Fig 1.1). Electrohydraulic, electromagnetic and piezoelectric techniques can all generate focused shock waves, and all have been approved for medical use in Europe (Seil et al. 2006). Energy flux and pulse energy are used to describe the temporal and spatial distribution of the pressure profile (Delius 1994). The energy flux density is defined as the maximum amount of acoustic energy transmitted through an area of $1mm^2$ per pulse (Shrivastava and Kailash 2005). Pulse energies are commonly in the range of 10–100mJ (Folberth et al. 1992). The total energy delivered is the energy per pulse multiplied by the number of pulses (Ogden et al. 2001).

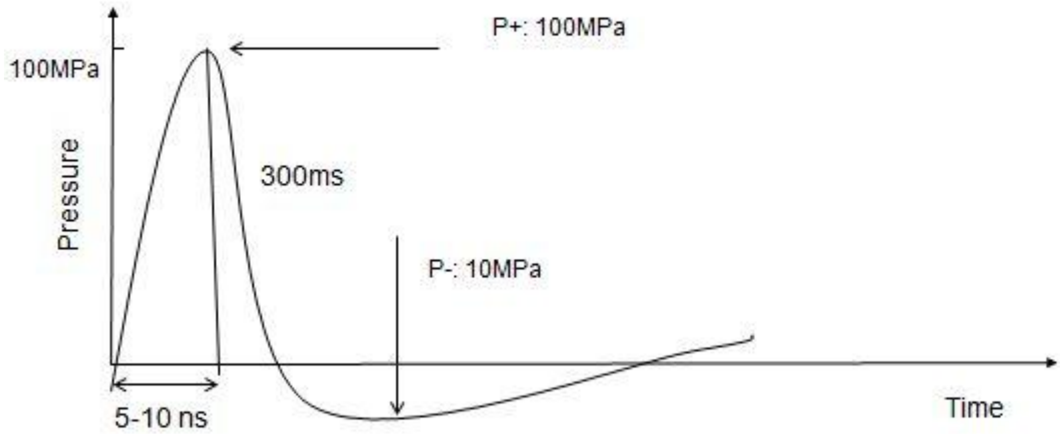


Figure 1.1 Graphic representation of a shock wave. There is a very rapid pressure rise (<10ns) to a high peak pressure (>10MPa), followed by a variable negative pressure, which may cause cavitation.

1.3.3 Therapeutic effects of ESWT

Rompe et al. (1996) first reported the use of ESWT in treating patients with plantar fasciitis. He reported a higher success rate after 3 sessions of ESWT with 1000 impulses of 0.08mJ/mm^2 compared with a sham group (receiving 10 pulses). The same author later reported a higher success rate at 6-month and 5-year follow-ups in the treatment group than in the sham group (Rompe et al. 2002). Cosentino et al. (2001) also found that, after six weekly sessions of ESWT, only the patients in the treatment group had significant pain reduction, not those in the control group. Similar results in terms of pain reduction have also been reported when athletes are treated and compared with a low energy ESWT (sham) treatment group (Rompe et al. 2003). In more recent studies, around 50 to 70% of patients were declared successfully treated at 3-month post intervention follow-ups (Hammer et al. 2003; Labek et al. 2005; Liang et al. 2007; Rompe et al. 2003, 2005). Hammer et al. (2003) used 3 weekly ESWT sessions, each with 3000 shocks at 0.2mJ/mm^2, and about 63% of patients reported less pain in their daily activities. Using 2000 shocks per session at 0.09mJ/mm^2, Rompe et al. (2005) observed that 67% of patients had at least a 50% improvement in pain. Liang et al. (2007) reported a 57% success rate at their 3-month follow-up after application of ESWT, furthermore, they found that less pain was related to thinner fascia. The different success rates in these studies may be due to the different ESWT protocols and different equipment. The criteria for success should also be taken into account.

1.3.4 Factors influencing the efficacy of ESWT

Despite the considerable success rates reported, differences in treatment regimens, treatment intensities, patient selection, the definition of treatment outcomes, as well as evaluation times, mean that direct comparison of treatment outcomes has been inappropriate (Seil et al. 2006). In general, ESWT is either high energy with local anesthesia or repetitive at low energy. But only in studies with ESWT at low to medium intensity, on multi-session at weekly basis, in chronic patients, all of them reached both statistically and clinically significance in treating plantar fasciitis (Cosentino et al. 2001; Gollwitzer et al. 2007; Ogden et al. 2004; Rompe et al. 2002, 2003). In addition, at low energy, ESWT without local anesthesia has been proved superior to ESWT with local anesthesia (Rompe et al. 2005; Labek et al. 2005). The weekly application of lower energy shock waves without local anesthesia, for at least 3 weeks, is therefore the accepted ESWT regimen for treating patients with plantar fasciitis (Rompe 2007).

From the literature review, the number of treatment sessions varies from 1 to 6, and the treatment intensity (the applied energy flux density and the number of shocks) ranges from 0.08mJ/mm^2 to 0.56mJ/mm^2 and 1000 to 3800 shocks respectively. ESWT's biological effects are related to the applied energy flux density and the number of shocks delivered. Rompe et al. (1998) observed a shift from no change to marked inflammatory reactions when the delivered energy was increased from low to high intensity in tests with rabbits. Similarly, when 0.17mJ/mm^2 energy was applied to cultured cells, the cell count increased in the 500 shocks group but decreased in the 1000 and 2000 shocks groups (Han et al. 2009). Such findings indicated that the effects of ESWT could be bi-directional and dose-dependent. In human studies, Liang et al. (2007) reported comparable success rates when ESWT was applied at either low (0.12mJ/mm^2) or high intensity (0.56mJ/mm^2) to patients with chronic plantar fasciitis. The maximum tolerable energy density was found to be more effective than either a low or fixed energy density for pain reduction and functional recovery (Chow and Cheing, 2007).

Most studies have reported continued improvement with the longer follow-up period (Chuckpaiwong et al. 2009; Hammer 2003, 2005; Moretti et al. 2006). Two years after ESWT, about 94% of patients reported decreased pain during daily activities, compared with only 63% at a 3-month follow-up (Hammer et al. 2003). Recently, Chuckpaiwong et al. (2009) also reported a 77.2% improvement in pain and foot function at a 12-month follow-up compared with 70.7% at 3 months. Aside from pain and function, fascia thinning has also been observed at 6 months post intervention (Hammer et al. 2005). A year after treatment, 61% of those who showed evidence of inflammation before treatment had a complete disappearance of inflammation signs by ultrasound examination (Moretti et al. 2006). But most of studies on long-term effect did not have any control group. Hence, the progressive improvement may relate to natural healing rather than the effects of ESWT.

1.3.5 Physiological effects of ESWT in treating planar fasciitis

Nowadays, even with a huge increase in the application of ESWT in treating tendinopathies and plantar fasciitis, research on its biological mechanisms is inadequate. Its therapeutic mechanism remains a topic of speculation (Roehrig et al. 2005). The analgesic effect may be achieved either by hyper-stimulation of the nociceptors, or by inducing nerve fiber degeneration and destroying nerve endings (Speed 2004). Hyper-stimulation analgesia is ascribed to "central biasing mechanism", which exert the inhibitory projection system at brainstem level, to inhibit pain transmission at spinal cord as well as higher levels (Melzack, 1982). ESWT induced healing may be promoted via interstitial and/or extracellular disruption, causing hematoma and local cell death. New tissue formation is stimulated with the recruitment of appropriate stem cells, and diseased tissues are allowed to adapt to biological and biomechanical demands (Ogden et al. 2001). Increased diffusion of cytokines across vessel walls into the painful region may be promoted, and angiogenesis and healing responses may be reinforced (Chen et al. 2004). Neovascularization may help to remove the breakdown products of the local cell death (Younger 2006) and/or induce the cellular repair of degenerate tissue (Fenwick et al. 2002). The latter two suggestions are related to vascularity changes after the application of ESWT.

Wang's group first demonstrated that one session of ESWT could induce neovascularity at the tendon-bone junction in dogs (Wang et al. 2002) and stimulate an in-growth of new blood vessels in rabbits (Wang et al. 2003). This research group also observed angiogenesis mediators such as nitric oxide and vascular endothelial growth factors one week after the application of ESWT. However, recently, it has been reported that a significant reduction in oxygen saturation after 3 sessions of ESWT in patients with supraspinatus tendinopathy (Notarnicola et al. 2011). The reduced oxygen saturation was quantified by an oximetry after the first session of ESWT, and the change in oxygen saturation was associated with pain reduction. Despite confirmation of ESWT-induced neovascularization, there is inadequate information as to whether vascularity is up-regulated or down-regulated following a course of ESWT.

1.4 Vascularity and tissue healing

There have been more studies of tendon than of fascia healing, but plantar fasciitis is in some ways similar to tendonitis (Wright and Rennels 1964). Based on the continuum model proposed by Cook and Purdam (2009), there are three phases in the pathological model of tendinopathy: reactive tendinopathy, tendon disrepair and degenerative tendinopathy. As different pathogenesis and characteristics in different phase, the corresponding intervention should be relatively different. In the early reactive/early dysreapair phase, which present with hyper activity and increase cellular response, i.e. tendon swollen and mildly hypoechoic/small focal hypoechoic areas with no or minimal vascular changes, the treatment aims for down regulating the cellular response, such as load management and non steroidal anti-inflammatory drugs; while in the later dysrepair/degenerative phase, which have matrix disorganization and filled with vessels, acellularity and little collagen, and from ultrasound exam, tendon with large discrete areas of hypoechogenicity, multiple vessels. Treatment in this stage should target for stimulate cell activity, increase protein production and restructure of matrix, e.g. exercise or injection of various substances around or into the tendon has been proposed (Cook and Purdam 2009).

Changes in vascularity have been followed in subjects with Achilles tendinopahty after a course of eccentric exercise (Ohberg and Alfreson 2004) and after sclerosing injections (Alfredson and Ohberg 2005). Increased intratendinous vascularity is observed initially (Alfredson and Ohberg 2006). It starts from day 1 after the intervention (training or injection) and persists for 2 to 3 weeks, following by a decline in successfully treated cases (Alfredson and Ohberg 2006). Such observations highlight the association between vascularity and healing. However, only 40% of patients with plantar fasciitis have detectable increased vascularity (Walther et al. 2004), so whether there is regulation of vascularity only in vascularized patients during healing is still unknown.

Despite the promising results in treating plantar fasciitis with ESWT, the optimal protocol has not been determined. In view of the vascularity changes associated with ESWT and the observation that modulation in vascularity is associated with successfully treated individuals, modulation in vascularity should be assessed for any association with changes in pain in patients with plantar fasciitis. Aside from vascularity, fascia thickness should also be assessed, as fascia thickness is associated with pathological changes in the plantar fascia (Liang et al. 2007). To clarify the temporal effects of ESWT, these evaluations should be conducted at different time points.

1.5 Measuring vascularity

The most direct and valid way to evaluate tissue vascularity involves histological study such as angiography on specimens from surgery or in animal models (Leach et al. 1986; LeMelle et al. 1990; Tounas and Fornasier 1996; Wang et al. 2003), but such methods are impractical in the clinic. Laser Doppler flow measurement is less invasive, but it still requires inserting a needle percutaneously into the tendon (Aström et al. 2000). Radioisotope tracking is another semi-invasive alternative (Langberg et al, 1998). All of these, however, are quite invasive considering that more than 80% of PF patients receive conservative treatment (Rompe 2009). In contrast, colour flow imaging is a non-invasive method that provides a Doppler sonogram in real time (Martinoli et al. 1998; Tegeler et al. 1991; Teh 2006; Rubin 1999). Power Doppler ultrasonography uses colour flow imaging to assess vascularity in the musculoskeletal system (Joshua and Lassere 2006; Martinoli et al. 1998; Newman et al. 1996; Silvestri et al. 2003; Walther et al. 2004).

1.5.1 Power Doppler ultrasonography

Power Doppler ultrasonography (PDU) uses amplitude shifts to create a Doppler signal. By using the amplitude component of the signals received to represent the number of moving blood cells, PDU can detect blood signal from the background, and assess the blood flow, vessel density and perfusion (Hsiao et al. 2009; Ota et al. 2007; Pairleitner et al. 1999). Because it has little angle-dependence and is not susceptible to aliasing, PDU has better sensitivity and superior vascular delineation with low or irregular flow, especially in observing serial vascular changes related to therapy (Martinoli et al. 1998). It has been proved that less than 10% variability in estimating kidney vascularity (Rubin et al. 1997) and correlating well with the histopathological grading of the vascularity of the synovial membrane in patients with arthritis (Walther et al. 2001).

1.5.2 Application of PDU in musculoskeletal-related studies

PDU has been used previously to quantify vascularity in patients with plantar fasciitis (Walther et al. 2004), but also in studying tendinopathy (Boesen et al. 2006; De Vos et al. 2007; Fahstrom et al. 2003; Newman et al. 1996; Ohberg and Alfredson 2002), the synovial tissues of patients with rheumatoid arthritis (Ellegaard et al. 2009; Qvistgaard et al. 2001; Stegbauer et al. 2008; Terslev et al. 2004) and in osteoarthritis studies (Walther et al. 2001, 2002). Most of those studies used Newman's grading scale to grade tissue vascularity on a scale from 0 to 3. Zero represents normal or minimal tissue perfusion with either no signal or only a local dark red PDU signal; one represents mild hyperemia with a dark red to red signal and/or a single vessel signal; two represents moderate hyperemia with a red to orange signal or a confluent vessel signal; three represents marked hyperemia with an orange to yellow signal or a marked vessel signal (Newman et al 1996; Walther et al. 2002, 2004; Stegbauer et al. 2008). Despite its simple and common use, Newman's grading system may not be sensitive enough to differentiate subtle vascularity changes (Cardinal et al. 1996).

Recently, computerized methods have been used to quantify tissue vascularity with ultrasonography. Tissue vascularity is quantified by computing a vascular index (VI), which is the ratio of the number of colour pixels to the total number of pixels within the region of interest in patients with soft tissue problems (Ellegaard et al. 2009; Terslev et al. 2004). Note that such studies have used colour Doppler ultrasonography. PDU is superior to frequency-based colour Doppler ultrasonography, especially in tissues with low blood flow such as the plantar fascia (Derchi et al. 1997; Walther et al. 2004). Ying et al. (2009) has reported the feasibility of the computerized quantification of vascularity in thyroid tissues with PDU. It is essential to evaluate whether this computerized quantification of vascularity can be applied to musculoskeletal tissue such as the plantar fascia.

1.6 Rationale and objectives of this study

1.6.1 Limitations of past findings

1. Although plantar fasciitis is a common foot disorder, its etiology and pathogenesis are not well understood. Vascularization has been reported in some patients with plantar fasciitis and Walther et al. (2004) has associated it with self-perceived pain. How vascularization relates to other mechanical loading factors as well as to morphological changes, however, remains unclear. Such information would provide a better understanding of the inter-relationships between mechanical loading and the pathogenesis of plantar fasciitis, so that evidence-based interventions could be proposed.
2. Changes in vascularity have been observed with ESWT, but the observations are contradictory. Up-regulation of vascularity was observed in animal studies, but down-regulation occurred in a human study of tendinopathy. Treatment intensity might affect outcome evaluations. The effects of ESWT on vascularization might depend on treatment intensity,

such as the number of treatment sessions.

3. Cook and Purdam (2009) proposed a continuum model for tendinopathy and highlighted the importance of classifying patients into different stages such that optimal intervention can be prescribed. ESWT has had considerable success in treating individuals with plantar fasciitis, but there is no consensus or rationale about treatment protocols, particularly treatment intensity. More information is required to guide treatment protocols that can fit the patients at different stages.

The results of previous research suggest that vascularity in the plantar fascia may be increased in some, but not all, patients with plantar fasciitis. Possible modulation in vascularity might be revealed when individuals with plantar fasciitis receive a course of ESWT. Classification of individuals with plantar fasciitis, according to the presence or absence of vascularization, might delineate the optimal ESWT protocol. In addition, it is important to establish whether or not the outcome measures associated with ESWT change with time during and after treatment.

1.6.2 Aims of the study

The studies reported here aimed to investigate vascularity in the proximal plantar fascia of patients with chronic plantar fasciitis and any vascularity changes after extracoporeal shock wave therapy. The study was also designed to investigate in patients with different treatment dosages, the significance of vascularity changes during the healing process. The intention was to contribute not only to the understanding of the pathogenesis and healing process of plantar fasciitis, but also to the planning of treatment for plantar fasciitis in the clinic.

1.6.3 Hypotheses

1) Patients with plantar fasciitis will display increase vascularity in their proximal plantar fascia.
2) The vascularity of the proximal plantar fascia of patients with planar fasciitis will change after a course of ESWT.
3) Any changes in vascularity will depend on the pre-intervention vascularity and ESWT treatment dosage.
4) Any regression of vascularity in the proximal plantar fascia will be observed only in patients who are treated successfully.
5) Any regression of vascularity in the proximal plantar fascia will be related with the time after treatment.

1.6.4 The structure of the enquiry

The study involved 5 experiments.

Study 1 (Chapter 2): Vascularity examination using power Doppler ultrasonography and Newman's scaling to establish test-retest reliability

Objective 1: To establish a quantitative method to measure vascularity at the proximal insertion of the plantar fascia.

Objective 2: To quantify the minimum detectable difference in vascularity and cut-off score for classifying patients into with and without vascularization using the method.

Objective 3: To correlate the method with Newman's scaling.

Study 2 (Chapter 3): Physical characteristics and sonographic examination of patients with chronic plantar fasciitis: differences from healthy controls

Objective 1: To compare the physical characteristics of patients with chronic plantar fasciitis with those of healthy controls.

Objective 2: To compare vascularity and fascia thickness in patients with chronic plantar fasciitis and healthy controls.

Objective 3: To explore temporal effects of vascularity and plantar fascia thickness in patients with chronic plantar fasciitis.

Study 3 (Chapter 4): Modulation of vascularity in patients with plantar fasciitis: the cumulative effects of extracorporeal shock wave

therapy

Objective 1: To explore the effects of ESWT on the vascularity of the proximal plantar fascia in patients with chronic plantar fasciitis.

Objective 2: To quantify any cumulative changes in vascularity after 2 different courses of ESWT.

Objective 3: To quantify any cumulative changes in perceived pain after 2 different courses of ESWT.

Study 4 (Chapter 5): Vascularization quantified by Power Doppler ultrasonography in patients with plantar fasciitis: its role on treatment planning

Objective: To examine whether pre-intervention vascularization quantified by power Doppler ultrasonography could assist treatment planning for patients with chronic plantar fasciitis.

Study 5 (Chapter 6): Factors influencing pain reduction in patients with chronic plantar fasciitis at 3- and 6-month post intervention

Objective 1: To document the effects of shock wave therapy in treating patients with chronic plantar fasciitis 3 and 6 months after shock wave therapy.

Objective 2: To assess changes in vascularity 3 and 6 months after the conclusion of ESWT

Objective 3: To assess factors influcing pain reduction in patients with chronic plantyar fasciitis 3 and 6 months after the conclusion of ESWT

The 5 intra-related studies are reported in subsequent chapters according to the sequence listed under 1.6.4. The main findings of all 5 studies are highlighted and summarized in Chapter 7, the contributions of this study are generalized, and recommendations are made for further research.

CHAPTER 2

VASCULARITY EXAMINATION USING POWER DOPPLER ULTRASONOGRAPHY AND NEWMAN'S SCALING TO ESTABLISH TEST-RETEST RELIABILITY

2.1 Abstract

Objectives: The purpose of this study was to establish a correlation between computerized vascular index and Newman's scaling using Power Doppler ultrasonography (PDU) imaging and its test-retest reliability.

Methods: PDU was performed on 44 patients (age range 30-66 years; mean age 47 years) with plantar fasciitis and 17 healthy subjects (age range 35-59 years; mean age 47 years). The vascularity was quantified using ultrasound images by a customized software programme and graded by the Newman's grading scale. Vascular Index (VI) was calculated from the software programme as the ratio of the number of colour pixels to the total number of pixels within a standardized selected area of proximal plantar fascia. The 17 healthy subjects were examined twice, with 7-10 days between these examinations. Statistical analyses were performed using Spearman's rank correlation coefficient and the intraclass correlation coefficient (ICC).

Results: Good correlation was found between the averaged VI ratios and Newman's qualitative scale (rho= 0.70; $p<0.001$). The intratester reliability was 0.72 (95% Confidence interval 0.43-0.86). The minimum detectable difference (MDD) of VI was 0.68%. A cut-off VI of 2.60% had a sensitivity of 100% and specificity of 81.80% (Area under curve (AUC) = 0.96; p= 0.00) in identifying plantar fascia with and without moderate to severe vascularization.

Conclusions: The computerized vascular index not only has a high level of

concordance with the Newman's grading scale, but is also reliable in reflecting the vascularity of proximal plantar fascia. This index can be used to classify patients with chronic plantar fasciits as having or not having moderate to severe vascualrization. It can also characterize the changes in the vascularity of patients with plantar fasciitis, and may be helpful to evaluate treatment and monitor the progress after intervention in future studies.

2.2 Introduction

Plantar fasciitis is the most common cause of heel pain, and about two million patients receive treatment every year because of it (Pfeffer et al. 1999). Besides mechanical loading, vascular disturbance with consequent metabolic impairment and hypoxia is thought to play an important role (Wearing et al. 2006). Indeed, fibrovascular hyperplasia and vascular proliferation have been observed from microscopic specimens obtained from operative resection (LeMelle et al. 1990; Lemont et al. 2003; Tountas and Fornasier 1996). Walther et al. (2004) was the first group to evaluate plantar fascia vascularity non-invasively using power Doppler ultrasonography (PDU).

PDU is one of the colour flow imaging techniques which encodes the amplitude of the power spectral density of the Doppler signals (Kollmann et al. 1998). This method has been used to assess soft tissue vascularity and treatment efficacy with a variety of musculoskeletal related problems. Changes in vascularity in synovial tissues in patients with rheumatoid arthritis (Ellegaard et al. 2009; Qvistgaard et al. 2001; Stegbauer et al. 2008; Terslev et al. 2004), osteoarthritis (Walther et al. 2001, 2002), as well as in patients with tendinopathy (Boesen et al. 2006; De Vos et al. 2007; Fahstrom et al. 2003; Newman et al. 1996; Ohberg and Alfredson 2002), and plantar fasciitis (Walther et al. 2004) have been reported. Modulation in vascularity was observed in patients with tendinopathy after a course of intervention (Alfredson and Ohberg 2005, 2006;

Boesen et al. 2006; De Vos et al. 2007; Ohberg and Alfredson 2002). Most of these studies used Newman's grading scale to grade the tissue vascularity (De Vos et al. 2007; Newman et al. 1996; Ohberg and Alfredson 2002). This qualitative grading for the PDU images had a high correlation with the histopathological grading of vascularity of the synovial membrane in patients with arthritis (Terslev et al. 2004). Nevertheless, Newman's grading system, as a qualitative approach, is a relatively rough estimation, and may not be sensitive enough to differentiate subtle vascularity changes.

Recently, computerized methods have been used to quantify tissue vascularity with ultrasonography. Tissue vascularity was quantified by computing a vascular index (VI), which is calculated as the ratio of the number of colour pixels to the total number of pixels within the region of interest in patients with soft tissue problems (Boesen et al. 2006; Ellegaard et al. 2009; Qvistgaard et al. 2001; Terslev et al. 2004). Note that most of these studies were conducted using colour Doppler ultrasonography. In this connection, PDU is superior to frequency-based colour Doppler ultrasonography, especially in tissues with low blood flow such as the plantar fascia (Derchi et al. 1997; Teirlinck et al. 1998; Walther et al. 2004). Ying et al. (2009) reported the feasibility of the computerized quantification of vascularity in thyroid tissues with PDU. We were interested to evaluate whether the computerized quantification of vascularity could be applied on musculoskeletal tissue, such as the plantar fascia. Therefore, the purpose of the present study was to correlate the computerized VI and Newman's qualitative grading scale in quantifying plantar fascia vascularity using PDU. Meanwhile, the smallest differences that will reflect real changes and optimal cut-off points for the identification of plantar fascia with and without moderate vascularization were also identified.

2.3 Methods and materials

2.3.1 Patient selection

44 patients (27 females, 17 males; mean age 47 years; range, 30 - 66 years) with a clinical diagnosis of plantar fasciitis by experienced orthopaedic surgeons were recruited from a local hospital. The inclusion criteria were patients who had plantar fasciitis for more than 3 months, were in good health and had no history of any systemic disease with manifestations similar to plantar fasciitis, including gout or seronegative arthritis. Patients having diseases which may affect the lower limb vascularity, such as diabetes mellitus, peripheral vascular disease, or foot trauma, were excluded from the study. Seventeen healthy subjects (13 females, 4 males; mean age, 47 years; range, 35 -59 years) with no history of heel pain for the previous 3 months were invited to have PDU examinations of their plantar fascia. These examinations were conducted twice, with 7-10 days between the two. This study was approved by the Human Subject

Ethics Sub-committee of the university and hospital (Appendix I). Written consent was signed from each subject after verbal explanation about the study (Appendix II and III).

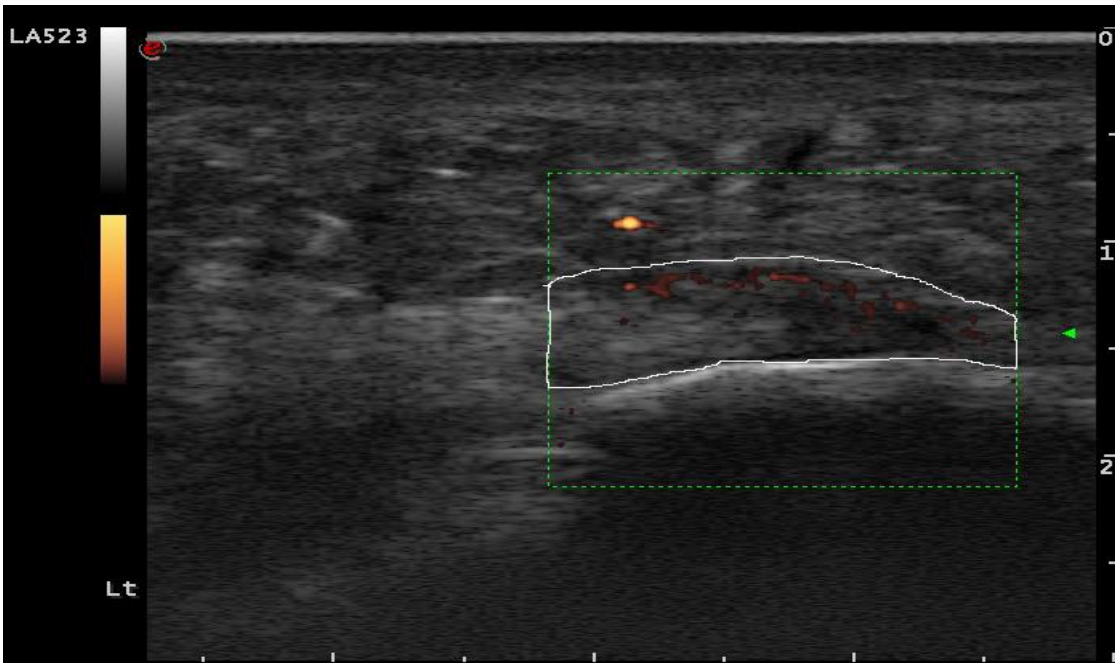
2.3.2 Ultrasonography

Grey scale and power Doppler ultrasonography were performed using an Esaote MyLab 70 X-view ultrasound unit in conjunction with a 4-13 MHz linear transducer (Esaote, Genova, Italy). In the ultrasound examination, the positioning of the proximal plantar fascia was adopted as described by O'Neill (2008). The transducer was in the longitudinal plane parallel to the long axis of the plantar foot. A clear image with both the contour of the medial tubercle of the calcaneus and the proximal part of the plantar fascia, which can be seen to be most legible, was acquired. Vascularity was examined using the power Doppler mode. The size of the colour box was standardized to 1.5 x 1 cm, and was placed over the insertion of the plantar fascia, i.e. the middle point of the right line of the colour box is just on the most prominent point of the calcaneus. Settings of the PDU were standardized for high sensitivity, with a low wall filter to allow the detection of vessels with low blood flow. The pulsed repetition frequency (PRF) was 370 Hz, and medium persistence was used. The colour gain was first increased to a level that showed colour noise, and then decreased until the noise disappeared (Wewers and Lowe 1990; Ying et al. 2009). For each subject, 5 images with the most abundant vascularity and consistent Doppler signals were selected and recorded. In addition, the room temperature was set to 22^{0}C, and subjects were required to stay in the room for 30 minutes before the ultrasound examination.

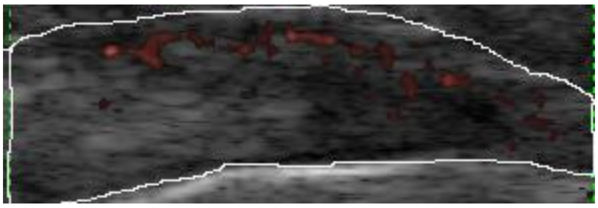
2.3.3 Image processing

The total number of pixels, as well as the colour pixels within the region of interest (ROI), were counted by a customized software programme (Matlab, version 7.3.0.267R2006b) (Figure 2.1 a to c). The vascular index (VI) was the ratio of the number of colour pixels to the total number of pixels within the ROI (Ying et al. 2009). The ROI was defined as the total area of the fascia within the 1.5 x 1 cm colour box. The averages of all 5 images (VI_5); the first 3 images (VI_3); and the maximum value of the five images (VI_{max}) were computed. The power Doppler ultrasound images were also graded by 2 examiners independently on a scale of 0-3 (Newman et al. 1996; Stegbauer et al. 2008). When determined scores by the 2 examiners did not match, joint evaluation was conducted to reach a consensus grade.

(a)



(b)



(c)

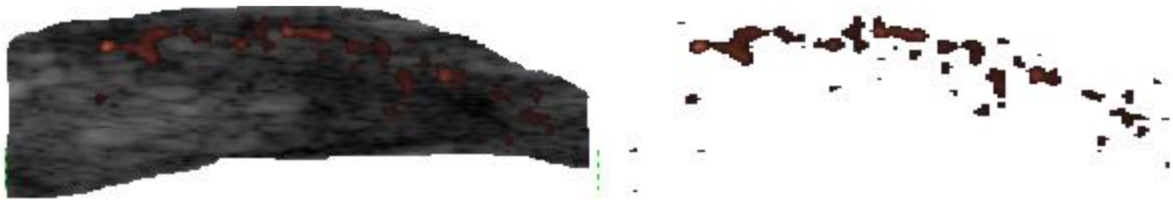


Figure 2. 1 The process of power Doppler image data reduction was carried out by using the customized algorithm. (a) The region of interest (ROI, the insertional part of the fascia to the bone) was extracted by outlining the boundaries (White line). (b) The ROI was initially extracted by trimming the unwanted area from the power Doppler window (green box). (c) The ROI was extracted further by trimming the unwanted area from the outlined area, and the total number of pixels within the ROI was counted (Left image). The colour pixels were extracted further by eliminating the gray-scale pixels, and the colour pixels were counted by the algorithm.

2.4 Statistical analysis

Spearman's rank correlation test was used to assess the level of correlation between the VI and Newman's grading scale. Intraclass correlation coefficient (ICC) model 3 was used to evaluate the intra-tester reliability (Portney and Watkins, 2008). Standard error measurement was computed (using the following formula: $SEM = SD \times \sqrt{1-ICC}$; SD and ICC represented the standard deviation and intraclass correlation coefficient), and minimal detectable difference was calculated based on the following formula: $MDD = 1.96 \times SEM \times \sqrt{2}$. Receiver operating characteristic (ROC) curves analyses were used to determine a cutoff point of VI to delineate subjects with and without moderate to severe vascularity. Subjects were graded as having moderate to severe vascularity based on the Newman's scale (of grade 2 and above). Youden's index was computed from the sensitivity and specificity values obtained. The highest index that represented the best overall sensitivity and specificity was the cut-off point. The area under the curve (AUC), the cut-off scores together with the sensitivity and specificity values were reported. The level of significance was at $p<0.05$.

2.5 Results

Demographic data of patients and healthy subjects are shown in table 2.1.

Table 2. 1 Demographic data of patients and healthy subjects.

		Patient group (n=44)	Control group (n=17)
Age, y (Mean±SD)		47.36±7.32	46.71±7.90
Body Mass Index, kg/m^2 (Mean±SD)		25.71±3.40	22.96±2.93
Gender, n	Female	27	13
	Male	17	4
Duration of symptoms, months (Mean, range)		13.11 (3-36)	
Affected foot,n	Unilateral	34	
	Bilateral	10	

SD denotes for standarded deviation; n denotes for number of subjects.

2.5.1 Correlation between computerized findings and Newman scaling on vascularity using Power Doppler Ultrasonography

A total of 440 images were collected from these 44 patients with 5 images on each side of every subject. VI_5 calculated from these 44 patients illustrated good correlation with the Newman's grading scale (rho = 0.70, p=0.00) (Fig 2.2).

