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The medical management of patients with chronic plantar fasciitis

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The medical management of patients with chronic plantar fasciitis

By

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for the award of Doctor of Philosophy
of Loughborough University

June 2019

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The medical management of patients with chronic plantar fasciitis

Background

Plantar fasciitis is a common cause of under-surface heel pain with a lifetime prevalence of 10%, and arises from dysrepair of the plantar fascia leading to abnormal thickening and structure.(1-3) Whilst most cases will settle over 6-12 months, a significant proportion of patients will go on to have much longer symptoms.(4-6) A wide range of treatment options for patients with plantar fasciitis exist, with a variable evidence base for their use.(2, 7)

Methods

This thesis first reviews the evidence base for a range of treatment options for patients with plantar fasciitis. Following this review, the thesis describes of six clinical studies, involving nearly 300 participants, investigating the outcomes for patients with plantar fasciitis, who were treated in a single secondary care NHS hospital clinic in the UK, with three different interventions: Tension Night Splint (TNS), radial-Extra-Corporeal Shockwave Therapy (rESWT), or Autologous Blood Injection (ABI). Each intervention has a pair of experimental studies: a case series study, followed by a randomised controlled trial. Additionally, the results following rESWT and ABI are compared in a prospective cohort study using data from the interventional RCTs to assess if differences occur between these two, relatively new, interventions.

Results

Results are available from the three RCTs comparing the different studied interventions against control groups. Although a number of within-group differences were seen, the time*group ANOVA analyses for each of the three RCT studies has failed to demonstrate any significant differences between the intervention and control groups at any time-point studied.

Discussion

The results from the clinical studies presented here demonstrate significant improvements from baseline in a number of the outcome measures studied, however they did not show significant differences between the intervention and control groups in any of the three RCTs. These studies have failed to demonstrate effectiveness of any of these three treatments in the management of patients with chronic plantar fasciitis treated in this department which raises important questions about effective treatment options in this condition.

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Glossary of terms used

Term (Acronym)	Definition / explanation
Aponeurosis	Typically, this is a flat sheet of fibrous connective tissue comprised primarily of collagen that connects muscles with a wide area of attachment to bone in place of a tendon, or serves to separate adjacent muscles, and can be considered a sub-type of the “deep fascia”. This term is also sometimes used to describe the intra-muscular portion of a tendon inside skeletal muscle, which is also known as the “central” tendon, thereby differentiating it from the “free” tendon.(14-16)
Autologous Blood Injection (ABI)	An injection of (normally a small quantity) of the patients own blood, most typically to an area of damage of a tendon or other similar structure, used to promote a healing response.
Computerised Tomography (CT)	A CT scan (also known as a “CAT scan”) is a diagnostic test which uses x-rays to create a 3-Dimensional image of bodily structures, most commonly used to investigate bony architecture.
Dry needling / Dry needle fenestration	This term has variable usage in the published literature, from the use of acupuncture needle for (myofascial) trigger point release(17, 18) to the fenestration of tendons using a large gauge needle, designed to provoke low grade localised injury and acute inflammatory response.(19-21) For the purposes of this thesis, the latter i.e. the fenestration procedure is what is meant, using a needle to repeatedly puncture the plantar fascia potentially creating an acute inflammatory response as a stimulus for healing.
Eccentric (loading)	Eccentric loading exercises are a form of rehabilitation exercises where force is generated by a muscle as it elongates through a range of movement (such as heel drop exercises where gastrocnemius is under load as the calf muscle elongates.) This form of rehabilitation training typically requires a steady increasing volume of load by increasing the number of repetitions performed to stimulate tissue healing and recovery.

Enthesis	The organ of attachment of a tendon into a bone.
Extra-Corporeal Shockwave Therapy (ESWT)	The therapeutic use of high-energy pulsed acoustic waves generated outside the body and transmitted through the skin and structures to target a specific structure. These are thought to improve healing of a range of conditions including tendinopathy. This treatment exists in at least two forms, Focal-ESWT (F-ESWT) and radial-ESWT (rESWT) with differences in the propagated wave form, and how the wave is created.(13, 22) This modality is discussed in section 2.2.2
Fascia	Fascia is loose-connective tissue that surrounds skeletal muscles and organs. Although different classification systems exist,(23) at its simplest level fascia can be divided into two sub-types, that of superficial facia which is comprises of loose areolar tissue and adipose tissue that connects the dermis to the underlying deeper structures including the deep fascia. The deep fascia in a layer of often well-defined layers, and in the limbs forms fibrous sheaths around muscles and divide limbs into compartments. Fascia has historically been considered a passive structure, but recent evidence has suggested important roles in proprioception, pain perception, and force transmission linking adjacent skeletal muscles aligned along a series in a “kinetic” or “myofascial” chain.(24, 25)
Greater Trochanteric Pain Syndrome (GTPS)	A clinical condition characterised by pain of the lateral hip. Traditionally this has been referred to as “trochanteric bursitis” however in recent years the focus has moved away from the adjacent bursa to the insertion of the hip abductors, most typically gluteus medius. This is treated in similar way to other classical tendinopathies.
Heavy Slow Resistance (training programme) (HSR)	A form of rehabilitation exercises, typically performed 2-3 times per week, which utilises high loading forces, often about 80% of the 1-rep max limit, to stimulate healing of tendinopathy. See two papers by Kongsgaard et al (26, 27) for further information.

High-Volume Image Guided Injection (HVIGI)	An injection of a high volume of injectate, typically in the order of 50 mL for an Achilles tendon procedure, designed to inject between the tendon, paratenon and adjacent fat pad to reduce pain.
Isometric (loading)	The specific loading of a structure (typically a muscle-tendon unit) without the length changing.
Magnetic Resonance Imaging (MRI)	An MRI scan is a non-invasive diagnostic image which creates a picture of body tissue using a strong magnetic field and radio-waves, rather than ionising radiation. This is most commonly used to investigate soft-tissue architecture, and bone stress injuries.
Minimum Important (Clinical) Difference (MCID / MID)	The MCID (sometimes referred to as MID) represents the smallest change in a treatment outcome that an individual patient would identify as important and which would indicate a change in the patient's management.(28)
National Institute for Health and Care Excellence (NICE)	(previously the National Institute for Health and Clinical Excellence) Originally set up in 1999 to reduce variability in health-care, this government appointed body develops guidance and sets standards in health and social care in the UK. See: https://www.nice.org.uk/about/who-we-are
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	A class of medications, which act on the COX1 and COX2 pathways, that have specific analgesic and anti-inflammatory effects. Examples include ibuprofen, diclofenac, and naproxen.
Numerical Rating Scale (NRS)	A simple numerical score, typically scored 0 ("no pain") to 10 ("worst pain") which can be asked verbally or in written format to rapidly assess levels of pain.(29, 30) This has been found to have a very close association with the Visual Analogue Scale of pain (VAS), and both of which are superior to an alternative brief

	method of assessing pain, that of a four-point verbal rating scale.(31)
Pacinian corpuscle	Sometimes called Lamellar corpuscles, these are one of the four major types of mechanoreceptor cells in mammals, which are sensitive to both pressure and vibration. These were named after the Italian anatomist who first identified them, Filippo Pacini.
Patient Reported Outcome Measure (PROM)	These are tools that patients complete themselves, typically through such means as written questionnaire(s), which measure aspects of quality of life such as levels or pain or function. These are able to assess the quality of care delivered from the patient perspective. Nationally NHS England mandates the national collection of PROM data for patients undergoing hip or knee replacements (see: https://www.england.nhs.uk/statistics/statistical-work-areas/proms/) In addition a wide range of these tools are used in a number of different clinical and research settings to assess patient outcome following intervention. These are reviewed in section 2.3
Plantar fascia	This is a thick band of aponeurotic tissue which runs from the undersurface of the heel to the metatarsal heads, with attachments also to multiple other structures including the dermis layers, the flexor sheaths and the transverse metatarsal ligament into the dermis. Whilst not anatomically truly a tendon, it has certain properties of one, and is often treated in similar ways to other tendinopathies.
Plantar fasciitis	This is a condition in which there is dysrepair and pain from the plantar fascia. This name literally means “inflammation” of the plantar fascia, and so some authors use terms of plantar fasciosis, or plantar fasciopathy, which may better represent the histological findings and processes involved.(2)

Platelet-Rich Plasma injection (PRP)	An injection of a fraction of a patient's own blood, typically using a centrifuge to obtain a small fraction of plasma, that is thought to be enriched with platelets and growth factors but having have the red blood cells removed. Different propriety preparation techniques exist giving rise to different, and often unknown, concentrations of injectate with limited comparative evidence between different preparations.(32-35)
Prolotherapy	A therapeutic injection of a chemical (most commonly using high concentration dextrose) which creates a fibrotic reaction within the tissue, and is thought to strengthen/stiffen damaged ligaments and tendons.
Ruffini corpuscles / nerve endings	Also known as Bulbous corpuscles, these are a type of mechanoreceptor found in tissue, which are sensitive to stretch forces, and to heat sensation.
Research Ethics Committee (REC)	"A research ethics committee is a group of people appointed to review research proposals to assess formally if the research is ethical. This means the research must conform to recognised ethical standards, which includes respecting the dignity, rights, safety and well-being of the people who take part." See: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213753/dh_133993.pdf
Seronegative arthropathies	A diverse collection of autoimmune conditions causing inflammation and damage to joints, typically involving the axial and peripheral joints and entheses. These include psoriatic arthritis, ankylosing spondylitis, and the arthritis associated with inflammatory bowel disease. These can be mistaken for a mechanical insertional tendinopathy, particularly in the early stages which present with pain, before the onset of inflammation and tissue destruction.

Sport & Exercise Medicine (SEM)	A medical speciality, which has three main areas of special interest; the medical management of musculoskeletal disorders, the use of exercise as a therapeutic tool, and athlete/team care. See: http://www.fsem.ac.uk
Tendon	A highly-organised type of connective tissue, comprised predominantly of Type I collagen and much smaller quantities of elastin and cells, aligned in groups of fibres aligned proximal to distal, and which connect skeletal muscle to bone allowing force transmission.(8, 9, 16)
Tendinopathy	A group of disorders affecting a range of different tendons, resulting in a failed repair / dysrepair process, and with clinical signs of pain and dysfunction, most typically at the onset or during activity. An alternative which is sometimes used is “tendinosis”. There has been a shift away from “tendinitis” as this suggests an inflammatory-driven process.
Tension Night Splint (TNS)	A device, typically worn for a period of time during the night, which keeps a muscle-tendon unit under a degree of tension, and which is used to reduce symptoms for both plantar fascia / heel pain, and Achilles pain. These can come in a variety of forms either off-the-shelf, or custom-made. Examples include a prefabricated rigid boot, or a Strasburg sock.
Ultrasound / Ultrasound Scan (US / USS)	A non-invasive diagnostic investigation which uses sound waves to create two dimensional pictures of structures based on their reflective properties.

Visual Analogue Scale (VAS)	A measurement of pain which is formally undertaken by drawing a 10cm line, with “No pain” indicated at one end and the “Worst pain” at the other.(30, 36) The patient indicates their level of pain by making a mark on the line and this is measured in mm with the value indicating their current pain level, and this value is either reported as /100 or converted to /10. When compared to a four-part categorical pain scale, a VAS score of 3 or less relates to “mild pain”, more than 3 and less than 7 as “moderate pain”, and 7 or more as “severe pain”.(37, 38) The VAS is widely used due to its simplicity, but may be limited in older populations due to cognitive or motor impairments, and can only be administered face to face.(30)

Chapter 1 – Introduction

Plantar fasciitis is the most common cause of under-surface heel pain and is a very common condition with a lifetime prevalence of 10%.(1, 2) Whilst the majority of cases will settle over a period of six to twelve months, this condition can have a significant impact on a patient's quality of life during the time of their symptoms, causing significant pain and affecting mobility(39) and at least 10-20% of patients have ongoing symptoms that limit them beyond the one-year period.(4, 5) There is some evidence suggesting that this figure may be much higher and that the under-reporting of ongoing symptoms may be common.(6)

Plantar fasciitis most commonly affects people aged 40-60 years, it is slightly more common in women than men, and can affect both sedentary and active populations.(2, 40-43) Patients with plantar fasciitis typically report a gradual onset of pain on the medial aspect of the undersurface of the heel, which is normally most sore when they first start to weight-bear in the morning or after a period of sitting, with pain which can be unilateral or bilateral.(2, 40, 44) Like many tendon conditions, the pain of plantar fasciitis can often ease initially with some level of activity, but tends to be worse towards the end of a day or sometimes the day following activity.(7, 40, 45)

Predominantly plantar fasciitis can be reliably diagnosed clinically, based on its typical history and examination findings.(2, 46) The examination findings are commonly that of localised pain at the plantar fascia attachment to the undersurface of the calcaneus, often associated with calf muscle tightness and a reduction of ankle dorsiflexion.(2, 40, 44) Investigations such as ultrasound or MRI may have some use in ruling out other conditions, or in quantifying the extent of the plantar fascia thickness, but poorly correlate to the severity of symptoms or to prognosis.(2, 40, 46, 47)

The plantar fascia can be considered anatomically as a ligament, linking the calcaneus with the metatarsal heads and through this it has a role in supporting the longitudinal arch of the foot.(11, 48, 49) However,

functionally it also has similar properties to a tendon, allowing force transmission along a kinetic chain, and many treatments used in the management of patients with plantar fasciitis are the same as those used for treating established tendinopathies.(2, 50) There are a wide range of treatments which are commonly used for treating patients with plantar fasciitis. For early cases, simple conservative therapy such as a home exercise programme and insoles can reduce the pain and potentially support recovery.(41, 46) However, for the patients with more chronic symptoms a number of different treatment strategies exist, with a variable quality evidence-base.

This thesis first reviews the evidence for the treatment of patients with chronic plantar fasciitis, before investigating three different treatments that are used, these are: Tension Night Splints (TNS), Extra-Corporeal Shockwave Therapy (ESWT), and Autologous Blood Injections (ABI). In the United Kingdom, the National Institute of Health and Care Excellence (NICE) has previously given guidance for the treatment of patients with ESWT(51) or ABI(52), and in both sets of guidance the mixed-quality evidence base and areas of uncertainty were highlighted, and calls for further robust research were made. Given the limited, and often inconsistent, evidence base for these three treatments, and their use in clinical care, these three treatments were identified as worthy of further study.

The existing evidence for each of these treatments is considered in the background and literature review sections of this thesis (chapter 2). In this chapter the evidence that is available from primary studies (including case series, cohort studies and RCTs) is reviewed as well as the evidence from published systematic reviews and meta-analyses. Gaps in the published literature, or conflicting evidence from different studies are highlighted, identifying areas where evidence may be less certain.

This thesis contains data from three case series studies which examine each of these three interventions in routine clinical care. In addition, each of these three interventions is examined within formal randomised controlled

trials for the treatment of patients with chronic plantar fasciitis in an NHS Secondary Care Sports Medicine Clinic. This novel experimental data for TNS interventions are located in Chapter 5, for ESWT in Chapter 6, and for ABI in Chapter 7. Further direct comparison of the outcomes seen following either ESWT or ABI are presented in Chapter 8. A number of different outcome measures are used in the RCT studies in an effort to assess any changes not just in local foot pain, but other wider markers of quality of life, such as mood, sleep quality, and activity levels.

Chapter 2 – Background and literature review

This chapter examines the condition of plantar fasciitis with reference to the published literature. In this chapter, the nature and anatomy of the plantar fascia, its similarity and differences to tendons, and the role of the plantar fascia in foot stability and foot function are all presented. The evidence of the aetiology of plantar fasciitis and the different risk factors that may predispose to its development are reviewed, linking these where possible to rationales for treatment options. The evidence for a number of treatment options for this condition are evaluated, including commonly used options such as rehabilitation, orthotic insoles, corticosteroid injections or surgery, as well as other novel therapies such as hyaluronic acid injections, topical nitric oxide or radiotherapy. This chapter then specifically reviews in detail three different treatment options that are used in the experimental studies presented here: Tension Night Splint (TNS), Extra-Corporeal Shockwave Therapy (ESWT), and the injection of blood products such as Autologous Blood Injection (ABI). In addition to examining the different treatment options available, this chapter also presents evidence about how patients with plantar fasciitis can be assessed using a range of different outcome measures, some of which are subsequently used in the different experimental studies presented here.