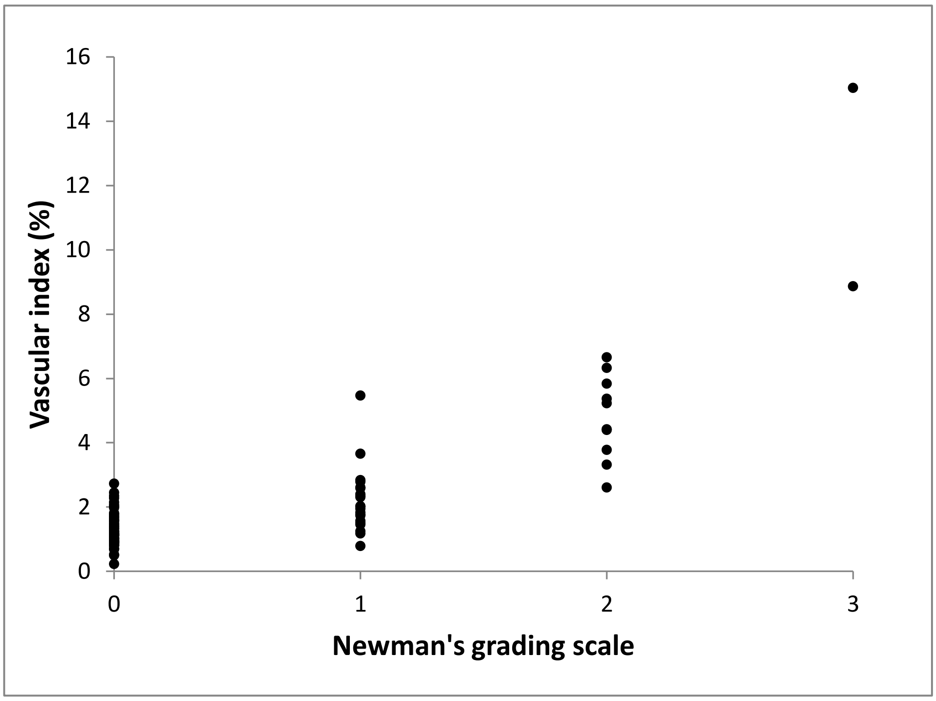


Figure 2. 2 Scatter plot of the vascular index (VI) and Newman's grading scale in patients with plantar fasciitis.

2.5.2 Intra-tester reliability

Seventeen healthy subjects had test-retest examinations with 7-10 days between the two tests. VI that was calculated from averaging the 5 images got the highest ICC rating (Table 2.2). Hence, this suggests that VI_5 is most reliable among VI_3 and VI_{max}. The mean difference between the first and second VI_5 was 0.19 on a range of -1.00 to 0.77.

Table 2. 2 Intraclass correlation coefficient (ICC) analysis of the intra-tester reliability

	Test 1	Test 2	*p*-value	Intra-tester ($ICC_{(3,1)}$)	95% confidence interval
VI_5	1.55±0.45	1.75±0.54	0.11	0.72	(0.433,0.859)
VI_3	1.54±0.44	1.70±0.55	0.19	0.70	(0.407,0.852)
VI_{Max}	1.90±0.56	2.21±0.62	0.03	0.67	(0.337,0.835)

VI_5, VI_3 and VI_{Max} denote vascularity index from averaging all 5 images, first 3 images and the maximum vascularity of all 5 images, respectively

2.5.3 Minimum detectable difference & ROC

The corresponding MDD computed from the 17 subjects was 0.68%. ROC curves were constructed to determine the optimal cutoff point of VI in identifying fascia with and without moderate to severe vascularization from the 44 patients. The area under the curve was 0.96 (p=0.00) (Fig. 2.3). Table 2.2 indicates VI of 2.60% yielded a sensitivity of 100% and specificity of 81.80%.

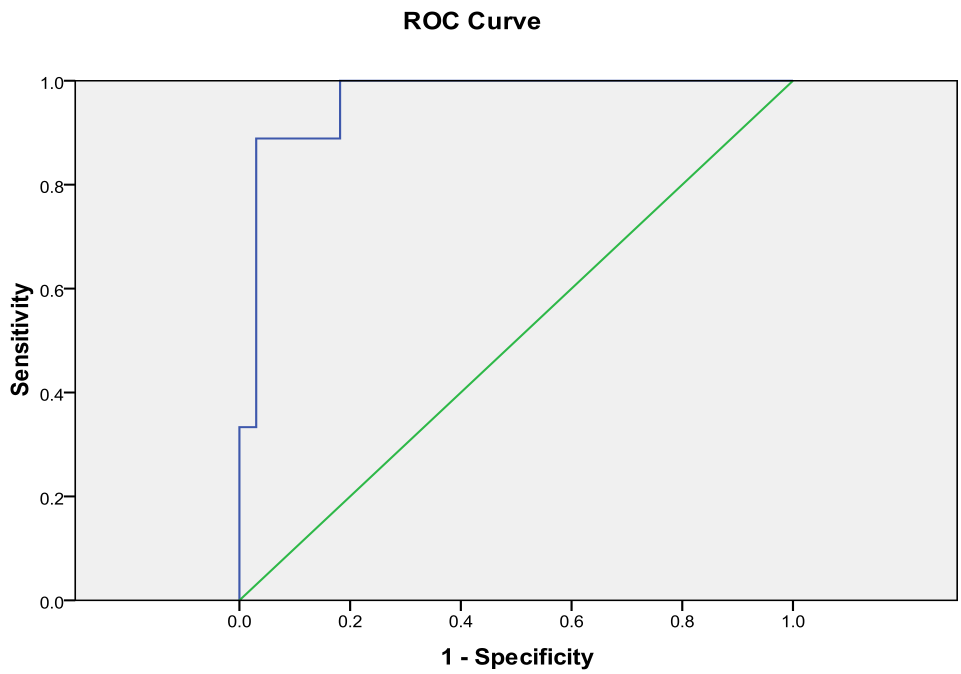


Figure 2. 3 The receiver operating curve shows VI of 2.60% for identification of feet with and without moderate vascularization with sensitivity of 100% and specificity of 81.80%.

Table 2. 3 Percentage of patients with plantar fasciitis correctly identified as having or not having moderate vascularity using different cut-off VI.

VI (%)	Sensitivity (%)	Specificity (%)	Youden's index
2.43	100	78.80	0.758
2.52	100	78.80	0.788
2.60	**100**	**81.80**	**0.818**
2.61	88.90	81.80	0.707
2.67	88.90	84.80	0.737
2.76	88.90	87.90	0.768
2.81	88.90	90.90	0.798

2.6 Discussion

The results from this study indicate that VI, which reflects the vascularity of proximal plantar fascia, has a high level of concordance with Newman's grading scale and demonstrated good intra-tester reliability on 17 healthy subjects. In addition, an optimal cut-off value of 2.60% was identified to delineate fascia with and without vascularization.

Since 1994, PDU has been suggested as a potential useful alternative to colour Doppler ultrasonography (Rubin et al. 1994). This method has become popular in assessing blood flow patterns to assist diagnosis and evaluate treatment efficacy in musculoskeletal disorders (Alfredson and Ohberg 2003, 2005; Ellegarrd et al. 2009; Lee et al. 2008; Qvistgaard et al. 2001; Stegbauer et al. 2008; Terslev et al. 2004). Increases were reported in vascularity in the Achilles tendon in patients suffering from Achilles tendinopathy (Alfredson and Ohberg 2003, 2005) and in the plantar fascia in patients with plantar fasciitis with symptoms for more than 6 months but less than 1 year (Walther et al. 2004). Hereto, hyperemia change was used to categorize the patients in addition to clinical signs (Alfredson and Ohberg 2005) as well as to monitor treatment effectiveness, in patients with tendinopathy (Alfredson and Ohberg 2006; Boesen et al. 2006; Fahstrom et al. 2003). Note that most of these studies used the qualitative grading method proposed by Newman (Newman et al. 1996). The Newman's grading scale, based on PDU imaging, was found to correlate with histological findings in an animal study by Lee et al. (2008) and in human subjects with arthritis by Walther et al. (2001). In the arthritis rabbit knee model, synovial vascularity using contrast-enhanced PDU and histological findings were correlated significantly (Lee et al. 2008). In patients with osteoarthritis and rheumatoid arthritis, Walther et al. (2001) reported a good correlation coefficient (of 0.81) on tissue vascularity between the Newman's grading scale based on PDU images and tissue sections obtained when patients received surgery. Although the grading scale had a high correlation with the tissue section, it was commented that the grading scale was not able to detect subtle changes in vascularity. In view of the increasing use of PDU in making diagnoses and evaluate treatment efficacy in musculoskeletal disorders, a quantified method was needed to reduce subjectivity in the grading process, as well as to evaluate changes in vascularity during its recovery. Our study, based on the computation approach used in the detection of vascularity on the thyroid gland, reported a good correlation (rho= 0.70) on tissue vascularity in plantar fascia obtained from our customized software programme based on PDU images and the Newman's grading scale.

Test-retest reliability is important for any scale designed to measure change over time. Test-retest reliability reflects measurement error associated with repeated measurement by the same operator (intra-tester reliability). Findings from this study indicated good intra-tester (ICC = 0.72 from averaged value of 5 images) reliability. Ultrasonography is well known for being a very operator-dependent technique (Koski et al. 2006; Naredo et al. 2006). The intra-reader reliability for the Doppler signal has been reported to vary from 0.58 to 0.96, which indicates good to excellent intra-tester agreement (Koski et al. 2006; Naredo et al. 2006; Portney and Watkins 2008). As plantar fascia is a hypovascular area, picking up the power Doppler signal is not as easy as for the big vessels in other organs. Although we adjusted the colour gain at the level at which colour noises were not apparent, for each image required, the averaging of 5 images could lower any error induced from one image, which may also help to explain why VI_5 showed higher repeatability and reproducibility than VI_3. Hence, the scanning of 5 images is recommended for computation of VI. In addition, the movement of the transducer during imaging may induce artifacts, which is unavoidable (Rubin et al. 1997). Such movement is more profound on an uneven surface, such as the epicondylar region. So using a light touch and trying to stabilize and well support the operator's wrist during imaging are also very essential.

This study also explored the minimum detectable change in VI that represents the minimum differences. A VI of more than 0.68% reflects the true change of vascularity in proximal plantar fascia instead of the measurement error. This value provided a reference value for us to evaluate vascularity change after intervention in the subsequent studies. Furthermore, a cut-off value of 2.60% yielding a sensitive of 100% indicates that subjects with VI of 2.60% must have moderate to severe vascularity. There would only be less than a 20% chance that subjects with a VI lower than 2.60% would have moderate or severe vascularity. Such findings support the use of computerized VI to delineate subjects having or not having moderate to severe vascularization at their plantar fascia.

2.7 Conclusion

We concluded that the computerized method that we used is reliable and has a high level of concordance with Newman’s grading system in evaluating proximal planar fascia vascularity. With vascular index, we can categorize patients into vascularized and non-vascularized groups. In addition, the minimum detectable changes identified can help to evaluate the true difference between subject groups and to assess treatment efficacy and monitor intervention progress in future studies.

CHAPTER 3

PHYSICAL CHARACTERISITCS AND SONOGRAPHIC EXAMINATION OF PATIENTS WITH PLANTAR FASCIITIS:

DIFFERENCES FROM HEALTHY CONTROLS

3.1 Abstract

Background: Plantar fasciitis is one of the most common causes of heel pain with unclear etiology and pathogenesis. This study was designed as a comprehensive examination of the intrinsic factors and fascia related physiological changes associated with plantar fasciitis.

Objectives: To compare plantar fasciitis sufferers and healthy controls in terms of body mass index (BMI), navicular mobility, range of motion in the ankle and first metatarsal phalangeal joints, and the vascularity and thickness of the plantar fascia. An additional objective was to explore temporal changes in vascularity and plantar fascia thickness in the patient group.

Study Design: This was a cross-sectional observational study.

Methods: Thirty-nine patients with unilateral plantar fasciitis and 21 healthy controls matched for age and gender were examined. Navicular mobility, range of ankle dorsiflexion, range of first metatarsal phalangeal joint extension, proximal plantar fascia vascularization and fascia thickness were assessed. Univariate analyses of variance were used to compare the patients with the healthy controls. Leg, gender and group were fixed factors with BMI entered as covariate. Contrast analysis was used to locate the source of significance. Kruskal-Wallis H tests were conducted to assess differences in vascularity and tendon thickness with duration of symptom.

Results: BMI was significantly greater in the patient than the control group (mean BMI = 25.37kg/m^2 and 23.25 kg/m^2 in the patient and control groups, respectively). More than half of these patients reached obesity with BMIs > 25kg/mm^2. They also had significantly greater active and passive extension ranges at the first metatarsal phalangeal joint than the healthy controls. Increased vascularization was detected in the affected fascia. The affected feet also had significantly thickened proximal fascia. Regression of vascularization was observed in patients whose symptoms had lasted more than 12 months.

Conclusions: Increased BMI and larger metatarsal phalangeal joint range are risk factors for developing plantar fasciitis. Vascularization and thickened fascia are evident in patients with plantar fasciitis. Strategies to modulate these factors are much needed in view of the high prevalence of plantar fasciitis in sedentary as well as active individuals.

Key words: plantar fasciitis, risk factors, vascularity, plantar fascia thickness

3.2 Introduction

Plantar fasciitis is one of the most common painful foot conditions. It affects both active and sedentary adults with a peak incidence between 40 and 60 years of age (Cole et al. 2005; Davis et al. 1994; Gill 1996). Each year about two million individuals suffer from this condition in the United States (Riddle and Schappart 2004). Plantar fasciitis is characterized by pain localized at the medial tubercle of the calcaneus which is exacerbated at weight bearing activities that initially after periods of non-weight bearing (Neufeld et al. 2008; Wearing et al. 2006). Most patients recover within 6–18 months (Davis et al. 1994; Martin et al. 1998), with 5–10% of recalcitrant cases requiring surgery (O'Malley et al. 2000).

Mechanical origin has been thought to play an important role in developing plantar fasciitis (Wearing et al. 2006). The plantar fascia acts as a tie-bar to form part of the passive mechanism maintaining the medial longitudinal arch during static stance (Hicks 1954; Wearing et al. 2006). Environmental or intrinsic factors which lower the medial longitudinal arch induce tension in the fascia, and can lead to the development of plantar fasciitis (McGonagle et al. 2002; Wearing et al. 2006). In addition, due to a “windlass” effect, tension in the plantar fascia increases when the toes are dorsiflexed (Hicks 1954). Reduction in ankle dorsiflexion would induce foot pronation, lower the arch and causes tension at the fascia (Sarrafian 1987; Wright and Rennels 1964; Riddle et al. 2003). Tension of the fascia could also be increased with extension of the big toe (Hicks 1954). Excessive toe extension might induce more tension at the fascia. Therefore, reduced ankle dorsiflexion or increased extension of the first metatarsal phalangeal joint (MTP) are suggested as intrinsic risk factors. However, inconclusive findings have been reported from analyses of whether there would be reduction at the ankle joint (Irving et al. 2007; Pohl et al. 2009; Riddle et al. 2003; Rome et al. 2001) or increase at the first MTP joint (Allen and Gross 2003; Creighton and Olson 1987).

Aside from arch mechanics, impaired vascularity with subsequent metabolic disturbance has been proposed as one of the mechanisms (Archambault et al. 1995; Fenwick et al. 2002). Animal studies have shown that inhibiting vascular perfusion can induce tendon degeneration (Kraus-Hansen et al. 1992). However, moderate or marked increases in vascularity in 40% of patients with plantar fasciitis at 1 cm proximal to the plantar fascia insertion was first reported by Walter et al. (2004). Such increased vascularity typified those having the problem for less than 12 months. Similar vascularization has been observed in patients with Achilles tendinopathy (Ohberg and Alfredson 2004) and patellar tendinopathy (Alfredson and Ohberg 2005). Alfredson (2004) proposed vascularization in diseased tendons as one of the potential mediators of pain in cases of tendinopathy. He proposed that nerve ingrowth associated with new vessels causes the pain these patients report. Further studies have confirmed that the intensity of pain with chronic tendinopathy is greater in vascularized patients compared with those not vascularized patients (Cook et al. 2004; Zanetti et al. 2003). In the vascularized plantar fasciitis, a higher Newman's grading has been associated with greater intensity of pain (Walther et al. 2004), and this was also seen with patellar and Achilles tendinopathy (Alfredson et al. 2003, 2005). Information from these studies highlights a possible association between vascularization and plantar fasciitis.

In addition, the affected fascia is thickened in patients with plantar fasciitis (Akfirat et al. 2003; Karabay et al. 2007; Walther et al. 2004). Such changes could relate to the reparative process of microtears, to fiber degeneration or to edema (Cardinal et al. 1996). Fascia more than 4 mm thick is considered to correspond with plantar fasciitis (Karabay et al. 2007). As reductions in thickness have been shown after intervention (Genc et al. 2005; Hammer et al. 2005; Liang et al. 2007), thickening of the plantar fascia is thought to be a pathological origin and correlated with symptoms (Liang et al. 2007).

The present study was designed to generate a better understanding of the intrinsic factors associated with plantar fasciitis and their possible relationship with the observed vascularization and changes in fascia thickness with duration since onset. The first objective of this study was to compare plantar fasciitis sufferers and healthy controls in terms of body mass index (BMI), range of motion in the ankle, range of motion in the first metatarsal phalangeal joint, navicular height, and the vascularity and thickness of their proximal plantar fascia. A second objective was to document changes in vascularity and fascia thickness in patients with different durations of symptoms. It was hypothesized that the heavier loading associated with a high BMI, reduced ankle range and increased MTP range would be observed in patients with plantar fasciitis. Changes in vascularity and tendon thickness might occur in patients with plantar fasciitis, and they might be related to the duration since onset.

3.3 Methods

3.3.1 Study design

The study was a cross-sectional observational one.

3.3.2 Subjects

Thirty-nine patients with plantar fasciitis were recruited from a local hospital. They had been diagnosed by experienced orthopaedic surgeons. Patients were considered eligible to participate if they fulfilled all of the following conditions: 1) age over 18; 2) only one foot affected; 3) symptoms having lasted more than 3 months; 4) intensity of pain equal or greater than 3 as self-assessed using a visual analogue scale (VAS); 5) no history of any systemic disease with manifestations similar to those of plantar fasciitis (including gout and seronegative arthritis). Patients with diseases which may affect lower limb vascularity, such as diabetes meliitus, peripheral vascular disease and foot trauma, were excluded from the study.

Twenty-one healthy subjects, with no history of heel pain in the previous 3 months and matched with age and gender, were invited to form the control group using convenience sampling from the community.

This study was approved by the Human Subject Ethics Sub-committees of the university and hospital (Appendix I). Written consent was obtained from each subject after verbal explanation of the study (Appendix II and III).

3.3.3 Procedures

The study was conducted at the ultrasonography laboratories of the university and a regional hospital. Each participant was invited to supply information on their age, gender, body weight, height and activity level. Each was assigned to a category of physical activity level (light, moderate or active) depending on the metabolic demands of the reported activities (DuBose et al. 2004). Each participant was also examined by a single examiner. X-rays were taken at the cooperating hospital with front/back review and lateral review to exam whether there is heel spur at the calcaneus.

3.3.3.1 Navicular Mobility

Navicular mobility was used to reflect foot pronation in a static position (Rome et al. 2001; Vicenzino et al. 2000). Navicular height was measured in sitting and in maximal weight bearing using a digital height gauge (Mitutoyo

American Corporation, U.S.A.). The seat height was adjusted such that the knee joint was at 90^0. Measurements in maximal weight bearing were conducted with the subject standing. The subject was instructed to align his/her feet along the sagittal plan with the untested foot on a stool. He/she was encouraged to shift his/her body weight to the test leg as much as possible (Crossley et al. 2007). The distance from the navicular tubercle to the floor was measured (Fig. 3.1) in 3 trials. Averaged navicular heights in sitting and maximum weight bearing were computed for use in the analysis. Navicular mobility was defined as the difference between the navicular height in sitting and in maximal weight bearing standing (Crossley et al. 2007; Headlee et al. 2008). Test-retest analyses on 17 subjects indicated good reliability with the ICC = 0.81.

a) b)

Figure 3. 1 Measurement of navicular height. a) The navicular tuberosity was identified by palpation and marked; b) Navicular height was measured as the distance from the floor to the navicular tuberosity.

3.3.3.2 Active and passive ankle flexion and first MTP extension

Range of joint motion was measured using a universal goniometer (Baseline, New York) (Creighton et al, 1987; Allen et al. 2003). The subject was supine lying with the knee in extension, and was instructed to dorsiflex the ankle and to extend the first MPT joints as far as possible for the active joint range measurements (Pascual et al. 2008). During the extension of the first MTP joint, the ankle joint was kept at 90^0 by a tailor-made brace (Fig. 3.2). For passive joint motion, the examiner moved the tested joint until resistance was felt. Three trials were performed measuring the active and passive ranges of the ankle and the first MPT joints of each foot. Averaged values were computed from the 3 trials

(Elveru et al. 1988; Rome et al. 2001).

a) b)

Figure 3. 2 Measurement of ankle and first MTP ROM. a) measurement of ankle dorsiflexion; b) measurement of first MPT extension with the ankle fixed in a neutral position.

3.3.3.3 Ultrasound examination of vascularity and plantar fascia thickness

An ultrasound unit with a 4–13 MHz linear transducer (MyLab 70 X-view, Esaote, Genoa, Italy) was used for ultrasound scanning. Details of the procedure have been described in Chapter 2. In brief, the subject was prone lying with the knee extended and the ankle fixed in a neutral position. The transducer was placed in the longitudinal plane parallel to the long axis of the proximal plantar fascia. A B-mode image was captured first, with the most legible contour of the medial tubercle of the calcaneus and the proximal part of the plantar fascia. Five images of the proximal plantar fascia were captured for off-line analysis.

Plantar fascia thickness was measured at the insertion of the plantar fascia to the calcaneus (Fig. 3.3) (Akfirat et al. 2003; Cardinal et al. 1996; Walther et al. 2004). Test-retest analyses on 17 subjects indicated good reliability with the ICC = 0.86.

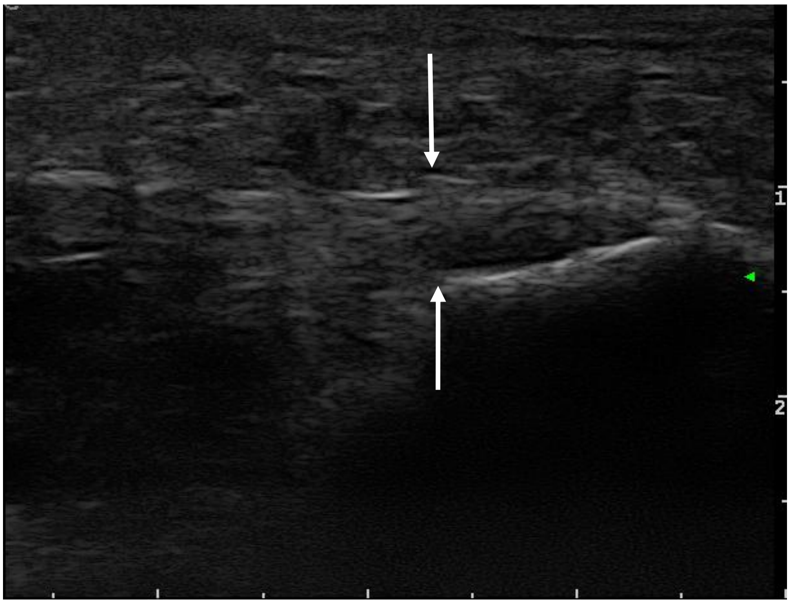


Figure 3. 3 Plantar fascia thickness was measured at its insertion with the calcaneus (the distance between the two white arrows).

Vascularity was examined by switching to the power Doppler mode. The power Doppler ultrasonography settings were standardized for high sensitivity, with low wall filtering to allow the detection of vessels with low blood flow. The pulse repetition frequency (PRF) was 370 Hz, and medium persistence was used. The colour gain was first increased to a level that showed colour noise, and then decreased until the noise disappeared (Ying et al. 2009). For each subject, 5 images with the most abundant vascularity and consistent Doppler signals were selected and recorded. Off-line measurements were conducted using the images captured. The room temperature was held at 22^{0}C, and the subjects were required to stay in the room for 30 minutes before the ultrasound examination.

A vascularity index (VI) was computed using a customized algorithm and software programme (Matlab version 7.3.0.267R2006b, The MathWorks Inc., Natick, MA, USA). Details have been described in chapter 2. The test-retest reliability for the VI had an ICC = 0.72.

3.3.4 Statistical analysis

Descriptive statistics were used to summarize all the measured variables. Independent t-tests and Mann-Whitney U tests were performed to compare average BMI and physical activity levels between the patient and control groups respectively. Paired t-tests were used to compare side-to-side differences in the control subjects' navicular mobility, ROM, VI and plantar fascia thickness. If side-to-side differences were detected, univariate analysis of variance was conducted with leg (dominance/non-dominant), gender (female and male) and group (dominant foot being affected (D_P), non-dominant foot affected (ND_P) and control group) as fixed factors. BMI, gender or physical activity level would be regarded as a covariate if there was a significant group finding. Contrast analysis was used to locate the source of any significant differences. In patients with plantar fasciitis, analyses were conducted to assess possible difference on

VI and tendon thickness in patients with symptom lasting for different duration i.e. less than 6 month; 6-12 months and more than 12 months. Because of the small number of patients in the "more than 12 months" group, Kruskai Wallis H tests were used. The level of significance was at $p \leq 0.05$. The statistical analysis was performed with the PASW statistics 17 software packages.

3.4 Results

3.4.1 Patient characteristics

Table 3.1 shows the characteristics of patients and the control group. A total of 39 patients (mean age 45.69 years; range 25-66 years) satisfied the inclusion criteria and were recruited. Meanwhile 21 healthy subjects (mean age 45.14 years, range 33-58 years) participated as the controls. The two groups had comparable age and gender distributions, but the patient group had a significantly greater average BMI (by 9.09%) than the controls. In addition, more individuals in the patient group (43.59%) than the control group (14.29%) claimed to participate actively in physical activity. About half of the patients (53.85%) had plantar fasciitis on their dominant side, and 48.72% of them had bone spurs. Of the 39 patients, 15.38% had experienced plantar fasciitis for more than 12 months.

Table 3. 1 Participant Characteristics

		Patient group (n=39)	Control group (n=21)	*p* value
Age, y		45.69±9.48	45.14±7.70	.82
Gender†	Female Male	25 14	9 12	.11
BMI, kg/m^2		25.37±3.12	23.25±2.80	**.01**
Physical Activity†	Light Moderate Active	10 12 17	7 11 3	.10
Duration of symptoms†	3-6 months 6-12 months >12 months	18 15 6		
Affected foot†	(D/ND)	21/18		
Bone Spur†	(Present)	19		

Abbreviations: BMI = body mass index; D= dominant; ND = non-dominant
Values are mean± SD, except where otherwise indicated.
†Values are numbers of subjects

Among the healthy controls, significant side-to-side differences in navicular mobility, range of motion of the ankle and range of motion of the first MTP were observed ($p \leq 0.05$) (Table 3.2). There was significantly greater navicular mobility (by 1.51mm, or 37.47%) in the non-dominant foot compared with the dominant foot. Greater active ROM was observed in the non-dominant foot (by 2.3^0) and also passive ROM (by 1.4^0) in ankle dorsiflexion. But the ROM of the first MTP was significantly smaller in active motion (by 3.3^0) and passive motion (by 4.5^0) for the non-dominant foot. No significant differences in VI or fascia thickness were detected among the controls.

Table 3. 2 Side-to-side comparisons of navicular mobility, joint range of motion, vascularity and plantar fascia thickness in the healthy controls.

		Dominant foot (n=21)	Non-dominant foot (n=21)	*p* value
Navicular Mobility, mm		4.03±3.29	5.54±3.81	.03
Ankle	AROM, degrees	8.10±3.60	10.40±3.70	.00
	PROM, degrees	13.10±4.50	14.50±3.70	.06
1st MTP	AROM, degrees	72.30±7.90	69.00±6.70	.00
	PROM, degrees	83.60±8.30	79.10±8.10	.00
VI, %		1.59±0.36	1.71±0.38	.11
Plantar fascia thickness, mm		2.90±0.60	3.00±0.50	.15

AROM = active range of motion; PROM = passive range of motion; MTP = metatarsal phalangeal joint; VI = vascular index

3.4.2 Comparisons of patients with plantar fasciitis and healthy controls

Univariate analysis of variance revealed no significant difference in navicular mobility or the range of ankle dorsiflexion between the patients and the healthy controls (Fig. 3.4). However, patients with symptom at the non-dominant feet had larger 1st MTP extension when compared with healthy control as well as in patients with dominant feet being painful ($p \leq 0.05$) (Fig. 3.5). The average increase was 6^0 when the non-dominant foot was painful (the ND_P group) compared with non-painful non-dominant feet (D_P group and control) (Table 3.3); for 8^0 increase in the non-painful dominant feet (ND_P group) than the painful dominant feet (D_P group) and non-painful dominant feet of the control (all $p \leq 0.05$) (Table 3.4).

Table 3. 3 Contrast analyses on active extension of 1st MTP joint

Leg		Mean Difference (95% CI)	Contrast comparison *p* value
Dominant	Dominant leg affected vs. Non-dominant leg affected	6.291 (0.500,12.082)	0.034
	Non-dominant leg affected vs control	6.727 (0.719,12.738)	0.029
Non-dominant	Non-dominant leg affected vs control	5.487 (0.843,10.131)	0.021

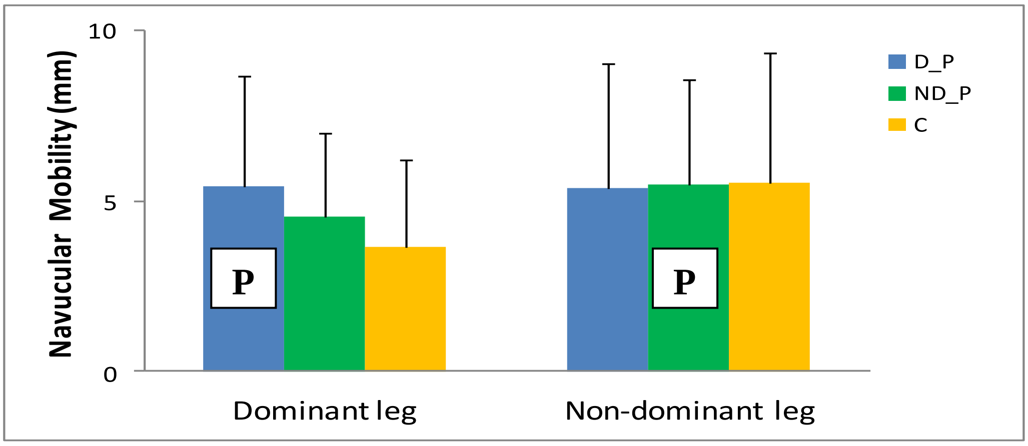
CI denotes for confidence interval

Table 3. 4 Contrast analyses on passive extension of 1st MTP joint

Leg		Mean Difference (95% CI)	Contrast comparison *p* value
Dominant	Dominant leg affected vs Non-dominant leg affected	8.204 (3.058,13.350)	0.002
	Non-dominant leg affected vs control	7.794 (0.719,12.738)	0.029
Non-dominant	Dominant leg affected vs. Non-dominant leg affected	5.40 (-0.693,11.494)	0.081
	Non-dominant leg affected vs control	6.544 (0.219,12.868)	0.043

CI denotes for confidence interval

a)



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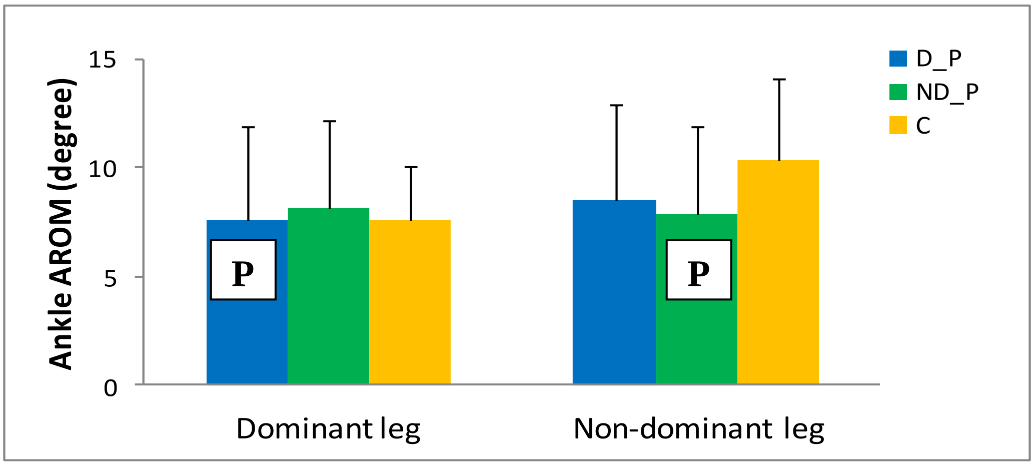


c)

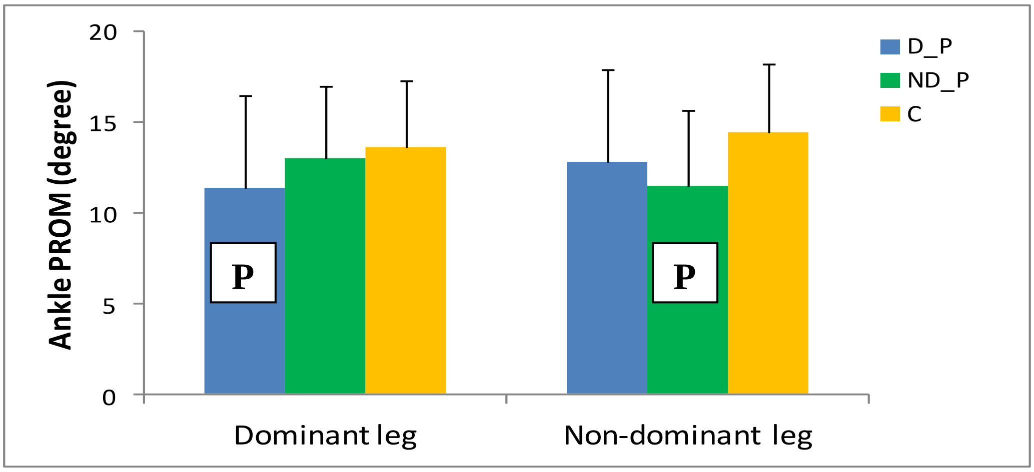
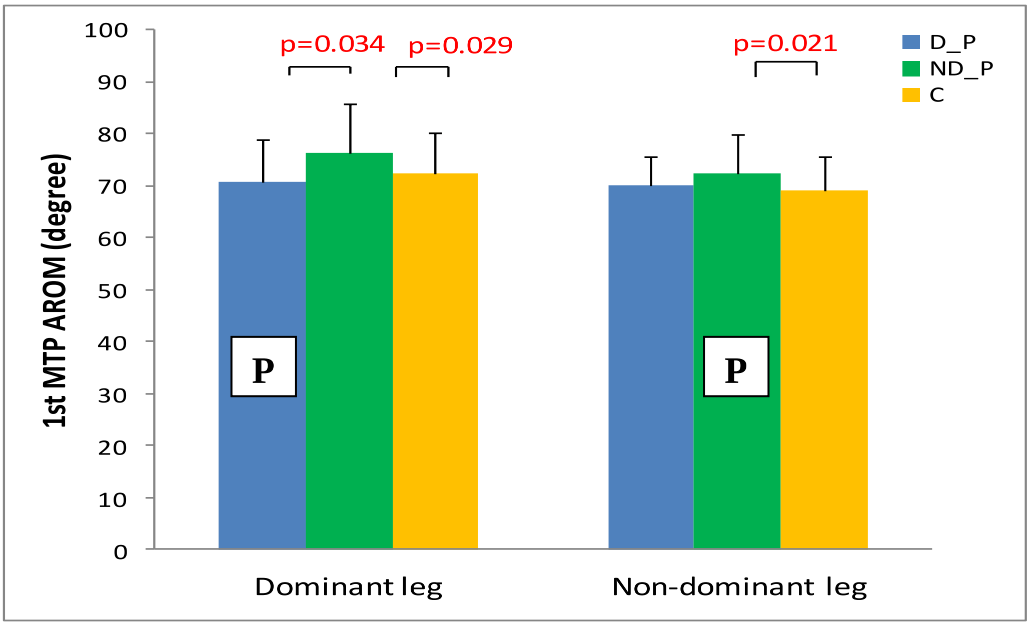


Figure 3. 4 Navicular mobility and ankle dorsiflexion showed no significant difference among the groups. a) Navicular mobility among three groups of subjects; b) active range of ankle dorsiflexion among the three groups; c) passive range of ankle dorsiflexion among the three groups. N_P= patients with dominant affected; ND_P= patients with non-dominant affected; C= healthy controls; AROM =active range of motion; PROM=passive range of motion. Painful side is highlighted.

a)



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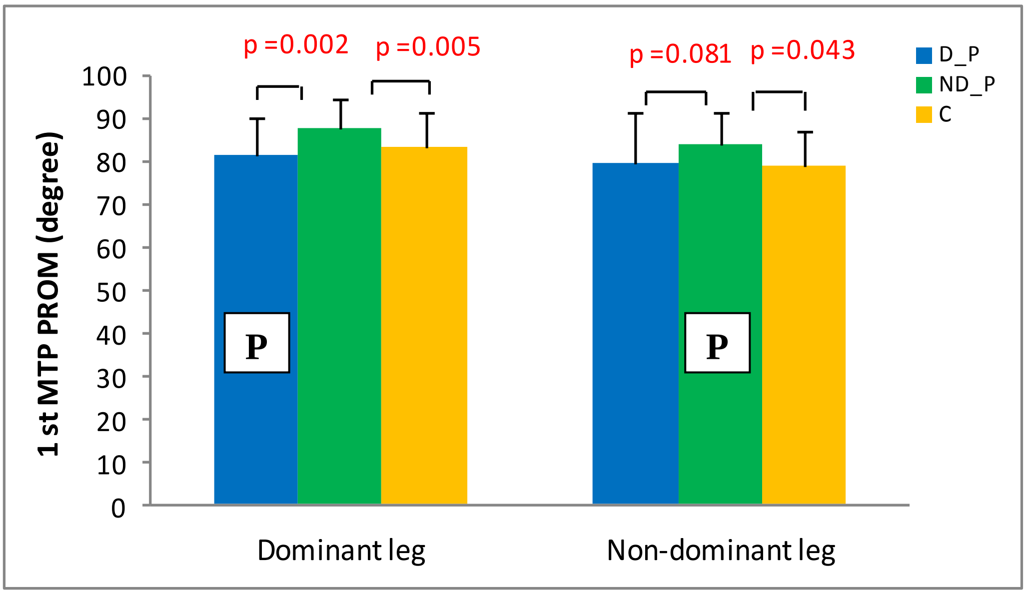


Figure 3. 5 Patients with the non-dominant foot affected had larger ranges of both active and passive motion in the first MTP ($p \leq 0.05$). N_P= patients with dominant affected; ND_P= patients with non-dominant affected; C= healthy controls; AROM= active range of motion; PROM= passive range of motion. Painful side is highlighted.

3.4.3 Sonographic comparisons between patients with plantar fasciitis and healthy controls

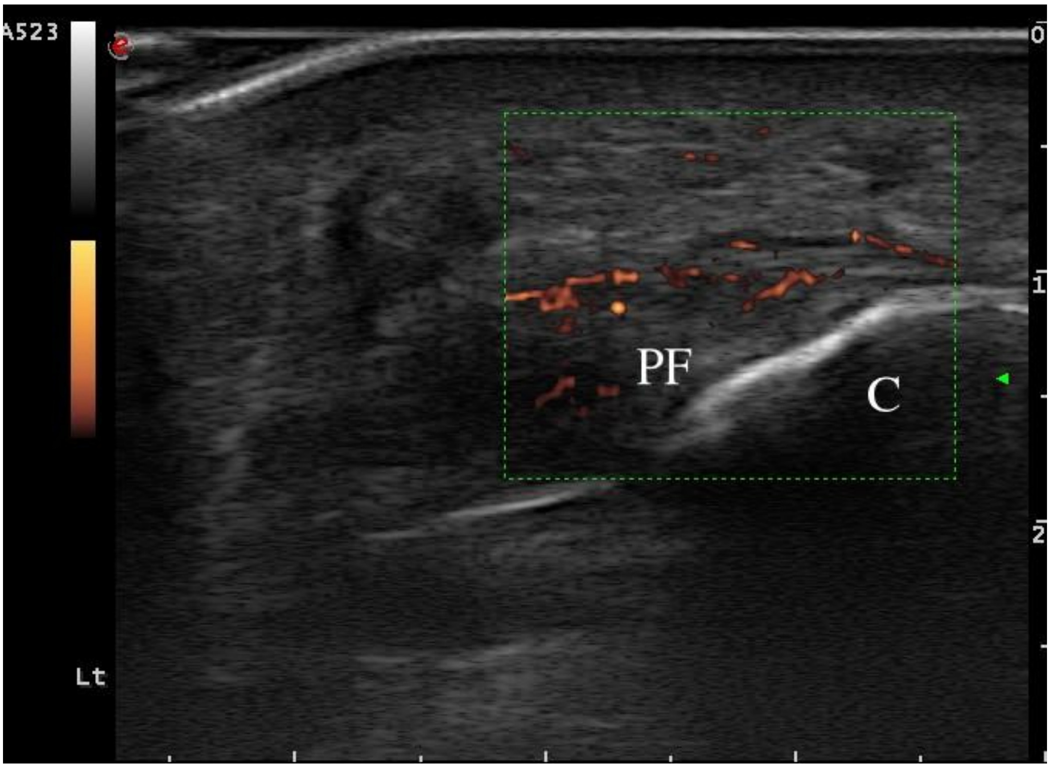
Figure 3.6 demonstrates representative vascularity images in a patient (Fig. 3.6 a) and a healthy subject (Fig 3.6 b). Table 3.5 shows the VI and fascia thickness results. Among the patients, the average VI of affected side was significantly higher than for the unaffected side, by 107.69% in the ND_P group and 87.40% in the D_P ($p \leq 0.05$) (Table 3.6). The VI almost doubled, from 1.35% on the unaffected side to 2.68% on the affected one. The VIs on the patients' affected side were also significantly higher (by 49.69% and 73.68% respectively) than those on the corresponding side in the healthy controls ($p \leq 0.05$) (Fig 3.7).

Table 3. 5 Vascular index and fascia thickness in the patient and control groups.

	D_P group		ND_P group		Healthy controls	
	D	ND	D	ND	D	ND
VI (%)	2.38±1.26	1.27±0.47	1.43±0.48	2.97±1.95	1.59±0.36	1.71±0.38
Thickness (mm)	4.7±1.1	3.5±0.7	3.2±0.6	5.4±1.5	2.9±0.6	3.0±0.5

Abbreviation: D_P group, patients with dominant leg affected group; ND_P group, patients with non-dominant leg affected group; D: dominant leg; ND: non-dominant leg; VI, vascular index. Values are mean± SD

a)



b)

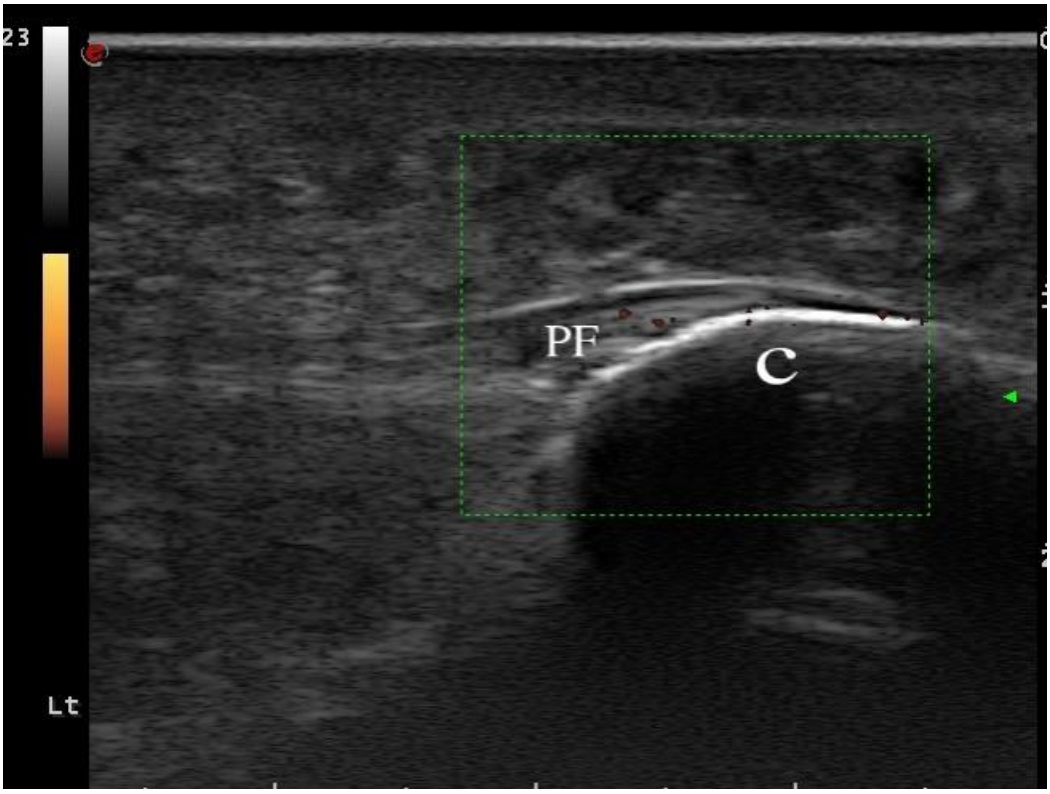


Figure 3. 6 Representative images of vascularity of proximal plantar fascia. a) image of a patient; b) image of a healthy subject. PF= plantar fascia; C= calcaneus

Table 3. 6 Contrast analyses on vascular index

Leg		Mean Difference (95% CI)	Contrast comparison p value
Dominant	Dominant leg affected vs control	0.740 (0.187,1.292)	0.01
Non-dominant	Non-dominant leg affected vs control	0.772 (0.043,1.501)	0.038
Dominant	Dominant leg vs. non-dominant leg	1.803(0.473,1.692)	0.001
Non-dominant	Dominant leg vs. non-dominant leg	1.143(0.179,2.107)	0.02

CI denotes for confidence interval

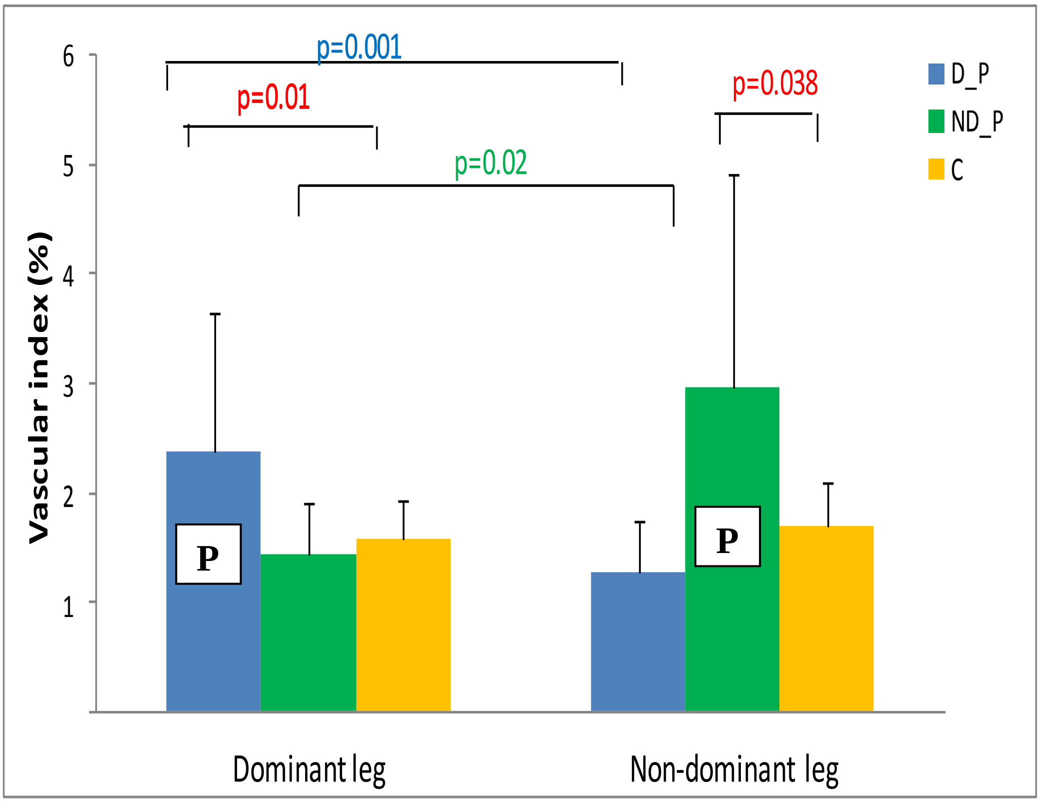
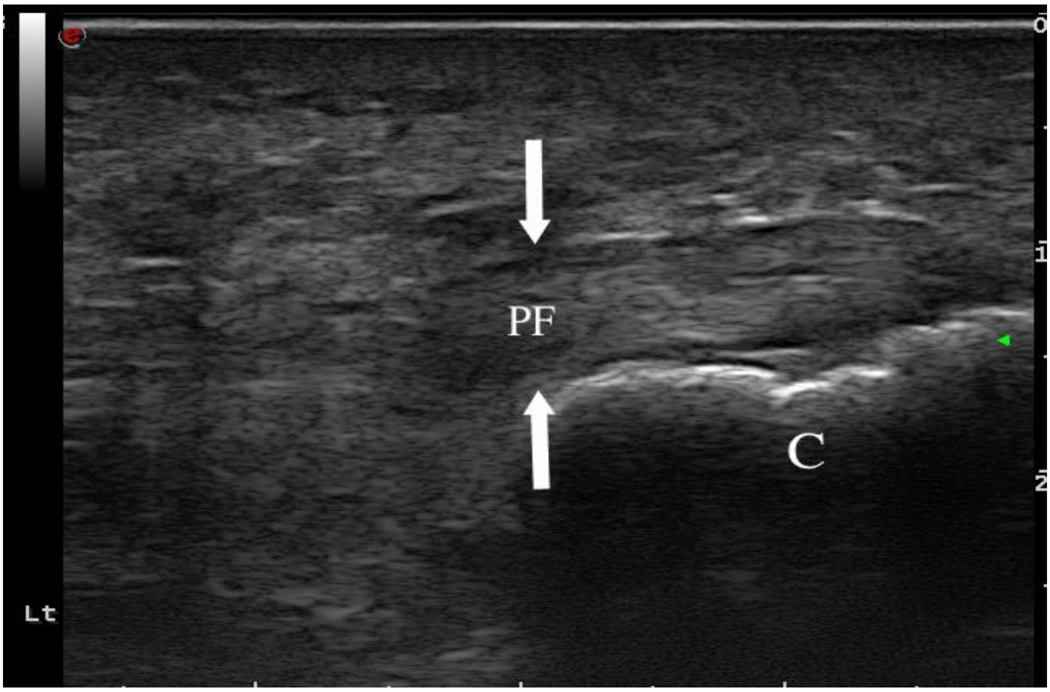


Figure 3. 7 The VI of the affected side was significantly higher, on average, than that of the unaffected side in patients, whichever foot was affected ($p \leq 0.05$); the average VI on the patients' affected side was significantly higher than on the corresponding side of the healthy controls ($p \leq 0.05$). Painful side is highlighted.

Figure 3.8 demonstrates representative images of the plantar fascia thickness in patients and healthy subjects. The mean thickness of the affected fascia was more than 4mm in both the ND_P and D_P groups, both of which were significantly thicker than the average for the unaffected side ($p \leq 0.05$) as well as for the corresponding side in the healthy control ($p \leq 0.05$) (Fig 3.9) (Table 3.7). There were, however, no significant differences in the VIs or plantar fascia thicknesses of the patients' unaffected side compared with the corresponding side in the healthy controls.

a)



b)

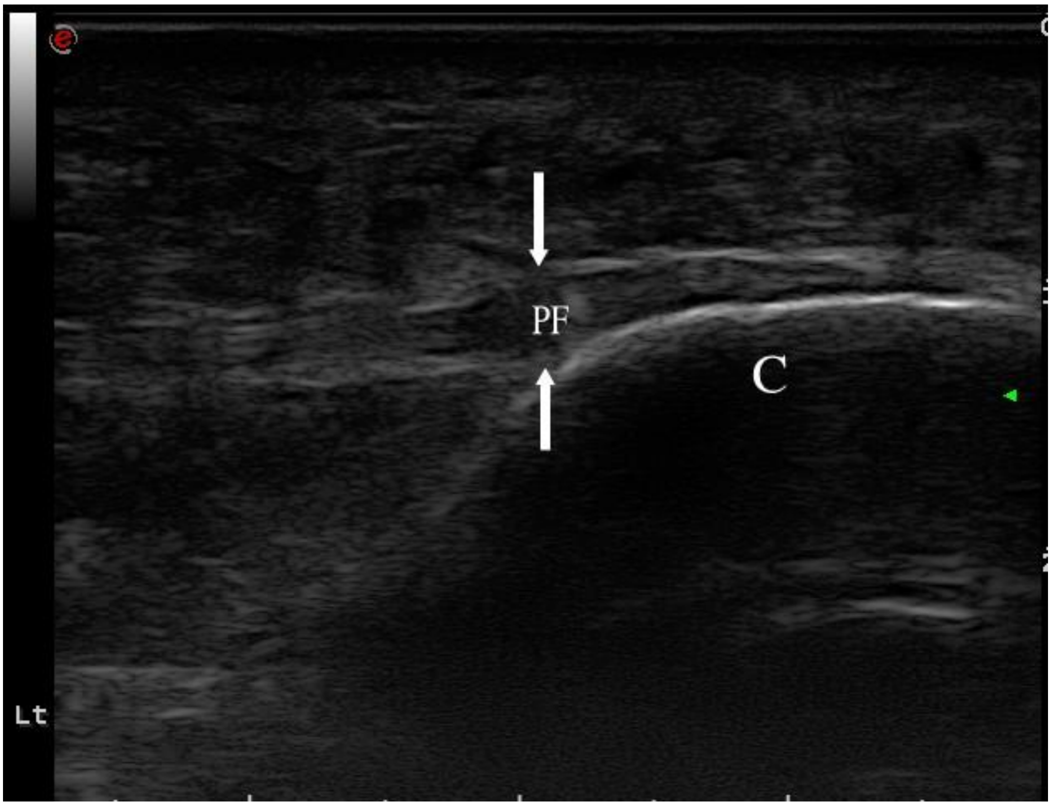


Figure 3. 8 Representative images of thickness of proximal plantar fascia.
a) image of a patient; b) image of a healthy subject. PF= plantar fascia; C= calcaneus. Distance between the two white arrows is measured as the thickness of plantar fascia.

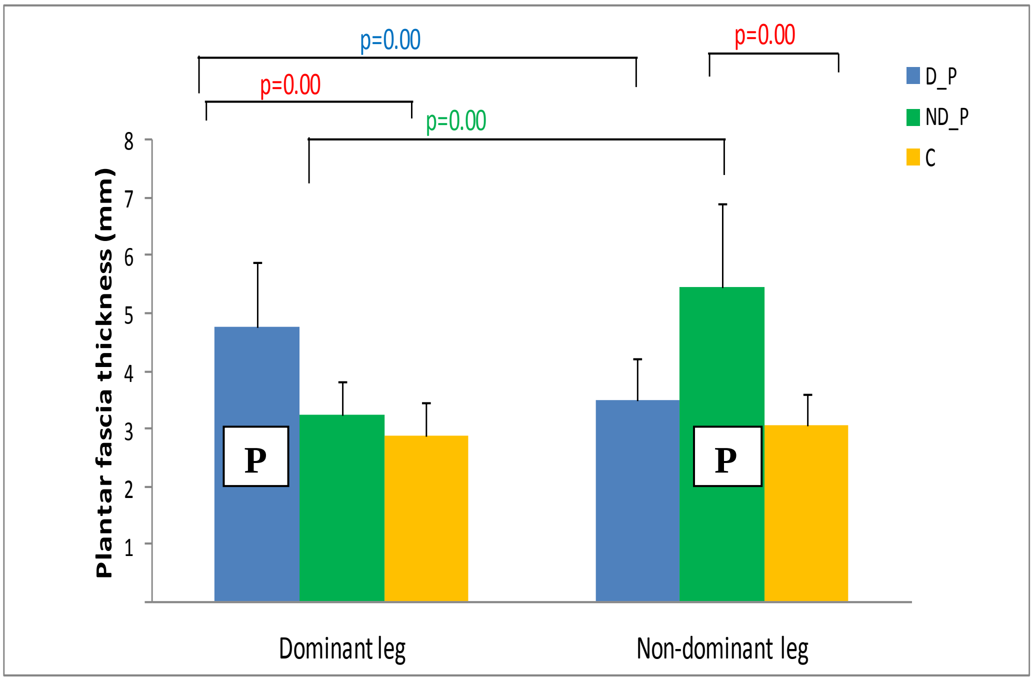


Figure 3. 9 Average plantar fascia thickness on the patients' affected side was much greater than that on the unaffected side whether the dominant or non-dominant foot was affected ($p \leq 0.05$). The affected side was also significantly thicker than the corresponding foot among the healthy controls ($p \leq 0.05$). Painful side is hightlighted.

Table 3. 7 Contrast analyses on fascia thickness

Leg		Mean Difference (95% CI) (cm)	Contrast comparison p value
Dominant	Dominant leg affected vs control	0.171 (0.105,0.237)	0.00
Non-dominant	Non-dominant leg affected vs control	0.236(0.153,0.318)	0.00
Dominant	Dominant leg vs. non-dominant leg	0.122(0.064,0.181)	0.00
Non-dominant	Dominant leg vs. non-dominant leg	0.218(0.13,0.304)	0.00

3.4.4 The relationship between vascularity, fascia thickness and duration of symptoms

Significant regression of vascularity was observed in patients who had experienced symptoms for more than 12 months ($p \leq 0.05$) (Fig. 3.10). In patients with symptoms for less than a year, the VI was similar to those with less long lasting symptoms ($p \leq 0.05$), but significantly higher than patients with symptoms for more than 12 months (Fig. 3.11). The thickness of the affected fascia was similar in all symptomatic patients.

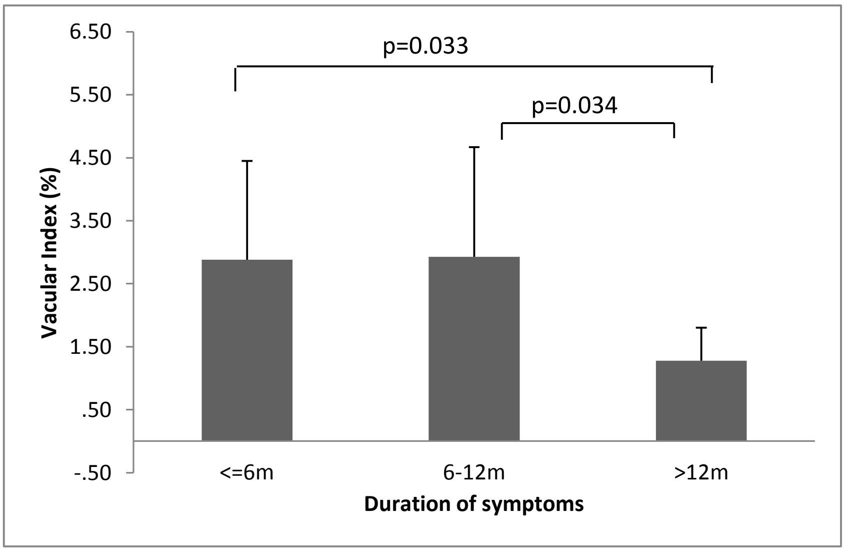


Figure 3. 10 Vascularity in patients with symptoms of different duration

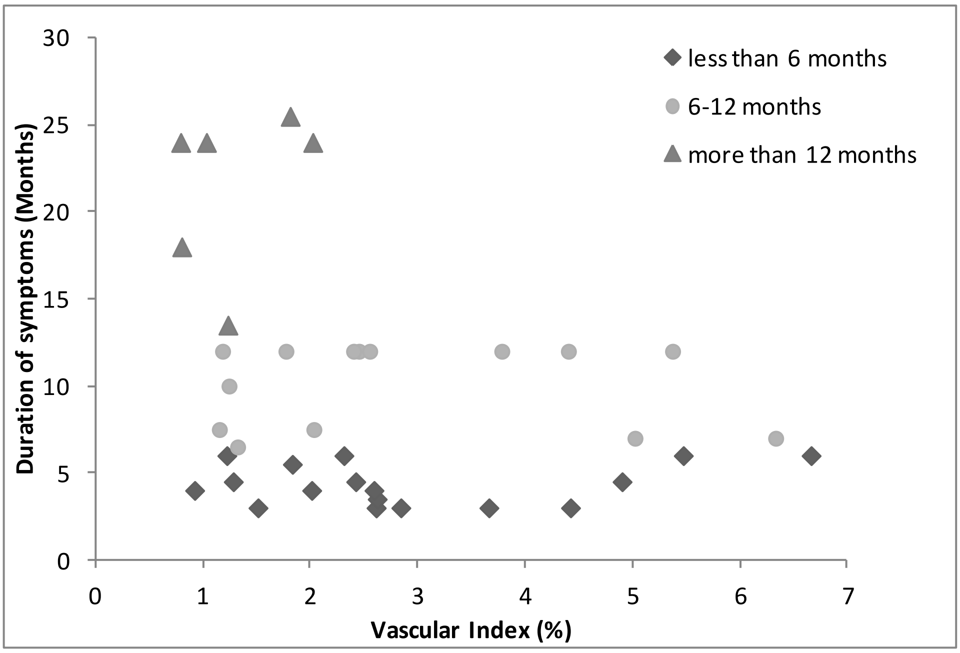


Figure 3. 11 Scatter plot of Vascular index and duration of symptoms

3.5 Discussion

This study was designed to delineate anatomical and physiological differences between patients with unilateral plantar fasciitis and healthy subjects. The larger BMI and increased in extension range of the 1^{ST} MTP J were observed in patients with plantar fasciitis when compared with healthy control. In addition, biological and morphology differences such as vascularity and fascia thickness were detected between the two study groups.

The ratio of male to female was higher in the control than the patient group. Despite statistically insignificant, but 64% versus 43% of female in patient and control groups, respectively seems to be something that could be clinically relevant. In view of such difference, further analyses were conducted with gender as one of the covariates.

Increased BMI is reported frequently in patients with plantar fasciitis (Irving et al. 2007; Riddle et al. 2003). Theoretically, heavier individuals place more loading on the medial longitudinal arch, and this might increase the risk of developing plantar fasciitis (League 2008; Cullen and Singh 2006). Riddle et al. (2003) have reported that an increase of BMI by more than 30 kg/m^2 predicts a 5.6 fold increase in the risk of having plantar fasciitis. However, Rome et al (2001) group reported no significant difference in average BMI for runners with and without heel pain. Irving et al. (2007) have concluded that BMI predicts heel pain only in a non-athletic population. In this study, the majority of the patients were not athletes, yet we found significantly higher BMIs (average 25.37kg/m^2) in the patient group compared with the healthy controls (23.25kg/m^2). Note that in Asia people with a BMI of more than 25kg/ m^2 are regarded as obese (Shiwaku et al. 2004). In this study, then, about 56.41% of the patients belonged to the obese group and suffered from proximal heel pain associated with plantar fasciitis.

Hicks, in 1954, proposed the “windlass” effects of the foot during locomotion, that an increase in foot arch as a result of digital dorsiflexion (extension) would induce greater stress to the plantar fascia. Many years later, Allen et al. (2003) found comparable passive ROMs of the first MTP in affected and unaffected feet. The present study shows that patients with plantar fasciitis on the non-dominant side have greater extension range in the first MTP joint in both active and passive motion. But this greater ROM is found in both their affected and unaffected feet. There is a possibility that an increased ROM in the first MTP joint might induce greater stress to their plantar fascia during locomotion. With time, this might lead to plantar fasciitis (Healey and Chen 2010; Wearing et al. 2006). But why would such a phenomenon not be observed in patients whose dominant feet are affected? We can only speculate that, since the non-dominant side is also the balance leg, greater stress might be imposed on the plantar fascia of that leg. In addition, the differences are in the range of 6^0 to 8^0. Note that the error of goniometer measurement is in the range of 5 degree. Results from our present study would be taken with caution. On the other hand, heavier people will also load the fascia more and lead to greater toe extension as the fascia lengthened. The cause and effect of increased 1st toe extension and incidence of plantar fasciitis requires longitudinal study to confirm.

Our findings on increased vascularity in the affected fascia concur with those of previous studies. Walther et al. (2004) have been the only group investigating changes in vascularity with planter fasciitis, and they found marked hyperemia in symptomatic feet, but not in asymptomatic feet or in healthy subjects. Plantar fasciitis is often, though not always, similar to tendonitis (Wright and Rennels 1964). Vascularization or new vessels have been frequently reported in patients with tendinopathies. Increased in vascularity was detected in patients suffered from Achilles tendinopathy (Ohberg et al. 2001) and patellar tendinopathy (Alfredson and Ohberg 2005). Such studies, however, usually use qualitative grading to categorized patients, most often Newman's grading. In this study we quantified vascularity based on the number of colour pixels detected by power Doppler within a pre-determined region of interest with reference to the calcaneus bone. Vascular index as a continuous data can be more accurate to detect vascularity change than categorical data such as Newman's grading. In Chapter 2, we have reported the useful intra-tester reliability of this approach. Using this, we have not only demonstrated significantly greater vascularity in the affected plantar fascia, but also quantified the differences.

In addition, most studies have observed increased vascularization in some, but not all, subjects. Walther and his colleagues observed moderate or marked hyperemia in 8 out of 20 patients with plantar fasciitis, all of whom had experienced symptoms for less than 12 months (Walther et al. 2004). In this study, regression in vascularity was observed in patients with symptoms for more than 12 months. This finding suggests that the natural progression of the disease involves modulation in vascularity. Vascularization is evidenced in diseased tissue, but this is time limited. Such observations pose a question as to whether the pain experienced by patients with symptoms for less than or more than 12 months is of different origin. Cook et al. (2004) have classified tendinopathy into 3 stages: normal ultrasonographic appearance with pain; abnormal ultrasonography without neovascularization; and abnormal ultrasonography with neovascularization.

Aside from vascularization, thickening of the affected plantar fascia is one of the sonographic characteristics of plantar fasciitis (Akfirat et al. 2003; Karabay et al. 2007; Walther et al. 2004). The mean plantar fascia thickness in normal individuals is from 2.2 mm to 3.6 mm (Gibbon and Long 1999; Wall et al. 1993). In patients with plantar fasciitis it ranges from 4.6 mm to 6.1 mm (Akfirat et al 2003; Karabay et al. 2007; Liang et al. 2007; Walther et al. 2004). In general, patients with plantar fascia thicker than 4 mm are regarded as having plantar fasciitis (Karabay et al. 2007; McNally et al. 2010). Our results were in accord with those previous studies, as the mean fascia thicknesses were 3.0 mm in the controls and 5.1mm at the affected heels. Unlike vascularization, however, there was no observable difference in the fascia thicknesses of patient groups with symptoms of different durations.

This study adopted navicular mobility, the difference of navicular height between non-weight bearing and maximal weight bearing, rather than navicular height to reflect foot pronation. Headlee et al. (2008) has suggested that such an approach provides a composite measure of pronation and excludes possible effects of laxity of the longitudinal arch. We observed no significant differences in navicular mobility between the patients and the healthy controls, and no difference between the patients' affected and unaffected sides. This agrees with the findings of Rome's group. The authors reported that excessive foot pronation is not associated with plantar fasciitis (Rome et al. 2001). Taunton et al. (2002) retrospectively analyzed 159 patients with plantar fasciitis and found that only 30 (19%) had an abnormal arch structure. Shama et al. (1983), however, based on radiographic findings, observed that 81% of patients with heel pain had evidence of foot pronation. The difference may be due to different ways of measuring pronation. With the limited evidence that foot pronation is associated with plantar fasciitis, further studies along this direction seem warranted.