2.1 - Introduction to plantar fasciitis and the plantar fascia

Plantar fasciitis is a common condition causing under-surface heel pain, resulting from chronic damage to the plantar fascia, which is a tough band of aponeurotic connective tissue in the sole of the foot.(2, 5, 46) The plantar fascia originates at the medial process of the tuberosity of the calcaneus in three portions (medial, central and lateral) and inserts in slips to the bases of each of the proximal phalanxes, (Fig 2.1) with fibres also blending with multiple other structures including the dermis layers, the flexor sheaths and the transverse metatarsal ligament.(45, 53-55) The central portion of the plantar fascia adheres to the underlying flexor digitorum brevis muscle, wrapping around this to form the medial and lateral intermuscular septae, and has important roles in intrinsic foot muscle structure and function.(54,

55) The medial and lateral portions of the plantar fascia are much thinner than the central band, and also serve as fascial coverings for the abductor hallucis and abductor digiti minimi.(56)

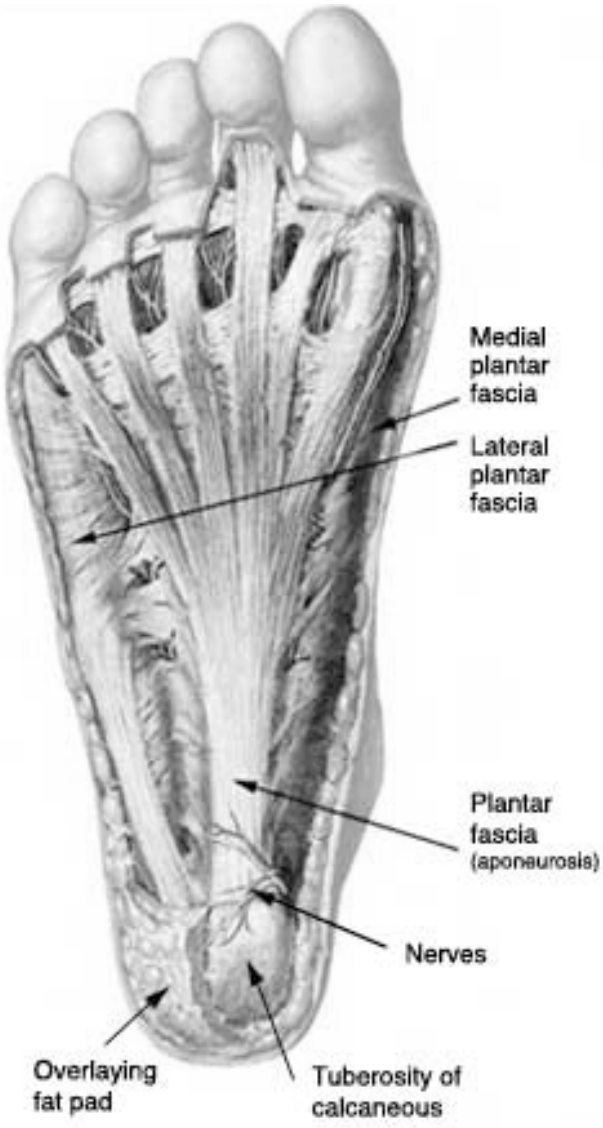


Figure 2.1: Anatomy of the plantar fascia

The plantar fascia is one of the main stabilising structures of the longitudinal arch of the foot absorbing strain forces, particularly during mid- and late-stance.(11, 48, 49, 57) Models suggest that the plantar fascia carries up to 14% of the total load on the foot during phases of the gait cycle.(58) The plantar fascia has a vital role in the “windlass effect”, with toe dorsiflexion causing tightening of the plantar fascia, which in turn causes a rise in the longitudinal arch and the depression of the metatarsal heads.(59) The plantar fascia is subject to tensile forces during weight-bearing, particularly

in late stance phase with dorsiflexion of the metatarsophalangeal joint, this tensile force causes elongation of the plantar fascia which subsequently contracts passively aiding propulsion during the gait cycle.(45, 59) In addition, at toe-off with the dorsiflexion of the toes, the plantar aspect of the forefoot is under significant compression and the tightening of the plantar fascia with its attachment into the skin layers tethers the skin to the skeleton, reducing shear-stress and giving protection to underlying nerves and blood vessels.(53, 55) In addition to this mechanical and force transmission effect, the plantar fascia is involved in proprioception and peripheral motor coordination and contains Pacinian and Ruffini corpuscles, which are sensitive to pressure, vibration, heat and stretch stimuli.(54)

Whilst the plantar fascia is not anatomically a classical tendon, as it does not solely connect muscle to bone, it has certain functional characteristics of a tendon including a role in force transmission, and plantar fasciitis is often treated in a similar manner as “true” tendinopathy conditions such as Achilles tendinopathy or tennis elbow.(2, 50) There are possible links between the plantar fascia and the Achilles tendon, both functionally and structurally. Originating as it does from the under-surface of the calcaneus, the plantar fascia can potentially be viewed as the functional end-point of the Achilles tendon, which is attached to the posterior margin of the calcaneus. Increasing tension in the Achilles tendon increases strain within the plantar fascia and this is believed to be a contributing factor to the development of plantar fasciitis.(60, 61) Additional evidence has shown that patients with plantar fasciitis have an increased likelihood of tightness of the hamstrings and calf muscle groups compared to those without plantar fasciitis.(62, 63) However the evidence is mixed and the direction of potential causality remains unclear.

At a microscopic structural level, superficial fibres directly connecting the plantar fascia to the Achilles tendon or tendon sheath have been found which persist well into adult life, although these decrease in elderly populations, and any significance of these fibres and their decrease during aging remains unclear.(54, 64) In addition, a cadaveric anatomical study has demonstrated the plantar fascia to be significantly thicker in patients

with co-existing Achilles tendinopathy compared to those without Achilles tendinopathy suggesting a link between these two conditions.(54) However, these findings have been challenged in a recent case-control study which identified that the plantar fascia was less thick at the calcaneal insertion, and there was a reduction in the size of the calcaneal fat pad, in patients with Achilles tendinopathy compared to controls.(65) These studies indicate a possible link between the plantar fascia and Achilles tendon, although possible confounders such as change in activity level in those with Achilles pain could contribute to thinning of the undersurface heel structures and so causality remains unclear.

The aetiology of various tendinopathy disorders has been studied extensively over the last decade, with a number of different causal factors being postulated rather than purely as a result of inflammation or mechanical overload. As a result of this research, there has been a move away from the previous title of “tendinitis” which suggested an inflammatory process to “tendinopathy” which represents the picture of a more degenerative process, with similar processes found in tendinopathies from different anatomical sites.(12, 66, 67) The same appears to be true for plantar fasciitis as histological findings in patients with chronic plantar fasciitis are typically that of myxoid degeneration, rather than those seen in inflammatory processes, and the development of plantar fasciitis is akin to an “over-use” or “under-recovery” type of condition, rather than a single acute injury.(2, 3, 7) Due to the lack of a predominantly inflammatory-driven primary process, this clinical condition is sometimes referred to as “plantar fasciosis” or “plantar fasciopathy” in some published works, and this mirrors the discussions in the published literature regarding classical tendons, described variably as “tendinitis”, “tendinosis”, and most recently “tendinopathy”.(68-70) In addition, the term “fasciitis” is itself questioned as the plantar fascia is closer to an aponeurotic structure (a broad sheet of connective tissue serving as an attachment to bone), rather than a true tendon or fascial structure.(45) However the phrase “plantar fasciitis” is used throughout this thesis as this remains the most widely used term, although the limitations of this term are recognised.(71)

- **Incidence and prevalence of plantar fasciitis**

Musculoskeletal (MSK) conditions as a group are one of the most common reasons for consulting primary care medical services, totalling one-fifth of all primary care consultations.(72, 73) It has also been found that 15% of the UK population in one primary care database had at least one current recorded musculoskeletal condition in their medical notes.(74) Musculoskeletal problems are common, have a high burden of disability across both developed and developing countries,(75-78) and are a common cause of loss of time from employment or lost productivity.(79) Whilst many musculoskeletal problems will settle, these conditions can also lead to chronic morbidity, with at least ten per cent of patients with plantar fasciitis or other tendinopathies going on to develop persisting symptoms of more than 12 months duration.(4, 41, 80, 81)

Plantar fasciitis is the one of the most common causes of under-surface heel pain with a lifetime prevalence of 10% and accounts for 8% of all primary care musculoskeletal consultations in the UK.(1, 73) There were an estimated 307million appointments in UK primary care Oct 2017-Oct 2018,(82) therefore from the previous research it is calculated that plantar fasciitis alone may contribute in excess of 4million primary care consultations each year in the UK. Plantar fasciitis is also common in other countries, with research that investigated the prevalence of lower-extremity tendinopathies in a Danish general practice population demonstrated that plantar fasciitis was the most common of these conditions, accounting for 39% of all lower-extremity tendinopathies, with an average of more than 30 new cases of plantar fasciitis each year in a typical Danish GP surgery of 5000 patients.(83) Research has previously identified that 10% of the population in the United States had reported previous symptoms of plantar fasciitis, with treatment costs of estimated between $192-376million in 2010.(84) Further recent research has estimated that in the USA just under 1% of the population reported having suffered with foot pain that was diagnosed as plantar fasciitis in the previous month alone, of which 25% had “severe” pain, 45% “moderate” pain, and 28% “mild” pain.(43) This is not a new phenomenon, with data from 15 years ago showing that patients

with new cases of plantar fasciitis accruing a total of approximately 1 million patient visits per year to healthcare professionals in the United States in 2004, with about two-thirds of these occurring in primary care.(41) Other tendon conditions are also common in the western world, with an annual incidence of presenting in primary care of 1.85 cases per thousand patients of Achilles tendinopathy,(85) and 4-7 cases per thousand patients for tennis elbow.(86)

Plantar fasciitis and other tendinopathies affect both sedentary and active populations, and are one of the most common running-related musculoskeletal injuries. Runners have an incidence of between 4.5-10% for plantar fasciitis, with a point prevalence of 6.2-9.5%, compared to an incidence of 9.1-10.9% for Achilles tendinopathy.(87) Runners have a 30-fold increase in risk of developing Achilles tendinopathy below the age of 45 compared to non-runners, with comparable figures not available specifically for plantar fasciitis.(88) Other tendinopathies are also common in active populations, with patella tendinopathy affecting 2.4% of elite soccer players each year corresponding to an incidence of 0.12 injuries/1000hours, often with a high recurrence rate in elite athletes.(89) Recent work performed at the Rio2016 Olympic Games highlighted the high incidence of a number of tendinopathy conditions in elite competing athletes, with the most commonly reported conditions including tendinopathy of the rotator cuff, Achilles or patella tendons, and with Track and Field athletes having the highest incidence reported.(90)

There are a number of similarities and differences between plantar fascia and tendon across aspects of structure, function, and pathology. These are discussed in the next sections.

- **Tendon histology – similarities and differences to the plantar fascia**

Tendons are found throughout the body, linking skeletal muscle to bone to allow movement and function. Tendons have a very low metabolic rate, which is more than 10-fold lower than skeletal muscle, and have a highly specialised anaerobic capacity enabling tendons to undertake prolonged

ischaemic load tolerance, which comes at the cost of slow rates of healing post-injury for tendons and the plantar fascia.(91-94) Living tendons contain approximately 70% water content, with the remaining dry mass being made up predominantly of Type I collagen (60-80% dry mass) and much smaller quantities of elastin (about 2% dry mass) and cells.(9) In comparison, the dry mass of the plantar fascia is also made up predominantly of Type I collagen, arranged mainly in a proximal to distal direction, with a small amount of Type III and Type IV collagen located mainly at areas of looser connective tissue where different directions of force exist, such as the perimysium of the plantar muscles.(54, 95) In addition there is the presence of some elastic fibres and the glycosaminoglycan hyaluronan in the plantar fascia.(54)

Recent histological work has identified fibre and cellular differences between plantar fascia in the central region (the “core”) and that of the surrounding region (the “sheath”).(95) There is the presence of loosely organised thin mesh-like cross-linked collagen fibres and blood vessel-like tissue present in the sheath, however the structure of the core showed an absence of blood vessels, and had densely-packed collagen fibre bundles aligned in a well-organised structure with similarities to tendon structure.(95) There were also differences in the stem cells derived from these two locations of the plantar fascia, with those within the sheath regions growing faster, forming larger colonies, and maintain stemness compared to those from the core region.(95) In addition there were differences in the subtypes of collagen in the two regions, with a higher proportion of collagen-I in the core, and increased collagen-IV in the sheath regions of the plantar fascia.(95)

- **Tendinopathy histopathology – similarities and differences to plantar fasciitis**

There are common histopathological findings found across a range of tendinopathy conditions. These include an increased number and abnormally shaped, often rounded, tenocytes which show signs of oxidative damage, an accumulation of water, proteoglycans and glycosaminoglycans (GAGs), plus collagen fibre thinning and disorganisation.(50, 96-100) There

is a greater proportion of Type III collagen seen in tendinopathy samples compared to healthy tendons, along with increased expression of fibronectin, tenascin C, aggrecan and biglycan.(50, 101, 102) Tendinopathy samples from a range of tendinopathy sites typically demonstrate features of disorganised and ineffective healing, and the balance between the effects of the matrix metalloproteinases (MMPs) involved in remodelling the extracellular matrix of tendons and the tissue inhibition factors is thought to be important, though poorly understood.(96, 101) There has also been found to be a significantly higher rate of apoptosis in the cells of injured rotator cuff tendons and patella tendinopathy, compared to healthy tendons when compared to uninjured tendons.(97, 103) Although the histopathology of plantar fasciitis has not been as well studied as that of tendinopathies, in patients with plantar fasciitis there are similar histopathological features to those seen in tendinopathies, with features of degeneration, angiofibroblastic proliferation, matrix calcification, and collagen necrosis.(3, 104-106)

The early pathophysiological processes in tendinopathy were modelled in rabbit tendons in a repeated loading pattern and were found to contain micro-tearing which it was thought could be the start of a degenerative process.(107) This mechanical overload is identified in a range of tendinopathies although the combination of adverse loading conditions including duration, magnitude and frequency remain poorly defined,(108) with uncertainty as to whether there is an over-stimulation or under-stimulation of tendon cells which provide the initial triggers for the development of tendinopathies.(109)

As well as the disorganised structure seen with tendinopathies, there is often an increase in surrounding microvessels which often penetrate the abnormal tendon, this is termed neovascularity.(110, 111) This neovascularity has been thought to correlate with pain and is a potential target for therapies as it is proposed that the ingrowth of new blood vessels brings with it neural structures associated with pain sensation that a range of therapies can target to facilitate recovery.(112, 113) Two reviews however have reported that the extent of neovascularity did not have any

additional diagnostic or prognostic value as they did not correlate with pain, only weakly associated with a functional scale measured in patients with Achilles tendinopathy on the VISA-A scale, and did not correlate with treatment outcomes reliably.(114-116) This neovascularity that affects some patients with chronic Achilles and Patella tendinopathy has not been as regularly identified in patients with plantar fasciitis,(117) and any implications of this remain unclear, although histologically the presence of blood vessel-like tissue has been found in the periphery (the “sheath”) of the plantar fascia.(95)

- **Tendon architecture and biomechanics – similarities and differences to the plantar fascia**

Typically tendon structure is comprised of highly organised collagen fibrils into groups of fibres, which are grouped into primary and then secondary and tertiary fibre bundles, which make up the main tendon unit structure, this sub-structure is displayed in Figure 2.2, taken from Galloway 2013.(8)

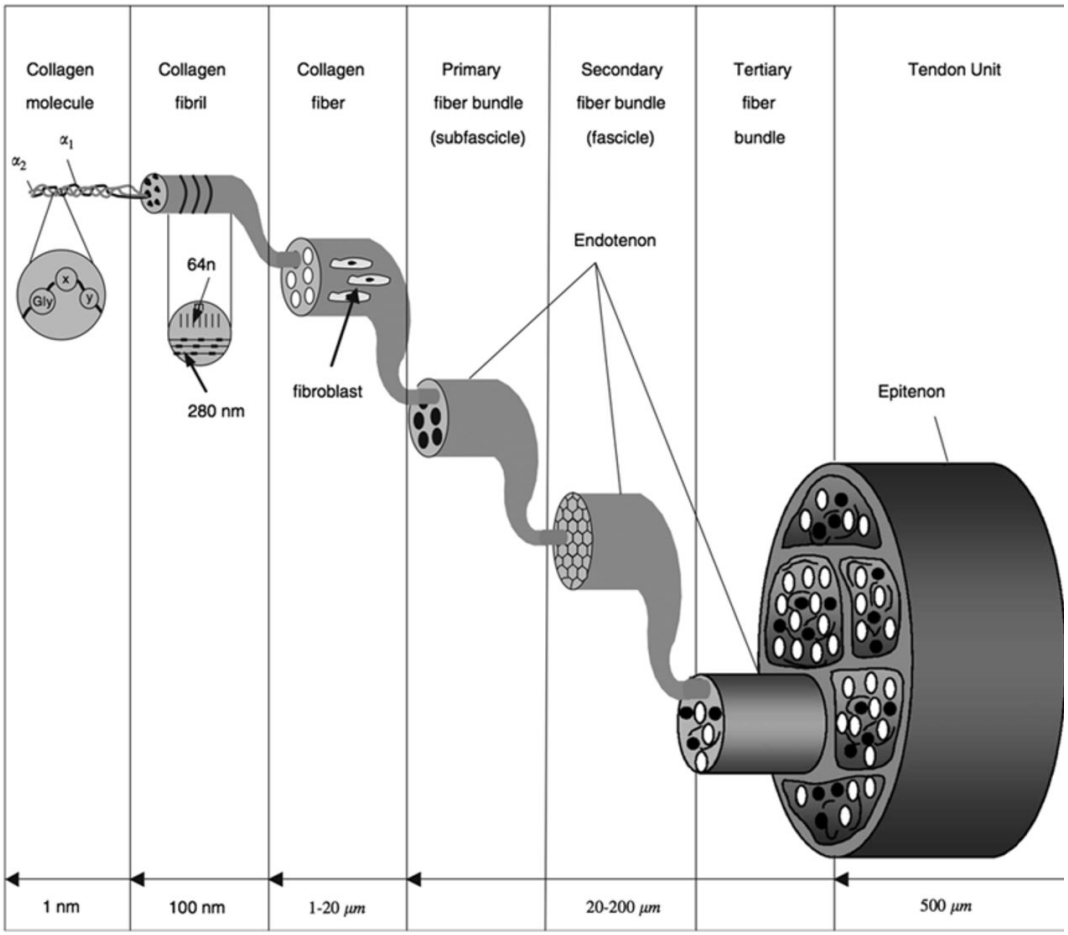


Figure 2.2: The structures of tendon architecture – from Galloway 2013 (8)

The plantar fascia structure and its connections differ from those seen in tendon structure. Macroscopically, the plantar fascia is composed of three bundles where the plantar fascia originates from a tuberosity on the plantar aspect of the calcaneus.(Fig 2.1) The plantar fascia, in particular in the "core" region, has densely packed collagen fibres laid predominantly in a longitudinal axis along the foot from proximal to distal.(42, 54, 95) These collagen fibres are firmly attached to the superficial muscles of the sole of the foot at the proximal part, and there are also several intermuscular and intramuscular septae originating from the inner aspect of the plantar fascia and extending into the deep fascia of the foot giving multiple connections, rather than just a single muscle-bone interface seen with a classical tendon.(54) The various muscle insertions of the plantar fascia have been suggested to facilitate the coordination of the different superficial and deep muscles of the plantar aspect of the foot.(54)

Tendons connect muscle to bone, and both transmit and withstand forces during muscle contraction. Whilst tendon architecture is similar in a range of different locations, tendon properties such as their stiffness, cross-sectional area and the sliding mechanics between fascicles vary greatly between tendon sites, suggesting that they are specialised for different activities.(118) The precise mechanisms by which they withstand force is poorly understood but are thought to involve crimping and de-crimping of the tendon microfibril structure.(119, 120) Without load applied, collagen fibrils and fibres exist in a crimped configuration, which de-crimp when load is placed upon the tendon. Tendons have viscoelastic properties displayed by a non-linear stress-strain relationship. There is an initial concave stress-strain relationship in the elastic "toe phase" (phase I) as the collagen initially de-crimps which occurs up to about 2% strain, after this point, de-crimping has already occurred and tendon structure deforms in a more linear fashion in an elastic capacity up to about 4% strain (Phase II), beyond 4% strain microscopic damage occurs, with macroscopic failure occurring beyond 8-10% strain (Phase III) which varies depending on a range of individual

factors including age.(9, 119-124) Figure 2.3 is from Sharma 2005 (9) and displays this stress-strain relationship of tendons. The extent of deformation is also dependent on the rate at which the external load is applied, with a more gradual increase in load allowing time greater time for tissue to adapt and deform to a larger extent, compared to more rapid increases in load.(50)

Although having some behaviour and functions similar to that of tendons, the plantar fascia is believed to mechanically respond differently from tendons under strain conditions. Work performed 50 years ago demonstrated the modulus of elasticity of the plantar fascia increased with greater load, and this is displayed in figure 2.4 (from Wright 1964 (10)) demonstrating the stress-strain curve for the plantar fascia compared to the fascia latae. Further in vivo studies have demonstrated that the plantar fascia undergoes continuous elongation from the stand-stance to the toe-off phases of the gait cycle, reaching deformation of between 9-12% during normal gait, which is greater than that seen in tendons.(125)

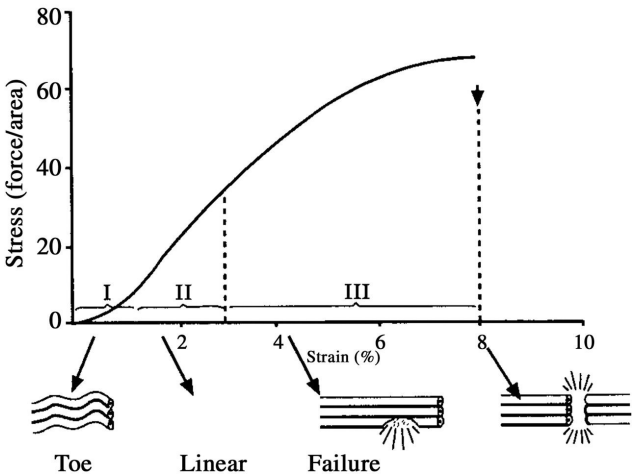


Figure 2.3: Stress-strain curve for Achilles tendon – from Sharma 2005 (9)

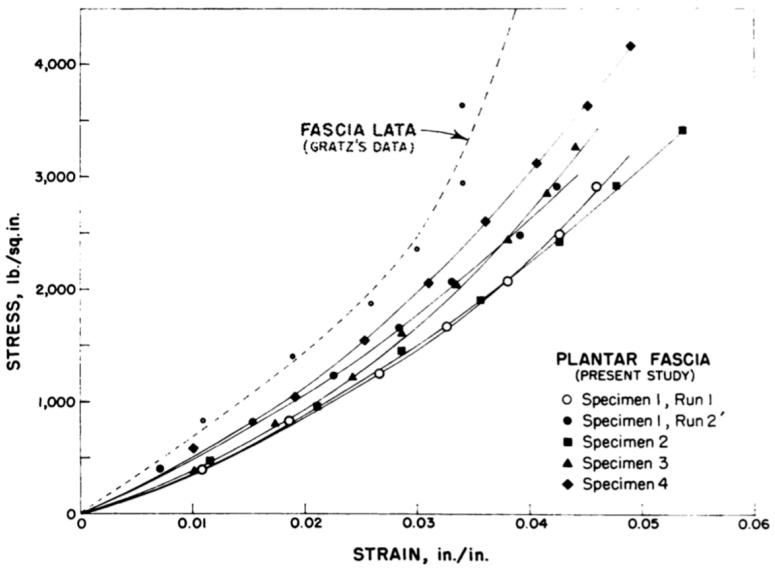


Figure 2.4: Stress-strain curve for plantar fascia – from Wright 1964 (10)

Biomechanical testing in vivo of the tibialis anterior tendon in healthy individuals demonstrate that, during normal physiological loading, tendons operate predominantly within the elastic “toe” region of the stress-strain curve.(126) During active loading the length change of the tendon unit greatly exceeds that of the aponeurosis, suggesting that this may transfer force onto the tendon which lengthens absorbing the elastic energy which is released during unloading.(127) This demonstrates that the stress-strain curve modelled above (Fig 2.3) may only relate to the tendon architecture itself, and other tissue types need to be considered in vivo. Furthermore, this stress-strain curve relates to a single bout of loading, and whilst tendons can be injured either suddenly, such as overstretch injury or mechanical trauma, they can also develop a chronic pathological state of tendinopathy, which is akin to a delayed or poor healing from repeated minor injury.(100)

Unlike tendons, the plantar fascia demonstrates a more linear relationship between the load and the amount of deformation that ensues.(11) Figure 2.5 demonstrates that after 0.6 mm of deformation there is a linear relationship between force applied to the plantar fascia and the amount of resulting deformation.(11)

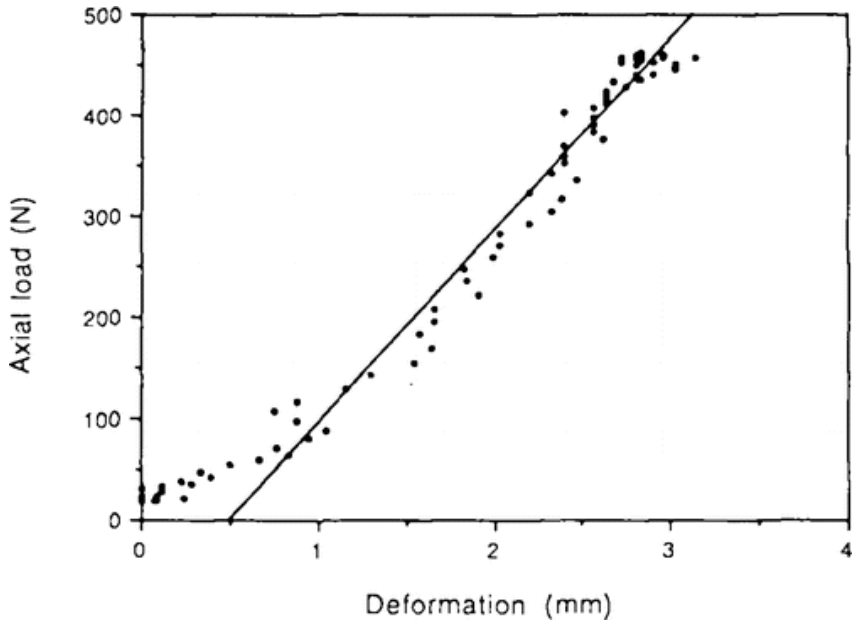


Figure 2.5: Load-deformation curve for plantar fascia – from Kitoaka 1994 (11)

The precise mechanism of this elastic deformation is unclear as anatomical studies have shown relatively few elastic fibres within the plantar fascia itself.(54) The collagen and elastic fibres in the plantar fascia are present in the form of longitudinal strands and wavy bundled networks, which change orientation from wavy to straight under load conditions.(56) Work has theorised that the elastic and collagen fibres in the plantar fascia are aligned in such a way that the elastic fibres are subjected to early stress and the collagen fibres later stress, causing the combined elastic modulus seen for the plantar fascia as a whole.(10, 55) Therefore, whilst the plantar fascia has certain tendon properties and plantar fasciitis is often treated in similar ways to tendinopathies, it is clear that some differences in mechanical function may exist. However, if this may relate to a clinical impact in the response to treatments compared to that seen in other tendinopathy conditions remains unknown.

As well as the de-crimping effect of loading on collagen fibres, the mechanical loading of tendon results in an up-regulation of collagen production, mediated by the amount of strain that the fibroblast cells are subject to, and this effect peaks 24-hours after exercise, but remains raised for 72-hours.(96) Rehabilitation programmes using graded loading, such as

eccentric/concentric ± isotonic that are commonly used in patients with Achilles and Patella tendinopathy tend to have a maximum of a once-daily or alternate-daily loading period and then a recovery period, during which other exercise forms may be undertaken.(128) This approach may give more of a difference between the tendon loading and recovery phases which may promote recovery, however further research is needed in this area to optimise rehabilitation programmes and also to study whether similar upregulation that has been demonstrated in tendon disorders is seen in patients with plantar fasciitis.

- **Tendons and response to mechanical load**

Tendons respond to load placed upon them, although the rate of adaptation may depend on the volume, intensity, frequency and duration of load as well as age, individual and genetic factors.(129-132) Under low-tensile loading conditions, both the muscle and tendon are elongated, and during active loading conditions the rate of elongation of the free tendon exceeds that of the aponeurosis highlighting the elastic storage of energy within the tendon itself.(127)

Achilles tendons have been shown to undergo significant hypertrophic changes during a six-month elite infantry training period,(133) representing evidence of the adaptation of tendons in this training model. However as athletes with a unilateral patella tendinopathy have been found to have a larger and stiffer tendon on the affected side compared to their non-affected side,(134) tendon pathology cannot be reliably determined from the hypertrophy alone. The magnitude of load is suggested as the key determinant of tendon adaptation, with an increase in tendon stiffness induced as an adaptation to load.(135) It is not known if the same increase in stiffness seen in tendons as an adaptation to load is seen in the plantar fascia, which has not been as well researched currently as other tendon conditions.

A clinical pathology model of tendinopathy was proposed in 2009 and the development of tendinopathy was proposed as being related strongly to mechanical (over)load and failure of tendon adaptation to this load.(12) This

model included a “reactive tendinopathy” phase involving a non-inflammatory proliferative response in the cellular components and matrix structure of tendons, with an abnormal thickening of the tendon, with a potential to advance to tendon dysrepair or resolve depending on internal and external factors. This model also proposed a weakened “stress-shielded” tendon state, which was a result of lack of loading, and which was susceptible to damage from forces that were considered normal due to a loss of its inherent robustness.(12) Figure 2.6 displays this tendinopathy model in graphical form.

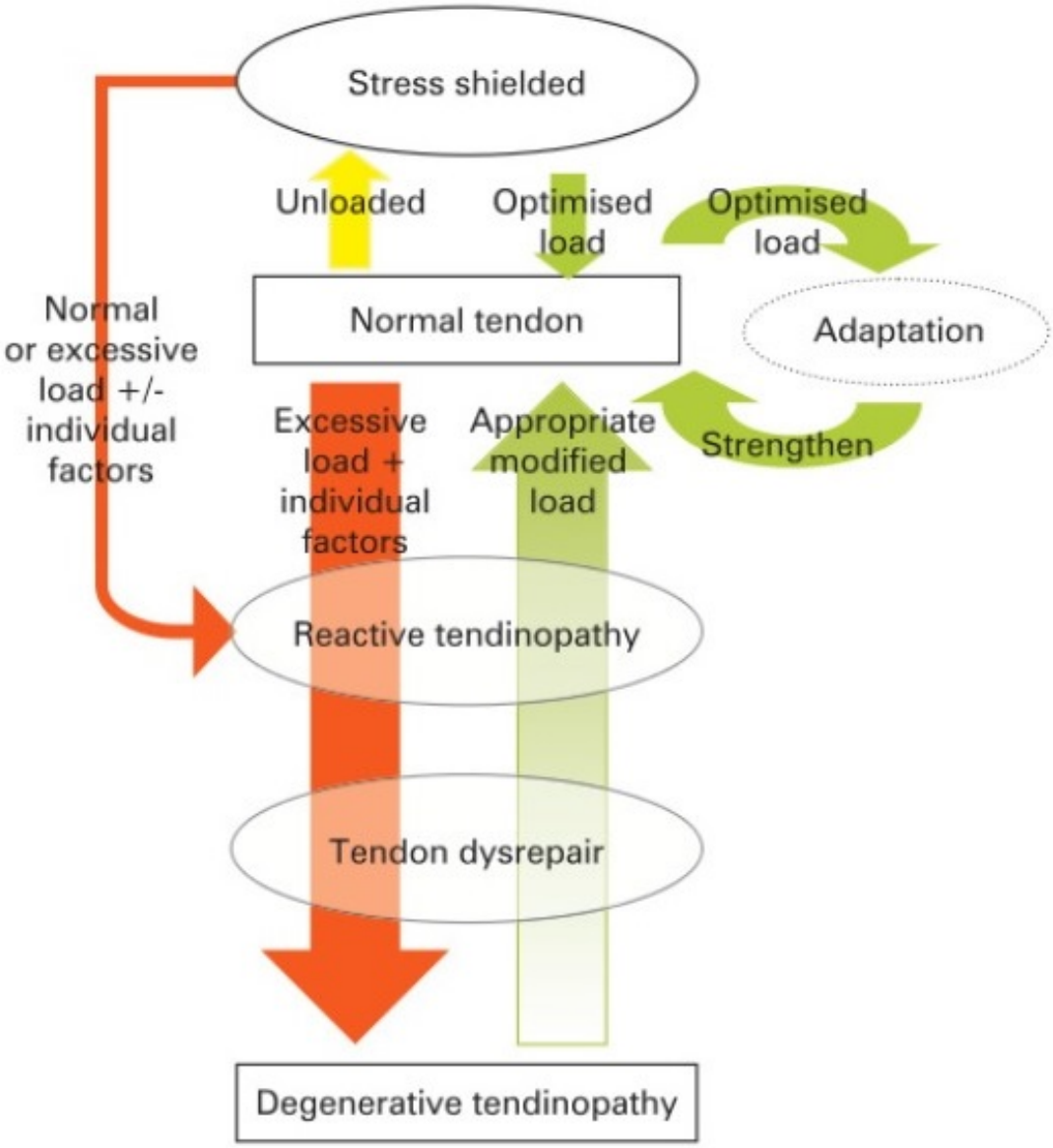


Figure 2.6: Tendinopathy continuum paradigm - from Cook 2009 (12)

This model demonstrates the transition from “normal tendon” through stages to “degenerative tendinopathy” and highlights the potential for reversibility, although this is thought to be more likely to possible only early on rather than once degenerative tendon dysrepair has occurred.(12) Whilst this model has been specifically developed for classical tendinopathies, failing the existence of a more specific model, this could have application in the development and management of plantar fasciitis, although uncertainties remain.