We also could not detect significant differences in ankle dorsiflexion in the affected feet of patients compared with their unaffected feet or the health controls. Rome et al. (2001) similarly reported no difference when testing an athletic population. Among five similar studies, 2 reported increased dorsiflexion (Irving et al. 2007; Pohl et al. 2009) and 3 others showed decreases (Kibler et al. 1991; Riddle et al. 2003; Warren 1984). Note that Pohl was testing a group of runners who were pain-free at the time of the assessment, and Irving used a dorsiflexion lunge test to measure the range indirectly. Riddle and his colleagues, aside from reporting a decrease in ankle dorsiflexion range in the patient group, also suggested that a reduction of 1 to 5 degrees in ankle dorsiflexion would increase the possibility of developing plantar fasciitis 8 fold. Although we didn't find a statistically significant difference in ankle dorsiflexion, reductions in both the active and passive ankle dorsiflexion ranges were observed on the affected side compared with the unaffected side (1° for the active range and 2° for the passive range). As with the navicular mobility, there was no conclusive relationship between the ankle dorsiflexion range and the incidence of plantar fasciitis.

3 .6 Clinical and research implications

Findings from this study indicate increased in vascularity in patients with plantar fascia when compared with healthy control. Knowing that normal fascia is hypovascular tissue, it seems logical that intervention strategies could aim to decrease vascularization in the affected fascia. Physical agents such as extracorporeal shock waves (Wang et al. 2002, 2003) have been demonstrated to induce neovascularity changes. It would be valuable to study the effects of such physical agents in modulating vascularity and the clinical symptoms of patients with plantar fasciitis. Weight control is another means to reduce loading and stress on the plantar fascia, but weight-bearing exercises might increase the impact on it. Indeed, any increase in physical activity has been identified as one of the risk factors for plantar fasciitis (Healey and Chen. 2010; Irving et al. 2006; Riddle et al. 2003). Non-weight bearing exercises with, for example, a stationary exercise bike, can reduce weight (Templeton et al. 2010) without inducing mechanic loading on the fascia could be an alternative for these individuals.

3.7 Limitations

This was a cross-sectional observational study, so no cause and effect relationships could be established. The findings do, however, highlight possible factors inducing plantar fasciitis and physiological changes associated with the condition.

Power Doppler was used to quantify vascularity in the proximal plantar fascia. Operator dependent is one the drawback of ultrasonography (Koski et al. 2006; Naredo et al. 2006; Ota et al. 2007). Therefore, in this study only one examiner was used to conduct all the ultrasound measurements to diminish the intertester variability.

Only a small number of the patients had experienced symptoms for more than 12 months. Kruskal-Wallis H tests were used to compare patients with symptoms of different durations. Interestingly, most patients with symptoms lasting at least 12 months had bilateral symptoms. Further studies are warranted to investigate the causes for patients having bilateral symptoms.

3.8 Conclusions

This study compared the demographic characteristics, vascularity and fascia thickness in patients with unilateral plantar fasciitis and healthy controls. Increased body mass index and a larger range of first MTP extension were observed in patients with plantar fasciitis, suggesting that these are potential risk factors for developing plantar fasciitis. Vascularization and thickened plantar fascia were evident in the patient group. In those patients with symptoms for more than 12 months there was a regression in vascularization, but not in fascia thickness. Strategies to modulate the identified factors are much needed in view of the high prevalence of plantar fasciitis in sedentary as well as active individuals.

CHAPTER 4

MODULATION OF VASCUALRITY IN PATIENTS WITH PLANTAR FASCIITIS:

CUMULATIVE EFFECTS OF EXTRACORPOREAL SHOCK WAVE THERAPY

4.1 Abstract

Background: Earlier studies have shown that the modulation of vascularity is associated with extracorporeal shock wave therapy (ESWT) in both animals and humans. However, little is known about the dosage effects of ESWT on the regulation of vascularization.

Objectives: The purposes of this study were: (1) to explore the effects of ESWT on vascularization in patients with chronic plantar fasciitis; and (2) to determine its cumulative effects in regulating vascularity and reducing pain.

Study design: Prospective randomized controlled study

Methods: Forty-six subjects with chronic plantar fasciitis with a mean age of 45.33 years and mean duration of symptoms of 9.98 months participated in this study. The subjects were randomly assigned into 3 study groups. Subjects being assigned into $ESWT_3$ and $ESWT_6$ groups received 3 and 6 sessions of ESWT, respectively. The control group received no active treatment for 6 weeks. Power Doppler was used to measure vascularization of the proximal plantar fascia. A vascular index (VI) was computed to represent the percentage of vascularization in the fascia. A visual analog scale was used to assess the intensity of pain. Pre- and post-intervention evaluations were conducted by the same evaluator.

Results: Modulation on vascularity was detected in 60% of the subjects following ESWT, but in only 28.6% of patients in the control group, a statistically significant difference (Odds ratio 4.35, 95% confedence interval 1.13,

16.85). In the 3-session group, 50% of the patients showed some vascular regulation, with the majority showing up-regulation. In the 6-session group, 43.75% had vascular down-regulated and 25% showed an up-regulation of vascularity. In the latter group, a cut-off pre-intervention VI score of 2.72% demonstrated excellent sensitivity of 100% and specificity of 88.9% in predicting whether patients with chronic plantar fasciitis would have or not have down-regulation of vascularity. A pre-intervention VI score of less than 2.23% indicated the best sensitivity (75%) and specificity (75%) in predicting whether there would or would not be an up-regulation of vascularity.

Pain reduction by 40% was reported for those in the 2 treatment groups, but by only 8.6% of the control group (Pain change in Rx group: 2.76 ± 0.37, 95% confedence interval 2.00, 3.52; in control group: 0.55 ± 0.56, 95% confedence interval -0.65, 1.76). In addition, 64.5% of the patients were treated successfully in the two ESWT groups verse compared to only 26.67% in the control group.

Conclusion: This study has been the first to demonstrate bi-directional regulation of vascularity in the treatment of chronic plantar fasciitis. The direction of regulation depends on the treatment dosage and baseline vascularization. Successful treatment occurred in 64.5% of the patients. Further studies are suggested to explore the long term effects of ESWT on vascularization and its association with long-term success in treating chronic plantar fasciitis.

Key words: vascularization, plantar fasciitis, extracorporeal shock wave therapy, cumulative effects, pain

4.2 Introduction

As mentioned in Chapter 1, chronic plantar fasciitis is one of the most common painful foot conditions that affect both active and sedentary adults (Cole et al. 2005; Crawford and Thomson 2003) leading to pain, limited mobility or even disability lasting for 6 to 18 months or even longer (Wearing et al. 2006). There are many commonly adopted conservative strategies for treating plantar fasciitis, but therapeutic ultrasound, low-intensity laser irradiation and many other therapies are only supported by limited scientific evidence (Crawford and Thomson 2003, League 2008). Extracorporeal shock wave therapy (ESWT) is a relatively new physical treatment modality approved by the U.S. Food and Drug Administration only since 2000 (Seil et al. 2006).

Shockwaves are defined as transient increases in positive pressure of high magnitude (up to more than 100MPa) with short durations (less than 10 ns), followed by a decrease to negative pressure values of roughly -10MPa (Ogden et al. 2001). Three techniques can generate focused shock waves: electrohydraulics, electromagnetics and piezoelectrics, all of which have been approved for medical use in Europe (Seil et al. 2006). Independent of the device, significantly greater reductions in pain or a larger fraction of patients with chronic platnar fasciitis successfully treated have been reported with repetitive, focused, low energy ESWT than with placebo treatment (Cosentino et al. 2001; Rompe et al. 1996, 2003) and low number ESWT (Rompe et al. 2002). At 3-month follow-ups, around 50% to 69% of patients have been found to be treated successfully (Hammer et al. 2003; Labek et al. 2005; Liang et al. 2007; Rompe et al. 2003, 2005) despite considerable differences in treatment regimens, treatment intensity, patient selection, and definitions of treatment outcome. Furthermore, most studies have reported better outcomes when subjects were evaluated at a longer follow-up period (Hammer et al. 2003; Moretti et al. 2006; Ogden et al. 2001). Aside from the time factor, other intrinsic factors such as gender (Höfling et al. 2008) and fascia thinness (Liang et al. 2007) have been shown to influence the successfulness of repetitive ESWT.

While numerous studies have examined ESWT's therapeutic effects, research on its biological mechanism is much less common. Several working mechanisms, such as micro-trauma (Ogden et al. 2001), inhibition of pain receptors (Rompe et al. 2007; Speed 2004), and promotion of soft tissue healing (Chen et al. 2004; Wang et al. 2002, 2003) have been proposed. ESWT induced neovascularization might promote tissue healing by removing the breakdown products of cell death (Younger 2006) as well as in inducing the cellular repair of degenerate tissue (Fenwick et al. 2002; Rompe et al. 1998). Wang's group first demonstrated that one session of ESWT could induce neovascularity at the tendon-bone junction in dogs (Wang et al. 2002) and stimulate an in-growth of new vessels in rabbits (Wang et al. 2003). In addition, the research group also observed angiogenesis mediators such as nitric oxide and vascular endothelium growth factors 1 week after the application of ESWT. On the other hand, a significant reduction in oxygen saturation has been detected after 3 sessions of ESWT in patients with supraspinatus tendinopathy (Notarnicola et al. 2011). The reduction in oxygen saturation quantified by an oxymetry began after the first session of ESWT, and the change in oxygen saturation was found to be associated with pain reduction. Despite evidence of ESWT-induced neovascualrization, there is inadequate information on whether there would be an up- or a down- regulation in vascularization following a course of ESWT. Such information would enhance our understanding of the vascularization changes ESWT induces and might thereby form a more scientific basis for clinical application.

In this connection, ESWT-induced biological effects are related to the applied energy density. Rompe et al. (1998) observed a shift from no change to marked inflammatory reactions when the delivered energy was increased from low to high intensity in a rabbit model. Similarly, when the energy density of 0.17mJ/mm^2 was applied to cultured cells, the cell count increased in a 500 shocks group but decreased in the 1000 or 2000 shocks groups (Han et al. 2009). The effects of ESWT could be bi-directional and dose-dependent. On the other hand, in human studies, Liang et al. (2007) has reported comparable success rates when ESWT was applied at either low (0.12 mJ/mm^2) or high intensity (0.56 mJ/mm^2) to patients with chronic plantar fasciitis, and no adverse effects were observed in those patients. However, the maximum tolerable energy density was found to be more effective than a low or fixed energy density for pain reduction and functional recovery (Chow and Cheing 2007). A question therefore arises as to whether the modulation in vascularization and pain by ESWT are dose-dependent.

ESWT was found to have clinical and statistic significant effects when applied with low intensity at weekly basis for at least 3 sessions to patients with plantar fasciitis for more than 6 months. In addition, changes in vascularity were detected in animal and human studies after application of ESWT. So, this study was set to explore possible changes in biology (vascularity) and clinical symptoms in patients with chronic plantar fasciitis. The objectives of this study were (1) to explore the ESWT-induced effects on vascularization in patients with chronic plantar fasciitis; and (2) to delineate dose-dependent effects in governing regulation on vascularity and pain. We hypothesized that in patients with chronic plantar fasciitis there would be ESWT-induced regulation in vascularization and that there would be a dose-dependent effect of ESWT on the modulation in vascularization and pain. The study was designed to provide a more scientific basis for the application of ESWT in cases of chronic plantar fasciitis.

4.3 Methods

4.3.1 Subjects and study design

A prospective, randomized, single blinded, controlled trial was performed on 46 subjects with chronic plantar fasciitis. They were referred from a regional hospital and diagnosed by orthopaedic doctors with more than 10 years of experience. To be included, patients were required to be above 18 years of age, and to have had the symptoms of plantar fasciitis for at least 3 months and less than 2 years. Patients were excluded if they had a history of a systemic disease such as gout or seronegative arthritis with manifestations similar to those of plantar fasciitis, or other systemic diseases such as diabetes mellitus or peripheral vascular disease which may affect lower limb vascularity. Subjects with a history of foot trauma, calcaneal stress fracture or corticosteroid injections were also excluded, as were those currently pregnant. This study was approved by the Human Subject Ethics Sub-committee of the university and hospital (Appendix I). Written consent was obtained from each subject after verbal explanation of the study (Appendix II and III).

4.3.2 Procedure

All assessments were conducted at the Ultrasonography Laboratory of the Hong Kong Polytechnic University by a single examiner before and within 7 days after the last session of ESWT, or 6 weeks after the first evaluation for the controls. This examiner was blind to the treatment condition.

Demographics

Demographic information such as age, sex, weight, height and activity level was obtained by interviewing the subjects.

Vascularization and fascia thickness

The equipment and procedures described in Chapter 2 were used to evaluate vascularization and fascia thickness. The vascular index (VI) was computed by expressing the number of colour pixels as a percentage of the total number of pixels. Our previous study of 44 patients with chornic plantar fasciitis and 17 healthy subjects revealed good intra-tester reliability for this index with an intraclass correlation coefficient of 0.72 (for details please refer to Chapter 2). The minimum detectable difference was 0.68%. Hence, vascular regulation was suggested when changes in VI exceeded 0.68%. An increase in VI of 0.68% or more was defined as up-regulation; a decrease in VI of 0.68% or more indicated down-regulation of vascularization.

Intensity of pain

Intensity of pain was self-rated using a visual analogue scale (VAS) (Wewers and Lowe 1990). The VAS was used to reflect the self-perceived intensity of pain on a 100mm horizontal line. Based on earlier work by Crossley et al. (2004), a change of 20mm or more was taken as indicating clinical improvement. Treatment was regarded as successful when the VAS reading dropped by 20mm or more, or by 30% or more (Metzner et al. 2010).

Treatment group and treatment protocol

According to gender, patients were invited to draw an unsealed envelope that indicated to which group they had been assigned (Fig. 4.1). The first male subject would draw from an envelope to decide whether he would enter 3-session, 6-session or control group. The first female subject also got 3 tickets in the envelope. For the second male, he would have 2 choose to draw from. For the third male, he would draw the only ticket in the envelope to reveal which group that he would enter. Patients in the $ESWT_3$ and $ESWT_6$ groups received 3 and 6 sessions of ESWT, respectively. Three treatment sessions have commonly been adopted in previous studies, while 6 is the maximum number of treatment sessions reported previously. Subjects made 6 weekly visits to a regional hospital in order to standardize the length of the intervention and any psychological influences. Subjects in the control group (C) were told they had a 6-week waiting period for receiving ESWT.

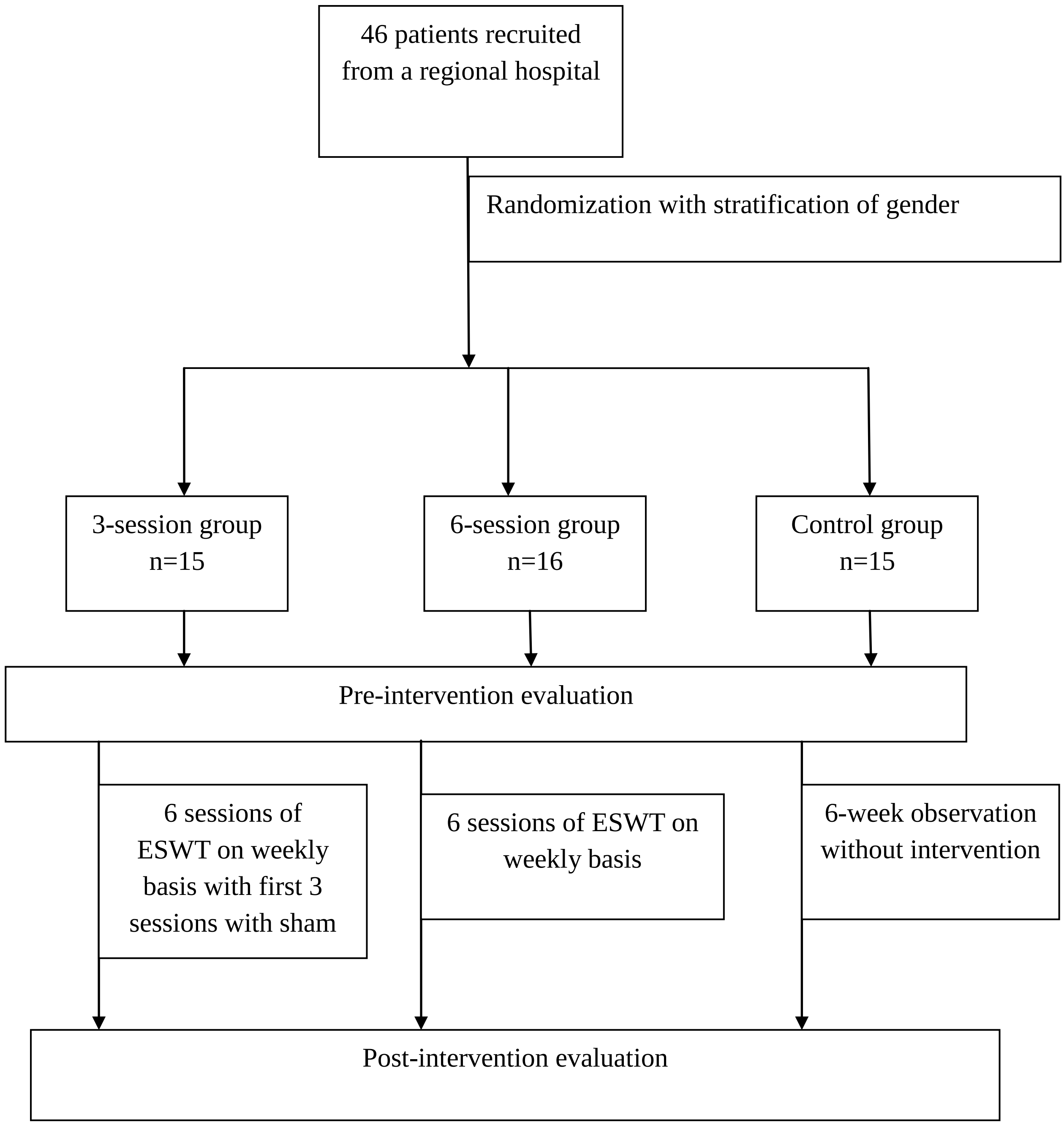


Figure 4. 1 Flow chart showing the grouping procedure. A total of 46 subjects completed the programme.

Extracorporeal shock wave therapy

The shock waves were delivered by an electromagnetic extracorporeal shock wave machine (Duolith SL1, Storz Medical, Switzerland) guided by an ultrasound unit (Aloka SSD-900, Hitachi Aloka Medical, Japan). The energy flux density ranged from 0.08-1.1 mJ/mm^2. Patients were treated in a prone position, lying with their feet hanging off the edge of the treatment plinth (Fig 4.2). Clinical focusing was used to localize the delivery of the shock waves (Rompe et al. 2007). The treatment head was placed perpendicular to the most painful area with the aid of patient feedback. Fine adjustment was made with feedback from the on line ultrasound. The treatment protocol for the $ESWT_3$ group consisted of 3 sessions of sham intervention followed with 3 sessions of actual treatment. The sham sessions consisted of 400 impulses at minimal intensity (0.01 mJ/mm^2) delivered at 1 Hz. The actual treatment consisted of 1500 impulses at maximum intensity delivered at 4 Hz. The first 200 shocks were used to adjust the intensity to the maximum tolerable pain level according to the patients' feedback. Patients in the $ESWT_6$ group received 6 sessions of maximum intensity of ESWT with 1500 impulses delivered at 4 Hz.

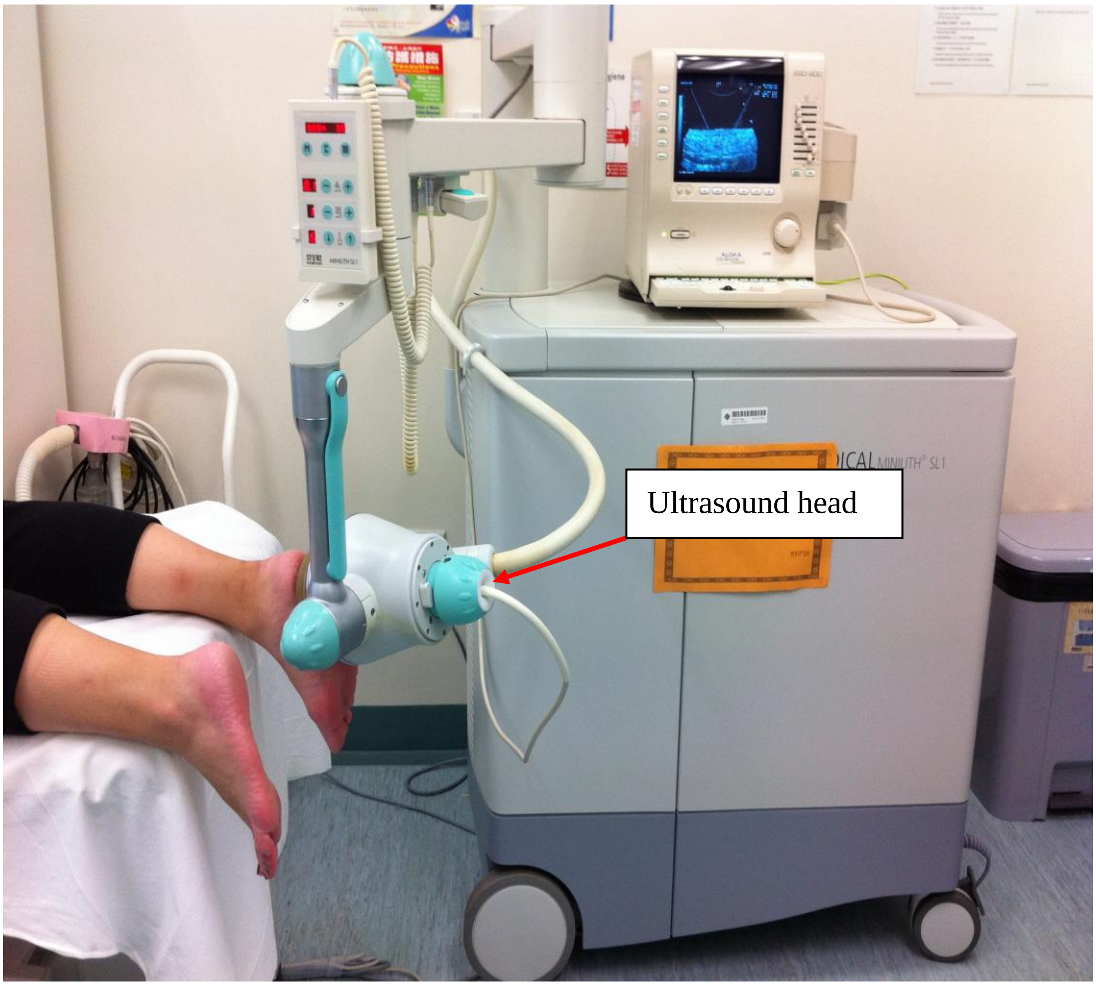


Figure 4. 2 Position of the patient and the treatment head of the extracorporeal shock wave machine for delivering treatment to the plantar fascia.

4.3.3 Statistical analysis

Descriptive statistics were used to examine the mean and variability of all measured variables. One way ANOVA was used to compare the ages, body mass indexes (BMIs), duration of symptoms, as well as the outcome variables among the three groups before the intervention started. Chi-square tests were used to assess intergroup differences in vascular regulation and the efficacy of the treatment. Post hoc test with Bonferroni correction was conducted between $ESWT_3$ and $ESWT_6$, $ESWT_3$ and control, $ESWT_6$ and control with adjusted p-value to 0.0167 to avoid type 1 error. Separate receiver operating characteristic (ROC) curves were constructed to identify the cut-off pre-intervention VI scores for vascular regulation in the 2 treatment groups. As an up-regulation or a down-regulation might occur, dummy variables (DVs) were created. DV_1 referenced the group with up-regulation to the group with no regulation; DV_2 referenced the group with down-regulation to the group with no regulation. The areas under the ROCs, the cut-off scores, and the associated sensitivity and specificity values were generated calculated using the PASW software package. Analysis of covariates (ANVOVA) was used to analyze pain reduction with time as within and group as between factors and age, sex, and height as covariates. The level of significance was set at $p \leq 0.05$. The PASW 17 statistical software package was used for all statistical analyses.

4.4 Results

Subject characteristics

A total of 46 patients (29 female) volunteered to participate in this study, and all of them completed the programme. The subject characteristics are detailed in Table 4.1. Comparable BMIs, duration of symptom, VI, VAS, and fascia thickness were observed among the 3 groups. There were, however, significant group differences in age and height. Patients in the $ESWT_6$ were older and shorter on average than the controls. Ten subjects had bilateral symptoms with 1, 4 and 5 of these subjects being assigned to the $ESWT_{3,}$ $ESWT_6$ and control groups, respectively. The activity levels ranged from sedentary to extremely active, but with insignificant intergroup differences.

Table 4. 1 Subject characteristics

Variable	$ESWT_3$ (n=15)	$ESWT_6$ (n=16)	Control (n=15)	*p* value
Demographics				
Age, years (Median)	45.80±6.68 (46)	49.25±5.01 (48.5)	40.67±9.10 (43)	0.006
Gender (Female,male)	11,4	12,4	6,9	0.079
Weight, kg	66.20±15.70	65.04±10.71	65.68±10.47	0.967
Height, m	1.59±8.23	1.59±6.56	1.66±9.90	0.021
Body mass index (kg/m^2)	26.07±4.14	25.72±2.65	23.69±2.43	0.094
Physical Activity (n)				
Sedentary & light	5	6	2	
Moderate	3	4	6	0.586
Active & extremely active	7	6	7	
Plantar fasciitis characteristics				
Duration of symptoms (months)	9.80±6.09	10.13±7.68	10.00±7.89	0.992
Affected side (left/right/both; n)	11/3/1	5/7/4	3/7/5	
Sonographic findings				
Vascularity index, %	2.01±1.32	3.22±1.83	2.74±2.17	0.203
Plantar fascia thickness, mm	5.40±1.42	4.96±1.45	4.23±1.07	0.074
Pain				
Visual analog scale	6.33±1.59	7.38±1.50	6.47±1.93	0.180

*Except where indicated otherwise, values are the mean±SD

Vascularity

Table 4.2 shows the pre- and post- intervention VIs of the 3 groups. In the $ESWT_3$ group, 50% of the patients showed some vascular regulation—40% showed up-regulated vascularity with only 2 patients showing vascularity down-regulated. In the $ESWT_6$ group, 68.75% had vascular regulation, with 43.75% showing down-regulation. Up- regulated vascularity was observed in 25% of the $ESWT_6$ group, with 31.25% showing no regulation. In the control group, 71.42% showed no regulation of vascularity, but three patients (21.43%) did show an up-regulation. The percentage of subjects showing some vascularity regulation was significantly higher in the treatment groups than in the control group (p=0.028, Odds ratio 4.35, 95% CI 1.13, 16.85) (Table 4.3). Further analysis indicated that the differences between the $ESWT_6$ and control groups (p=0.019) was close to the alpha level set on vascular regulation (p=0.0167) but no difference was found between the $ESWT_6$ and $ESWT_3$ groups (p=0.379) and between the $ESWT_3$ and control groups (p=0.136).

Table 4. 2 Pre- and post-intervention vascular index of the affected heel*

	$ESWT_3$ (n=15)		$ESWT_6$ (n=16)		Control (n=15)	
	Pre-	*Post-*	Pre-	*Post-*	Pre-	*Post-*
1	3.78	*6.01*	0.71	*0.90*	1.23	*1.79*
2	1.18	*3.99*	2.61	*2.82*	1.32	*1.30*
3	0.79	*3.71*	1.14	*2.02*	2.42	*2.09*
4	2.31	*1.70*	2.84	*1.77*	1.98	*2.10*
5	2.61	*4.44*	3.66	*4.77*	2.03	*2.47*
6	0.80	*2.16*	1.03	*1.74*	2.79	*2.49*
7	1.51	*1.32*	5.84	*4.04*	1.15	*1.19*
8	**15.04**	*10.64*	6.33	*3.82*	**8.87**	*2.68*
9	1.77	*1.84*	2.02	*3.46*	1.81	*5.97*
10	2.59	*5.43*	4.42	*3.72*	1.83	*1.44*
11	5.37	*2.99*	5.47	*2.83*	1.28	*1.15*
12	0.92	*0.78*	2.45	*2.12*	4.9	*2.38*
13	0.75	*0.65*	4.40	*3.34*	5.89	*8.66*
14	2.55	*2.11*	2.01	*1.54*	1.55	*1.72*
15	1.24	*1.33*	1.57	*1.92*	2.08	*3.40*
16			5.02	*2.69*		
Mean	2.01	*2.75*	3.22	*2.72*	2.74	*2.72*
SD	1.32	*1.71*	1.83	*1.07*	2.17	*2.03*

*The more affected heel of patients with bilateral symptoms are presented.
The two outliers that are highlighted in bold were excluded from the mean calculation.

Table 4. 3 Number of patients with regulation of vascularity

Regulation of vascularity	Intervention Groups			Control
	ESWT $_3$	ESWT$_6$	Total	
No regulation	7	5	12	10
Down-regulation	2	7	8	2
Up-regulation	6	4	10	3

Receiver Operating Curves

Separate ROCs were constructed to determine the optimal pre-intervention VI cutoff scores for identifying vascular up-regulation and down-regulation in the 2 treatment groups (Table 4.4). For up-regulation, the areas under the curves were 0.479 and 0.771 for the ESWT$_3$ and ESWT$_6$ groups, respectively. The cut-off scores of 1.21% and 1.36% provided low sensitivity of 50% but high specificity of 75% and 91.70% for the ESWT$_3$ and ESWT$_6$ groups, respectively. A further increase in cut-off score to 2.23% substantially increased the sensitivity to 75% but decreased the specificity to 75% for the 6 –session group. For down-regulation, the area under the curve was 0.984 for the ESWT$_6$ groups. Table 4.4 indicates that a pre-intervention VI score of 2.72% had excellent sensitivity of 100% and specificity of 88.9% for predicting down regulation after 6 sessions of ESWT. No analysis was conducted for the ESWT$_3$ group because only two subjects had vascular down-regulation.

Table 4. 4 Percentage of patients with plantar fasciitis correctly identified as having or not having vascular regulation using different cut-off pre-intervention vascular indexes for the ESWT3 and ESWT6 groups

	Up-Regulation (%)	No regulation (%)
$ESWT_3$ group cutoff		
1.21	**50.0**	**75.0**
1.38	50.0	62.5
1.64	50.0	50.0
2.04	50.0	37.5
$ESWT_6$ group cutoff		
1.09	25.0	91.7
1.36	**50.0**	**91.7**
1.79	50.0	83.3
2.01	50.0	75.0
2.23	**75.0**	**75.0**
2.53	75.0	66.7

$ESWT_6$ group cutoff	Down-regulation (%)	No regulation (%)
2.23	100.0	66.7
2.53	100.0	77.8
2.72	**100.0**	**88.9**
3.25	85.7	88.9
4.03	85.7	100.0

Pain reduction

Significant reduction in pain was reported by about 40% of the patients in both treatment groups, but not in the control group. For details, please refer to Table 4.5. The number of patients treated successfully is also listed in Table 4.5. A significantly greater portion (64.52%) of patients was treated successfully in the treatment groups (60% in the $ESWT_3$ group and 68.75% in the $ESWT_6$ group) when compared with the control group (26.67%) ($p \leq 0.05$). The percentage of successfully treated patients was significantly greater in the $ESWT_6$ group than the controls ($p \leq 0.05$). Further analysis indicated that the differences between the $ESWT_6$ and control groups (p=0.019) was close to the alpha level set on vascular regulation (p=0.0167) but no difference was found between the $ESWT_6$ and $ESWT_3$ groups (p=0.611) and between the $ESWT_3$ and control groups (p=0.065) (Table 4.6).

Table 4.5 Intensity of pain and the efficacy of a course of ESWT in pain reduction

	$ESWT_3$ (n=15)	$ESWT_6$ (n=16)	Control (n=15)
VAS score			
Pre-intervention	6.33 ±1.59	7.38±1.50	6.47±1.93
Post-intervention	3.84±3.01	4.37 ±2.44	5.91±1.68
Within group, *p* value	0.000	0.000	0.343
Mean difference (95% CI)	2.49 (1.39,3.958)	3.01 (1.937, 4.076)	0.55 (-0.551,1.658)

*The differences among the three groups were significant at the 5% level of confidence

Table 4. 6 Number of successfully treated patients among three groups

<table>
<tr><td></td><td>ESWT₃ (n=15)</td><td>ESWT₆ (n=16)</td><td>Control (n=15)</td></tr>
<tr><td>Number of successfully treated patients</td><td>9</td><td>11</td><td>4</td></tr>
<tr><td rowspan="3">Contrast comparison p value, Odds ratio (OR) (95% CI)</td><td colspan="2">0.611, OR 0.682,(0.156,2.989)</td><td></td></tr>
<tr><td></td><td colspan="2">0.019 , OR 0.165 (0.035, 0.785)</td></tr>
<tr><td colspan="3">ESWT₃ VS. control: 0.065, OR 0.242 (0.052,1.133)</td></tr>
</table>

4.5 Discussion

This study was designed to delineate ESWT-induced vascular regulation in patients with chronic plantar fasciitis. This is the first report observing bi-directional regulation of vascularity following 6 sessions of ESWT. The direction of regulation apparently depends on the baseline vascularity. Our findings also suggest dose-dependent effects of ESWT on vascularization and successful treatment. Such findings support a role for vascularity in tissue healing.