A subsequent review by the authors of the “tendinopathy continuum model” discussed not just the tensile forces which cause the maladaptation leading to tendinopathies, but also that tendons are subject to compressive forces which may be implicated in the development of tendinopathy.(136) Initial suggestions highlight that many of the insertional tendinopathies, such as insertional Achilles tendinopathy which affects the enthesis (the insertion of tendon into bone) are subject to compression in certain positions, whereas mid-substance tendinopathy (such as a mid-substance Achilles tendinopathy) may be subject to internal compression from an internal tendon shear force between tendon bundles from the two different calf muscles. The plantar fascia, arising as it does from the undersurface of the calcaneus, is highly subject to compressive forces during weight-bearing. The authors conclude that reducing compression load on a tendon, may be as important as reducing tensile load, and give some clinical suggestions of how this can be done in clinical practice.(136) This reflects earlier work that suggested that certain joint positions were more likely to place tensile stress on the areas of the tendon affected by tendinopathy, and proposed that alternative rehabilitation positions could load these vulnerable areas more uniformly.(137)

However the model of a tendon as a single viscoelastic structure is believed to be too simplistic, as work has shown that the free-Achilles tendon and the proximal Achilles tendon are placed under differing amounts and directions of strain during contraction of the calf muscle complex, with the proximal Achilles tendon in particular being placed under transverse as well as longitudinal strain from the action of the muscle contraction.(138) The

plantar fascia is subject to strains in multiple directions, as demonstrated by the collages fibre alignment lying predominantly proximal to distal, but with fibres also aligned obliquely, transversely and vertically.(42) From its position on the under-surface of the foot, the plantar fascia is also subject to significant compressive forces from body-weight and ground reaction forces. How these different forces may relate to pathology or treatment remains unclear.

- **Inflammatory model**

The role of inflammation and chronic tendon disease has been controversial, with evidence coming full circle since the early days of "tendinitis", to discarding the role of inflammatory pathways, to newer evidence that suggests inflammation may play an important role in the development of tendinopathy after all. An alternative to the "mechanical loading" hypothesis model suggests that whilst tendinopathy is not primarily inflammatory-driven as had been historically suggested with the term "tendinitis", the role of various inflammatory mediators may remain very important in the development of tendinopathy. A review has highlighted the changes in the perceptions of causality of tendinopathies over time, and that recent advances had demonstrated the presence in tendinopathy samples of macrophages, both T- and B-lymphocytes, as well as macrophage-derived Interleukin-1 (Il-1), Cyclo-Oxygenase-1 (COX1), COX-2, IL-6, Transforming Growth Factor-B (TGF-B), and increased Substance-P.(66) These are all part of the inflammatory cascade, and their presence suggests that the inflammatory response is a key component of tendinopathy.(66) Additional work in patients with Achilles tendinopathy and hamstring tendinopathy has shown increased expression of CD14+ (e.g. monocytes) and CD68+ cells (e.g. circulating macrophages) and the increased expression of various interferon target genes in both tendinopathic and ruptured Achilles tendons compared to healthy tendon controls.(139)

Research has shown that there is the presence of various inflammatory and angiogenic proteins in both tendinopathic and ruptured Achilles tendons, further strengthening the argument that inflammatory processes play an

important, if not well understood, process in the development of some tendinopathies.(139) This differs from work performed in shoulder rotator cuff tears which did not show the same angiogenic markers seen in those with Achilles tendinopathy,(140) which suggests that differences may exist between different tendinopathy sites. The plantar fascia has not been as extensively studied as certain tendinopathies have, and it is not clear if the same mediators may be present in plantar fasciitis. However in vitro histological studies have demonstrated that under mechanical overloading conditions the cells within both the core and sheath regions of the plantar fascia underwent inflammatory and catabolic responses, including an increased production of IL-6 and PGE_2.(95) The research demonstrating a role of the inflammatory pathways in patients with certain tendinopathy conditions could potentially guide alternative therapeutic strategies in managing plantar fasciitis and tendinopathies in the future.(141)

- **Other aetiological models**

A further concept is that of tendon hyperthermia, in which tendons become damaged due to heat build-up within the tendon core from stresses and mechanical strain during use. Conservative mathematical modelling has calculated that the core of the Achilles tendon could reach up to 41 degrees Celsius during running from the forces transmitted through the tendon, which may be sufficient for tendon hyperthermia to be a direct cause of tendon injury, or be one of a number of contributory factors in the development of tendon injury.(142) However, clinical work has not yet been performed to confirm this hypothesis and if proven how this could be best managed.

Separate from the mechanical-models, such as the tendinopathy continuum model by Cook (12) and the inflammatory-models, is the concept that some patients with chronic musculoskeletal disorders may have either a central or peripheral sensitisation component to their symptoms with a disordered pain sensation process being a part of the symptoms.(143, 144) However there is conflicting evidence for the existence of this concept in patients with tendinopathy conditions.(145) One study in patients with Achilles tendinopathy found no evidence of neural sensitisation in the participants

that they studied, however this was a small study of only 8 patients and 8 control participants.(146) Another point-prevalence study found that of more than 280 patients with chronic lower limb tendinopathy, including 126 with chronic plantar fasciitis, 28% of the overall group (including 29% of the patients with chronic plantar fasciitis) were suggestive of having a neuropathic pain component using the painDETECT questionnaire.(147) Subsequent work has suggested that Central Sensitisation may play a role in 24% of patients with chronic plantar fasciitis using the Central Sensitisation Inventory (CSI), which is a similar proportion to patients with Greater Trochanteric Pain (GTPS), and is higher than that of patients with chronic Achilles tendinopathy.(148) However the high false positive rate from this questionnaire is recognised and so some caution with this figure may be required.(149) Recent research involving patients with Achilles or Patella tendinopathy has found alterations in pain sensation locally, but not remotely, in patients with tendinopathy suggesting that tendinopathy may be associated with a peripheral rather than centralised pain state (150), however the limited research in this area makes this an area in which further work is required for clarification, and any impact this could have on treatment outcomes.

- **Risk factors for the development of plantar fasciitis**

The development of plantar fasciitis and other tendinopathies is often multi-factorial although soft-tissue tightness, particularly that of the posterior chain (hamstrings and calf muscle groups) is an important consideration in patients with plantar fasciitis, both as a possible contribution to causality and to consider in treatment planning.(2, 44) Poor flexibility of the hamstrings and calf muscle groups has been shown to be significantly more frequent in patients with plantar fasciitis compared to those without.(62) A prospective cohort study has demonstrated that patients with hamstring tightness as assessed by popliteal angle measurements were more than eight-times more likely to experience plantar fasciitis, although this was an association and causality was not proven.(63) One study has specifically highlighted the importance of calf flexibility, and has concluded that a reduced range of ankle dorsiflexion is one of the most significant risk factors for the development of plantar fasciitis.(151) Further work has shown a very

strong association with isolated gastrocnemius tightness as assessed by the Silfverskiöld test(152) and plantar fasciitis when comparing patients with plantar fasciitis to those with other foot/ankle pathology and also those without any foot/ankle pathology.(153, 154) Additional work has demonstrated strong associations between a reduction in ankle dorsiflexion or reduced first metatarsophalangeal joint (MTPJ) movements and the development of plantar fasciitis.(44, 155)

Given this body of evidence, the role of muscle tightness in the posterior muscle chain, including gastrocnemius, soleus and the hamstring muscle groups, is an important consideration in the management of patients with plantar fasciitis.(2, 45, 156) This tightness may be modified either from stretching or potentially through the use of devices such as the Tension Night Splints (TNS). This latter treatment is investigated in Chapter 5.

In addition to soft-tissue tightness, the development of plantar fasciitis may have multiple different and overlapping risk factors. One prospective study which involved Thai military conscripts undergoing 10 weeks of military training has shown multiple different risk factors predisposed to the development of plantar fasciitis, these included a higher body mass index, those with a lower degree of femoral anteversion, those with poorer levels of control of movement, and those with lower levels of physical fitness prior to conscription.(157) A leg-length discrepancy has been postulated as a risk for the development of plantar fasciitis,(158) although the significant issues with poor intra-observer and inter-observer error in these measurements makes this risk factor subject to question.(159, 160) Other work has shown that an overpronated foot position may predispose to the development of plantar fasciitis(161), potentially giving an important role for orthotics in managing this condition.

In addition to mechanical factors in the development of plantar fasciitis or tendinopathies, other factors including metabolic factors may play an important role. Plantar fasciitis can affect sedentary individuals as well as active individuals, suggesting that mechanical overload itself is not the sole causative issue and other factors may need to be considered.(2, 40) Other

intrinsic risk factors that have been shown in the development of plantar fasciitis or tendinopathy include: obesity, hypertension (associated in female patients only), and diabetes mellitus.(155, 161-167) One systematic review of risk factors for the development of plantar fasciitis has shown an association between higher BMI (not just those who are obese) and plantar fasciitis, and highlighted that this specific risk factor could be from mechanical loading, or from a metabolic influence, or possibly both.(155) Other research has demonstrated an increased proportion of patients with Achilles tendinopathy have clinically significant dyslipidaemia compared to matched controls, suggesting that a range of metabolic factors may have an influence on the development of tendinopathy,(168) however similar work has not yet been undertaken in patients with plantar fasciitis. Psychological factors may also be important, with research demonstrating an association between symptoms of depression, anxiety and stress, and the presence of plantar aspect heel pain, however the temporal nature of this relationship remains unproven.(169)

In addition to these intrinsic and extrinsic risk factors, various medications have been specifically linked to the development of different tendon disorders, including tendinopathy and plantar fasciitis. One group of medications which has been specifically linked to the development of tendinopathy are the fluoroquinolone antibiotic group of medications, which have been shown to have an association with an excess risk of 3.2 cases per 1000 patient years, and this impact appears to be greatest in patients over the age of 60, in patients who are taking corticosteroids, or in patients with co-existing diabetes or renal impairment.(170-172) This effect appears to be from a direct toxic effect on collagen fibres and is independent of medication dose.(170-172) In the United Kingdom, the Medicines & Healthcare products Regulatory Authority (MRHA) have recently issued updated restrictions and precautions regarding fluoroquinolone antibiotics.(173) This guidance highlights the risk of disabling and potentially irreversible adverse reactions from this class of antibiotics including the development of tendinopathy or tendon rupture, and advises prescribers to advise patients stop taking these treatments at the first sign of tendon pain or inflammation, and advises against co-administration with corticosteroids

and in caution with those over 60 years or, those with renal impairment or with solid-organ transplants as these can increase the risk of tendon injury.(173) In addition to fluoroquinolones, the statin class of medications (including atorvastatin, simvastatin, pravastatin, fluvastatin and rosuvastatin) appear to have a small increased risk of the development of tendinopathy, most commonly in the first year of medication use.(174) For women, both the oral contraceptive pill (OCP) and hormone replacement therapy (HRT) have been found to increase the risk of the development of tendinopathy, although the absolute risk remains unclear.(162) Careful consideration therefore must be given in clinical practice about the medications that are used in people most at risk of developing tendinopathy or plantar fasciitis, and also in those patients who already have these conditions.

- **Plantar fasciitis and Baxter's neuropathy**

Heel pain may be associated with local nerve compression, including entrapment of the first branch of the lateral plantar nerve (the inferior calcaneal nerve), which is often called Baxter's neuropathy.(175) This is far less common than plantar fasciitis, and has symptoms which tend to be more proximal and medial and which may worsen with eversion of the foot.(176) Multiple aetiological factors have been proposed for this nerve entrapment, and a study which examined MRI evidence of abductor digiti minimi atrophy (ADMA) as a sign of peripheral nerve entrapment demonstrated significant association between plantar fasciitis and ADMA, and suggested a possible aetiological role of plantar fasciitis in the progression to Baxter's neuropathy.(177)

- **Plantar fascia and radiographic heel spurs**

The presence of a radiographic heel spur remains a controversial topic, with clinical opinion about its significance (or lack thereof) changing over time. Radiologically, plantar aspect calcaneal spurs have been found in 66-89% of patients with plantar fasciitis (178, 179) and in 40% of patients presenting with Achilles tendinopathy.(180) However plantar spurs were also found in 16-32% of normal asymptomatic populations,(178, 179) and so the significance of the presence of a calcaneal plantar spur remains unclear

and many researchers now regard this as an incidental finding.(45) One case-control study has found that patients with a spur visible on lateral x-ray had more foot pain and worse function (as assessed by the FAOS) compared to those without a spur, even when patients with plantar fasciitis was excluded.(181) Furthermore the cohort who had a heel spur had a higher body mass, were 4 times more likely to have diabetes and were 10 times more likely to have lower limb osteoarthritis than those without a spur.(181) An ultrasound-based study has found the presence of calcaneal spurs in 33% (n=7/21) of patients with plantar fasciitis, and 27% (n=8/30) of asymptomatic controls.(182) Other research has found that heel spurs are more common in people age 50 and over, are more common in women than in men, and are present in populations of various ethnicities.(183-185) The presence of a heel spur has not been shown to predict prognosis for patients with plantar fasciitis in a long-term follow-up study.(6)

Given this current evidence, the clinical significance of the presence of a calcaneal spur remains unclear. However, the evidence currently suggests that a plantar aspect heel spur is not pathognomonic of plantar fasciitis, nor does it necessarily have a role in predicting outcomes.

2.2 -

Treatment modalities

There are a wide range of treatment strategies available for the treatment of patients with plantar fasciitis and tendinopathies. Different centres and different publications have different individual treatment clinical pathways and protocols that they follow.(2, 46, 186-188) A recent systematic review and meta-analysis comparing treatments for patients with plantar fasciitis using therapeutic exercise, corticosteroid injections (CSI), or shockwave therapy (ESWT) found little evidence to support one treatment over another in terms of outcomes.(189) This section of this chapter seeks to explore the effectiveness of different treatments for patients with chronic plantar fasciitis.