Bi-directional regulation of vascularity

Our findings suggest that ESWT induced vascular changes in 60% of the patients with chronic plantnar fasciitis studied. Up-regulation of vascularity was observed following 3 and 6 weekly sessions of ESWT. Vascularity was observed as down-regulated only after 6 sessions of ESWT in patients with a baseline vascular index greater than 2.72%. These findings may partially explain the contradictory findings in previous studies. ESWT-induced neovascularization was first reported from Wang's research group (Wang et al. 2002, 2003). They used healthy Achilles tendons harvested from dogs and rabbits. Healthy tendons have low vascularization (Fenwick et al. 2002), and up-regulation of nitrous oxide (NO), vascular endothelial growth factor (VEGF) and new vessels was induced from a single session of ESWT. Notarnicola et al. (2010) applied ESWT to patients with chronic supraspinatus tendinopathy with symptoms lasting for 7 to 14 months. The oxygen saturation was much greater on the painful than the non-painful shoulder (O_2 = 80.1% and 45.7%, respectively). Similar to our findings, they observed ESWT-induced down-regulation of oxygen tissue saturation in patients with increased vascularization. However, the authors reported vascular regulation after the first session (Notarnicola et al. 2011). But we found down-regulation of vascularization to be rare (in only 2 patients) following 3 sessions of ESWT in our study. The differences might be associated with the tissues treated (tendon versus fascia), the equipment used to quantify vascularity (oxymetry versus power doppler) and the intensity of treatment (2000 impulses verse 1500). Nevertheless, our findings, taken together with previous reports, highlight that the regulation of vascularity is bi-directional and may depend on the initial vascular status of the injured tissues.

Dose-dependence of vascularization

It has been reported that high intensity ESWT induces inflammatory responses in the healthy Achilles tendons of rabbits (Rompe et al. 1998) and that excessive impulses cause cell death in culture (Han et al. 2009). On the other hand, cell proliferation only occurs when the intensity of treatment reaches a threshold (Han et al. 2009; Ogden et al. 2001). We found that 6 sessions of ESWT at the maximum tolerable intensity caused more subjects having vascular down-regulation than 3 sessions. The comparison between 6-sessions group and control group showed that p value was quite close to the set alpha level, but not in 3-session groups and control groups. As Bonferroni correction was used to avoid type I error, at the same time it also might increase the possibility of type II error, which means there may have real difference between 6-session group and control group, but we can not detect it from the statistical analsysis. Such a finding is not entirely surprising, as Chow and Cheing (2007) have previously reported dose-dependent effects on pain and foot function.

How does ESWT regulate vascularization?

Shockwaves induce sudden changes in pressure causing cavitation in soft tissues and result in vessel rupture and angiogenesis (Notarnicola et al. 2011). Another mechanism could be related to neurochemical factors. Vascular endothelial growth factor-A (VEGF), a potent angiogenic peptide, is expressed in patients with tendinopathy (Scott et al. 2008) as an element of the inflammatory response to soft tissue injury (Stein et al. 2000) or to mechanical loading (Petersen et al. 2004). Alexander et al. (2008) observed up-regulation of VEGF by 3 sessions of ESWT in the ischemic myocardium in vitro. At the same time, shockwaves enhance endogenous nitric oxide production (Mariotto et al. 2005). Like VEGF, nitric oxide (NO) is known as a mediator of the anti-inflammatory response and vasodilation. These findings provide a possible mechanism for ESWT-induced NO that limits the inflammatory process. Regression of the inflammation might then turn off the associated angiogenesis. Down regulation of vascularization might therefore be found during the course of ESWT (Notarnicola et al. 2011) and after a successful intervention (Alfredson et al. 2003; Alfredson and Ohberg 2005).

Dose-dependent effects on clinical symptoms

In both treatment groups, significant pain reduction (by 40%) was observed. The percentage pain reduction was significantly greater than among the controls. Such findings concur with previous studies (Chow and Cheing 2007;

Cosentino et al. 2001; Rompe et al. 2002, 2005). Like us, Cosentino's group reported significant pain reduction following 6 sessions of ESWT. Most studies have assessed treatment effects at longer follow up time, e.g. after 3 months or 6 months (Rompe et al. 2002, 2005). As micro-trauma induced by ESWT is thought to be one of its working mechanisms (Rompe et al. 2002), tissue repair and healing take time. Results from our study indicate an average of 64.5% of patients being treated successfully following 3 or 6 sessions of ESWT. The percentage would probably be greater at a later follow-up, as Metzner et al. (2010).

4.6. Research and clinical implications

Our findings substantiate the importance of vascularity for tissue healing. Optimization of the internal environment via up-regulation or down-regulation of vascularity can be achieved with the commonly used physical agents such as cold, heat, and ultrasound. It would be valuable to compare the effects of different physical agents in treating patients with plantar fasciitis with and without reference to baseline vascularity.

4.7 Limitations

In this study, we used a change in 20mm or more out of 100mm of the visual analogue scale was taken as clinical significant at post-intervention. This reference was based on the study from Crossley et al. (2004) on patients with patellofemoral joint pain. We assumed such reference could be made in patients with plantar fasciitis as both type of patients has dysfunction affecting the lower limb.

Second, each subject was assigned to either treatment or waiting groups at a Regional Hospital by a registered physiotherapist. This physiotherapist also delivered the ESWT to the patients. Both 3-sham-3-session and 6-session groups attended the hospital for 6 weeks. The pre- and post outcome measures on ultrasonographic evaluation and clinical outcomes were measured by another tester blinded to the grouping. The changes on vascularity and clinical measures on the 3-sham-3-treatment group would likely be a combination of sham and treatment effects. We used patients in the waiting list as control in order to observe natural changes in patients with plantar fasciitis within the same time frame.

Note that there were more subjects with bilateral symptoms assigned to the control group as the subjects were randomized only with gender stratification. Also, the subjects in the control group had no active treatment while waiting for 6 weeks. We cannot rule out psychological factors influencing pain perceptions. For the 3-session group, they received 3 sham treatments. Hence, the effect on vascularity and pain might be a combined effects from psychological and intervention.

Note also that the evaluations and the interventions were conducted at two different locations. Patients were invited to the testing laboratory before and after the treatment programme. The same evaluator conducted the pre- and post-intervention evaluations to minimize inter-tester variance, and she was blinded to the treatment condition. However, re-evaluation could not be done after each session. Hence only cumulative effects were assessed and we could not determine any session-to-session effects (Notarnicola et al. 2011).

4.8 Conclusions

This study has been the first to demonstrate bi-directional regulation of vascularity when ESWT is used to treat chronic plantar fasciitis. The direction of regulation depends on treatment dosage and baseline vascularization. Successful treatment occurred in 64.52% of the patients. Further studies are suggested to explore the long term effects of ESWT on vascularization and its association with the long-term successful treatment of chronic plantar fasciitis.

CHAPTER 5

VASCULARIZATION QUANTIFIED BY POWER DOPPLER ULTRASONOGRAPHY IN PATIENTS WITH PLANTAR FASCIITIS:

ITS ROLE ON TREATMENT PLANNING

5.1 Abstract

Background: Vascular changes have been proposed as one of the potential mediators of plantar fasciitis pain and was found increased in some but not all patients. Regression of vascularization was observed in successfully treated patients.

Objectives: This study aimed to examine whether pre-intervention vascularization quantified by power Doppler ultrasonography could assist treatment decision for patients with chronic plantar fasciitis.

Method: Thirty patients with unilaterally affected plantar fasciitis (age 46.00$\pm$ 7.88 years; BMI = 25.68$\pm$ 3.10 Kg/m^2) were divided randomly into receiving either 3- or 6- session Extracorporeal shock wave therapy. Vascularity of proximal plantar fascia, pain intensity and foot function were assessed at pre-, post and one month after intervention by the same evaluator. Receiver operating curves (ROC) were used to identify the cutoff VI scores for successful treatment for the 3- and 6-session groups.

Results: In 30 patients with chronic plantar fasciitis, 43.30% had significant increase in vascularity. The magnitude of vascularity was positively correlated to pain and foot function in patients with symptoms lasting less than 12 months. A vascularity index at the baseline of more than 1.55% was a predictor of unsuccessful recovery (sensitivity=83.30%, specificity=100%, area under the curve=0.92) with three sessions of extracorporeal shockwave therapy (ESWT);

but a VI score of more than 3.25% of unsuccessful recovery with six sessions of ESWT (sensitivity = 62.50%, specificity=100%, area under the curve=0.75). A similar VI index for unsuccessful intervention at 4-week follow-up based on pain reduction was observed.

Conclusions: These findings highlight the importance of using power Doppler ultrasonography on treatment planning. Our findings also indicate that treatment efficacy depends on pre-intervention vascularity and the number of treatment sessions. As plantar fasciitis has a substantial impact on a patient's quality of life, treatment planning based on baseline evaluation can give a patient appropriate expectation.

Key words: Neovascularization, plantar fasciitis, treatment planning, Extracorporeal shock- wave therapy

5.2 Introduction

Plantar fasciitis is the most common cause of heel pain (Rompe 2009) and vascular changes have been proposed as one of the potential mediators of that pain (Alfredson et al. 2003). Recent advances in ultrasonography (US) can detect increased vascularization in patients with plantar fasciitis (Walther et al. 2004) and chronic tendinopathies (Alfredson and Ohberg 2005; De Vos et al. 2007; Divani et al. 2010; Zanetti et al. 2003; Zeisig et al. 2006). However, vascularization has been found to have increased in some but not all patients. In patients with chronic plantar fasciitis, Walther et al. (2004) observed moderate to severe hyperemia in 40% of the patients studied. Such findings suggest that vascularization could be one of the physiological changes typifying patients with chronic plantar fasciitis. Doppler US images can thus assist clinicians and researchers to classify patients.

Pain has been found to be more intense in patients with vascularization than in those without (Cook et al. 2004; Zanetti et al. 2003). Based on Newman's grading, a higher grade is associated with greater intensity of pain in patients with plantar fasciitis (Walther et al. 2004) and Achilles tendinopathy (Peers et al. 2003; Reiter et al. 2004). Regression of vascularization has also been observed in those treated successfully (Alfredson and Ohberg 2005). Notarnicola et al. (2011) have recently reported using an oximeter to monitor tissue oxymetry values in patients with supraspinatus tendinopathy during a course of extracorporeal shock wave therapy (ESWT). Reduced oxygen saturation was observed after each treatment session, and the reduction in oxygen saturation was associated with clinical improvement. If Doppler US can assist clinicians in classifying patients according to their extent of vascularization, perhaps treatment planning could be at least partially guided by pre-intervention vascularization. To date, there is no information on planning treatment based on vascularity for patients with plantar fasciitis.

ESWT has been approved for treating patients with plantar fasciitis in the U.S. by their Food and Drug Administration since 2000 (Rompe et al. 2003). Its efficacy in reducing pain in patients with plantar fasciitis has been proven amply with ESWT applied at low to medium intensity, from 1000-2000 impulses on multi-session at weekly basis in chonic patients (Cosentino et al. 2001; Gollwitzer et al. 2007; Ogden et al. 2004; Rompe et al. 2002, 2003). The number of required treatment sessions varies. The majority of the reported studies used 3 sessions (Gollwitzer et al**.** 2007; Metzner et al. 2010), but Cosentino et al. (2001) reported using six sessions to treat their patients.

The present study was designed to examine whether pre-intervention vascularization quantified by power Doppler US could assist in making treatment decisions about patients with plantar fasciitis. It tested the proposition that initial vascularization can inform whether patients requires 3- or 6-session of extracorporeal shock wave therapy for a satisfactory clinical outcome at post-intervention and 1 month follow-up. The findings were intended to form a scientific basis for patient management based on Doppler US imaging.

5.3 Methods

5.3.1 Study participants

Thirty patients with unilateral plantar fasciitis (20 females, 10 males) participated in the study. Their ages ranged from 25 to 60 years (mean age 46 years). These patients were recruited from a regional hospital and diagnosed by experienced orthopaedic doctors. Only patients with unilateral symptoms were included in this study. To be included, patients were required to be above 18 years of age, and to have had the symptoms of plantar fasciitis for at least 3 months. Patients were excluded if they had a history of systemic disease such as gout or seronegative arthritis with manifestations similar to those of plantar fasciitis, or other systemic diseases such as diabetes mellitus or peripheral vascular disease which may affect lower limb vascularity. Subjects with a history of foot trauma, calcaneal stress fracture, corticosteroid injections were also excluded, as were those currently pregnant. This study was approved by the Human Subject Ethics Sub-committee of the university and hospital(Appendix I). Written consent was obtained from each subject after verbal explanation of the study (Appendix II and III).

5.3.2 Assessments

All assessments were conducted at the Ultrasonography Laboratory of the Hong Kong Polytechnic University. Demographic data such as age, weight and height were recorded, and a standard assessment protocol was conducted by a single researcher at baseline, post-intervention and 4 weeks later as a follow-up. The assessment protocol consisted of ultrasound examination, patient rated pain on a visual analogue scale (VAS) (Wewers and Lowe 1990) and foot function evaluation using the Chinese version of the foot function index (FFI) (Wu et al. 2008). The VAS was used to reflect the self-perceived intensity of pain. Based on earlier work by Crossley et al. (2004), a change in 20mm was taken as indicating clinical improvement. A decrease of 30% of the initial VAS score is approximately 2 cm in length on the VAS line (Farrar et al. 2001). Therefore, the successful treatment was defined as patients having a VAS reduction of either more than 20mm or more than 30% of the pre-intervention level. The FFI is a 23-item self-administered questionnaire. It comprises pain, disability and activity limitation subscales, and a higher score indicates greater dysfunction (Budiman-Mak et al. 1991). It has been used widely in evaluating foot function especially in patients with plantar fasciitis (Landorf and Radford 2008; Liang et al. 2007; Man-Son-Hing et al. 2002).

5.3.3 Ultrasonography

We adopted the same protocol as that reported in Chapter 4. In brief, Power Doppler ultrasonography was performed using an Esaote MyLab 70 X-view ultrasound unit with a 4-13 MHz linear transducer (Esaote, Genova, Italy). During the assessment, patients were prone lying with the ankle fixed at a neutral position. The size of the colour box was standardized to 1.5 x 1 cm, and was placed over the insertion of the plantar fascia. Settings of the PDU were standardized for high sensitivity, with a low wall filter to allow detection of vessels with low blood flow. Pulsed repetition frequency (PRF) was 370 Hz, and medium persistence was used. For each subject, 5 images with most abundant vascularity and consistent Doppler signals were selected and recorded.

5.3.4 Data reduction

A vascularity index (VI) was computed off-line using a customized algorithm and software programme (Matlab version 7.3.0.267R2006b, The MathWorks, Inc., Natick, MA, USA). As described in Chapter 2, a range of interest (ROI) was drawn manually along the boundary of the proximal plantar fascia within a colour box in each image. The programme extracted the ROI and counted the total number of pixels within it. The colour pixels within the ROI were then extracted and counted. The VI was calculated as the ratio of the number of colour pixels to the total number of pixels within the ROI (Ying et al.

2009). Patients were categorized as belonging to the vascularization group if their VI scores exceeded 2.60%. In Chapter 2, we reported delineating 2.60% as the optimal cut-off VI for indentifying patients with and without moderate to severe vascularization.

5.3.5 Extracorporeal shock wave intervention

The extracorporeal shock wave therapy was delivered at a regional hospital. Patients were assigned randomly into 3- or 6-session groups. All of them made 6 weekly visits to the hospital in order to standardize the length of the intervention and any psychological influences. The treatment protocol for the three-session group consisted of three sessions of sham intervention followed with three sessions of actual treatment. The sham sessions consisted of 400 impulses at minimal intensity (0.01 mJ/mm^2) delivered at 1 Hz. The actual treatment consisted of 1500 impulses at maximum intensity delivered at 4 Hz. The maximum intensity was determined by the highest level of energy flux density that the patient could tolerate (Chow and Cheing 2007). The 6-session group received six sessions of maximum intensity of ESWT with 1500 impulses delivered at 4 Hz. The treatment was delivered at the most painful point of the heel using a Storz Duolith SL1 shock wave apparatus (Storz Medical, Gottlieben, Switzerland). For details of treatment procedure, please refer to Chapter 4.

5.3.6 Statistical analysis

Descriptive statistics were used to examine the means and variability of all measured variables in the subjects. Pearson's correlation coefficient was evaluated to explore relationships among VI, VAS and FFI in the patient group. Independent *t*-tests were conducted to compare differences in VAS and FFI between patients with and without vascularization. Receiver operating curves (ROC) were used to identify the optimal cutoff VI scores for successful treatment for the 3- and 6-session groups. Treatment was considered successful with either VAS reduced more than 20mm or more than 30% of the pre-intervention level. Various VI cutoff scores, with their respective sensitivity and specificity values, were generated. Youden's indexes were computed by subtracting the specificity from the sensitivity values for the 3- and 6-session groups at post-intervention and at the 4-week follow-up. The optimal VI cutoff scores for each group were determined from the ROC curve based on the highest Youden's index. All statistical tests were performed using the PASW statistics 17 software package. The level of significance was set at $p \leq 0.05$.

5.4 Results

Subject characteristics

The 30 patients were tested between October 2009 and December 2010

(Table 5.1). The mean duration of symptoms among the patients was 9.62 months (ranging from 3 to 24 months). In the patient group, the mean VI of the affected side was significantly greater than that of the un-affected side (by 97%; $p \leq 0.05$).

Table 5. 1 Subject characteristics

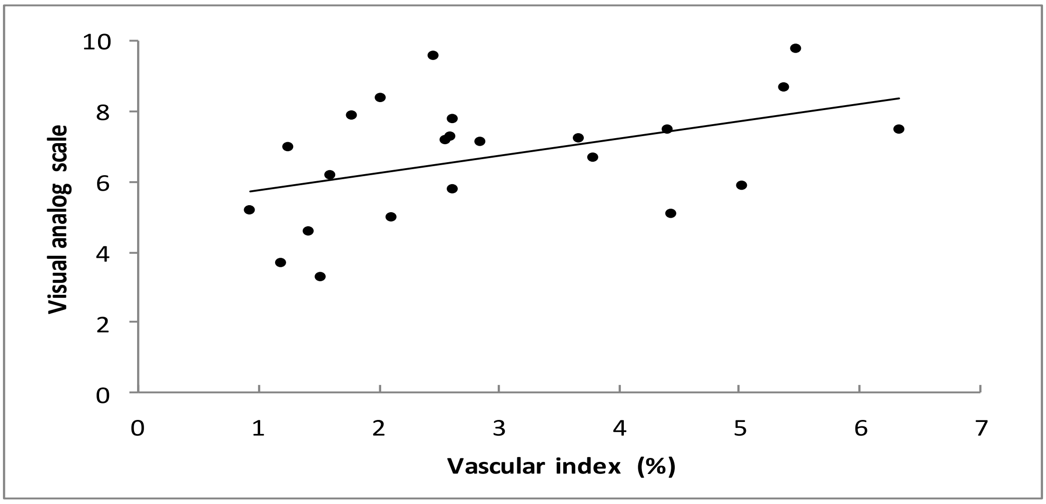
Variable \ Group	$ESWT_3$ (n=15)	$ESWT_6$ (n=15)	p Value
Age, years	44.87±8.44	47.13±7.39	0.44
Body mass index (kg/m^2)	25.21±3.82	26.14±2.21	0.42
Duration of symptoms (month)	9.83±6.05	9.40±8.13	0.87
Vascularity index, %	2.01±1.29	3.33±1.50	0.02
Visual analog scale	6.26±1.57	6.82±1.65	0.35
Foot function index	44.80±19.87	51.95±14.72	0.27

*Except where indicated otherwise, values are the mean±SD

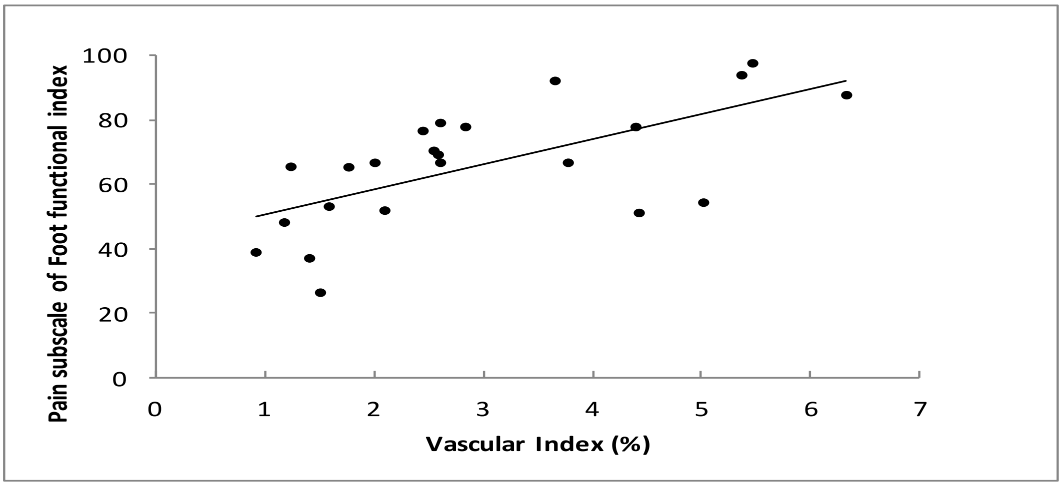
Relationships among vascularization, pain and foot function

As in Chapter 3, we found that VI was similar to patients with shorter duration of symptoms (<=12 months) and higher than patients with symptoms for more than 12 months. There were only 6 out of these 30 patients with duration of symptoms more than 12 months. The number was too small to do the analysis, so we only focused on patients with symptom durations of less than 12 months. Figure 5.1 showed that, in 24 patients with symptoms for less than 1 year, VI was positively correlated with pain and functional ability in patients with duration of symptoms for less than 12 months (Fig. 5.1). A higher VI was associated with greater intensity of pain (r=0.44, *p*=0.035), with the pain subscale of the FFI (r=0.65, *p*=0.001) and FFI as a whole (r=0.57, *p*=0.004).

a)



b)



c)

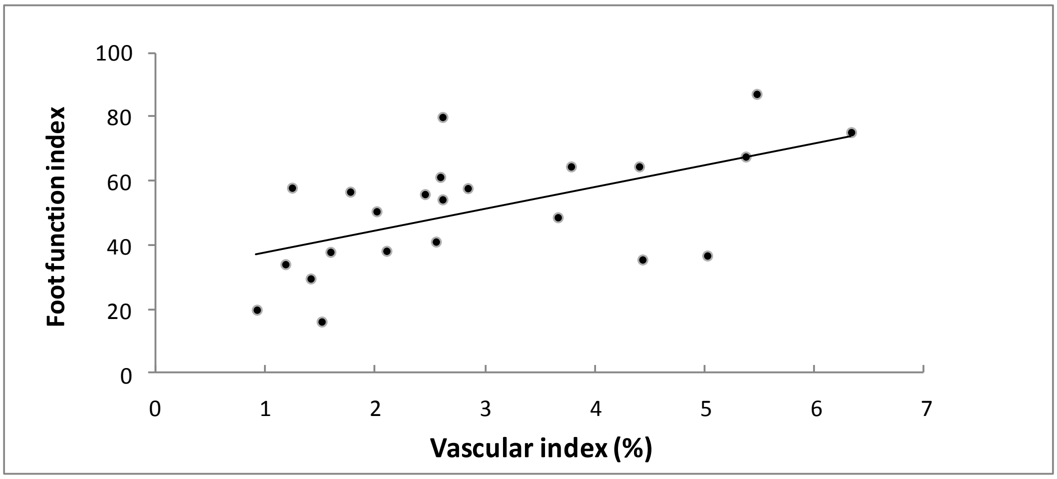


Figure 5. 1 Relationships among vascularization, pain and foot function: VI is positively correlated with (a) VAS; (b) pain subscale of FFI; (c) Foot function index.

Thirteen of the 30 patients (43.30%) showed greater vascularization. These patients had VI scores beyond 2.60% (This was the threshold for the moderate or severe vascularization reported in Chapter 2). Patients with vascularization reported significantly more intense pain based on the pain subscale of the FFI (p=0.002) and dysfunction (p=0.003) than the non-vascularized patients (Table 5.2). These findings indicate that patients with vascularization were more impaired and dysfunctional measured at baseline.

Table 5. 2 Patients categorized into with and without neovascularization group

Group / Variable	Patients with vascularization†	Patients without vascularization‡	p Value	Mean difference	95% Confidence interval
Numbers (%)	13(43.3)	17 (56.7)	N/A		
VAS	6.92±1.52	6.28±1.66	0.288	0.64	-1.85, 0.57
FFI_pain	75.52±15.34	55.59±15.89	0.002[§]	19.93	-31.75, -8.11
FFI	59.01±16.39	40.50±14.19	0.003[§]	18.50	-29.95, -7.05

VI=vascular index; VAS=visual analogue scale; FFI=foot function index
†Patient without neovascularization defined as VI less than 2.60%
‡ Patient with neovascularization defined as VI more than 2.60%
[§]Significant difference between groups, $p<0.05$
CI denotes for confidence interval

Prediction of treatment successfulness

ROC curves were constructed to determine the optimal VI cutoff scores for successful treatment post-intervention and at the 4-week follow-up for 3- and 6-session treatment groups in patients with duration of symptom less than 12 months. Table 5.3 shows the treatment outcomes based on clinical improvement after ESWT. The area under the VI curve was 0.92 for the 3-session and 0.75 for the receiving 6-session group. Post-intervention for the 3-session group, the optimal cutoff value of baseline VI was 1.55% (the highest Youden's index) for excellent sensitivity (of 83.30%) and specificity (of 100%). Hence, patients with a baseline VI score of more than 1.55% would be unlikely to experience a successful outcome after only 3 sessions of ESWT. For the 6-session group, the VI of 3.25% had the higher Youden's index 0.625 (Table 5.3). All patients with a baseline VI beyond 3.25% would expect unsuccessful treatment with 6 sessions of ESWT based on clinical measures, and 62.50% of patients with a baseline VI below 3.25% would be treated successfully. At the 4-week follow-up the baseline VI cut-off scores were similar to those post intervention (Table 5.4). Specifically, the VI cut-off scores ranged from 1.46% to 1.55% for the 3-session group and from 2.72% to 3.25% for the 6-session group.

Table 5.3 VI scores at baseline to identify percentage of patients being successful and unsuccessful managed post ESWT

ESWT	AUC	Youden's index Cut-off VI score	Successful % (Sensitivity)	Unsuccessful % (Specificity)
3	0.92	1.55	83.30	100
6	0.75	3.25	62.50	100

Table 5.4 VI scores at baseline to identify percentage of patients being successful and unsuccessful managed at 4-week follow up after ESWT

ESWT	AUC	Youden's index Cut-off VI score	Successful % (Sensitivity)	Unsuccessful % (Specificity)
3	0.89	1.46	66.70	100
6	0.68	2.72	57.10	100

5.5 Discussion

This study has been the first to show that vascularization can be used for planning the treatment of patients with plantar fasciitis. The vascularity index can be used to guide the number of ESWT sessions required to achieve clinical success at post and 1-month after ESWT. Doppler US assessment can thus aid in planning the treatment of patients with plantar fasciitis.

The findings also elucidate the relationships among vascularization, impairment and dysfunction caused by plantar fasciitis. Baseline Doppler US readings revealed vascularization in 43.30% of the patients studied. Despite using a new system to define vascularization, these results concur with the findings reported by Walther et al. (2004). Those authors reported moderate to marked hyperemia in 8 of their 20 patients with plantar fasciitis. Our method of quantifying vascularity has good intra-tester reliability, and can provide objective and continuous measures of vascularity (as reported in Chapter 2). Plantar fascia is often, though not always, similar to tendonitis (Wright and Rennels 1964). Vascularization or neovessels are present in at least 55% of symptomatic Achilles tendonitis cases (Alfredson and Ohberg 2005; De Vos et al. 2007; Peers et al. 2003; Zanetti et al. 2003). De Vos et al. (2007) has suggested that differences in US frequency, the position of the patient and the pressure of the US probe are all possible causes of diversity in US readings. Information on the equipment, patient positioning and probe pressure should always be reported in such studies.

Only one previous study has reported a possible relationship between vascularity and clinical symptoms in patients with plantar fasciitis (Walther et al. 2004). That study found a significant association between hyperemia of the plantar fascia and the intensity of pain in patients with planar fasciitis less than 12 months. The findings from our study are in accordance with Walther’s report; we also found an association between vascularity and the pain level in patients with the same duration, which is less than 12 months, and the correlation coefficient is higher in a more specific pain scale for the foot function index than the VAS pain scale. The reason may be that the pain subscale of the FFI solicits information on the self-perceived intensity of pain at the first step in the morning and after a long period of sitting. The pain subscale of the FFI may, therefore, enable patients to quantify the intensity of pain across more pain-provoking activities and be more sensitive to pick up the change of pain.

The data also indicate that higher vascularity was associated with greater dysfunction. Similar observations have been reported with patellar and Achilles tendinopathy patients. Reiter et al. (2004) has reported lower Victorian Institute of Sport Assessment (VISA) scores among symptomatic patellar tendon patients with vascularization. A weak correlation between vascularization and VISA-A questionnaire replies has also been observed among those with Achilles tendinopathy (Peers et al. 2003) and at a 12-week follow-up of patients with mid-portion Achilles tendinopathy (De Vos et al. 2007). Our findings extend such relationships between vascularity and dysfunction to patients with plantar fasciitis. Zanetti et al. (2003) has previously compared changes in VAS scores 3 and 6 months after completion of a 12-week standard treatment protocol for patients with Achilles tendinopathy with and without vascularity. The duration until follow-up in that study might have been long enough to wash out any group differences in VAS scores.

Power Doppler US, aside from assessing blood flow patterns to assist diagnosis, can also help evaluate treatment efficacy in soft-tissue disorders (Alfredson et al. 2003; Alfredson and Ohberg 2005; Zanetti et al. 2003). The present study has shown that three sessions of ESWT are often inadequate when the baseline VI is greater than 1.55%. For patients with baseline VI scores above 1.55%, the chances of success after only three treatments are unlikely (with a specificity of 100%). Note that the VI score of 1.55% was slightly above the group mean of the unaffected heels (VI = 1.39%) and below the threshold for vascularization. So patients presenting with vascularization would be less likely to have successful treatment with 3 sessions of ESWT. Six sessions of ESWT can successfully treat 62.50% of patients with a baseline VI score below 3.25%.

According to the continuum model proposed by Cook and Purdam (2009), vascular change is one of the main features of individuals with tendinopathy entering the late tendon disrepair/degenerative stage. In-growth of nerves in the newly formed vessels is one of the causes of pain (Alfredson et al. 2003), and down-regulation of vascularity seems necessary for pain reduction in these individuals. In previous chapter, noticeable down-regulation of vascularity seems to have occurred only in patients receiving six but not three sessions of ESWT. Results from this study suggested that in individuals with vascularized fascia, 6 sessions of ESWT is required to induce tissue healing. This group of patients requires interventions that could stimulate cell activity and increase protein production (Cook and Purdam 2009). ESWT has been found to increase transforming growth factor and insulin-like growth factor-1 expression and to stimulate fibroblast production (Chen et al. 2004). All assist in tenocyte metabolism and extracellular matrix formation (Bosch et al. 2007) and stimulate cellular activity.

Cook and Purdam catergorized less vascularized patients as a reactive/early tendon disrepair group. They proposed that substances such as glutamine acting on nerve receptors might induce pain in this cellularly active stage. The application of ESWT can modulate the expression of cytokines and the synthesis of interleukin-1 and metalloproteinases, which are markers of tendinopathy and may have a crucial role in degrading collagen matrix (Archambault et al. 2002; Han et al. 2009; Li et al. 2000). Findings from our study also indicated the treatment effects of 3 sessions of ESWT on non-vascularized patients with chronic platnar fasciitis.

5.6 Clinical and scientific implication

Our findings provide evidence of the significance of baseline vascularity of proximal plantar fascia in treatment planning. It can not only help assist clinicians and researchers to classify patients, but also give information to guide treatment session of ESWT. Categorization of patients into with and without vascularization implies that there may be different stages of pathology underneath within these two groups of patients. Therefore, treatment should correspond to different categories rather than a global guideline, so that patients in different phase of pathogenesis can be treated appropriately.

5.7 Limitations

In this study, our main goal was to investigate whether patients with chronic plantar fasciitis with and without moderate vascularity response differently to either 3- or 6-session of ESWT. Findings from this study suggest that for patients belong to the vascularized group are unlikely to have significant clinical improvement after 3-session of ESWT. For patients belong to the vascularized group, 6-session of ESWT was found to improve 63% of patients. Whether the portion of patients being successfully treated could be changed if more sessions of ESWT were given await for further investigation. However, in this study, we didn’t include a control group such that for the non-vascularized group, we could not ascertain whether natural recovery would have similar result as the 3-session group.

This study included only patients with unilateral symptoms, and changes in pain and function were related to the affected foot. The findings cannot, therefore, automatically be generalized to patients with bilateral symptoms.

Only the cut-off VI values for three and six sessions of ESWT were assessed because these are the most commonly used ESWT protocols with plantar fasciitis. Further study is required to assess whether the cut-off VI values can be increased with more sessions.

5.8 Conclusions

Most patients with plantar fasciitis (43.30%) have significantly greater vascularity than normal**.** The magnitude of vascularity is related positively to pain and foot function. A VI score >1.55% at the baseline is a strong predictor of unsuccessful recovery with only 3 sessions of ESWT. But 62.50% of the patients with VI score <3.25% would have successful recovery with six sessions of ESWT. Power Doppler US readings at baseline are a useful treatment planning tool. Further study is required to include other parameters in supporting clinician in making treatment plan. This study made a step in making treatment plan on either 3- or 6-session of ESWT would be required to patients with chronic plantar fasciitis based on pre-intervention fascia vascularity. Plantar fasciitis has substantial impact on a patient's quality of life, so treatment planning based on baseline evaluation can give a patient appropriate expectation. Vascularity apparently changes from plantar fasciitis post intervention and at four weeks, but a longer follow-up period is required to delineate the recovery process in patients with plantar fasciitis.

CHAPTER 6

FACTORS INFLUENCING PAIN REDUCTION IN PATIENTS WITH CHRONIC PLANTAR FASCIITIS 3 AND 6 MONTHS POST INTERVENTION

6.1 Abstract

Background: The success rate of extracorporeal shock wave therapy in treating chronic plantar fasciitis has been reported as being time dependant following treatment.