Many of the same treatments that are used for more classical tendinopathies, such as Achilles tendinopathy or tennis elbow, are also used in the management of patients with plantar fasciitis.(2, 50) The mechanical models of tendinopathy emphasise the importance of load modification in the management of tendinopathies,(12) which will normally occur alongside a range of other treatment modalities in clinical practice. In general, simple conservative management options are routinely tried first including a graded rehabilitation programme often involving forms of eccentric loading or heavy slow resistance(190) before progressing on to more interventional procedures such as the use of injection modalities. Finally, for chronic tendinopathies that have not resolved with other conservative options, there are the options for novel therapies such as shockwave therapy or novel injections such as Autologous Blood Injections (ABI) / Platelet Rich Plasma (PRP) Injections, and in Achilles and patella tendinopathy conditions High-Volume Image-Guided Injections (HVIGI). A range of different surgical options for a number of chronic tendinopathies are reported in the literature and this has been undertaken for chronic plantar fasciitis as well.

To attempt to stratify the different options for patients with plantar fasciitis along a care pathway, figure 2.7 displays a range of some of the available treatment options based on available published literature as well as clinical experience, split for methodological purposes into early or first line treatments, before progressing to more interventional treatments in second / third line treatment options. The exact order / sequence of treatments is certainly open to debate, but this demonstrates some of the more commonly used treatments options, many of which are discussed later in more detail.

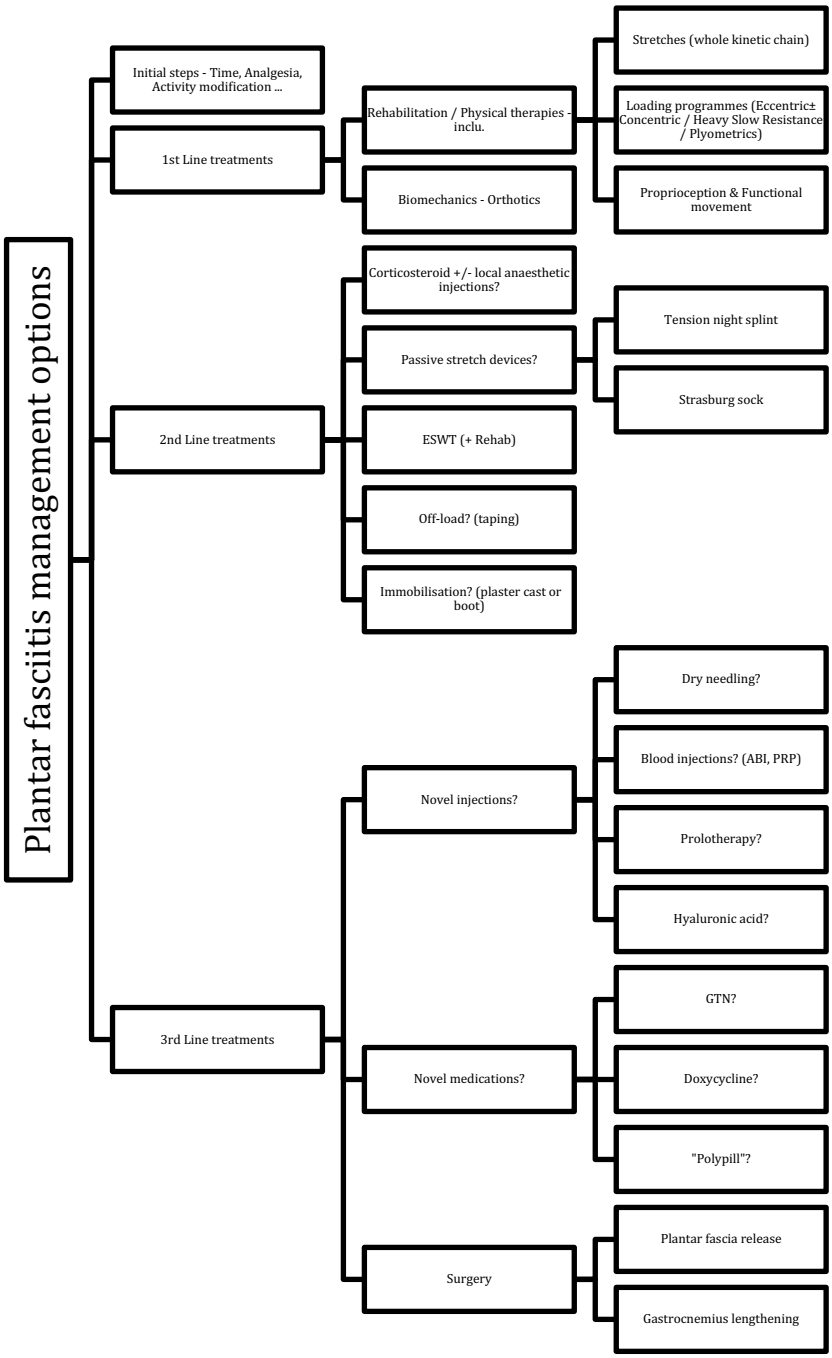


Figure 2.7: Example treatment options for patients with plantar fasciitis

Treatment options for patients with plantar fasciitis

- **Rehabilitation**

Tight posterior chain muscles (hamstrings, gastrocnemius, soleus) are often found in patients with plantar fasciitis,(62, 191, 192) with a reduction in ankle dorsiflexion being one of the most significant risk factors for the development of plantar fasciitis.(151) Addressing any particular tightness in the calf muscle is therefore a key consideration in the management of patients with plantar fasciitis, with improvements in tightness correlating well to improvements in pain in these patients.(193) In general principles, rehabilitation along with other available treatments looks at reducing pain, offloading tissue stress, and restoring flexibility and muscle strength.(194) Understanding and correcting any abnormal biomechanical movements that are contributing to the continuance of the plantar fasciitis symptoms are a key part of any rehabilitation programme.(195) As a part of this treatment approach it is common for rehabilitation of patients with plantar fasciitis to include stretches of all the muscles in the posterior chain including the calf muscles and Achilles complex, as well as stretches of the plantar fascia.(4, 5, 193, 196, 197) Research has shown specific benefits in the short-term of a specific plantar fascia stretch-based rehabilitation programme, and these benefits continued at a two-year review period.(4, 156) However it is not clear how stretching actually works, and rather than by increasing range of movement by causing structural change, it may instead improve stretch or load tolerance.(198)

In addition to the stretch-based component, rehabilitation programmes normally include intrinsic foot muscle strengthening and proprioceptive training exercises, both of which seek to improve the control of forces through the foot.(199) However, isometric exercises, which have been found to induce an analgesic effect in certain tendinopathy conditions,(200-202) were found to be no more effective than either isotonic exercises or walking in a small study involving patients with plantar fasciitis.(203) A recent editorial has also raised questions about the focus on isometric load programmes for pain reduction in tendinopathy management at the expense

of other forms of rehabilitation, and highlights the importance of individualised progressive strengthening programmes.(204)

Research in patients with plantar fasciitis has also shown that off-load taping was superior in reducing pain when compared to a stretch-based rehabilitation.(202, 205, 206) However, these studies have had only a relatively short-duration of follow-up, which may suggest that this modality may be useful in managing an acute flare of pain, but that a rehabilitation programme remains a vital part of longer-term management. Research in the form of a single-blinded RCT that used a dry-needling technique to myofascial trigger points in the calf in patients with plantar fasciitis compared to a home exercise programme identified improved levels of pain but did not find any differences or range of movement between the two groups studied, suggesting no benefit of the addition of dry-needling to calf trigger points to address calf muscle tightness, although foot pain may be improved.(207) This differs from a systematic review and meta-analysis which found no significant difference between acupuncture / dry-needling and placebo interventions for myofascial pain,(17) the reasons for this difference are not known.

- **Analgesia**

The use of pain control is actively promoted in guidance for treating plantar fasciitis.(2, 45, 208) However, although non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for pain from a range of sources including musculoskeletal pain, the addition of a NSAID in addition to a conservative treatment programme (involving stretching, insoles, and night-splints) did not provide any additional benefit to patients with plantar fasciitis over a placebo when measured at 1-, 2- and 6-months.(209)

- **Insoles / Orthotics**

Orthotic insoles are commonly used in patients with plantar fasciitis, both bought over the counter and sometimes prescribed with bespoke devices manufactured by podiatrists. The evidence for the use of orthotics has been considered within several published systematic reviews, with the earliest systematic review showing a reduction in pain and improvement in

measures of functional outcomes following the use of orthotics in patients with plantar fasciitis, drawing evidence from 4 RCTs.(210) However two recent systematic reviews and meta-analyses, both published in 2018, have shown conflicting results, with one review demonstrating evidence of benefit from the use of orthotics in treating patients with plantar fasciitis in the medium term, but not the short-term(211), and the other concluding that that foot orthoses were not superior to sham devices or other forms of conservative treatment.(212) Both of these recent reviews have drawn on the same literature base and have highlighted methodological limitations in many of the studies that were considered for inclusion, with small sample sizes, and many were thought to have a high risk of bias from their designs. The difference in findings from the recent systematic reviews was discussed in a recent editorial which suggested that this stemmed from the different views taken by the authors in the different reviews about primary outcome measures in the studies.(213) A recent RCT study compared the use of corticosteroid injections versus orthotics for the treatment of patients with plantar fasciitis.(214) This study identified at 4 weeks there was superior benefit in the group treated with steroid injection but this did not continue, and at 12 weeks there was superior benefit in the group receiving orthotics, which reached statistical difference, but this did not reach the minimally important difference identified, meaning that patients may not notice a difference between the two treatment options.(214)

Overall, there is inconsistent evidence of benefit from the use of orthotics in the management of patients with plantar fasciitis, despite these commonly being recommended, and commonly used in the management of patients with plantar fasciitis.(2, 40, 42, 45)

- **Corticosteroid and other injections**

Corticosteroid and local anaesthetic injections are often used in patients with plantar fasciitis, and a variety of differing techniques and broad outcome figures for success rates are reported in the literature, however, some papers report a plantar fascia rupture rate of up to 10% indicating that some caution may be needed.(215-218) Corticosteroid injections can be performed with palpation-guided, ultrasound-guided or x-ray guided

approaches, with one study demonstrating favourable outcomes following any of these approaches with no difference found between groups.(219)

A review of injection therapies for tendinopathies and plantar fasciitis, has concluded that the evidence for patients with plantar fasciitis, much like a range of other tendinopathies, has shown moderate evidence of benefit following corticosteroid injections for short-term relief of pain (up to 1 month), but with very limited evidence of benefit at longer time periods.(220) Other work has shown that there remains insufficient evidence to recommend corticosteroid injections over other treatments.(189, 221)

A recent systematic review and meta-analysis of injection therapies for plantar fasciitis has considered the evidence from a total of 22 studies involving a range of different injection therapies, which have often been compared with corticosteroid injections. This review and meta-analysis has shown mixed but potentially promising results for some injections including PRP, Botulinum toxin-A, and dehydrated human amniotic/chorionic membrane.(21) However, many of these treatments have a very limited evidence base and lie outside the remit of this thesis, although the role of blood injections is considered further within this chapter (section 2.2.3) and the results from two intervention studies involving autologous blood injections are presented in Chapter 7.

- **Surgery**

Surgery has traditionally been used to treat patients with recalcitrant plantar fasciitis, although this is often a treatment of last resort due to the recovery needed following surgical intervention. The results of surgery are reported predominantly in the format of case series utilising a range of different partial/sub-total or total fasciotomy procedures performed either open or endoscopically.(106, 222-231) Two of the largest case series studies, with 68 / 74 responses respectively and an average follow-up of 7 years / 4 years post-surgery, have both shown very positive self-reported patient responses, with 73-84% of patients reporting that they were satisfied with their symptoms post-operatively respectively, even though up to 44% of

patients were identified in the second study as continuing to have post-operative complications.(229, 230)

To potentially mitigate recovery time and reduce cost from surgical interventions options such as a percutaneous or endoscopic plantar fascia release are being examined, with suggestions of good improvements in a variety of open and minimally-invasive surgical options.(232, 233) A recent study has also demonstrated that in cadaveric feet it was possible to perform a partial plantar fasciotomy with a standard hypodermic needle, without any associated nerve injury, indicating this could potentially be a treatment option offered in the future.(234)

Plantar fasciotomy surgery however is not without possible complications. Several cadaveric studies have demonstrated that that even partial plantar fasciotomy decreased the arch supporting function of the plantar fascia, reduces arch height, and can lead to a collapse of the arch, which can be more problematic in those with pre-existing pes planus.(49, 235-237) Further cadaveric studies have shown significant changes to the medial and lateral columns with a release of only the medial third of the plantar fascia, which appears to lead to a strain of the calcaneo-cuboid ligament and joint capsule which is a possible cause for persisting lateral mid-foot pain seen following some surgeries.(238) However the protocols of these studies did not necessarily simulate normal functional biomechanics and are not readily able to take into account either the dynamic stabilisers or functional control mechanisms in vivo, and it is not clear how the findings seen in cadaveric studies relate to in vivo populations.

To avoid the potential problems following plantar fasciotomy, more recent work has been performed to investigate if a surgical release of the gastrocnemius muscle, thereby increasing calf flexibility, can be effective in treating cases of recalcitrant plantar fasciitis and has shown good results from case series and cohort studies in several sub-populations.(239, 240) One retrospective cohort study has suggested that the gastrocnemius lengthening surgery may have better outcomes than the traditional plantar fasciotomy/ fasciectomy surgical approach.(241) One RCT has also shown

at 12-month follow-up greater improvements in patients with plantar fasciitis following a proximal gastrocnemius release plus stretching versus a stretching programme only.(242) However, many of these different surgical treatment options have not yet been subject to rigorous study design, or direct comparison with other interventional treatments, and the costs and the risks of surgery are known to be greater than that from less invasive treatments.(5, 223, 225, 243)

Intervention studies that have involved surgical management of conditions are difficult to run as double-blinded placebo-controlled trials due to issues with blinding, as well as ethical considerations, and as a result there is a paucity of published literature of surgical studies in this format. A couple of systematic reviews have considered the evidence of surgery versus sham surgery for a range of medical conditions and have noted the limited number of published studies to draw conclusions from across a range of conditions, but have highlighted areas in which further work is required to assess outcomes of surgical management versus a more robust control group.(244, 245) Both of these reviews have focussed on non-musculoskeletal conditions but a recently published systematic review has examined the outcomes of surgical intervention versus sham surgery or physiotherapy specifically for patients with a range of different tendinopathy conditions.(246) This systematic review which focussed on the surgical management of tendinopathy has demonstrated superior outcomes from surgery compared to other treatments only in the short-term, with similar effects to sham surgery for pain and function in the medium term, and to physiotherapy for a range of outcome measures including pain and function in the medium and longer terms.(246) This systematic review included a total of 12 studies involving patients with rotator cuff tendinopathy, tennis elbow, patella tendinopathy or Achilles tendinopathy, but did not identify any suitable studies involving patients with plantar fasciitis that met its inclusion criteria. However, the lack of certain benefit of surgery over other treatment options in the medium and longer-term for other tendinopathies raises important questions for the surgical treatment of patients with plantar fasciitis that are not fully answered from the current published literature.

- **Other treatment options**

If simple measures prove unsuccessful in treating patients with plantar fasciitis, and to avoid the need for invasive surgical intervention, several other treatment options have been suggested including Tension Night Splints (TNS), Extra-Corporeal Shockwave Therapy (ESWT), or Autologous Blood Injections (ABI) and the specific evidence for each of these is considered in subsequent sections. However, directly comparing outcomes from these different options is often difficult due to the heterogeneity of patient populations, treatment interventions, and follow-up, and many of these have not been subject to rigorously designed investigation, or there may be conflicting results from different studies.

The purpose of this thesis is to review these treatments in a population with symptoms of chronic plantar fasciitis, and to construct methodologically robust study of them in this clinical population.

2.2.1 - Treatment option: Tension Night Splint (TNS)

Patients with plantar fasciitis may be recommended to use Tension Night Splints (TNS) as a part of their treatment package.(42, 44, 46) These are devices that are typically worn throughout the night on consecutive nights, most commonly for periods of six-weeks or longer. TNS may have a plausible rationale for their use by stretching the calf musculature over prolonged periods of time, as tight calf-musculature has been found to be an important risk factor for plantar fasciitis.(62, 191, 192) During the time that they are worn they keep the ankle in a neutral or dorsiflexed, rather than a plantarflexed, position, holding the calf in a stretched position, potentially facilitating recovery due to prolonged periods in this elongated position.(247) However, despite tension night splints being in routine clinical use, there is inconsistent evidence of benefit found in published works to date of this intervention in patients with plantar fasciitis, particularly in those with chronic symptoms.