Objectives: To investigate the temporal effects of ESWT in terms of modulating vascularity and tendon thickness and to document the factors influencing treatment success.

Study design: A double-blinded randomized controlled trial

Methods: Twenty four patients with chronic plantar fasciitis received either three or six sessions of ESWT at weekly intervals. A visual analog scale was used to quantify their pain perceptions, and foot function index scores were monitored, as were vascularity and plantar fascia thickness. All were evaluated before treatment and three and six months after treatment had ended. Repeated measures analysis of variance was used to analyze the temporal and inter-group differences in pain, foot function, vascularity and fascia thickness. Treatment results were termed "excellent" when self-reported pain was reduced by 70% of the individual patient's pre-treatment level. The groups were compared in terms of treatment success using a Chi-square test. Correlation analyses were performed to explore the relationship between demographic factors and pain reduction.

Results: By three months, 62.50% of the patients reported successful treatment.

By six months that had increased to 91.67%. More patients who received six sessions of treatment (n=10) reported success compared with the 3-session group (n=5), but the difference was not statistically significant (likelyhood ratio p= 0.09) at 3-month follow-ups. At 6-month follow-ups, 12 patients in 6 session group and 10 patients in 3 session group being treated with excellent reduction in pain. Six sessions were, however, significantly more effective in treating patients displaying greater vascularization before treatment. Both groups observed a regression on VI at 3-month follow-ups (p=0.012), but greater reduction was observed in the 6-session group (p=0.017). In most successfully treated patients the VI had regressed to a level similar to that in the unaffected foot by six months after the end of treatment. Significant reductions in fascia thickness were also observed at six months. About 90% of the patients with a heel spur reported excellent results after six months, but only 33% of those without a heel spur.

Conclusions: Regression of vascularity was evident after three months and it continued at least until six months post intervention. Patients with excellent treatment results had normal vascularity after six months. Fascia thinning was evident after three months, and about 50% of the patients regained normal fascia thickness by six months post intervention. Regression of vascularity and fascia thinning could be a combined effect of natural healing and treatment effect. Among highly vascularized individuals, treatment efficacy at six months post intervention depends on the number of treatment sessions. The presence of a

bone spur also influences treatment success. Six sessions of ESWT are suggested for individuals who have vascularized plantar fascia and have symptoms for less than 12 months.

Key words: plantar fasciitis, vascularity, fascia thickness, extracorporeal shock wave therapy, heel spurs

6.2 Introduction

As mentioned in Chapter 4, extracorporeal shock wave therapy (ESWT) has been used widely in treating patients with plantar fasciitis as it alleviates pain and restores function in a noninvasive way (Odgen et al. 2001; Toomey et al. 2009; Wang et al. 2006). The success rates being reported have ranged between 56% and 94% (Rompe et al. 1996; Theodore et al. 2004; Weil et al. 2002; Yucel et al. 2010). In addition to differences in the treatment regimens, the wide spread in success rates may relate to differences in the definition of success and the follow-up time.

Pain is the main concern of patients with chronic plantar fasciitis, and pain intensity measured using a visual analogue scale is commonly used to assess treatment effectiveness. Treatment is regarded as successful if pain is reduced to some pre-set threshold. Most studies use 50% reduction of the level before treatment as the threshold (Metzner et al. 2010; Odgen et al. 2001; Rompe et al. 2005; Yucel et al. 2010). Metzner et al. (2010) used a 30% reduction in the initial pain, therefore they reported a success rate of more than 80%. In addition, excellent recovery has been defined when pain reduction was more than 50% (Cosentino et al. 2001; Chuckpaiwong et al. 2009) or from 70-100% (Morretti et al. 2006). Self-perceived satisfaction scores, such as the Roles and Maudsley scale, have also been used to judge treatment success. An intervention was viewed as a success if the patient gave a good or excellent response were rated from patients (Chuckpaiwong et al. 2009; Dorotka et al. 2006; Haake et al. 2003; Rompe et al. 2002). Based on these criteria, about 60% of patients with plantar fasciitis are being treated successfully with ESWT as measured at a 3-month follow-up (Rompe et al. 2007).

Longer follow-up period yields greater reduction in pain and a better success rate. Hammer et al. (2003) reported an increase in pain reduction from 63–69% to more than 90% when assessments were done at 3 and 24 months, respectively. The success rate was also found to increase from 85% to 95% when assessment was conducted from 3 month follow-up to 12 months follow-up (Ogden et al. 2004). Theodore et al. (2004) reported a larger reduction in pain intensity (from 56% to 91%) when evaluations were done at 3 months and 12 months follow-up. In that study they used 3800 shocks at 0.36mJ/mm^2 with nerve blocking all in one session. So a pronounced improvement in treatment effect is detected with a longer follow-up period when plantar fasciitis is treated using ESWT. However, all of these reported studies didn't have a control group. The reported changes might relate to natural recovery of the condition in addition to the effects of ESWT. Only the study from Rompe et al. (2003) reported 1-year follow-up with a control group. The authors found in treatment group, the pain reduced from mean value of VAS 6.9 to 2.1 at 6 months follow-up, compared from 7.0 to 4.7 in control group; at 1year follow-up, paints in treatment group have a mean VAS of 1.5, while 4.4 in control group, the difference between two groups are significant ($p<0.0001$). Findings from this study suggested progressive improvement on pain longer follow-up after intervention.

Chapter 4 reported regression in vascularity after a course of ESWT in patients with plantar fasciitis. Regression of vascularization to a level similar to the unaffected side has also been reported in those treated successfully for chronic Achilles (Ohberg and Alfredson 2004) and patellar tendinopathy (Alfredson and Ohberg 2005). In Chapter 5, we reported possible association of baseline vascularity with treatment outcomes at post- and 1-month follow-ups after ESWT. Aside from vascularization, reduced fascia thickness has been found among patients who reported less pain after 6 months (Hammer et al. 2005). Even though there was no control group and there might be natural history set in for the change in fascia thickness. Liang et al. (2007) further demonstrated an association between thinner fascia at baseline and pain reduction after ESWT. The authors commented that the thickening of the plantar fascia is of pathological origin.

The current study was designed to examine modulation in vascularity and tendon thickness associated with ESWT in patients with chronic plantar fasciitis 3 and 6 months after ESWT. A second aim was to assess factors affecting vascularity and tendon thickness as well as the effects of treatment sessions on success in patients with plantar fasciitis after receiving ESWT.

6.3 Methods

6.3.1 Subjects and study design

The subjects were the same individuals introduced in Chapter 4. Only patients who had experienced symptoms for less than 12 months were followed up for 6 months. The study was approved by the Human Subject Ethics Sub-committees of the University and the hospital (Appendix I). Written consent was obtained from each subject after verbal explanation of the study (Appendix II and III).

6.3.2 Procedures

After stratification by gender, patients randomly drew an unsealed envelope which indicated the number of their treatment group. There were two treatment groups, grouping patients receiving either 3 ($ESWT_3$) or 6 sessions of ESWT ($ESWT_6$). Evaluations included pain and foot function, and an ultrasound examination. The evaluation was performed for each patient at baseline, and then repeated 3 and 6 months after the completion of the ESWT. A VAS and the FFI questionnaire were used to assess pain and foot function respectively. B-mode and power Doppler ultrasonography were used to measure fascia thickness and vascularity. For a more detailed description of the testing, please refer to Chapter 2.

6.3.3 Extracorporeal shock wave therapy

The intervention procedure was described in Chapter 4. In brief, extracorporeal shock waves were delivered by an electromagnetic shock wave machine (Duolith SL1, Storz Medical, Tägerwilen, Switzerland) guided by an ultrasound unit (Aloka SSD-900, Hitachi Aloka Medical, Tokyo, Japan). Patients were lying prone with their feet hanging off the edge of a plinth. Clinical focusing was used to localize the delivery of the shock waves (Rompe et al. 2007). The treatment protocol for the $ESWT_3$ group consisted of 3 sessions of sham intervention followed by 3 sessions of actual treatment. The sham sessions consisted of 400 impulses at minimal intensity ($0.01mJ/mm^2$) delivered at 1 Hz. The actual treatment consisted of 1500 impulses delivered at 4 Hz at maximum pain tolerance of the patient under ESWT. The first 200 shocks were used to adjust the intensity to the maximum tolerable pain level according to the patients' feedback. Patients in the $ESWT_6$ group received 6 sessions of maximum intensity of ESWT with 1500 impulses delivered at 4 Hz.

6.3.4 Data reduction

Treatment was regarded as satisfactory when pain was reduced by 50 to 70% based on the VAS scale self-reports (Chuckpaiwong et al. 2009; Yucel et al. 2010; Wang et al. 2006). Excellent treatment was defined as pain reduced by more than 70%.

The vascularity index (VI) was described fully in Chapter 2. In brief, it was based on the images from the power Doppler scanning. The index was defined as the ratio of the number of colour pixels to the total number of pixels within the region of interest. It was an average computed from 5 images (details please refer to chapter 2). As reported in Chapter 2, a VI value of 2.60% was used as the threshold of patients with or without moderate to severe vascularization.

Fascia thicknesses were assessed using the method described in Chapter 3. The measurement was from the insertion of the plantar fascia to the calcaneus and expressed in millimeters (Akfirat et al. 2003; Cardinal et al. 1996; Walther et al. 2004).

6.3.5 Statistical analysis

All descriptive data were expressed as means or proportions as appropriate. Independent T-tests were used to compare differences in age, BMI, duration of symptoms, VAS, FFI, VI, and plantar fascia thickness between the two treatment groups at baseline. Repeated measures analysis of covariance was used to compare the changes in the outcome measures with time (pre-intervention, at 3- and 6-month follow-up) as the within group factor and group (3- and 6-session groups) as the between group factor. Variables with significant differences at the baseline were used as covariates, i.e. VI. Chi-square tests were conducted to compare group effects on the number of patients treated successfully at the 3- and 6-month follow-ups either by group, or when patients were categorized into vascularized and non-vascularized groups. Chi-square tests were also used to compare group differences in the number of patients with fascia reduced to the normal level (4 mm) (Wall et al. 1993). Whether the presence of a bone spur was related to the success of treatment was also assessed with the Chi–square statistic. The level of significance was set at $p \leq 0.05$. The analyses were done using the PASW 17 statistics software package.

6.4 Results

A total of 24 patients satisfied the inclusion criteria and completed the pre- and post evaluations. Table 6.1 shows the characteristics of these patients. Significant inter-group differences in VI were observed ($p \leq 0.05$), which were considered as a covariate in following analyses.

Table 6. 1 Characteristics of the two treatment groups

		$ESWT_3$ n=12	$ESWT_6$ n=12	*p* values
Age , years		45.25±7.19	49.25±6.47	0.166
BMI, kg/m2		25.91±4.16	25.36±2.04	0.685
Gender (Female, male)		9,3	8,4	0.653
Duration of symptoms (Mean ±SD)		8.50±4.08	7.00±3.48	0.343
Affected side	Unilateral	11	10	0.466
	Bilateral	1	2	
Physical Activity, n	Light	5	5	0.666
	Moderate	2	4	
	Active	5	3	
Baseline VI , %		2.28±1.37	3.85±1.57	0.019
Fascia thickness, mm		5.60±1.49	5.57±1.33	0.955
Presence of heel spur, n		8	8	0.495
Intensity of pain VAS		6.68±1.46	7.62±1.48	0.132
FFI-pain subscale		67.32±18.64	71.55±13.71	0.533
FFI-total score		54.17±19.41	56.15±15.01	0.783

Abbreviation: BMI= body mass index; VAS=visual analog scale; FFI= foot function index, n denotes the number of subjects

Except for the count data, the values are the mean±SD.

Fig. 6.1 shows the self-rated intensity of pain (Fig. 6.1a), the pain sub-scores of the FFI (Fig. 6.1b) and the FFI total scores (Fig. 6.1c) before treatment and at the 3- and 6-month follow-ups after 3 or 6 sessions of ESWT. After 3 months the average VAS had decreased 50.13 % for the 3-session group and 70.08% for the 6-session group. Both decreases are statistically significant (Table 6.2) ($p \leq 0.05$). Continued reductions in pain were observed between 3 and 6 months with the overall pain reduction reaching 71.01 % and 83.86% for the 3- and 6-session groups at 6 months post intervention respectively (all $p \leq 0.05$). Greater reduction in pain was observed in the 6 session group when compared with 3-session group ($p = 0.098$ and 0.094 at 3- and 6 month post-intervention, respectively). The average FFI pain sub-scores had also decreased significantly in both groups after 3 months. There were further significant decreases from 3 to 6 months in both treatment groups (Fig. 6.1b). Fig. 6.1c illustrates the changes in average FFI total scores. Scores were significantly lower (indicating better function) after 3 months, and had further decreased significantly after 6 months in both intervention groups ($p \leq 0.05$). There were no significant differences between the groups in terms of the changes in the average pain sub-score or the average total FFI score.

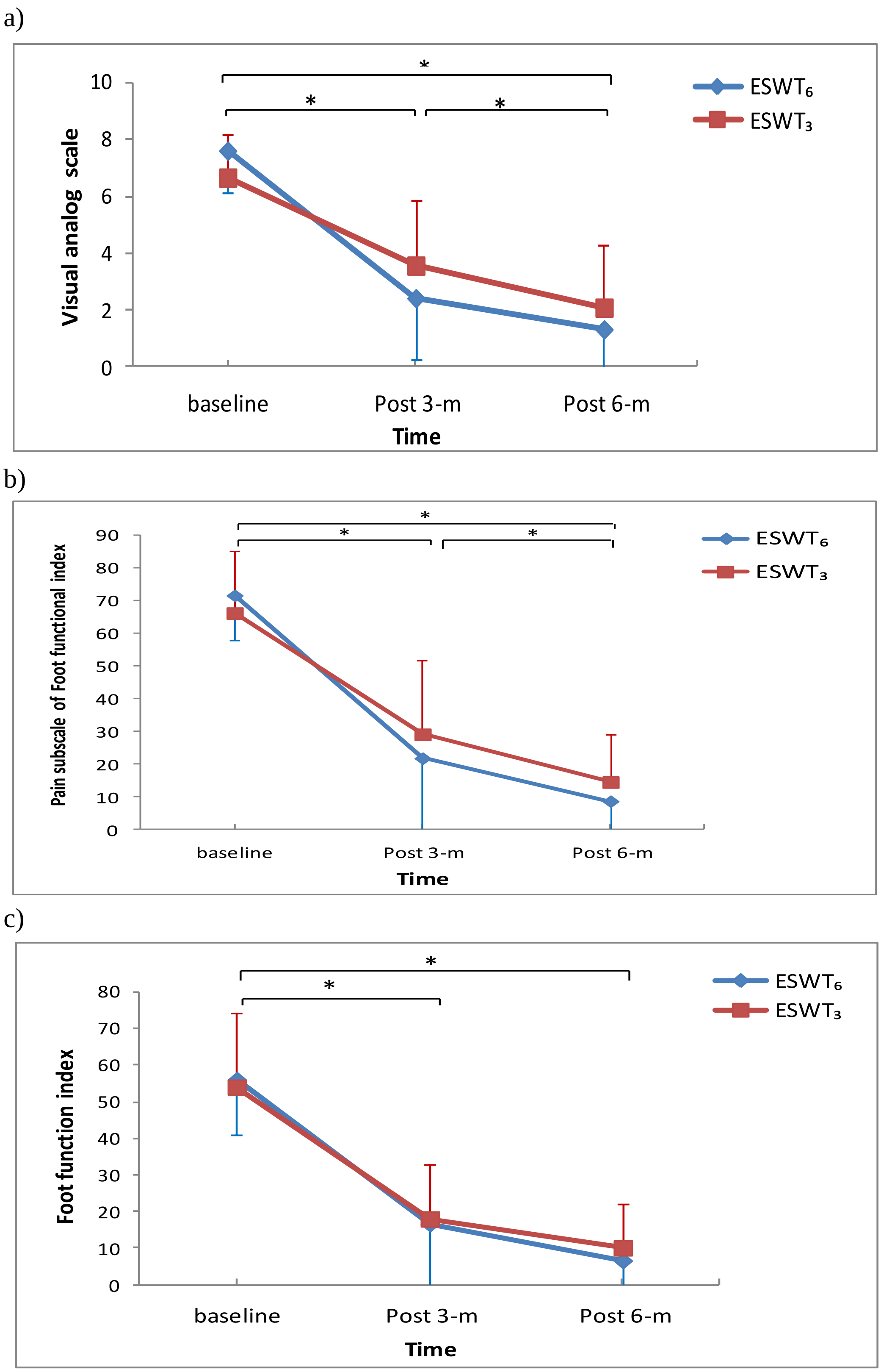


Figure 6. 1 Average intensity of pain, FFI pain sub-score and FFI total score before treatment and at the 3- and 6-month follow-ups. a) The VAS decreased in both groups; b) Significant reduction of scores on the pain subscale of the foot function index after treatment; c) Both groups had significant foot function improvement after treatment.
* indicates a significant difference between two time points. Post 3-m and post 6-m denote post 3 months and 6 months after a course of ESWT respectively. Error bars represent the standard deviation.

Table 6.2 Pain reduction in two treatment groups after 3 and 6 months after intervention

	VAS	$ESWT_3$	$ESWT_6$
Pre- Post 3-month	Mean Difference (95% CI*)	3.10 (1.33,4.87)	5.20 (3.80,6.59)
	Contrast comparison *p* value	0.026	0.012
Post 3-month-Post 6-month	Mean Difference (95% CI)	1.48 (-0.23, 3.19)	1.10 (-0.11, 2.31)
	Contrast comparison *p* value (95% CI)	0.095	0.078
Pre-Post 6-month	Mean Difference (95% CI)	4.58(3.18,5.99)	6.30(4.75,7.84)
	Contrast comparison *p* value (95% CI)	0.000	0.007

*CI denotes for 95% confidence interval

Table 6. 3 Number of patients rating the treatment satisfactory or excellent 3 and 6 months later

	$ESWT_3$	$ESWT_6$	*p* value
3- month follow-up			
Satisfactory	1	3	0.090
Excellent	4	7	
6- month follow-up			
Satisfactory	3	1	0.067
Excellent	7	11	

* Values are expressed as Number of patients that were successfully treated, p value reported are results from likelyhood ratio.

Table 6.3 shows the success rates at satisfaction and excellent levels in the $ESWT_3$ and $ESWT_6$ groups. The treatment was rated satisfactory or better by 62.50% of the patients after 3 months and 91.67% after 6 months. The portion of patients giving excellent ratings in the 3- and 6-session groups was 33.3% and 58.33% respectively after 3 months and 58.33 % and 91.67 % after 6 months. The 6-session group had more patients giving satisfactory or excellent ratings; the differences from the 3-session group were not statistically significant but demonstrate a strong trend (likelyhood ratio 0.067).

Table 6.4 shows success rates when the patients were categorized according to their pre-intervention vascularization. In vascularized patients, significantly more patients in the 6-session group rated the treatment excellent after 6 months than in the 3-session group ($p \leq 0.01$). On the contrary, there were no significant inter-group differences among the non-vascularized patients. In patients with base-line vascularized plantar fascia, Table 6.5 showed regulation on vascularity at 3 and 6 months after treatment in two groups.

Table 6.4 Number of vascularized and non-vascularized patients who rated the treatment excellent

	$ESWT_3$	$ESWT_6$	*p* value
Vascularized patients			
3- month follow-up	1	6	0.164
6- month follow-up	1	9	0.003
Non-vascularized patients			
3- month follow-up	3	1	0.898
6- month follow-up	6	2	0.782

* Values are the number of patients that were treated successfully

Table 6.5 Regulation on vascularity in patients with base-line vascularized plantar fascia

	$ESWT_3$	$ESWT_6$
	Up/down /no	Up /down / no
3- month follow-up	1/1/1	0/8/0
6- month follow-up	0/2/1	0/8/0

Table 6.6 shows the temporal changes in the VI. Both groups showed significant reductions from pre-treatment to the 3-month, as well as from the 3-month to the 6-month follow up (all $p \leq 0.05$). Greater average reductions were observed in the 6-session than in the 3-session group (overall $p \leq 0.05$). Fig. 6.2 shows that, when assessed after 6 months, a VI cut-off of 1.52 could predict which patients had excellent results with a sensitivity of 75% and a specificity of 83.3%.

Table 6. 6 Vascular index before treatment and at 3 and 6 month follow-ups

	$ESWT_3$	$ESWT_6$
Pre-intervention	2.13±1.35	3.96±1.59
3-month follow-up	1.73±0.86	1.70±0.81
6-month follow-up	1.51±0.80	1.56±0.40
The between group difference p=0.017		

	Within group difference (Time effect)						Overal time effect p value
	Level 1-2		Level 2-3		Level 1-3		
	Mean difference, 95% CI	Contrast comparison p value	Mean difference, 95% CI	Contrast comparison p value	Mean difference, 95% CI	Contrast comparison p value	
$ESWT_3$	0.40 (-0.27,1.06)	0.325	0.22 (-3.96,0.84)	0.928	0.62 (0.27,0.97)	0.002	0.091
$ESWT_6$	2.26 (1.73,2.80)	0.000	1.44 (-0.53,0.82)	1.000	2.41 (2.06,2.76)	0.000	0.074

*Values except the p values are expressed as the Mean±SD. Level 1-2: Pre--intervetion to the 3-month follow-up; Level 2-3: 3-month follow-up to the 6-month follow-up; Level 1-3: Pre-intervention to the 6-month follow-up. CI denotes for confidence interval.

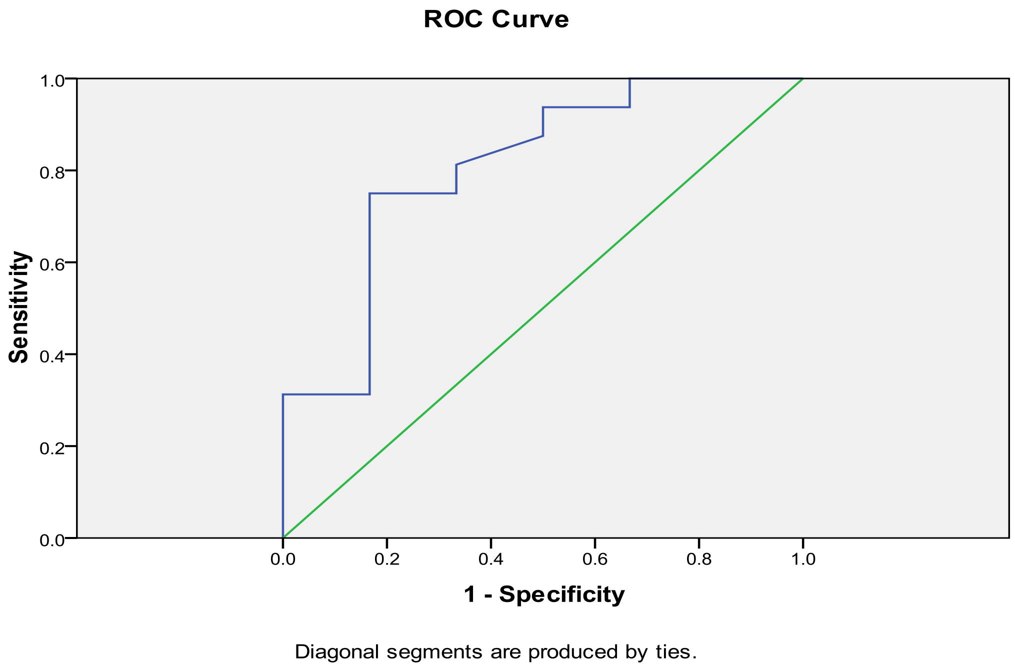


Figure 6. 2 The receiver operating characteristic (ROC) curve shows that at 6 months post intervention a VI of 1.52 indicates patients with excellent treatment results with a sensitivity of 75% and a specificity of 83.3%.

Small and insignificant changes in average plantar fascia thickness were observed at the 3-month follow-up, but by 6 months they were significant when compared with pre-intervention ($p \leq 0.05$) (Fig. 6.3 and Table 6.7). Prior to the intervention, all patients had plantar fascia thicker than 4mm. At the 3-month follow-up, 3 patients had plantar fascia less than 4 mm thick. A total of 14 patients (9 in the 6-session group) had plantar fascia thickness below 4mm 6 months after treatment. More number of patients having plantar fascia thickness less than 4mm was observed in the 6-session group when compared with the 3-session group although did not reach to the statistically significant levle (p=0.098).

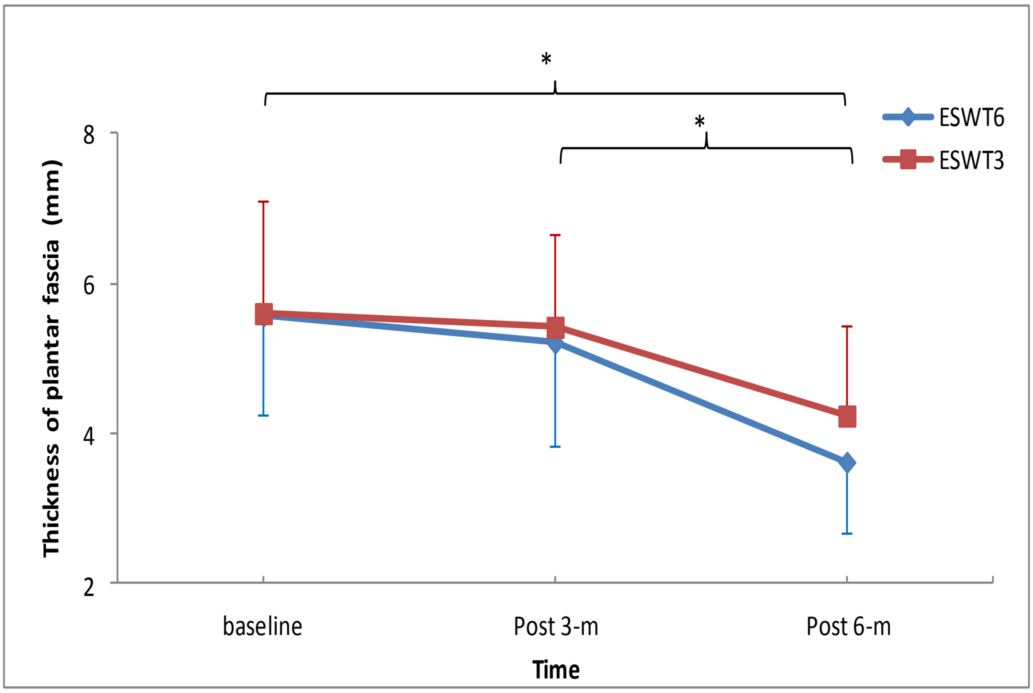


Figure 6. 3 Plantar fascia thicknesses decreased with time after receiving 3 or 6 sessions of ESWT. Post 3-m and post 6-m denote post 3 months and 6 months respectively after a course of ESWT. * denote for the significant fascia thinning between two time levels in each group.

Table 6. 7 Average plantar fascia thickness at pre-intervention, after 3 and 6 months

	$ESWT_3$	$ESWT_6$
Pre-intervention	5.60±1.49	5.67±1.33
3-month follow-up	5.42±1.23	5.21±1.37
6-month follow-up	4.23±1.21	3.62±0.94
The between group difference *p*=0.424		

	Within group difference (Time effect)						Overal time effect *p* value
	Level 1-2		Level 2-3		Level 1-3		
	Mean difference, 95% CI	Contrast comparison *p* value	Mean difference, 95% CI	Contrast comparison *p* value	Mean difference, 95% CI	Contrast comparison *p* value	
$ESWT_3$	0.18 (-0.60,0.97)	0.523	1.59 (0.39,2.79)	0.000	1.37 (0.45,2.28)	0.001	0.021
$ESWT_6$	0.36 (-0.01,0.09)	0.065	1.18 (0.61,1.76)	0.003	1.95 (0.76,3.14)	0.001	0.584

*Values except the *p* values are expressed as the Mean±SD. Level 1-2: Pre-intervention to the 3-month follow-up; Level 2-3: 3-month follow-up to the 6-month follow-up; Level 1-3: Pre-intervention to the 6-month follow-up. CI denotes for confidence interval.

No significant correlation could be established between pain reduction and factors such as age, gender, BMI, physical activity or the duration of symptoms at 6 month post intervention. About 90% of the patients with a heel spur reached the excellent level by 6 months after treatment, but only 33% of those without bone spurs were treated successfully ($p \leq 0.05$) (Table 6.8).

Table 6. 8 The presence of a bone spur affects the treatment outcome

	Heel spur		*p* value Odds ratio (95% Confidence interval)
	Present	Absent	
Excellent treatment	14	2	0.011 0.071 (0.008,0.680)
Less than excellent treatment	2	4	

6.5 Discussion

This investigation demonstrated temporal effect on pain reduction, vascular regression and plantar fascia thickness modulation after ESWT. The factors affecting treatment effects included baseline vascularization, number of treatment sessions and the presence of a heel spur. Treatment efficacy of 3- or 6-session of ESWT on patients with chronic plantar fasciitis was associated with baseline vascularity. The presence of a heel spur was correlated with better treatment results 6 months after the intervention.

The findings indicate ongoing pain reduction (from 60% to 77%)

between 3 and 6 months post treatment for patients with plantar fasciitis. The portion of patients with satisfactory or excellent results increased from 62.50% to 91.67% over the same period. These findings not only concur with previous reports on the percentage of pain reduction and patients being treated satisfactorily, they also agree on the temporal factor on treatment effects. The pain reductions reported in previous studies ranged from 56% to 73.2% after 3 months (Gollwitzer et al. 2007; Hammer et al. 2003; Hyer et al. 2005) and up to 79% at 6 months after shock wave therapy (Hammer et al. 2005). These results and our present findings, taken together, highlight the temporal effects in the efficacy of ESWT. Differences in treatment protocols may explain some of the wide spread in success rates reported previously (Rompe et al. 2007). This study has also demonstrated differences in pain reduction when ESWT is applied for 3 or 6 sessions. After 6 months, the portion of patients reaching the excellent results level was 58% in the 3-session group and 92% in the 6-session group.

This has been the first study providing quantitative measures of microcirculation and observing vascular changes for 6 months. Increased vascularity has been reported in patients with plantar fasciitis (Walther et al. 2004), patellar tendinopathy (Alfredson and Ohberg 2005) and Achilles tendinopathy (Ohberg and Alfredson 2004). Regression in vascularity was observed in Achilles tendinopathy patients treated successfully with eccentric exercise (Ohberg and Alfredson 2004), as well as in patients with patellar tendinopathy after sclerosing intervention (Alfredson and Ohberg 2005). In this study we found significant vascular regression 3 months after the intervention. The decline in vascular index continued at least up to 6 months. Furthermore, the average changes in vascularity were greater and faster for the 6-session group than for the 3-session group. These results suggested that ESWT induces vascular modulation aside from the natural healing process. Our findings concur with previous reports that increased vascularization regresses in successfully treated patients. In this study, all but one subject with excellent results showed a regression of vascularity to levels similar to that in the unaffected foot. It seems that the pain associated with plantar fasciitis is partly related to vascular changes.

Another interesting finding from the comparison of successfully treated patients is that more highly vascularized patients had better improvement after 6 months when they had received 6 sessions of treatment. Such differences could not be detected in the less-vascularized patients. These results echo the findings being reported in Chapter 5. There we reported treatment effects after treatment and one month later. The bi-directional regulation of vascularity reported in Chapter 4 might partially explain the differences in treatment outcomes observed here and in the experiments reported in Chapter 5. The results from this study are substantiated further for the patients in the vascularization group, 6 sessions of ESWT being more beneficial for them even from a long-term (i.e. 6 months after a course of ESWT) perspective.

The results of this study suggest that the treatment of less vascularized individuals with plantar fasciitis is similar to the reactive/early disrepair phase in tendinopathy. The treatment aims at down regulating the cellular response and decreasing cell proliferation. Three sessions of ESWT may be appropriate to induce cytokines to decrease cell proliferation and protein production. In the late disrepair or degenerative stage, in order to stimulate a healing response and increase cell activity, 6 sessions of ESWT are required to initiate cell proliferation for tissue healing in the fascia.

Such dose-dependent effects have been demonstrated by Rompe et al. (1998). Using rabbits, they observed a shift from no change to marked inflammatory reaction when the delivered energy was increased from low to high intensity. Similarly, a group led by Han observed that when shock waves at 0.17 mJ/mm^2 were applied to cultured cells, the cell count increased in response to 500 shocks but decreased in response to 1000 or 2000 shocks (Han et al. 2009). Taken together, these findings highlight the importance of delivering an appropriate dosage of shock waves to individuals with plantar fasciitis.

Aside from vascular regression, changes in fascia thickness were observed from 3 month post intervention. Interestingly, changes in tendon thickness have been reported as early as one month post intervention by Cosentino et al. (2001) but only after 6 months by Hammer et al. (2005). Such discrepancies may be attributed partly to differences in equipment or treatment protocol. Nevertheless, results from this and previous studies support the view that plantar fascia thickness is reduced after ESWT. At 6 months post intervention, about half of our treated patients had plantar fascia of normal thickness (about 4 mm). Is there any relationship between plantar fascia thickness and patients' pain perceptions? Despite increased plantar fascia thickness being reported in most patients with plantar fasciitis (Akfirat et al. 2003; Karabay et al. 2007; Walther et al. 2004), its relationship with pain remains unclear. Liang et al. (2007) has shown that plantar fascia thickness predicts pain reduction with ESWT, but the present study and another by Chuckpaiwong et al. (2009) could not establish relationship between fascia thickness and pain. In view of the delayed changes in plantar fascia thickness, further studies with longer follow-up periods might be needed to delineate the possible relationship between fascia thickness, self-perceived pain and function.

This study recruited patients whose symptoms had lasted for 3 months or more. Our present study shows sequential modulation in vascular and fascia thickness. Regression in vascularity is evident immediately after the intervention (as reported in Chapter 4) and continued until at least 6 months after the intervention. Two-thirds of the patients were non-vascularized by 3 months, and 79% had regained a vascular index similar to those in their healthy feet by 6 months post intervention. Changes in fascia thickness started later and only about 50% had returned to normal thickness at the 6-month follow-up. These findings indicate that modulation of vascularity occurs earlier than tendon thinning. Normalization of tendon thickness might take longer than 6 months.