An initial study was published in 1991 in the format of a small case series, and which suggested benefit from the use of night splints in patients with recalcitrant plantar fasciitis.(248) Following this there has been mixed evidence from randomised controlled trials, and also some lower quality evidence from further case series published.

Individual studies that have shown benefits from tension night splints include a prospective RCT involving 40 patients published in 1996 which showed improved outcomes in a group treated with night splint alongside other treatments which included stretching, NSAIDs, and a heel cup, compared to a group without a splint, using clinical outcome measures.(249) Further to this a smaller RCT with 28 patients published in 2012 examining groups with orthotics plus tension night splints versus orthotics alone found better results in the combined approach with an eight-week follow-up.(250)

In addition to these studies, a cross-over study published in 1998 and which used the AOFAS ankle-hindfoot rating and the Mayo Clinical Scoring System demonstrated improvements with the addition of the splint devices.(251) A retrospective study sought to compare the outcomes from a simple stretch-based programme and those from the use of a TNS, and this found quicker recovery time and fewer further treatments were required in the TNS group, although the retrospective nature of this study and the lack of randomisation means that these results are subject to greater bias than other studies.(252) Lastly, a small case series of 12 patients using a specific TNS device was published in 2002 suggesting good results with both pain and a functional scale and high levels of tolerability from this device, but the small study size and lack of control or comparison group limits the impact of this research.(253)

However not all of the published evidence has given favourable results. A large RCT involving more than 100 patients published in 1999 showed no difference in the outcomes of treatment with the addition of a tension night splint using both clinical outcome measures and the SF36 questionnaire.(254) In addition, a larger three-arm RCT published in 2001 and involving more than 250 patients, compared two different orthotic devices and a tension night splint device, and found overall there were no differences between the groups in terms of outcome, but a higher discontinuation rate in the TNS group.(255)

Most recently a systematic review published in 2015, using a search undertaken in November 2013, demonstrated that overall there was uncertain evidence for the use of tension night splint devices to treat patients with plantar fasciitis.(256)

The following table (2.1) displays a summary of the published evidence concerning the use of tension night splints for these patients suffering with plantar fasciitis.

Table 2.1: Summary of published evidence for use of Tension Night Splints (TNS) in patients with plantar fasciitis

1st author (Year)	Design / intervention	Number	Patient demographics, including age gender,	Symptom duration	Follow-up period	Outcome measures	Notes	TNS Conclusion	Ref
Wheeler (2017)	*Single-blinded RCT* *Rehab +/- TNS (otc rigid TNS)*	*40 patients*	*Mean (SD) age 52.1 (10.3) range: 33-72* *33% male*	*Mean 25 months*	*3 months*	*Pain (VAS), Stiffness (VAS) – including subscales* *Function: MOXFQ, FFI-r, FAAM* *Activity: IPAQ* *Mood: HAD* *Sleep; PSQI* *Measures of physical flexibility & plantar fascia thickness*	*No significant improvement with the addition of TNS in pain, flexibility or function*	*Ineffective*	*(257)*
Landorf (2015)	Systematic review (search date Nov 2013)			.				Unknown effectiveness	(256)
Wheeler (2014)	*Retrospective case-series* *Custom-made TNS*	*Results from 17/20 identified cases*	*Mean(SD) age 49.9 (12.3) range: 28.5-76.6* *55% male*	*mean 30 months*	*6-18 months f/u* *Aim to wear TNS for 3months*	*Pain (VAS) – average pain and pain first thing sub-scores* *Self-reported % function scores, symptom changes, Satisfaction scores,*	*mean reduction in pain first thing in the morning of 2.8 points, and pain overall of 1.9 points on a 0-10 visual analogue scale. Overall function improved by 17 percentage points. one-third of patients having significant sleep disturbance whilst wearing the tension night splint, 30% ceasing to wear the splint within one month.*	*Possibly effective, but compliance is an issue*	*(258)*
Lee (2012)	RCT Orthoses +/- TNS	28 patients	Mean(SD) age 43.9(6.4) range: 30-54	average symptoms of 7.4 months	8 weeks	FFI questionnaire	Orthotics + TNS more effective than orthotics alone	Effective	(250)

	(adjustable dorsiflexion night splint)		7.1% male						
Berlet (2002)	Prospective case series TNS for 1 month (ankle dorsiflexion dynasplint)	12 patients	.	.	6 months	Pain (VAS), Modified plantar fasciitis functional assessment scale	75% report improvement at 1 month	Effective	(253)
Barry (2002)	Open retrospective cohort study Stretches or TNS (Strasburg sock)	160 patients total	Mean age 46.4yrs (range 6-80) 38.7% male	Mean 2 months (range 1 week – 1 year)	Max f/u 79 days (TNS) v 246 days (stretches only)	Assessed days to recovery, number of clinic visits, number of interventions (13% patients lost to follow-up)	TNS group – quicker recover, fewer additional interventions Duration of symptoms was predictive factor in outcome, and length of time to outcome No difference in outcomes seen for body weight, BMI, age	Effective	(252)
Martin (2001)	RCT (3-arm) Custom-made orthoses / arch supports / TNS	255 patients	.	.	3 months	.	No differences seen in outcomes between groups	Ineffective	(255)
Probe (1999)	RCT NSAIDs, stretching & shoe advice +/- TNS (3months) (5degree dorsiflexion)	116 patients	Mean 46 (SD 11) 30% male	Average 19 weeks	Average 19 months (range 12-28months)	Pain on 4-point scale SF36	Overall 68% patients improved No change with TNS Age>45 poor prognosis No difference in improvement in gender, duration of symptoms, bilateral symptoms, or spur	Ineffective	(254)

Powell (1998)	Cross-over study TNS for 1 month	37 patients	average age 48 (range 22-72) 24% male	Average 33.4 months (range 6-108)	6-month	Outcome measures included AOFAS ankle-hindfoot rating and Mayo Clinic Scoring system (/100)	88% patients improved	Effective	(251)
Mizel (1996)	Case series Night splint + shoe modification (steel shank & anterior rocker bottom)	57 patients 71 feet	Mean age 54 years 35% male	Average 10 months (range 0.5-132 months)	Average 16 months	Clinical outcome measures from 4 options (“resolved”, “improved”, “no change”, or “worse”)	Symptoms resolved in 59%, improved in 18%, not changed in 15%, and worse in 7% No change in outcome for age, gender, duration of symptoms, and bilateral involvement	A combination of TNS + shoe modification effective	(259)
Batt (1996)	RCT NSAIDs, heel cushion, + stretches +/- TNS	32 patients 33 feet	Mean age: 45.7 range 20-74	average 12.7 months	12 weeks	Outcome measures: pain (VAS), plantar fascia tenderness, ankle range of movement	16/16 initially treated with TNS “cured” in average 12 weeks versus 6/17 in control group in average 8.8 weeks	A combination of treatment involving TNS more effective	(249)
Wapner (1991)	Case series Custom-made TNS + NSAIDs, gel cups, liners, stretches	14 patients	Average age 37 64% male	average symptoms at least 1 year	Average 4 months	(clinical only)	“successful resolution” in 11/14 patients	A combination of treatment involving TNS more effective	(248)

Overall, the evidence of any benefit from a tension night splint device in treating plantar fasciitis remains inconclusive. Many of these studies were performed in private clinics, with patients paying for treatment, and typically presenting at much earlier stage in their symptomatology, both of which may influence compliance and results as the natural resolution of symptoms is more common in patients with short-duration symptoms.(5, 6, 252) These studies may therefore not be directly comparable to routine NHS clinical practice in a secondary care clinic. Some studies including two small RCTs have shown benefit from the use of a TNS.(249, 250, 252) However several trials, particularly the larger studies and those with a with more robust study design, have failed to show any additional benefit with the use of a tension night splint.(254, 255) The most recent systematic review has again highlighted that any overall benefits remained unclear.(256)

Despite the lack of robust evidence, TNS are still often used in clinical practice and many commercial products are available for sale. To date, there has been no published clinical work in an NHS population, which often involves those with chronic symptoms, that investigates the addition of tension night splints to routine care to see if there is any added benefit to this strategy.

One of the avenues of study in this thesis has been to assess any effect that the TNS may have when used to treat patients with chronic plantar fasciitis presenting to a secondary care clinic. This has been studied in the format of a pragmatic case series initially. Information from this was then used to develop a formal, single-blinded, randomised control trial to investigate this treatment more robustly. These two studies are presented in chapter 5.

2.2.2 - Treatment option: Extra-Corporeal Shockwave Therapy (ESWT)

Extra-Corporeal Shockwave Therapy (ESWT) is the use of high-energy, inaudible, sound waves generated from a commercially available musculoskeletal ESWT machine, external to the body and which are transmitted through the skin to an area of tissue damage such as that seen in patients with plantar fasciitis or other focal tendinopathy.

There are two sub-types of ESWT, that of radial Extra-Corporeal Shockwave Therapy (rESWT) and Focal Extra-Corporeal Shockwave Therapy (F-ESWT) and there may be differences between them that may influence outcome following treatment.(22, 260, 261) In radial shockwave therapy (rESWT), pressure waves are generated by the means of a pneumatic system with compressed air accelerating a projectile to high-speed against a transmitter head, which is held against the area being treated. This kinetic energy from the projectile, is transmitted into the local tissue where it spreads out into adjacent tissue as a radial wave aspherically. The radial wave loses power the deeper it passes into tissue, but can potentially cover a broad area through the expansion of the radial wave.(260) Focal shockwave (F-ESWT) generates focal shockwaves electromagnetically, typically using opposing magnetic fields and a cylindrical coil. This creates a small focal zone pressure wave directed to a specific anatomical location by adjusting the F-ESWT settings, typically directed through the use of real-time imaging with ultrasound. In F-ESWT the small focal zone allows the pressure wave to be specifically targeted, and this can potentially deliver more energy to deeper structures than is possible with rESWT.(13, 22) Treatment with F-ESWT has historically been performed under local or regional anaesthetic cover as this treatment can be painful,(22) whereas rESWT with its lower energy pressure waves has not typically required anaesthesia.(262, 263) The different energy waves created by the two types of ESWT are illustrated in figure 2.8

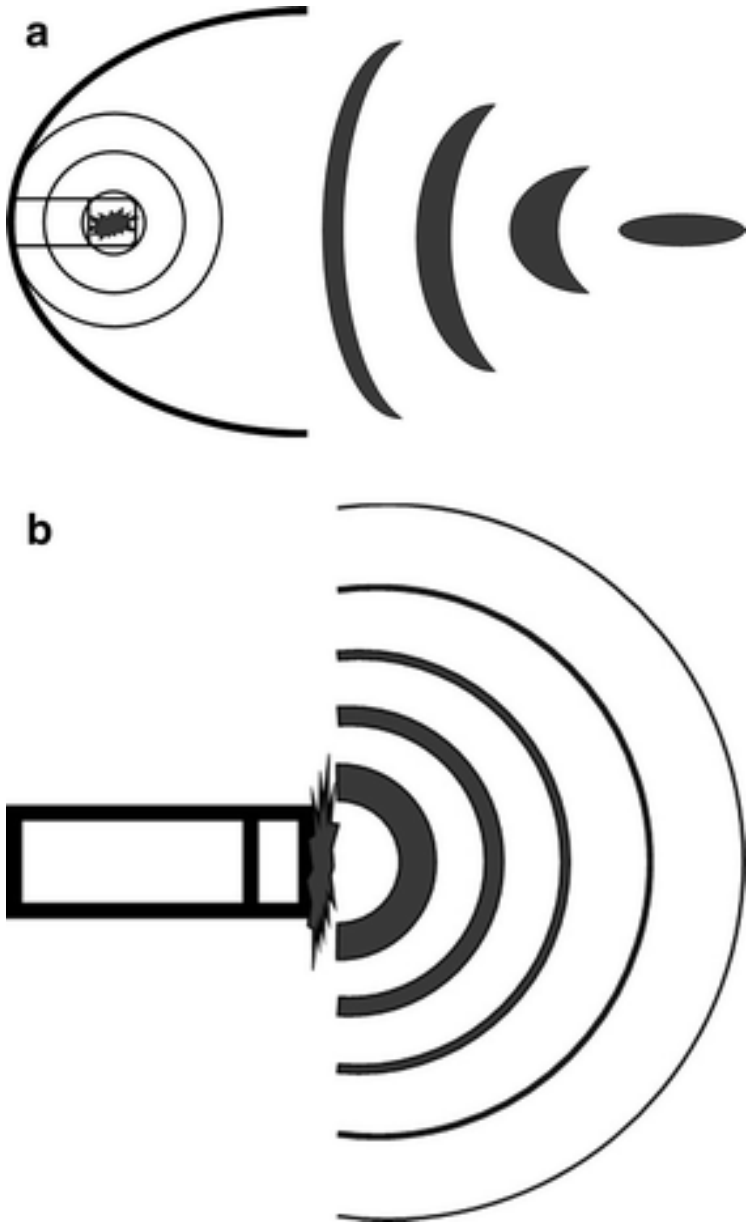


Figure 2.8: Example pressure waves generated from focal-ESWT (a) and radial-ESWT (b) – From van der Worp (13)

The underlying mechanism of action of ESWT in either plantar fasciitis or tendinopathy conditions remains unclear. There is evidence that ESWT can increase local blood flow, which may be from a modulation of endogenous nitric oxide (NO).(264) Previous work in rabbits, comparing those that received ESWT near to the Achilles-Bone junction to those that did not, has shown an increase in neovascularisation and improved blood supply, as assessed by the numbers of vessels and an increase in angiogenesis-related tissue markers such as endothelial nitric oxide synthesis (eNOS), vessel endothelial growth factor (VEGF) and also endothelial cell proliferation as

highlighted by an increase in proliferating cell nuclear antigen (PCNA).(265) The changes in eNOS and VEGF were seen within one week and remained high before falling by week 12, whereas the increases in PCNA and neovessels began at 4 weeks, and remained higher at week 12.(265) These two studies which suggest an increase in neovascularisation and local blood flow at face value run counter to the argument that the neovessels that are seen in chronic tendinopathy are a sign of dysrepair, although this hypothesis is itself questioned.(115) Subsequent work examining the effects of ESWT in rabbit patella tendons has demonstrated that ESWT may increase collagen synthesis and collagen cross-link formation (266), and work in rat Achilles tendons demonstrated a reduction in inflammatory cell infiltration into tendon, and increase in PCNA as well as elevations in Insulin-Like Growth Factor 1 (IGF-1) and Transforming Growth Factor beta1 (TGF-B1).(267) However it is not clear if results derived from animal models apply fully to human condition.(268) In human-derived cell lines in vitro studies have demonstrated a reduction in the abnormally high levels of several Matrix Metallo-Proteinases (MMPs) and interleukins that are seen in tendinopathy, including MMP-1, MMP-13 and IL-6.(269) Further studies have shown that ESWT has a range of biological effects in tendon tissue, including differentiation of mesenchymal stem cells (MSC), the release of angiogenetic factors and increase in neovascularisation, and a reduction in inflammatory mediators including various interleukins and MMPs.(268, 270) These biological effects have shown that ESWT in tendons has a different mechanism of action to that in renal stones, which is thought to be a mechanical disruption effect, however the precise mechanism of action of ESWT in tendon conditions, is not yet fully understood.

Although the mechanism of action may remain unknown, clinical studies have shown that the use of ESWT can reduce pain in many patients with plantar fasciitis or tendinopathy resistant to other treatments, with success rates reported between 65% and 91%(261, 271) There is evidence that the addition of ESWT to a rehabilitation programme leads to improvement in outcome compared to either treatment on its own, highlighting the importance of active rehabilitation, even with the additional of adjunct therapies such as ESWT.(272, 273)

The evidence for the use of ESWT in the treatment of patients with plantar fasciitis includes a number of case series and RCT studies, although many studies have included patients with short-duration of symptoms and/or with very short periods of follow up only.(20, 274-281) A systematic review has identified that the majority of studies reported outcomes only up to 6-months, leaving uncertainty as to longer-term outcome.(282) However since this review was published, an RCT and a multi-centre case series studies have been published which have follow-up periods of up to two-years demonstrating favourable results.(283-285)

There is evidence of benefit following ESWT for patients with plantar fasciitis from randomised controlled trials directly comparing ESWT against a range of other treatments including steroid injections, (278, 286) injections of blood products,(287) botulinum toxin injections,(288) or surgery.(289, 290) Additionally, there are several studies using ESWT versus a sham ESWT procedure with the use of either minimal dose, or the use of acoustic shielding attempt to create a placebo-ESWT.(291, 292) However, it is noted that sham ESWT appears to have a significant placebo effect in some studies.(293)

Overall, the side-effect profile from ESWT is favourable, with few serious side-effects reported in most primary studies, or systematic reviews that examined this area.(261, 271, 282) In a placebo-controlled study of more than 270 patients, reported side-effects included transitory reddening of the skin (21%) which was harmless and did not lead to treatment cessation, pain (4.8%), and small haematomas (3%), in addition there was a possibility of ESWT triggering migraine or possible fainting.(294) The risk of haematoma was reported following the use of a non-MSK specific machine, and newer more MSK-specific ESWT devices, appear to have a safer side-effect profile.(294) In the NICE guidance relating to the use of ESWT for recalcitrant plantar fasciitis (IPG311), it highlighted that 12% of patients receiving ESWT in one study had skin reddening, compared to 4% of patients receiving placebo ESWT.(51) Other reports of side-effects within the specific NICE guidance for lateral hip / trochanteric pain (IPG 376) report than in 2% of patients there was

increased pain of more than 1-day following ESWT treatment, and skin irritation in 33% of patients at 1-month.(295)

The practical administration of ESWT varies greatly between published research. This has been driven partly by improvements in technology over the last 20 years, as well as different designs of machine and manufacturer guidance. Some studies have used ESWT performed either under local or regional anaesthetic such as a medial calcaneal block,(286, 296, 297) or even conscious sedation,(290) whereas other ESWT studies have not used any anaesthetic.(276, 288) Partly this is from the form that the ESWT takes, with radial ESWT (rESWT) being less painful to administer than focal ESWT (F-ESWT), hence not requiring the use of co-administered anaesthetic, and partly with newer F-ESWT machines not requiring the use of local anaesthetics.(22, 298) In addition, there is some suggestion that local anaesthetic could adversely influence the outcomes following ESWT either by a direct potentially locally toxic effect of the local anaesthetic or by the act of numbing the area allowing either under-dosing or over-dosing of ESWT to occur.(51) This suggestion is supported from the results of one RCT which involved 86 patients with plantar fasciitis and found superior outcomes in the group that had ESWT performed without co-administered local anaesthetic compared to a similar group, receiving identical ESWT after local anaesthetic was administered.(299) Additionally, one study has compared outcomes following ESWT in patients with plantar fasciitis using either ultrasound-guided ESWT, or ESWT guided by the location of the patient's pain, and found no significant difference in outcomes between the two groups suggesting the use of ultrasound to guide ESWT gave no specific advantage.(300)

Different studies have used different energy doses and different treatment frequencies, again partly driven by technology and manufacturer guidance and possibly also by pragmatic booking issues.(301) There remains no evidence as yet that one specific ESWT regime or machine is superior to another, with no head-to-head prospective studies comparing results from different ESWT machines for patients with plantar fasciitis, although a small RCT study in patients with tennis elbow demonstrated a comparable reduction in pain between those treated with 3 sessions of either radial or focal

shockwave therapy.(302) One meta-analysis involving patients with plantar fasciitis treated with ESWT has suggested that rESWT is an appropriate alternative to F-ESWT and may have improved effectiveness as well as a lower cost for the rESWT device compared to F-ESWT.(303)

Table 2.2 gives a brief summary of some of the evidence for the use of ESWT in patients with plantar fasciitis from primary research studies. Where possible the type of shockwave therapy (rESWT or F-ESWT) is specified as well as the specific device that was used and, where specified in the study, the number of shocks, energy intensity, and number of treatment sessions.

Table 2.2: Summary of published evidence for the use of Extra-Corporeal Shockwave Therapy (ESWT) for the treatment of patients with plantar fasciitis – primary research studies

1st Author (Year)	Design	Intervention / design notes	number	Age in years (range)	Symptom duration in months	Follow-up period	Findings	Ref
Hanada (2019)	Retrospective cohort study	Comparing patients with plantar fasciitis at enthesis versus full-length symptoms F-ESWT (Epos Ultra) – 1 -5 sessions (sessions performed after 3 weeks if patients had not improved sufficiently) – no anaesthesia (1 session n=35 , 2 sessions n=35, 3 sessions n=29, 5 sessions n=2)	92 pts (99 feet)	Mean 59.9 (range 40-85)	*Not reported*	4 months	Outcome measures: VAS Greater improvements in those with pain only at enthesis rather than whole-length plantar fascia Equal benefits in those who were engaged in reactional sports or in activities of daily living only	(298)
Mishra (2019)	Prospective cohort study (non-randomised)	Injection of 40mg methylprednisolone versus rESWT (rESWT – 2500 impulses of "low energy ESWT" – single treatment session, machine not specified)	60 pts	Mean 44.2 (range 15-65)	*Not reported (min 2 weeks?)*	6 months	Outcome measures: VAS At 6weeks, 87% rESWT group and 53% CSI group had VAS<5 (p=0.005) At 3-months and 6-months, results also favoured ESWT over CSI	(304)
Cinar (2018)	Single-blinded randomised controlled trial	Control group ± 1 of 2 interventions (control group – full-length insoles for 3months, plus home exercise programme for 3 weeks) rESWT – Swiss DolorClast device (total of 2000 shocks weekly for 3 weeks) Low-level laser therapy (LLLT) – using a gallium-aluminium-arsenide (CaA1Aa) low-level diode laser	76 pts	45.4 ± 9.6	*Not reported* *Min: 1* *1month*	3 months	Outcome measures: pain-subscale of FFI Significant improvement in pain in all groups, with LLLT group having lower pain than control or ESWT group at 3-weeks, and lower pain than ESWT group at 3-months	(305)
Maffulli (2018)	Multicentre Case series	(insertional plantar fasciitis) rESWT – Swiss DolorClast device and Stortz devices 500 impulses at 1.5 bar then 2000 at 2.5bar or above 3 treatment sessions max gap of 2 weeks between treatments	198 pts	48.1 ± 17.9	*Not reported*	Max 24 months	Outcome measures: VAS, FFI, EQ-5D Follow-up at 3, 6, 12 and 24 months Significant improvements in VAS, FFI & some sub-sections EQ-5D	(284)
Maffulli (2018)	Multicentre Case series	(mid-substance plantar fasciitis) rESWT – Swiss DolorClast device and Stortz devices 500 impulses at 1.5 bar then 2000 at 2.5bar or above 3 treatment sessions max gap of 2 weeks between treatments	52 pts	Mean 53.4 ± 12.1	*Not reported*	Max 24 months	Outcome measures: VAS, FFI, EQ-5D Follow-up at 3, 6, 12 and 24 months Significant improvements in VAS, FFI & some sub-sections EQ-5D	(285)
Njawaya (2018)	Un-blinded randomised controlled trial	Comparing outcomes following ESWT performed under ultrasound guidance versus patient pain location (3-5 sessions at weekly intervals) rESWT – Chattanooga Intellect Radial Pressure Wave RPW	51 pts with PF + spur	Mean 52.1	*Not reported*	Max 6 months	Statistically significant improvement in both groups, reached at 3-months No differences between groups	(300)

Purcell (2018)	Case series	F-ESWT – 2000 shocks, at 24kV (98% has 1 session ESWT) (74% patients were active duty military personnel)	82 pts	Mean 42 ± 10 yrs	*Not reported*	Mean FU: 42±22 months	Outcome measures: VAS Improvement in VAS from 7.8±2 to 2.5±2 at FU Less improvements seen in active duty military population than non	(306)
Rahbar (2018)	Single-blind randomised controlled trial (investigator blinded)	Local dry needling with 18G needle versus rESWT – 2000 impulses, 10Hz, energy flux 0.25 all pts: shoes, stretches (including "rotator cuff muscles?")	72 pts	Mean 44.2 (range 23-65)	*Not reported* *Min: 1* *1month*	8 weeks	Outcome measures: VAS, FFI, Improvements in outcomes in both groups – favouring dry needling over ESWT at 8-week, but not at 4-week period	(20)
Vahdatpour (2018)	randomised controlled trial	Combination focal and radial ESWT (Storz Medical Duolith SD1 – F-ESWT: 2000 shocks, 0.2-0.3mj/mm^2 rESWT: 3000 shocks, 1-8-3mj/mm^2 ± topical corticosteroid ointment (Clobetasol) administered 30mins prior to ESWT	80 pts	Mean 49.8	*Not reported*	3 months	Outcome measures: VAS, Roles & Maudsley Score (RMS), PF thickness on ultrasound At one-month VAS (morning) & RMS improvements greater in group with steroid ointment, but no difference overall VAS At 3-months – no difference in outcomes between groups	(307)
Wheeler (2018)	*Case series*	*rESWT for patients with very chronic plantar fasciitis (median symptoms of 24months)* *ESWT = "Intelect" RPW ESWT machine (DJO Global Chattanooga)* *3 sessions, weekly intervals – "maximally comfortably tolerated dose"*	*35 pts*	*Median 50.9 (IQR: 43.8-54.9)*	*Median 24.0 (IQR: 12-30)*	*3 months*	*Outcome measures: VAS (various subscales), FFI-r, MOXFQ, IPAQ* *Effective?* *Statistically significant improvements in pain and PROMs – but no control group as comparator*	(276)
Ibrahim (2017)	RCT	rESWT v placebo (follow-up study to Ibrahim 2010) ESWT = EMS Swiss DolorClast ® (EMS Electro Medical Systems Corporation; Dallas, TX) 2 sessions, one-week apart, with 2000impulses/sessions, air pressure 3.5bar / 0.16mj/mm^2	50 pts	Mean 52.9 (range 26-87)	Min 6M	2 years	Outcome measures: VAS, Roles and Maudsley Score ESWT found to be effective Significant differences in VAS and RM score between groups at 1M, 3M, 6M, 12M, and 24M – favouring ESWT group	(283)
Saxena (2017)	(Pilot) Cohort study	rESWT – comparing those with symptoms <3M & those >6M rESWT = radial ESWT EnPuls; (Zimmer MedizinSysteme, Neu-Ulm, Germany) 3 sessions "at approximately weekly intervals" – total of 3000 pulses (including 500pulse ramp up) per session, at 160mj / approx. 4.0 bar	28pts	Mean 50.5	(Either <3M or >6M)	12 months	Outcome measures: VAS, Roles and Maudsley score Improvements in both groups Improvements in VAS and RM were better for the early group, but differences were not statistically significant	(308)
Ulusoy (2017)	RCT	RCT: ESWT v laser v US therapy ESWT = BTL-5000 SWT combined device (BTL Turkey, Ankara, Turkey) 3 sessions at weekly intervals, 2000 shocks, at 2.5bar	60 pts	Mean 52.9	Mean 16.2 (range 6-120)	1 month	Outcome measures: VAS, AOFAS ankle-hindfoot scale, Roles and Maudsley score, and MRI appearance Pain/function/MRI thickness improved in all groups	(280)

							ESWT & laser superior to US therapy	
Eslamian (2016)	Single-blinded RCT (investigator blinded)	RCT: rESWT v corticosteroid injection rESWT – Swiss DolorClast device, 2000 impulses, 2 pulses/sec, energy level as tolerated (0.2mj/mm^2) 5 sessions at 3-day intervals Or single steroid injection 40mgh methylprednisolone + 1ml 1% lidocaine	40 pts	Mean 42.1 (range 18-65)	Mean 9.5 weeks	8 weeks	Outcome measures: VAS, patient satisfaction (4-part Likert scale), modified FFI, Both groups improved significantly from baseline, with no statistical difference between groups at 8 weeks – ESWT group non-statistically improved FFI & more satisfied …	(279)
Roca (2016)	Open label RCT	RCT: F-ESWT v botulinum toxin (BoNT-A) F-ESWT = Piezoson 100 Single session of 3000 focussed shocks, flux intensity 12mj/mm^2	72 pts	Mean 52.4	Min 6M	Median 1 month (range 1-2M)	Outcome measures: VAS (several subscales including 1st step), Roles and Maudsley Score ESWT superior to botulinum toxin injection	(288)
Scheur (2016)	Cohort study	Cohort study 1 v 2 v 3 sessions F-ESWT Focal ESWT = Stortz Duolith SD1 Tower 1500 shockwave impulses / treatments of 0.15-0.25mj/mm^2	284 pts	Mean 50.2	*Not reported*	Mean 9.5 months (range 14-541days)	Outcome measure: numerical rating score for pain Three-quarters of patients reported satisfying pain relief 72% received single F-ESWT only No correlation between number of treatment sessions and outcome	(309)
Gollwitzer (2015)	RCT	F-ESWT Multicentre DB RCT: F-ESWT v placebo intervention ESWT = Duolith SD1 shock wave device (Storz Medical) 3 treatments at weekly intervals, 2000 shocks per treatment at 0.25mj/mm^2	250 pts	Mean 48.7	Min 6M	3 months	Outcome measures: VAS, Roles and Maudsley Score, pressure sensitivity score with F-meter F-ESWT found to be effective	(291)
Maki (2015)	Case series	ESWT with MRI findings pre/post ESWT = Epos Ultra® (Dornier MedTech, Tokyo, Japan) Approx. 3800 shocks, at 0.03-0.036mj/mm^2	50 pts	Mean 55.3 (range 16-79)	Min 3M Mean 23.8 (range 4-240)	6 months	Improvements seen in VAS & Japanese Society for Surgery of Foot (JSSF) Ankle-Hindfoot Score No change in MRI thickness A High Signal Intensity Area (HSIA)predicted symptom improvement more than other MRI findings	(275)
Mardani-Kivi (2015)	RCT	RCT: ESWT v corticosteroid injection with acute plantar fasciitis (<6weeks) (ESWT machine not stated) Performed 2000 shocks, 3 times at weekly intervals (total dose of 900mj/mm^2)	84 pts	Mean 44.3	max 6 weeks	3 months	Outcome measures: VAS Improvements seen in both groups, but better outcomes with steroid injection in early plantar fasciitis	(278)
Rompe (2015)	RCT	Single-Blinded RCT: rESWT v rESWT + PF stretches (rESWT = radial shock wave device (EMS ElectroMedical Systems, Nyon, Switzerland)	152 pts	Mean 51.6 (range 27-73)	Mean 12M (range 12-34M)	24months max	Outcome measures: VAS (1st step pain), FFI (pain subscale), Improvements seen in both groups.	(273)