The results also show that, aside from pre-intervention vascularity, the presence of a heel spur is significantly correlated with pain reduction. Patients who had a heel spur had significantly better success rates than those without (using a X^2 test, $p \leq 0.05$). ESWT has been reported to reduce or even eliminate calcification in shoulder tendonitis (Delius 1994; Peters et al. 2004). Cosentino et al. (2001) has also observed a reduction of more than 1mm in the diameter of enthesophytosis in patients with plantar fasciitis. The direct effects of ESWT on a bone spur might reduce pain associated with inflammation or mechanical stimulation of plantar soft tissue by the presence of the spur (Barrett et al. 1995; Moretti et al. 2006).

6.6 Limitation

This study lacked a control group. We did not include a control group because most of the patients had received other more conservative treatments without success. In addition, the aim of this study was to evaluate factors influencing treatment efficacy by ESWT on patients with chronic plantar fasciitis; as well as to assess possible association between regression of vascularity and treatment efficacy. The difference on vascular modulation by 3 and 6 sessions of ESWT helped to illustrate treatment effects from just natural healing.

A second limitation of this study was the small sample size. The numbers reporting better pain reduction and excellent treatment results were not sufficient to reach statistical significance because of the overall power of the study.

The follow-up period may also have been insufficient. Re-evaluation after 6 months showed modulation of fascia thickness in only 50% of the patients. Knowing that remodeling in tissue healing may take a year or more, the long term effects of ESWT need further study with a longer follow-up period.

Lastly, the patients studied here had experienced plantar fasciitis symptoms for less than 12 months. Vascularity was found reduced in patients who have had symptoms for more than 12 months, so the pattern of vascularization and fascia thickness modulation observed here might not apply to patients with symptoms persisting longer than 12 months.

6.7 Conclusions

The study provides some evidence on factors influencing treatment efficacy by 3- and 6-session of extracorporeal shockwave therapy in patients with plantar fasciitis. Patients with moderate to severe vascularization at baseline had greater portion of patients reaching excellent pain changes when receiving 6 sessions of ESWT than 3 sessions at 6-months follow-ups. Patients with excellent treatment results had normal vascularity at 6-month follow-ups. Among highly vascularized individuals, treatment efficacy after 6 months depends on the number of treatment sessions. The presence of a bone spur also influences treatment success. We suggest, therefore, using power Doppler to categorize individuals with plantar fasciitis, and we recommend 6 sessions of ESWT for individuals who have experienced plantar fasciitis symptoms for less than 12 months and demonstated vascularized plantar fascia.

CHAPTER 7

SUMMARY AND CONCLUSIONS

7.1 Introduction

7.1.1 Rationale of the study

Plantar fasciitis is one of the most common painful foot conditions. It affects both active and sedentary adults with a peak incidence between 40 and 60 years of age (Cole et al. 2005; Davis et al.1994; Gill 1996; Neufeld and Cerrato 2008). Each year about two million individuals suffer from this condition in the United States (Riddle and Schappart 2004). Even though most of these sufferers recover within 6 to 18 months with conservativie treatments (Davis et al. 1994; Martin et al. 1998), about 5 to 10% of recalcitrant cases progress to surgery (O'Malley et al. 2000).

The etiology and pathogenesis of plantar fasciitis are still not well understood (Schepsis et al. 1991; Wang et al. 2006; Wearing et al. 2006). Increasing mechanical load and increase tension in the fascia have been proposed as the main components leading to its development (McGonagle et al. 2002; Wearing et al. 2006). Individuals with a high body weight have been found to have an increased risk of developing plantar fasciitis. (Cullen and Singh 2006; Wearing et al. 2006). However, with regard to mechanical loading and tension it has proved difficult to confirm experimentally whether or not increased digital dorsiflexion (extension) and limited ankle dorsiflexion will induce greater stress in the plantar fascia.

In addition, fibrovascular hyperplasia and proliferation have been reported frequently, and these indicate increased vascularity (Lemont et al. 2003; LeMelle et al. 1990; Snider et al. 1983; Tountas and Fornasier 1996). Increased vascularity is evident 1cm proximal to the proximal plantar fascia (Walther et al. 2004), especially among those having had the problem for less than 12 months. The author used Power Doppler Ultrasonography (PDU) to capture the vascularity of small vessels and Newman's grading scale to grade tissue vascularity. Newman's grading scale may not be objective or sensitive enough to differentiate subtle vascularity changes (Cardinal et al. 1996).

In order to better understand possible modulation in vascularization in plantar fascia, an objective and quantified measurement of vascularity is necessary. Recently, computerized methods have been used to quantify tissue vascularity with Ultrasonography and the feasibility of computerized quantification of vascularity was only explored in thyroid tissues (Ying et al. 2009). It is essential to evaluate whether this computerized quantification of vascularity can be applied to musculoskeletal tissue such as the plantar fascia. With such a test, the possible modulation in vascularization could be examined quantitatively. Potential factors such as mechanical loading and fascia tension as well as vascularization were assessed in the same subjects to have a comprehensive understanding.

In addition, plantar fasciitis is often, though not always, similar to tendonitis (Wright and Rennels 1964). Similar vascularization has also been observed in patients with Achilles tendinopathy (Ohberg and Alfredson 2004) and patellar tendinopathy (Alfredson and Ohberg 2005). Alfredson (2004) proposed vascularization in diseased tendons as one of the potential mediators of pain in cases of tendinopathy. Changes in vascularity have been followed in subjects with Achilles tendinopahty after a course of eccentric exercise (Ohberg and Alfreson 2004) and after sclerosing injections (Alfredson and Ohberg 2005). Information from these studies highlights a possible association between vascularization and plantar fasciitis.

In this connection, extracorporeal shock wave therapy (ESWT) has been evidenced in treating plantar fasciitis (Rompe et al. 2003). One of its proposed mechanisms is its ability to induce vascularity modulation. It has been speculated that increased diffusion of cytokine crossed vessel walls after the application of ESWT might reinforce the angiogenesis and healing responses (Chen et al. 2004); and enhanced neovascularization could aim at removing the breakdown products of the focal cell death (Younger 2006) or in inducing the cellular repair of the degenerate tissue (Fenwick et al. 2002). Wess (2008) postulated that strong and repeated stimulation of synaptic junctions by ESWT may selectively erase the pathologic memory reflex pattern and give rise to increase circulation and metabolism due to the relaxation of vessel tonus. On the contrary, after the application of ESWT, Chao et al. (2008) reported up-regulation of the transforming growth factor β1 and the release of endogenous NO to stimulate tenocyte proliferation and collagen synthesis. NO is known as a powerful vasodilator, which might cause a decrease in vascularity after ESWT.

In addition, contrary findings on ESWT-induced vascularization changes were also reported in animal and human studies. Wang's group demonstrated increased neovascularity at the tendon-bone junction in healthy dogs and rabbits after the application of ESWT (Wang et al. 2002, 2003). Meanwhile, they also observed angiogenesis mediators, such as VEGF and proliferating cell nuclear antigen one week after ESWT. On the contrary, a significant reduction in oxygen saturation was detected after three sessions of ESWT in patients with supraspinatus tendinopathy (Notarnicola et al. 2011). The change in oxygen saturation was found to be associated with pain reduction. Hereby, modulation in vascularization was evidenced after the application of ESWT; that will be up- or down-regulated after a course of ESWT. In addition, this change in vascularity will possibly affect treatment effect.

It is worth noting that vascularization was found in some (40%) individuals with plantar fasciitis (Walther et al. 2004). The author also reported that in vascularized plantar fasciitis, a higher Newman's grading was associated with greater intensity of pain (Walther et al. 2004). This relationship has also been seen with patellar and Achilles tendinopathy (Alfredson et al. 2003, 2005). In addition, the intensity of pain with chronic tendinopathy has been found to be greater in vascularized patients compared with those not newly vascularized

(Cook et al. 2004; Zaneti et al. 2003). Information from these studies highlights a possible association between vascularization and self-perceived pain in plantar fasciitis.

Cook and Purdam (2009) have proposed a continuum model for tendinopathy. This involves three continuous stages: reactive tendinopathy, tendon disrepair and degenerative tendinopathy. The intensity of vascularity is one criterion in classifying tendinopathy. Generally, swollen tendons, mildly hypoechoic with no or minimal vascular changes, indicate the early reactive stage. The presence of multiple vessels in the affected tendon indicates the degenerative stage. The authors proposed that ideal interventions should be tailored for the different pathological phases. Hence, any modulation in vascularity might affect the treatment outcome after a course of intervention, such as ESWT.

Most studies have reported continued improvement with a longer follow-up period (Chuckpaiwong et al. 2009; Hammer 2003, 2005; Moretti et al. 2006). Two years after ESWT, about 94% of patients reported decreased pain during daily activities compared with only 63% at a 3-month follow-up (Hammer et al. 2003). Recently Chuckpaiwong et al. (2009) also reported a 77.2% improvement in pain and foot function at a 12-month follow-up compared with 70.7% at 3 months. Aside from pain and function, fascia thickening has also been observed at 6 months post intervention (Hammer et al. 2005). Any evaluation of treatment efficacy should include follow-ups for at least 6 months post intervention to assess possible changes in treatment effects on pain, function, fascia thickness, as well as vascularization. Despite better treatment effects were reported at a longer duration after treatment, without a control group, the findings from these studies could not rule out the effects of natural history. Rompe et al. (2003) was the only study had a control group. The authors reported in treatment group, the pain reduced from mean value of VAS 6.9 to 2.1 at 6 months follow-up, compared from 7.0 to 4.7 in control group; at 1year follow-up, paints in treatment group have a mean VAS of 1.5, while 4.4 in control group, the difference between two groups are significant ($p<0.0001$). Findings from this study suggested progressive improvement on pain longer follow-up after intervention.

7.1.2 Study design

This study aimed to contribute a better understanding of the change of vascularity in patients of plantar fasciitis as well as its role in the healing process. We hope that these results will not only contribute to the understanding of pathogenesis and the healing process of plantar fasciitis, but will also help the clinical treatment plan of patients with chronic plantar fasciitis.

Five inter-related studies were conducted at the Hong Kong Polytechnic University and one of the major regional hospitals in Hong Kong. In the first study, we evaluated the feasibility of a computerized quantification of vascularity that could be applied on plantar fascia and identified the minimum detectable change of this method, which was used to evaluate the true difference between subjects in the following studies. The optimal cut-off value that could differentiate individuals with and without moderate and severe vascularity was identified. Study 2 was conducted to investigate physical characteristics (such as body mass index, range of motion in the ankle and first metatarsal phalangeal joints, and navicular mobility) and sonographic examination of the vascularity and thickness of the plantar fascia in patients with plantar fasciitis and health controls. Study 3 focused on the evaluation of modulation in the vascularity of plantar fascia after a course of ESWT. Study 4 analyzed patients with unilateral affected fascia, based on their improvements at post-intervention and one month after, highlighting the importance of pre-intervention vascularity and the number of treatment sessions for treatment planning. Study 5 followed up the patients who had symptoms for less than 12 months for 3-, and 6-months after the application of ESWT. As well, treatment efficacy, temporal changes in vascularity and plantar fascia thickness were investigated.

7.2 Vascularity examination using power Doppler ultrasonography and Newman's scaling to establish test-retest reliability

Forty-four patients with chronic plantar fasciitis and 17 healthy subjects were recruited to test for any correlation between computerized findings on small vessel vascularity and Newman's scaling using Power Doppler ultrasonography (PDU) imaging and its test-retest reliability. The vascularity of their plantar fascia was examined using the testing procedure described in Chapter 2. For each subject, the 5 images with the most abundant vascularity and consistent Doppler signals were selected and the vascularity was quantified using the ultrasound images and a customized software programme. Each was also graded using Newman's grading scale. A vascularity index was calculated as the ratio of the number of colour pixels to the total number of pixels within a standardized selected area of the proximal plantar fascia. The 17 healthy subjects were examined twice, 7 to 10 days apart. The averaged VI ratios were found to be strongly correlated with the Newman's scale ratings (rho = 0.70; $p \leq 0.001$). Intratester reliability was 0.72. The minimum detectable difference of the VI was 0.68%. A cut-off VI of 2.60% had a sensitivity of 100% and specificity of 81.2% (Area under the curve = 0.963; $p \leq 0.001$) in identifying fascia with and without moderate to severe vascularization.

These findings indicate that the computerized vascular index not only has a high level of concordance with the Newman grading scale but is also reliable in reflecting the vascularity of the proximal plantar fascia. This index can be used to characterize changes in the vascularity of patients with plantar fasciitis, and it may also be helpful to evaluate treatment and monitor the progress after intervention in future studies. Hence, in subsequent studies any differences in VI greater than 0.68% can be interpreted as indicating a true difference or change. Individuals with a VI equal to or greater than 2.60% belong to the vascularized group.

7.3 The physical and sonographic characteristics of patients with chronic plantar fasciitis compared with healthy controls

Navicular mobility, range of ankle dorsiflexion, range of first metatarsal phalangeal joint extension, proximal plantar fascia vascularization and fascia thickness were all assessed in the 39 patients with unilateral plantar fasciitis and the 21 healthy controls matched for age and gender. The patients with plantar fasciitis had higher BMIs (mean 25.37kg/mm^2) and a greater extension range of their first metatarsal phalangeal joints than the healthy controls ($p \leq 0.05$), suggesting that increased BMI and larger MTP joint range are potential risk factors for developing plantar fasciitis. Vascularization and thickened plantar fascia were evident in the patient group ($p \leq 0.05$). The VI almost doubled from 1.35% on the unaffected to 2.65% on the affected side. The VIs on the patients' affected side were also significantly higher (by 60.6%) than on the corresponding side in the healthy controls ($p \leq 0.05$). The mean thickness of the affected fascia was more than 4mm in both, which was significantly thicker than the average for the unaffected side ($p \leq 0.05$) and among the healthy controls. In those patients with symptoms for more than 12 months, significant regression in vascularization was observed, but no significant fascia thinning.

It can be concluded that individuals with plantar fasciitis for more than 3 months had increased body mass index and larger range of 1^{st} MTP extension, suggesting that relationships between BMI, MPT joint range and patients with plantar fasciitis. The cause effect relationship could not be established by the present study. Vascularization and thickened plantar fascia were evident in the patient group, in particularly in those with symptom less than 12 months. Strategies to modulate the identified factors are much needed in view of the high prevalence of plantar fasciitis in sedentary as well as active individuals. Physical agents such as extracorporeal shock waves have been demonstrated to induce neovascularity changes. It would be valuable to study the effects of such physical agents in modulating vascularity and the clinical symptoms of patients with plantar fasciitis.

7.4 The cumulative effects of extracorporeal shock wave therapy on vascularity in patients with chronic plantar fasciitis

Forty-six subjects with chronic plantar fasciitis were assigned randomly to undergo either 3 or 6 weekly sessions of ESWT or function as a control subject. ESWT was delivered at a major regional hospital (for details, please refer to Chapter 4). The treatment in each session consisted of 1500 impulses at the maximum tolerable intensity delivered at 4 Hz.

Besides the vascularity of the subjects' plantar fascia, the same evaluator also assessed pain level using a visual analog scale pre- and post-intervention. Modulation of vascularity was detected in 60% of the subjects following ESWT, but in only 28.6% of patients in the control group ($p \leq 0.05$). In the 3-session group, 50% of the patients showed some vascular regulation. All but two of those subjects showed up-regulation. In the 6-session group, 43.8% had vascular down- regulation and 31.3% showed an up-regulation of vascularity. The direction of regulation seems to depend on pre-intervention vascularity. Subjects with a pre-intervention VI score of at least 2.72% were down-regulated; those less than 2.72% had no regulation after 6 sessions of ESWT. A pre-intervention VI score of less than 2.30% indicated the best specificity in predicting whether there would be an up-regulation of vascularity. About 70-80% of individuals with a pre-intervention VI of more than 1.21-1.31% would not be up-regulated after 3 or 6 sessions of ESWT. In treatment group, pain reduction is 40% compared with pre-intervention, while in control group, the pain reduction is only 8.6%.

This study was designed to delineate ESWT-induced vascular regulation in patients with chronic plantar fasciitis. This is the first report of bi-directional regulation of vascularity following 6 sessions of ESWT. The direction of regulation apparently depends on the baseline vascularity, as down-regulation could only be detected in individuals with a pre-intervention VI greater than

2.72%. In addition, only 6-sessions of ESWT could induce down-regulation in those individuals having a pre-intervention VI greater than 2.72%. These findings suggest dose-dependent effects of ESWT on vascularization. They support a role for vascularity in tissue healing that could be used for guiding treatment.

7.5 The role of power Doppler ultrasonography in treatment planning for patients with chronic plantar fasciitis

Thirty patients with unilateral plantar fasciitis were followed up four weeks after the completion of shock wave therapy. The vascularity of their proximal plantar fascia, pain intensity and foot function before treatment, right after treatment and one month later were compared by the same evaluator. Patients were categorized as vascularized if their pre-intervention VI was equal to or greater than 2.6%. Successful treatment was defined as a decrease in pain of either 20mm or more than 30% of the pre-intervention level on the visual analog rating scale.

A higher VI was associated with greater intensity of pain (r=0.44, $p \leq 0.035$), with the pain subscale of the FFI (r=0.65, $p \leq 0.001$) and with the FFI rating as a whole (r=0.57, $p \leq 0.004$). In addition, 13 of the 30 patients (43.3%) showed increased vascularization, i.e. patients who had initial VI scores beyond 2.60%. Patients with vascularization reported significantly more intense pain (based on the pain subscale of the FFI ($p \leq 0.002$) and dysfunction ($p \leq 0.003$) than the non-vascularized patients. A vascularity index before treatment of more than 1.55% was identified as a predictor of unsuccessful recovery (sensitivity=83.30%, specificity=100%, area under the curve=0.92) with 3 sessions of ESWT, while a VI score of more than 3.25% predicted unsuccessful recovery even with 6 sessions (sensitivity = 62.50%, specificity=100%, area under the curve=0.75). Similar VIs predicted unsuccessful intervention (based on pain reduction) as rated at the 4-week follow-up.

These findings highlight the importance of pre-intervention vascularity for treatment planning. Individuals with plantar fasciitis with VIs of more than 1.55% will require more than 3 treatment sessions to achieve satisfactory pain reduction at post intervention and 4-weeks follow-up. For individuals with a VI index greater than 3.25%, even 6 treatment sessions will probably be inadequate.

7.6 Factors influencing pain reduction in patients with chronic plantar fasciitis

Twenty-four of the patients were followed up 3 and 6 months after the intervention. In this study, treatment was regarded as satisfactory when pain was reduced by 50 to 70% based on the VAS scale, and excellent treatment was defined as pain reduced by more than 70%. All the patients had previously experienced symptoms for less than 12 months.

The results showed that by 3 months, 62.50% of the patients reported successful treatment, and by 6 months this had increased to 87.50%. Regression of vascularity was evident in both treatment groups after 3 months, and it continued at least until 6 months post intervention. The 6-session patients reported even larger vascularity decreases ($p \leq 0.05$). Patients with excellent treatment results had normal vascularity after 6 months. In addition, more patients in 6-session group reported success although did not reach to the significant level (p=0.067). Six sessions were significantly more effective for patients with greater vascularization before treatment, effective especially after 6 months ($p \leq 0.003$).

Fascia thinning was evident after 3 months, and about 50% of the patients regained normal fascia thickness by 6 months post intervention. Furthermore, about 90% of the patients with a heel spur reported excellent results after 6 months, but only 33% of those without a heel spur.

These results indicate that among highly vascularized individuals, treatment efficacy after 6 months depends on the number of treatment sessions. The presence of a bone spur also influences treatment success.

7.7 Limitations and future studies

These experimental protocols had three major limitations. First, the evaluations and the interventions were conducted at two different locations.

Patients were invited to the testing laboratory before and after the treatment programme. The same evaluator conducted the pre- and post-intervention evaluations to minimize inter-tester variance, and she was blinded to the treatment condition. However, re-evaluation could not be done after each session, so only cumulative effects could be assessed and we could not delineate the number of treatment sessions that could induce vascular regulation in a session-by-session manner.

Second, the recommendation to use plantar fascia vascularity level to plan ESWT treatment is based on observations of unilateral patients. The findings cannot, therefore, be generalized automatically to those affected bilaterally.

Third, generalization of the results on vascularization and fascia thickness modulation observed at 3- and 6-month follow-up should be confined to patients with duration of symptoms less than 12 months. In addition, the follow-up period may have been insufficient. Re-evaluation after 6 months showed modulation of fascia thickness in only 50% of the patients. Knowing that remodeling in tissue healing may take a year or more, the long term effects of ESWT need further study with a longer follow-up period.

For the treatment protocols, cut-off VI values were only estimated for 3 and 6 sessions of ESWT because these are the most commonly used ESWT protocols with plantar fasciitis. Further study is required to assess whether the cut-off VI values can be increased with more sessions.

7.8 Significance of the project

The results from this study substantiate the bi-directional regulation of vascularity after the application of extracorporeal shock wave therapy, but they also provide a scientific basis for selecting an appropriate treatment session of ESWT for treating patients with plantar fasciitis. The main contributions from the present thesis are highlighted as following:

First, to our knowledge, this has been the first study to quantify the vascularity of the proximal plantar fascia. With this approach, patients can be categorized successfully into those with and without vascularization groups, and such a classification may indicate different stages of the pathological changes.

Second, bi-directional regulation of vascularity after the application of ESWT has been observed. Such observation indicates that vascular modulation depends on baseline vascularity and treatment dosage in terms of number of treatment sessions, which further supports the important role of modulation of vascularization in ESWT's working mechanism and in the healing process of plantar fasciitis.

Third, patients' vascularization categories, together with the number of treatment sessions, have been shown to be two important factors that affect the effectiveness of treatment in terms of pain reduction and morphological changes such as plantar fascia thickness.

Finally, in terms of clinical application, based on the above findings, 6 sessions of ESWT are recommended for individuals who have had plantar fasciitis for less than 12 months and for whom power Doppler has demonstrated increased vascularity.

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APPENDIX I

THE HONG KONG
POLYTECHNIC UNIVERSITY
香港理工大學

Memo

To	FU Siu Ngor, Department of Rehabilitation Sciences		
From	NG Yin Fat, Chairman, Departmental Research Committee, Department of Rehabilitation Sciences		
Ref.	in	Your ref.	in
Tel no.	Ext. 6721	Fax no.	
Email		Date	

Ethical Review of Research Project Involving Human Subjects

I write to inform you that approval has been given to your application for human subjects ethics review of the following research project for a period from 18/6/2009 to 30/5/2011:

Project Title: Changes of proximal plantar fascia microcirculation after Extracorporeal Shock Wave Therapy in patients with proximal plantar fascillitis : A double-blinded randomized controlled trial

Department: Department of Rehabilitation Sciences

Principal Investigator: FU Siu Ngor

Please note that you will be held responsible for the ethical approval granted for the project and the ethical conduct of the research personnel involved in the project. In the case the Co-PI has also obtained ethical approval for the project, the Co-PI will also assume the responsibility in respect of the ethical approval (in relation to the areas of expertise of respective Co-PI in accordance with the stipulations given by the approving authority).

You are responsible for informing the Departmental Research Committee (DRC) in advance of any changes in the research proposal or procedures which may affect the validity of this ethical approval.

You will receive separate notification should you be required to obtain fresh approval.

NG Yin Fat
Chairman
Departmental Research Committee
Department of Rehabilitation Sciences

APPENDIX II

香港理工大學康復治療科學系科研同意書

科研題目：體外衝擊波治療後近端足底筋膜微循環的改變

科研人員：符少娥博士，導師。陳泓穎，博士研究生，學生。梁曉莛，研究助理

導師：符少娥博士

科研內容：本實驗欲研究對患有頑固性足底筋膜炎的病人，其足底筋膜於跟骨附著處血液微循環的情況，以及在進行衝擊波治療前後，該部位血液微循環的變化情況。

本實驗將分成幾個不同的階段，分別包括對（1）健康志願者（2）足底筋膜炎患者足底筋膜血液微循環的觀測，以及（3）進行衝擊波治療的足底筋膜炎患者，治療前後血液微循環的情況。如果您不是足跟痛患者，您將做為健康志願者參加測試；如果您患有足跟痛，您可能做為第二組或者第三組的受試者參加測試。

實驗過程：

對於第三組受試者，研究人員將其隨機分配成不同劑量衝擊波治療組，並在進行治療衝擊波治療前以及治療週期結束後，分別進行足底筋膜跟骨附著處微循環的檢測。

能量超聲觀測足底筋膜跟骨附著處血液微循環的過程

受試者俯臥於床，自覺舒適體位。踝關節固定于中立位。採用能量超聲波分別對兩側足底蹠筋膜於跟骨附著處進行檢測。整個過程無創無痛，總共需時約 30 分鐘至 1 小時。

參加試驗的足跟痛患者需符合以下條件：

1. 年齡 18－60 歲
2. 經醫生診斷為足底筋膜炎
3. 病程超過 6 個月，經其他保守治療方法無明顯效果

4. 沒有在治療區域進行過外科手術；沒有周圍血管疾病的病史；脛後動脈及足背動脈搏動正常；無毛細血管充盈障礙；無糖尿病、及外周神經性病變（包括風濕性關節炎、強制性脊柱炎等）；踝關節感覺缺失；妊娠；跟骨應力性骨折等

對項目參與人仕和社會的益處：不僅可以使參加者瞭解到自己足底筋膜的微循環狀況外，對於對衝擊波治療足底筋膜炎機制研究也有積極的促進作用。

潛在危險性：測試對參加者不會造成任何危險。

同意書：

本人＿＿＿＿＿＿已瞭解此次研究的具體情況。本人願意參加此次研究，本人有權在任何時候、無任何原因放棄參與此次研究，而此舉不會導致我受到任何懲罰或不公平對待。本人明白參加此研究課題的潛在危險性以及本人的資料將不會洩露給與此研究無關的人員，我的名字或相片不會出現在任何出版物上。

本人可以用電話 27666726 來聯繫此次研究課題負責人，符少娥 教授/博士。若本人對此研究人員有任何投訴，可以聯繫梁女士（部門科研委員會秘書），電話：27665397。本人亦明白，參與此研究課題需要本人簽署一份同意書。

簽名（參與者）：＿＿＿＿＿＿＿＿＿＿＿ 日期：＿＿＿＿＿＿＿＿＿＿

簽名（證人）：＿＿＿＿＿＿＿＿＿＿＿ 日期：＿＿＿＿＿＿＿＿＿＿

APPENDIX III

The Hong Kong Polytechnic University

Department of Rehabilitation Sciences

Research Project Informed Consent Form

Project title: **Changes of proximal plantar fascia microcirculation after Extracorporeal Shock Wave Therapy in patients with proximal plantar fascillitis : A double-blinded randomized controlled trial**

Investigator(s):

Dr Amy Fu, PhD, Assistant Professor, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University

Dr Michael Ying, PhD, Associate Professor, Department of Health Technology Informatics, The Hong Kong Polytechnic University

Dr Hok Ming Ho, Consultant, Department of Orthopaedic and Traumatology,l Tseung Kwan O Hospital

Ms Holly Chen, PhD student, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University

Project information:

- The effects of extracorporeal shock wave therapy in patients with chronic proximal heel pain will be conducted in the Department of Orthopaedic and Traumatology Unit of Tsang O Hospital in Hong Kong. The target group will be patients with age between 18 and 60 and suffered from proximal heel pain for more than 3 months.
- Physical examination on pain, range of ankle movement, as well as microcirculation will be conducted before, immediately after, at 3-, 6- and 12 months after having extracorporeal shock wave therapy. The study will last for 1 year.

- The physical assessment and examination on microcirculation will last for 30 minutes. No discomfort will be induced on the patients. Pain will be perceived during the application of extracorporeal shock wave therapy. The intensity of treatment will be adjusted according to patients' acceptance.
- The effectiveness of extracorporeal shock wave therapy for patients with proximal heel pain has been established. This study aims to find out the optimal intensity in terms of number of sessions of treatment for patients with proximal heel pain, as well as to have a better understanding on the therapeutic effects of this treatment.

Consent:

I, ____________________________, have been explained the details of this study. I voluntarily consent to participate in this study. I understand that I can withdraw from this study at any time without giving reasons, and my withdrawal will not lead to any punishment or prejudice against me. I am aware of any potential risk in joining this study. I also understand that my personal information will not be disclosed to people who are not related to this study and my name or photograph will not appear on any publications resulted from this study.

I can contact the chief investigator, Dr Amy Fu at telephone 27666726 for any questions about this study. If I have complaints related to the investigator(s), I can contact Mrs Michelle Leung, secretary of Departmental Research Committee, at 27665397. I know I will be given a signed copy of this consent form.

Signature (subject): Signature (witness):

Printed name (subject) Printed name (witness)

Date: Date:

APPENDIX IV

姓名　　　　　　　　　　　　　　　　　　　　日期

足部功能問卷 Foot Function Index

⌘　下列問題 1~9，每一個項目旁邊的直線代表過去一星期當中，在下列情況下，您的足部疼痛程度。直線的最左端代表「完全沒有疼痛」，最右端代表「極度無法忍受之疼痛」。請在直線上用箭頭↓做記號，代表過去一個星期當中，您的足部在下列情況下的疼痛程度。過去一星期當中，如果您從未進行該項活動，請註記為「不適用」。

⌘　您的足部疼痛程度?

1. 疼痛最嚴重的時候　　☐ 不適用

完全沒有疼痛 ______________________________ 極度無法忍受之疼痛

2. 早晨起床前　　☐ 不適用

完全沒有疼痛 ______________________________ 極度無法忍受之疼痛

3. 赤腳走路時　　☐ 不適用

完全沒有疼痛 ______________________________ 極度無法忍受之疼痛

4. 赤腳站立時　　☐ 不適用

完全沒有疼痛 ______________________________ 極度無法忍受之疼痛

5. 穿鞋走路時　　☐ 不適用

完全沒有疼痛 ______________________________ 極度無法忍受之疼痛

6. 穿鞋站立時　　☐ 不適用

完全沒有疼痛 ______________________________ 極度無法忍受之疼痛

7. 穿戴鞋墊或輔具走路時　　☐ 不適用

完全沒有疼痛 ________________________________ 極度無法忍受之疼痛

8. 穿戴鞋墊或輔具站立時　　☐ 不適用

完全沒有疼痛 極度無法忍受之疼痛
____

9. 一天結束、上床睡覺前　　☐ 不適用

完全沒有疼痛 極度無法忍受之疼痛
____

⌘　下列問題 10~18，每一個項目旁邊的直線代表過去一星期當中，您在從事該項活動時，感受到

的困難程度。直線的最左端代表「完全沒有困難」，最右端代表「極度困難」。請在直線上用

箭頭↓做記號，代表過去一個星期當中，因為您的足部問題，在從事下列活動時，感受到的

困難程度。過去一星期當中，如果您從未進行該項活動，請註記為「不適用」。

⌘　您感受到的困難程度如何?

10.在室內走路　　☐ 不適用

完全沒有困難 ________________________________ 極度困難

11. 出門走在不平的路面　　☐ 不適用

完全沒有困難 ________________________________ 極度困難

12. 走四條街或以上的距離　　☐ 不適用

14. 下樓梯　　　　　　　　☐ 不適用

完全沒有困難 ______________________________ 極度困難

15. 掂腳尖站著　　　　　　☐ 不適用

完全沒有困難 ______________________________ 極度困難

16. 從座椅上起身　　　　　☐ 不適用

完全沒有困難 ______________________________ 極度困難

17. 上下人行道的邊緣　　　☐ 不適用

完全沒有困難 ______________________________ 極度困難

18. 快步走或跑步　　　　　☐ 不適用

完全沒有困難 ______________________________ 極度困難

⌘　下列問題 19~23，每一個項目旁邊的直線代表過去一星期當中，您從事該項活動的頻率，直線的最左端代表「完全沒有」，最右端代表「所有時間都如此」。請在直線上用箭頭↓做記號，代表過去一個星期當中，您因為足部問題而進行下列活動的頻率。過去一星期當中，如果您從未進行該項活動，請註記為「不適用」。

⌘　您花多少時間：

19. 在室內使用枴杖或助行器　☐ 不適用

完全沒有 ______________________________ 所有時間都如此

20. 出外時使用枴杖或助行器　☐ 不適用

完全沒有 ______________________________ 所有時間都如此

21. 因為足部的問題，大部份時間不出門　☐ 不適用

完全沒有 ______________________________ 所有時間都如此

22. 因為足部的問題，大部份時間不下床　☐ 不適用

完全沒有 ______________________________ 所有時間都如此

23. 因為足部的問題，活動受到限制　☐ 不適用

完全沒有 ______________________________ 所有時間都如此

APPENDIX V

The British Journal of Radiology, *000* (2012), 1–5

Correlation between computerised findings and newman's scaling on vascularity using power Doppler ultrasonography imaging and its predictive value in patients with plantar fasciitis

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Objectives: The purpose of this study was to correlate findings on small vessel vascularity between computerised findings and Newman's scaling using power Doppler ultrasonography (PDU) imaging and its predictive value in patients with plantar fasciitis.
Methods: PDU was performed on 44 patients (age range 30–66 years; mean age 48 years) with plantar fasciitis and 46 healthy subjects (age range 18–61 years; mean age 36 years). The vascularity was quantified using ultrasound images by a customised software program and graded by Newman's grading scale. Vascular index (VI) was calculated from the software program as the ratio of the number of colour pixels to the total number of pixels within a standardised selected area of proximal plantar fascia. The 46 healthy subjects were examined on two occasions 7–10 days apart, and 18 of them were assessed by 2 examiners. Statistical analyses were performed using intraclass correlation coefficient (ICC) and linear regression analysis.
Results: Good correlation was found between the averaged VI ratios and Newman's qualitative scale (ρ=0.70; p<0.001). Intratester and intertester reliability were 0.89 and 0.61, respectively. Furthermore, higher VI was correlated with less reduction in pain after physiotherapeutic intervention.
Conclusions: The computerised vascular index not only has a high level of concordance with the Newman grading scale but is also reliable to reflect the vascularity of proximal plantar fascia, and can predict pain reduction after intervention. This index can be used to characterise the changes in vascularity of patients with plantar fasciitis, and it may also be helpful to evaluate treatment and monitor the progress after intervention in future studies.

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Plantar fasciitis is the most common cause of heel pain, and about 2,000,000 patients receive treatment every year because of this condition [1]. Besides mechanical loading, vascular disturbance with consequent metabolic impairment and hypoxia is thought to play an important role [2]. Indeed, fibrovascular hyperplasia and vascular proliferation were observed from microscopic specimens obtained from operative resection [3–5]. Walther et al [6] were the first group to evaluate plantar fascia vascularity non-invasively using power Doppler ultrasonography (PDU).

PDU is one of the colour flow imaging techniques that encodes the amplitude of the power spectral density of the Doppler signals [7]. This method has been used to assess soft tissue vascularity and treatment efficacy with a variety of musculoskeletal and related problems. Changes in vascularity in synovial tissues in patients with rheumatoid arthritis [8–11], osteoarthritis [12, 13], tendinopathy [6, 14–21] and plantar fasciitis [6] have been reported. Modulation in vascularity was observed in patients with tendinopathy after a course of intervention [14–21]. Most of these studies used the Newman's grading scale to grade the tissue vascularity [19–21]. This qualitative grading for the PDU images had high correlation with the histopathological grading of vascularity of the synovial membrane in patients with arthritis [11]. Nevertheless, Newman's grading system may not be objective and sensitive enough to differentiate subtle vascularity changes.

Recently, computerised methods were used to quantify tissue vascularity with ultrasonography. Tissue vascularity was quantified by computing a vascular index (VI), which is calculated as the ratio of the number of colour pixels to the total number of pixels within the region of interest in patients with soft tissue problems [8, 9, 11, 17]. Note that most of these studies were conducted using colour Doppler ultrasonography. In this connection, PDU is superior to frequency-based colour Doppler ultrasonography, especially in tissues with low blood flow, such as the plantar fascia [6, 22, 23]. Ying et al [24] reported the feasibility of computerised quantification of

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vascularity in thyroid tissues with PDU. We were interested in evaluating whether the computerised quantification of vascularity could be applied on musculoskeletal tissue, such as the plantar fascia. Therefore, the purpose of the present study was to correlate the computerised VI and Newman's qualitative grading scale in quantifying plantar fascia vascularity using PDU, to evaluate the intra- and intertester reliability of the computerised quantitative method and its predictive ability of recovery in patients with plantar fasciitis. Proximal plantar fascia, which is the most commonly affected area in individuals with plantar fasciitis, according to clinical examination [25,26] and previous B-mode ultrasonography [26, 27, 28], was chosen as the target testing area.

Methods and materials

Patient selection

44 patients (28 females, 22 males; mean age 48 years; range 30–66 years) with a clinical diagnosis (by experienced orthopaedic surgeons) of plantar fasciitis were recruited from a local hospital. The inclusion criteria were patients with planar fasciitis for more than three months in good health and having no history of any systemic disease with similar manifestations as plantar fasciitis, including gout and serogenative arthritis. Patients who had diseases that may affect the lower limb vascularity, such as diabetes mellitus, peripheral vascular disease and foot trauma, were excluded from the study. 46 healthy subjects (34 females, 12 males; mean age 36 years; range 18–61 years) with no history of heel pain for the previous three months were invited to have PDU examination on their plantar fascia twice with 7–10 days apart. 18 of them were examined by two examiners. This study was approved by the Human Subject Ethic Sub-committee of the university and hospital. Written consent was signed from each subject after a verbal explanation of the study.

Ultrasonography

Greyscale and PDU were performed using a MyLab 70 X-view ultrasound unit in conjunction with a 4–13 MHz linear transducer (Esaote, Genova, Italy). In the ultrasound examination, positioning of the proximal plantar fascia was adopted as described by O'Neill et al [29]. The transducer was in the longitudinal plane parallel to the long axis of the plantar foot. A clear image with both the contour of the medial tubercle of the calcaneus and the proximal part of the plantar fascia, which can be seen most legibly, was acquired. Vascularity was examined using the power Doppler mode. The size of the colour box was standardised to 1.5×1 cm, and was placed over the insertion of the plantar fascia (*i.e.* the middle point of the right line of the colour box is just on the most prominent point of the calcaneus). Settings of the PDU were standardised for high sensitivity, with a low wall filter to allow detection of vessels with low blood flow and to have low colour noise. Pulsed repetition frequency (PRF) was 370 Hz, and medium persistence was used. The colour gain was first increased to a level that showed colour noise, and then decreased until the noise disappeared [24, 30]. For each subject, five images with most abundant vascularity and consistent Doppler signals were selected and recorded. In addition, the room temperature was set to 22°C, and subjects were required to stay in the room for 30 minutes before the ultrasound examination.

Image processing

The total number of pixels as well as the colour pixels within the region of interest (ROI) were counted by a customised software program (Matlab, version 7.3.0.267R 2006b; Figure 1). The vascular index (VI) was the ratio of the number of colour pixels to the total number of pixels within the ROI [24]. The ROI was defined as the total area of fascia within the 1.5×1 cm colour box. Average VI for all five images (VI_5) and for the first three images (VI_3), and maximum VI value of the five images (VI_{max}), were computed. The PDU images were also graded by two examiners on a scale of 0–3 independently [19]. When determined scores by the two examiners did not match, joint evaluation was conducted to reach a consensus grade.

Extracorporeal shock wave therapy

Meanwhile, for the 44 patients with plantar fasciitis, extracorporeal shock wave therapy (ESWT; Duolith SL1, Storz Medical, Tägerwilen, Switzerland) was delivered for pain reduction. This device is a piezoelectric-type device with an energy flux density ranging from 0.08 to 1.1 mJ mm^{-2}. Patients were randomly divided into receive either 3 or 6 sessions of treatment once a week. Both groups received 1500 shocks per session, and treatment intensity was patient-guided with their most tolerable pain level. A self-administered 100 mm visual analogue scale (VAS) [31] was used to evaluate the pain level before and after treatment.

Statistical analysis

Spearman's rank correlation tests were used to assess the level of correlation between the VI and Newman's grading scale. Intraclass correlation coefficient (ICC) model 3 and model 2 were used to evaluate the intratester and intertester reliability, respectively [32]. Pearson correlation coefficient was used to detect relationship between baseline VI and intensity of pain. Linear regression analysis was performed with pain reduction as dependent variable and baseline VI as explanatory variables. The level of significance was at $p<0.05$.

Results

Correlation between computerised findings and Newman scaling on vascularity using Power Doppler Ultrasonography. A total of 220 images were collected from these 44 patients, with 5 images from each subject before intervention. The VI calculated from the 220 images illustrated good correlation with Newman's grading scale (ρ=0.70, p=0.000; Figure 2).

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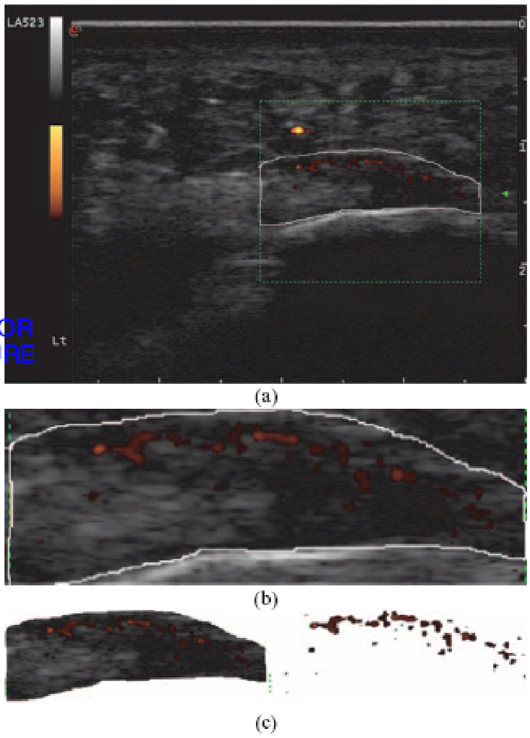

Figure 1. The process of power Doppler image data reduction by using the customized algorithm. (a) The region of interest (ROI; the insertional part of the fascia/tendon to bone) was extracted by outlining the boundaries (white line). (b) The ROI was initially extracted by trimming the unwanted area from the power Doppler window (green box). (c) The ROI was further extracted by trimming the unwanted area from the outlined area, and the total number of pixels within the ROI was counted (left image). The colour pixels were further extracted by eliminating the greyscale pixels, and the colour pixels were counted by the algorithm.

Intratester and intertester reliability

46 healthy subjects had test–retest examination with 7–10 days apart, while 18 of them were evaluated by two examiners. The intratester reliability of the two examiners showed an ICC greater than 0.75 ($p<0.05$) only when VI was calculated from averaging of five images (Table 1). Hence, VI_5 is more reliable than VI_3 and VI_{max}. VI_5 also achieved the highest intertester reliability of 0.61. The mean difference between the first and second VI_5 was 0.15 on a range of −0.13 to 0.42.

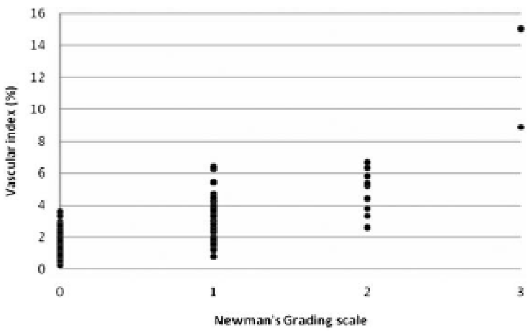

Figure 2. Scatter plot of the vascular index and Newman's grading scale in patients with plantar fasciitis.

Predictive value of vascular index on pain reduction

44 patients with duration of symptoms lasting from 3 months to 3 years (mean duration of symptoms: 13.11 months) received ESWT. The baseline VI was found related to the intensity of pain ($r=0.36$, $p=0.02$) in these 44 patients. Further analysis using linear regression analysis showed that baseline VI was related to pain reduction after a course of intervention with ESWT only in the 19 patients with duration of symptoms less than 12 months. Indeed, from the regression model, baseline VI can explain 49.2% of pain reduction after ESWT (Pearson's $r=-0.70$, $p=0.002$; Figure 3). Thus, a higher baseline VI was correlated with less reduction in pain in patients with symptoms less than one year.

Discussion

The results from this study indicate that VI, which reflects the vascularity of proximal plantar fascia, has a high level of concordance with Newman's grading scale. The VI also demonstrated good intratester reliability and moderate intertester reliability for 46 healthy subjects. In addition, our study is the first showing that VI can predict recovery in patients with plantar fasciitis.

Since 1994, PDU has been suggested as a potential useful alternative to colour Doppler ultrasonography [33]. This method has become popular in assessing blood flow pattern to assist diagnosis and evaluate treatment efficacy in musculoskeletal disorders [8–11, 14, 15, 34]. An increase in vascularity in the Achilles tendon was reported in patients suffering from Achilles tendinopathy [14, 15] and in the plantar fascia in patients with plantar fasciitis with symptoms for more than 6 months but less than one year [6]. Here, hyperaemia change was used, in addition to clinical signs [15], to categorise the patients, and also to monitor treatment effectiveness, in patients with tendinopathy [14, 16–18]. Note that most of these studies used a subjective grading method proposed by Newman et al [19]. Newman's grading scale based on PDU imaging was found to be correlated with histological

Table 1. Intraclass correlation coefficient (ICC) analysis of the intratester and intertester reliability 1

	Intratester ICC (3,1)		Intertester ICC (2,2)
	Tester 1	Tester 2	
VI_5	0.89	0.79	0.61
VI_3	0.72	0.48	0.38
VI_{max}	0.68	0.85	0.45

VI_5, VI_3 and VI_{max} denote vascularity index from averaging of all five images, of first three images and maximum vascularity of all five images, respectively.

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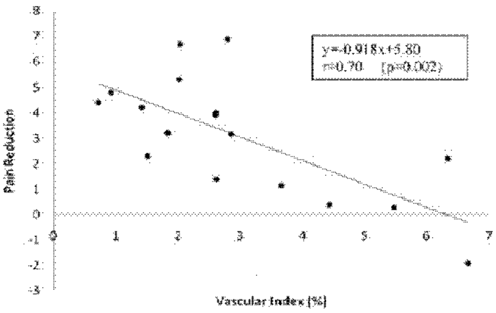

Figure 3. Scatter plot of the vascular index and visual analogue scale reduction in patients with duration of symptoms more than 3 months and less than 12 months. 2

findings in an animal study by Lee et al [34] and in a study of human subjects with arthritis by Walther et al [12]. In Lee et al's arthritic rabbit knee model, synovial vascularity using contrast-enhanced PDU and histological findings were significantly correlated [34]. In patients with osteoarthritis and rheumatoid arthritis, Walther et al. [12] reported a good correlation coefficient (of 0.81) on tissue vascularity between the Newman's grading scale based on PDU images and tissue sections obtained when patients received surgery. Although the grading scale has high correlation with tissue section, it was noted that the grading scale was not able to detect subtle changes in vascularity. In view of the increasing use of PDU in diagnosing and evaluating treatment efficacy in musculoskeletal disorders, a quantified method is needed to reduce subjectivity in the grading process, and also to evaluate changes in vascularity during its recovery. Our study, based on the computation approach used on detection of vascularity on thyroid gland, reported good correlation on tissue vascularity in plantar fascia obtained from our customised software program based on PDU images and Newman's grading scale. Direct comparison of our method with tissue section is difficult as a majority of patients (about 85%) with plantar fasciitis recovered with conservative treatment [2].

Test–retest reliability is important of any scale designed to measure change over time. Test–retest reliability reflects measurement error associated with repeated measurement by the same operator (intratester reliability) or a number of operators (intertester reliability). Findings from this study indicated good intratester (ICC=0.79–0.89 from averaged value of five images) and moderate intertester (ICC=0.66) reliability. Ultrasonography is well known for being a very operator-dependent technique [35, 36]. The intrareader reliability for the Doppler signal has been reported to vary from 0.58 to 0.96, and interreader reliability was 0.66, which indicated good to excellent intrareader agreement and moderate interreader reliability [35, 36]. Note that intratester reliability from both examiners in the present study had the highest test–retest reliability when VI was computed from averaging five images. As plantar fascia is a hypovascular area, the power Doppler signal picking up is not as easy as those big vessels in other organs. Although we adjusted the colour gain at the level for which colour noises were not apparent, for each image required, an averaging of five images could minimize any error induced from one image, which may also help explain why VI_5 showed higher repeatability and reproducibility than VI_3. Hence, scanning of five images is recommended for computation of VI. In addition, movement of the transducer during imaging may induce artefacts, which is unavoidable [37]. Such movement is more profound on an uneven surface, such as the epicondylar region. Therefore, it is essential to try to stabilise and support the wrist of the operator during imaging, and to apply a light touch.

This study also explored the role that vascularity plays in recovery of pain in patients with plantar fasciitis. An 3
increase in vascularity was associated with greater pain intensity in patients with Achilles tend tendinopathy on [14, 32, 38] and patellar tendinopathy [15]. In contrast, increased vascularity has also been found some time after effective treatments such as sclerosing injection [15, 16] and eccentric training [18, 38]. In patients with plantar fasciitis, Walther et al [6] first reported a moderate or severe hyperaemia in patients with less than 12 months duration of symptoms, and in these patients the grading of vascularity was related to the VAS. In line with Walther's observation, we observed an increase in vascularity in plantar fascia in patients with duration of symptoms below 12 months, and the baseline vascularity was also found to relate to the intensity of pain. Furthermore, the treatment outcome in patients with duration of symptoms below 12 months was related to the baseline vascularity. In patients with higher VI, less reduction in pain was observed after a course of either three or six sessions of ESWT. These findings demonstrated the role of vascularity in tissue recovery. Further study is needed to investigate whether baseline vascularity can be used to determine the success of intervention, as well as treatment intensity.

Conclusion

We concluded that the semi-quantitative computerised method that we used is reliable and has a high level of concordance with the Newman's grading system in evaluating proximal plantar fascia vascularity. The vascularity obtained is a strong predictor for pain reduction after a course of physiotherapeutic intervention in patients with plantar fasciitis with a duration of less than 12 months. Such findings may help the therapist to determine the prognosis of their treatment outcome in patients with plantar fasciitis.

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APPENDIX VI

World Confederation for Physical Therapy

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RR-PO-203-7-Thu. VALIDATION OF IN VIVO PATELLAR TRACKING WITH USE OF CUSTOM-MADE CLAMP: A FLUOROSCOPY STUDY. *Jiu-Jenq Lin, Taiwan*

RR-PO-203-5-Thu. THE LOCAL DYNAMIC STABILITY OF LOWER EXTREMITY ON TREADMILL WALKING WITH NONLINEAR ANALYSIS. *Yoshio Kobayashi, Japan*

RR-PO-202-19-Thu. ELECTROMYOGRAPHY ACTIVITY DURING DIFFERENT ANKLE PROPRIOCEPTION EXERCISES IN UNIPODAL SUPPORT. *Bianca Callegari, Brazil*

RR-PO-202-23-Thu. DEVELOPMENT OF MOTOR ABILITY SCALE FOR STROKE PATIENTS. *Munetsugu Kota, Japan*

SI-PO-203-13-Thu. NEW ELECTRICAL EVALUATION DEVICE COMBINING TWO TRIAXIAL ACCELEROMETER AND EMG. *Hiroshi Karasuno, Japan*

RR-PO-204-3-Thu. QUANTITATIVE/QUALITATIVE ANALYSIS OF STAIR ASCENT AND DESCENT USING A GAIT ANALYSIS SYSTEM WITH A 3-AXIS ACCELEROMETER AND AN EMG. *Kazunori Morozumi, Japan*

RR-PO-202-27-Thu. EFFECTS OF TOES FLEXION STRENGTH TO POSTURAL SWAY AND RANGES/AREA OF WEIGHT SHIFTS. *Yuji Tanaka, Japan*

RR-PO-203-1-Thu. SKIN MOVEMENT OF THE TRUNK DURING TRUNK ROTATION. *Tsutomu Fukui, Japan*

RR-PO-202-21-Thu. EXCITABILITY DYNAMICS OF THE CORTICAL MOTOR AREA DURING VOLUNTARY MUSCLE RELAXATION. *Naoshin Yoshida, Japan*

RR-PO-203-17-Thu. EFFECTS OF METHODS OF DESCENDING STAIRS FORWARDS VERSUS BACKWARDS ON KNEE JOINT FORCE IN PATIENTS WITH OSTEOARTHRITIS OF THE KNEE. *Masaki Hasegawa, Japan*

RR-PO-203-19-Thu. MOTION ANALYSIS OF STANDING UP IN PERSONS WITH ROUND BACK. *Yoshihide Tokuda, Japan*

RR-PO-203-21-Thu. CONTROL OF ABDOMINAL AND HIP MUSCLES IN HIP FLEXION. AN EXPLANATION FOR GAIT IMPAIRMENTS IN PATIENTS WITH PELVIC PAIN?. *Jaap van Dieen, Netherlands*

RR-PO-203-23-Thu. KINEMATIC ANALYSIS OF STAND-TO-SIT MOTION IN PEOPLE WITH KNEE OSTEOARTHRITIS. *Kazuki Tokuda, Japan*

RR-PO-203-25-Thu. CHANGES IN NATURAL BREATHING AND INTRA-ABDOMINAL PRESSURE-TIME CURVE DURING DYNAMIC LIFTING. *Masashi Kawabata, Japan*

RR-PO-204-1-Thu. WHICH BODY POSTURE IS RELATED TO SADNESS AND DEPRESSION?. *Jose Luis Pimentel Rosario, Brazil*

RR-PO-204-5-Thu. ACTIVITIES OF BACK MUSCLE AT STATIC MUSCLE CONTRACTION DURING PELVIC ANTERIOR TILT WITH NUTATION OF SACRUM. *Teppei Abiko, Japan*

RR-PO-204-7-Thu. THORACIC MANIPULATION DOES NOT INFLUENCE 3-D SCAPULAR KINEMATICS DURING ARM FLEXION IN HEALTHY SUBJECTS. *Paula Camargo, Brazil*

RR-PO-204-9-Thu. INTERACTION INTERFERENCE BETWEEN ARM AND LEG: DIVISION OF ATTENTION THROUGH MUSCLE FORCE REGULATION. *Hideaki Takebayashi, Japan*

RR-PO-203-3-Thu. THE CONTRIBUTION OF THE DYNAMIC JOINT STIFFNESS OF THE ANKLE JOINT TO GAIT IN PATIENTS WITH HEMIPARESIS. *Yusuke Sekiguchi, Japan*

RR-PO-203-27-Thu. ANALYSIS OF THE HUMEROSCAPULAR ANGULAR MOTION RATIO USING A NEW COMBINED PALPATORY AND PHOTOGRAMMETRIC MEASURING PROCEDURE. *Ulrich Betz, Germany*

MUSCULOSKELETAL: Lower Limb 5

RR-PO-302-16-Thu. PROXIMAL PLANTAR FASCIA MICROCIRCULATION IS MODULATED IN PATIENTS WITH PLANTAR FASCIITIS. *Hongying Chen, Hong Kong*

RR-PO-304-2-Thu. THE INFLUENCE OF FUNCTIONAL ANKLE INSTABILITY ON POSTURAL CONTROL DURING THE INITIAL PERIOD OF SINGLE-LEG STANDING. *Masahide Yagi, Japan*

RR-PO-302-22-Thu. VALIDATION OF THE KNEE INJURY AND OSTEOARTHRITIS OUTCOME SCORE (KOOS) FOR PATIENTS WITH KNEE SPRAINS. *Pernilla Svensson, Sweden*

RR-PO-304-16-Thu. ANKLE PROPRIOCEPTION IS NOT TARGETED BY EXERCISES ON AN UNSTABLE SURFACE. *Henri Kiers, Netherlands*

RR-PO-304-14-Thu. INFLUENCE OF CHAIR HEIGHT IN THE PEAK TORQUE FORCES PRODUCED BY THE LOWER LIMB JOINTS DURING THE CHAIR RISE MOVEMENT. *Cristina Melo, Portugal*

RR-PO-304-12-Thu. STRENGHT TRAINING OF THE IN- AND EVERSION MUSCLES AROUND THE ANKLE JOINT: A COMPARISON BETWEEN THE THERABAND® AND THE PHYSIOFLIP®. *Philip Roosen, Belgium*

RR-PO-304-10-Thu. ENERGY EXPENDITURE AND FATIGUE INDUCED PROPRIOCEPTIVE DEFECT FOLLOWING REHABILITATION OF THE RECONSTRUCTED ANTERIOR CRUCIATE LIGAMENT. *Tamer Shousha, Egypt*

RR-PO-304-6-Thu. AN EVALUATION OF THE LOWER EXTREMITY ALIGNMENT, ASSESSED BY THE POSTURAL ANALYSIS SOFTWARE AND BASED ON THE GDS METHOD. *Elizabeth Alves G Ferreira, Brazil*

RR-PO-303-4-Thu. HIP MUSCLE SIZE IN THE PRESENCE OF ACETABULAR LABRAL JOINT PATHOLOGY. *M. Dilani Mendis, Australia*

RR-PO-303-24-Thu. FIRST RAY MOBILITY IN INDIVIDUALS WITH PRONATED FOOT. *Huei-Ming Chai, Taiwan*

RR-PO-303-22-Thu. REHABILITATION USING ECCENTRIC TRAINING AND MAINTAINED STRETCHING ON CAPILLARIZATION IN RAT SKELETAL MUSCLES AFTER IMMOBILIZATION. *Anabelle S Cornachione, Brazil*

RR-PO-303-20-Thu. EFFECT OF WHOLE BODY VIBRATION TRAINING ON GASTROCNEMIUS AND VASTUS LATERALIS INTRAMUSCULAR TEMPERATURE. *J. Brent` Feland, United States of America*

RR-PO-302-24-Thu. INFLUENCE OF DAILY JOINT IMMOBILIZATION TIME FOR THE PREVENTION OF ANKLE JOINT CONTRACTURES IN RATS. *Takeya Ono, Japan*

RR-PO-302-12-Thu. DOSAGE-DEPENDENCE OF GRADED EXERCISE THERAPY IN PATIENTS WITH PATELLOFEMORAL PAIN SYNDROME A RANDOMIZED CONTROLLED CLINICAL TRIAL. *Berit Østerås, Norway*

RR-PO-304-4-Thu. EFFECTIVENESS OF LOW-LOAD ISCHEMIC RESISTANCE EXERCISE IN TREATING CHRONIC DISUSE ATROPHY OF KNEE EXTENSOR MUSCLES: A CASE REPORT. *Alan Kacin, Slovenia*

RR-PO-302-18-Thu. THE RELEVANCE OF FIVE MANUAL SHOULDER MANEUVERS USED TO IDENTIFY PATIENTS WITH SUBACROMIAL IMPINGEMENT SYNDROME. *Kajsa Johansson, Sweden*

RR-PO-303-18-Thu. THE EFFECTS OF REARFOOT POSITION ON LOWER LIMB KINEMATICS DURING BILATERAL SQUATTING IN ASYMPTOMATIC INDIVIDUALS WITH A PRONATED FOOT TYPE. *Amanda Clifford, Ireland*

RR-PO-303-2-Thu. THE LONG TERM OUTCOME OF A TWO-STAGED PHYSIOTHERAPY APPROACH TO THE TREATMENT OF PATELLOFEMORAL PAIN. *Marjon Mason, Australia*

RR-PO-303-12-Thu. MYOFASCIAL TRIGGER POINT PREVALENCE IN THE TRICEPS SURAE AND SPECIFIC DIAGNOSTIC CRITERIA IN A HEALTHY UNIVERSITY POPULATION; A CROSS-SECTIONAL STUDY. *Rob Grieve, United Kingdom*

RR-PO-303-6-Thu. ANKLE PROTECTION DURING AN INVERSION IS A TOTAL BODY RESPONSE. *Henk Nieuwenhuijzen, Netherlands*

RR-PO-303-8-Thu. INFLUENCE OF MECHANICAL PROPERTIES OF WATER ON MUSCLE ACTIVITY OF LOWER EXTREMITY AT STANCE AND SWING PHASES DURING WALKING. *Yoichiro Sato, Japan*

RR-PO-303-10-Thu. DYADIC INTERVENTION AND EDUCATION IMPROVE THE FLEXIBILITY OF HAMSTRING MUSCLE: A RANDOMIZED, CONTROLLED TRIAL. *Kiyokazu Akasaka, Japan*

RR-PO-303-16-Thu. EFFECT OF ELASTIC TAPING ON SHOCK ATTENUATION CAPACITY IN INDIVIDUALS WITH POOR-REBOUND HEEL PAD. *Jui-Chi Hsu, Taiwan*

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Quantitatively Measuring Proximal Plantar Fascia Microcirculation by Power Doppler Ultrasonography

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Purpose: To identify a quantitative method to assess microcirculation of plantar fascia (proximal insertion)

Material and Methods: Power Doppler ultrasonography (PDU) of the plantar fascia of 20 healthy subjects (aged 18-61 years old) was assessed by My Lab70 ultrasound unit (Biosound Esaote, Indianapolis, USA) with a 7.5-12MHz linear transducer. The region of interest (ROI) was defined as an area of 1.5cm * 1.5 cm centered at the calcaneal insertion of the plantar fascia. Five representative power Doppler images were acquired for each foot, and analyzed by a self-written software program (Mat lab 7.0.1). Microcirculation Index (MI) was expressed as a ratio of the number of pixels painted by PDU signals to the number of pixels of the whole ROI. Each subject was evaluated by 2 independent testers twice with 7 days apart.

Results: The intra-tester reliability was good with the average value of all five images (ICC =0.70, P<0.05), but not with the average of the firs three and the maximum value (ICC =0.65 and 0.62, p<0.05). The inter-tester reliability was fair (ICC =0.62, p<0.05)

Conclusion: Power Doppler ultrasonography demonstrates good test-retest reliability with the same tester using an averaged of 5 images. This method can be used to assess possible changes in microcirculation in patients with plantar fascillitis and effectiveness of treatment.

Materials and Methods: We scanned database of patients with superficial soft tissue masses from 2 different institutes. Lesions were evaluated on ultrasound and then confirmed surgically. 25 out of 431 masses were selected, of which initial interpretation was cystic or included cystic tumor and its pathology was solid tumor. All images were reviewed by two radiologists, regarding internal echogenecity of lesions, presence of posterior enhancement, margin, size, and internal vascularity.
Results: Twenty five masses were proven as benign fibrous histiocytoma (n = 2), fibroma and GCT of tendon sheath (n = 5), fibromatosis (n = 2), dermatofibrosarcoma protuberans (n = 2), dermatofibroma (n = 1), schwannoma (n = 4), angioleiomyoma (n = 3), granular cell tumor (n = 2), one of eccrine spiroadenoma, granulation tissue, lymphoma, myeloma. Masses were hypoechoic in 16 (homogenous in 10, heterogenous in 6), anechoic in 6 and isoechoic in 3. Posterior enhancement was present in 12 masses and 8 of them showed no internal vascularity on color Doppler images. Margin was smooth in 10, smooth with mild lobulation in 10 and lobulated in 5. Mean size was 2.09 cm.
Conclusion: Of cyst-like solid masses on ultrasound, fibrous tumor was the most frequent. Care should be given to these solid tumors that have cystic appearances even without internal vascularity on Doppler imaging.

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Ultrasonographic Diagnosis of Polyethylene Loose Body of Knee Prosthesis: A Case Report

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Polyethylene is an important component of knee prosthesis. Wear of polyethylene by long term repetitive force is a common complication of total knee replacement. However, because of radiolucent character of polyethylene, routine image tools usually don't provide correct diagnosis for its wearing.
Case Report: It was an 80-year-old lady who received surgery of total replacement of her both knees at 15 years ago. She visited the clinic with chief complaint of a mass at her left posterior knee. There was inflammatory sign with limited range of motion at her knee. Infection was suspected and antibiotics were given for 3 days before she was transferred to a medical center. Culture of the aspirated fluid from the mass was negative and the laboratory data was grossly normal. X-ray finding of her left knee was unremarkable and MRI depicted a 2.6 x 4.5 x 10.5 cm cystic mass. The mass was lobulated with much villi inside and PVNS or infectious bursitis was suspected. Much amount fluid with hypertrophy of synovial villi and hyperemia was noted under ultrasound. Furthermore, there was an 8 x 2 mm echogenic linear shape structure inside the mass and loose body from the torn polyethylene was highly suspected. After surgical removal of the mass, the pathologic report confirmed the diagnosis.
Conclusion: Ultrasound could detect small loose body from polyethylene in torn knee prosthesis while routine x-ray or MRI may not. Ultrasound is highly recommended as a routine image tool for follow up of the total knee replacement surgery.

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Power Doppler Ultrasonography and Stenosing Tenosynovitis

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Introduction: Power Doppler Ultrasonography (PDS) has been used to assess joint inflammation and tendonopathy. Stenosing tenosynovitis is a frequent disease associated with repetitive inflammation of the flexor tendon sheath in the finger.
Case Report: A 53 year old patient presented with stenosing tenosynovitis in the left and right ring fingers for 12 and 3 months respectively. This patient had pain and incidence of "triggering" during finger extension, in particularly, in the early morning. PDS signal showed mild hyperemia in the left but not the right side around the A1 pulley region. The PDS signal changed to moderate hyperemia on both fingers immediately after 3 weeks of extracorporeal shock wave therapy over the A1 pulley region on weekly basis. Substantial reduction in pain and incidence of "triggering" were reported in both fingers. The increased microcirculation flow returned to normal level after 6 and 4 months on the left and right fingers, respectively.
Conclusion: Changes in Power Doppler Ultrasonography signal were observed before and during the course of recovery in this case with stenosing tenosynovitis. PDS could be used to assess patients with stenosing tenosynovitis as well as treatment effectiveness.

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Sonography of the Hemiplegic Shoulder Undergoing Rehabilitation after a Recent Stroke

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Objective: The aim of this study is to determine the relationship between different motor function levels of hemiplegic shoulders and the clinical characteristics of stroke patients and to clarify the frequency of the surrounding soft tissue injuries in hemiplegic shoulders undergoing rehabilitation.

APPENDIX VII

Pre- and post-intervention pain score (visual analogue scale) of the affected heel of three groups in study 3 (Chapter 4)

	$ESWT_3$ (n=15)		$ESWT_6$ (n=16)		Control (n=15)	
	Pre-	*Post-*	Pre-	*Post-*	Pre-	*Post-*
1	8.70	9.90	7.20	7.70	4.80	8.70
2	7.90	7.80	9.80	9.50	3.50	5.40
3	6.70	6.30	5.10	4.70	3.30	4.60
4	3.70	2.60	5.70	4.80	5.80	6.80
5	6.80	5.50	7.25	6.10	8.00	8.50
6	7.20	5.90	9.70	7.80	3.30	3.20
7	7.80	6.40	7.50	5.30	6.30	6.00
8	5.20	2.10	6.00	3.20	7.40	7.00
9	3.30	.10	7.15	4.00	8.60	7.80
10	7.30	4.10	5.80	1.80	7.90	6.80
11	7.30	3.40	6.80	2.40	6.70	4.90
12	4.60	.40	7.50	2.20	8.00	6.00
13	5.20	.40	8.40	3.10	7.50	5.00
14	7.00	1.70	5.90	.40	6.90	4.10
15	6.30	1.00	8.60	3.00	9.00	3.90
16			9.60	3.90		
Mean	6.33	*3.84*	7.38	*4.37*	6.47	*5.91*
SD	1.59	*3.01*	1.50	*2.44*	1.93	*1.68*

*The more affected heel of patients with bilateral symptoms are presented.