		Weekly for 3 weeks, air pressure of 4bar, equivalent to positive energy flux density of 0.16mj./mm^2					Better results seen for ESWT + Stretching than for ESWT alone at 4 months, but no between groups changes at 24months	
Androsoni (2013)	Case series	rESWT = Swiss DolorClast Weekly for 4 consecutive weeks, 2000 impulses per session at 0.18mj/mm^2	30 pts	Mean 48.37 (range 33-78)	Mean 13.6 M (range 6-60M)	6 months	Outcome measures: AOFAS ankle-hindfoot scale, Roles and Maudsley score, US thickness	(274)
Chew (2013)	RCT	ESWT v Autologous Conditioned Plasma (ACP) v rehab alone ESWT = Dornier EPOS Ultra ESWT Machine (The ESWT Co, Piqua, OH) 2 sessions at weekly intervals, under US guidance, 2000 shocks/treatments, increasing from 0.02-0.42mj/mm^2	54 pts	Mean 46.1 (range 29-71)	Min 4M (range 6-24M)	6 months	Outcome measures: VAS, AOFAS, PF thickness on US Treatment with either ACP or ESWT better than rehab alone, although no differences between ACP & ESWT except PF thickness (greater reduction in ACP group)	(287)
Grecco (2013)	RCT	RCT: US v rESWT rESWT = Swiss DolorClast radial shock wave device 10 physio sessions, 2/week of US or 3 sessions radial ESWT at weekly intervals Both groups had stretches	40 pts	Mean 49.6 ± 11.8 (range 25-68)	Min 3M	12 months	At 12M both groups improved, with faster improvements in ESWT group Outcome measures VAS, duration of pain, analgesia use	(310)
Krishnan (2012)	Case series	ESWT = Storz D-Actor 200 ESWT with 5 sessions on alternate days 1000shocks/treatment at 0.16mj/mm^2	25 pts	Mean not stated (range 30-70)	Min 6M Mean 7.9M	4 weeks	Outcome measures: VAS, Roles and Maudsley Score High pt. satisfaction reported, significant improvement in VAS at 4w f/u	(277)
Radwan (2012)	RCT	F-ESWT v surgery (surgery endoscopic plantar fasciotomy)\ ESWT = OssaTron device (High Medical Technology, Kreuzlingen, Switzerland) Under conscious sedation - Total of 1500 shocks, at max 0.22mj/m^2	65 pts	Mean 38.7	Min 6M (range 6-60M)	12M (additional fu at 2 & 3yrs)	Outcome measures: VAS (morning pain), AOFAS ankle-hindfoot scale, Roles and Maudsley score Both groups improved at 3W, 3M, and 12M – no difference between groups	(290)
Saber (2012)	RCT	F-ESWT v Corticosteroid injection (2 sessions ESWT under LA injection or 2 injections 2 weeks apart) (ESWT not stated)	60 pts	Mean 34.3	Min 6M	Mean 20 weeks (range 12-24)	Outcome measures: Mayo scoring system, US thickness Both groups improved – no difference between groups	(286)
Saxena (2012)	RCT	F-ESWT RCT: surgery v ESWT v sham (surgery endoscopic plantar fasciotomy) focused shock wave device, DuolithTM ESWT = Storz Medical AG, Tägerwilen, Switzerland) 3 treatments at 7±3day intervals, 2000shocks/session, increasing to 0.24mj/mm^2	37 pts	Mean 46.0	Min 6M	Not clear – min 1 year	Outcome measures: VAS, Roles and Maudsley Score ESWT found to be effective Surgery > ESWT	(289)
Ibrahim (2010)	RCT	RCT: rESWT v sham	50 pts	Mean 52.9	Min 6M	6 months	Outcome measures: VAS, Roles and Maudsley Score	(292)

		ESWT = EMS Swiss DolorClast ® (EMS Electro Medical Systems Corporation; Dallas, TX) 2 sessions, one-week apart, with 2000impulses/sessions, air pressure 3.5bar / 0.16mj/mm^2		(range 26-87)			ESWT found to be effective Significant improvements seen in rESWT group – no changes in placebo group	
Othman (2010)	Cohort study	F-ESWT v surgery (ESWT under. LA) ESWT machine not specified, appears to be single session, 1500-3000 shocks	37 pts (ESWT = 20)	Mean 43.6	Min 6M	Range 6-11months	Outcome measures: VAS Recommended ESWT as earlier recovery	(296)
Rompe (2010)	RCT	Single-blinded RCT: stretching v rESWT for early plantar fasciitis (<6 weeks of symptoms) rESWT = EMS Electro Medical Systems, Nyon, Switzerland 3 sessions at weekly intervals 2000 shocks/session at 4bar – equiv. to 0.16mjj/mm^2	102 pts	Mean 51.5	max 6 weeks	15 months	Outcome measures: Foot Function Index (pain subscale), measures of pain and satisfaction Stretching > ESWT for early plantar fasciitis (all pts also got viscose heel pads in addition)	(311)
Chuckpaiwong (2009)	Retrospective case series	ESWT – preformed under tibial nerve block ESWT = Epos Ultra device (Dornier Med Tech. America, Inc., Atlanta, GA Single ESWT session of 3800 shocks, max 0.36mj/mm^2	225 pts	Mean 48.8 ± 10.1	Min 6M	12 months (max mean FU 30M)	Outcome measures: VAS (first steps), AOFAS ankle-hindfoot scale, Roles and Maudsley score Improvements seen following ESWT Diabetes, “psychological issues” and age – negative predictors of success	(312)
Greve (2009)	RCT	RCT: physio v rESWT rESWT = Swiss DolorClast radial shock wave device 10 physio sessions, including ultrasound, kinesiotherapy and stretching v. 3 sessions radial ESWT at weekly intervals + stretches	32 pts	Mean 47.3 ± 10.3 (range 25-68)	Min 3M	3 months	Both groups improved No difference between groups using VAS, duration of pain, use of analgesia	(281)
Gerdesmeyer (2008)	RCT	RCT: rESWT v placebo rESWT = Swiss DolorClast radial shock wave device 3 sessions at 2weeks ±4days apart Total 2000 shocks/session, at 0.16mj/mm^2	245 pts	Mean 52.2	Min 6M	12 months	Outcome measures: VAS, SF36, Roles and Maudsley score Effective - Primary outcome 12weeks, with 12M follow-up	(313)
Marks (2008)	RCT	DB RCT: rESWT v sham ESWT = Swiss DolorClast ; EMS, Nyon, Switzerland 3 sessions - 500 shocks 1st session, then 2000 shocks at sessions 2 and 3 at 3-day intervals, at 0.16mj/mm^2 / 2.5bar	25 pts	Mean 51.8 ± 12.5	Mean 30.3 days?	6 months	Outcome measures: VAS, Roles and Maudsley score Ineffective – both groups improved, but no difference between groups *(unclear duration of previous symptoms – table says days, text says months)*	(293)
Gollwitzer (2007)	RCT	DB RCT: F-ESWT v sham shockwave (ESWT = Duolith SD1 ESWT system (Storz Medical, Tägerwilen, Switzerland) 3 x weekly sessions 2000shocks/session at 0.25mj/mm^2	40 pts	Mean 56.4 (range 30-76)	Min 6M	3 months	Outcome measures: VAS, Roles and Maudsley score Found ESWT to be (non-significantly) effective, with 32% reduction in pain on top of that seen for placebo	(314)

Kudo (2006)	RCT	Multicentre DB RCT: ESWT v placebo (ESWT = Dornier MedTech Systems, GmbH, Germany Single session ESWT under LA medial calcaneal block, approx. 3800 shocks total – equivalent to total of 2330mj/mm^2 in total	114 pts	Mean 50.0	Min 6M Mean 29.2M	3 months	Outcome measures: AOFAS ankle-hindfoot score (pain/ROM domains), Roles and Maudsley Score, SF12, pain on palpation Effective	(315)
Malay (2006)	RCT	Multicentre DB RCT: ESWT v placebo ESWT = Orthospec (active ESWT) device ESWT - total of 3800 shocks without LA	172 pts (ESWT = 115)	Mean 51	Min 6M	3 months	Outcome measures: VAS – observer & participants scores ESWT more effective than placebo in those with radiographic heel spur only	(316)
Moretti (2006)	Case series	(case series of 54 running athletes) ESWT = electromagnetic lithotripter (Minilth SL1 by Storz Medical) 4 sessions of ESWT at weekly intervals – 2000 Pulses/sessions at average 0.04mj/mm^2	54 pts	Mean 35.2 (range 30-42)	Min 6M	Max 24 months	Outcome measures: VAS, US appearance Inclusion criteria required a radiographic heel spur Effective in all but 4 (3 required surgery, 1 declined)	(317)
Wang (2006)	RCT	Intervention group: single session ESWT (1500 impulses at 16kV) Control group: NSAIDs, orthotics, exercise programme, ± steroid injection	149 pts			60-72 months (5-6 years)	Outcome measure: 100-point composite pain/function score (pain - max 70 points, function - max 30 points) At follow-up, shockwave group (FU: 60-72 months) showed significant better pain / function than the control group (FU: 34-64months)	(318)
Rompe (2005)	RCT	3 weekly ESWT sessions performed either with or without local anaesthetic (2000 shocks, total energy flux density per shock at 0.09mj/mm^2	86 pts			3 months	Outcome measures: VAS Superior outcomes at 3-months in group without co-administered local anaesthetic	(299)
Theodore (2004)	RCT	Multicentre DB RCT: ESWT v sham ESWT (RCT data 3 months, ESWT f/u 12-month data) ESWT = Dornier Epos Ultra ESWT under LA medial calcaneal block, total of 3800 shocks (max 0.36mj/mm^2)	150 pts	Mean 51.5	"Min 6M" Mean 23M (range 3-120)	3 months	Outcome measures: VAS, AOFAS ankle-hindfoot score (pain/ROM domains), Roles and Maudsley Score, SF12, physical exam ESWT found to be more effective than sham -, particularly for those with symptoms >12M (Control group contained pts with symptoms <6M stipulated on inclusion criteria)	(297)
Haake (2003)	RCT	Multicentre single-blinded RCT: ESWT v placebo shocks ESWT = Dornier Epos Ultra lithotripter (Dornier Medizintech- nik, Wessling, Germany) 3 sessions at 2-weekly intervals (±2d) 4000 impulses (positive energy flux density 0.08mj/mm^2) under local anaesthetic	272 pts	Mean 53.0	Mean 13M (range 9-24M)	3 months / 1 year	Outcome measures: "success" defined by Roles and Maudsley Score, of 1 or 2, VAS (several domains), further Rx at 12m Ineffective – no difference between groups ¾ had god out comes at 1year	(319)

Hammer (2003)	Cross-over	ESWT v iontophoresis with diclofenac & oral NSAIDs – plus heel cups ESWT device = Piezoson 300 (Richard Wolf, Knittlingen, Germany), 3 sessions at weekly intervals without local anaesthetic (3000 impulses at 0.2mj/mm^2)	47 pts (49 feet)	Mean 48.5 (range 24-79)	Mean 9.2 (range 6-12)	24 months (cross-over after 3 months)	Outcome measure: VAS (several domains), Significant improvements seen in both groups, but no differences between groups for pain, but improved walking time Concluded that ESWT was effective	(320)
Rompe (2003)	RCT	RCT: ESWT v sham ESWT = Sonocur Plus, Siemens AG, Erlangen, Germany 3 sessions at weekly intervals of 2100 impulses (energy flux density of 0.16mj/mm^2)	45 pts	(Age not stated)	Min 12M	12 months	Outcome measure: VAS (first thing plus several other domains), AOFAS ankle-hindfoot score Study in recreational athletes Improved outcomes in ESWT group compared to sham at 6-months and 12-months	(321)
Speed (2003)	RCT	DB RCT: ESWT v sham ESWT = Sonocur Plus Unit (Siemens) 3 sessions at monthly intervals - 1500pulses at 0.12mj/mm^2	88 pts	Mean 52.1 (range 25-76)	Min 3M Mean 15.2 (range 12-312M)	3 & 6 months	Outcome measures: "success" – defined at 50% improvement in self-reported pain Both groups improved at 3-months and 6-months – ESWT not shown to be effective	(322)
Buchbinder (2002)	RCT	DB RCT: ESWT v placebo ESWT ESWT = Dornier MedTech EPOS (Extracorporeal Pain therapy and Orthopaedic System) Ultra (Dornier MedTech America Inc, Kennesaw, Ga) 3 sessions weekly – 2000-2500 shocks at 0.02-0.33mj/mm^2	160 pts	Mean 53.3	Min 6W (median 10M, range 2M – 18yrs)	3 months	Outcome measures: VAS, Maryland Foot Score, walking ability, SF-36, problem Elicitation Technique Score At 6 & 12 weeks – both groups improved, but no significant differences between groups for outcome measures studied ESWT not shown to be effective	(323)
Ogden (2001)	RCT	DB RCT: ESWT v placebo ESWT under ankle block anaesthetic ESWT = OssaTron® machine (High Medical Technology, Kreuzlingen, Switzerland) Single session of 1500 shocks at 18kv setting	302 pts	Mean 49.6 (range 20-79)	Min 6M (range 6m-18yrs)	3 months	Outcome measures: pain/pressure sensor, VAS, use of medication, self-assessment of activity Effective	(324)

Key: rESWT = Radial extra-corporeal shockwave therapy, F-ESWT = Focal / Focussed extra-corporeal shockwave therapy

In addition to the primary research studies, there have been a number of systematic reviews and several different meta-analyses published over the last 20 years which have examined the use of ESWT for the treatment of patients with plantar fasciitis in efforts to draw conclusions about its effectiveness. These have each drawn upon the evidence published to that date, and the more recent systematic reviews have suggested that ESWT appears to be both safe(282) and effective(189, 263, 325) in the treatment of patients with plantar fasciitis.

Limitations of the evidence-base as displayed in table 2.2, and which are specifically raised as an issue in one formal review,(301) include that while benefit is often shown, there are considerable differences in patient populations, including patient ages, duration of symptoms, duration of follow-up periods, as well as differences in the ESWT treatment regimens that were used in different studies. This makes formal conclusions harder from the information available. Furthermore, as there are no head-to-head studies of different ESWT machines / modalities / doses in patients with plantar fasciitis there is ongoing uncertainty when comparing different treatment protocols used in different studies.

Table 2.3 gives a very brief summary of the findings from these different reviews for the use of Extra-Corporeal Shockwave Therapy for patients with plantar fasciitis.

Table 2.3: Summary of published evidence for the use of Extra-Corporeal Shockwave Therapy (ESWT) for the treatment of patients with plantar fasciitis – systematic reviews / meta-analyses

1st Author (Year)	Design	Intervention / design notes	Findings	Ref
Babantunde (2019)	Systematic review and network meta-analysis	A total of 31 RCTs (n=2450 patients) included Comparing interventions for "plantar heel pain" – ESWT, CSI, NSAIDs, therapeutic exercise)	Available evidence does not suggest superiority of any one treatment over another Steroid injections ± exercise, and ESWT, were both most likely to have benefit in short-, medium, and long-term Exercise only – appeared to be effective only for longer-term pain	(189)
Xiong (2018)	Meta-analysis	Included 6 studies in meta-analysis Compared ESWT v CSI	Meta-analysis comparing ESWT and corticosteroid injections (CSI) for plantar fasciitis Both groups had significant. Improvements in pain and function – at 3months Significant improvement in VAS in ESWT compared to steroid injections – at 3months No significant differences between groups for PROMs studied – including FFI, MayoCSS or HFI	(326)
Roerdink (2017)	Systematic review	Included 39 studies (25 RCTs, 2 prospective & 1 retrospective cohorts Involving total of 2493 pts and average follow-up of 14.7 months	Systematic review examining complications following ESWT Concluded: "ESWT is likely to be safe" No complications are expected at 1-year follow-up, but any long-term complications are not known	(282)
Speed (2014)	Systematic Review	10 DB-RCTs included - (319, 323, 324), (292, 297, 313-316, 322)	Concluded that ESWT was effective in patients with plantar fasciitis, with some evidence of benefit from both Focussed ESWT (F-ESWT) and Radial ESWT (rESWT) Highlighted that the evidence suggests a dose-dependent response for F-ESWT	(263)
Aqil (2013)	Meta-analysis	7 prospective RCTs included (292, 293, 313, 314, 316, 321, 322) - total of 294 patients in ESWT group and 369 in placebo group, with minimum duration of symptoms of 3 months	Concluded that "ESWT is a safe and effective treatment of chronic plantar fasciitis refractory to nonoperative treatments " Significant improvements in VAS and Roles and Maudsley Scores v placebo – at 12 weeks post-ESWT Improves level of pain felt at first step by 60% & benefits are maintained for up to 12 months	(325)
Dizon (2013)	Meta-analysis	11 RCTs included involving patients with chronic plantar fasciitis	ESWT was effective in reducing morning pain Moderate-intensity ESWT was effective in reducing overall pain and activity-related pain Both moderate and high-intensity ESWT were effective in improving functional outcomes	(327)
Chang (2012)	Systematic review and Meta-analysis	12 RCTS (1431 patients) with plantar fasciitis comparing ESWT with placebo Focal ESWT (F-ESWT) and radial ESWT (rESWT)	Compared results of rESWT with F-ESWT (in 3 subgroups: low / medium / high intensity) Meta-analysis showed medium and high F-ESWT had reliably higher success rates and pain reduction than placebo, but low F-ESWT and rESWT less convincing due to large confidence intervals Meta-regression showed F-ESWT success rate not related to intensity, but elevated energy densities relived pain more rESWT "appropriate alternative (to F-ESWT) because of its lower price and probably better effectiveness"	(303)

NICE (2009)	Review	(IPG 311) The efficacy of 3 RCTs specifically are discussed, 2 comparing ESWT and sham ESWT, one versus conservative management Safety findings from 2 RCTs are discussed	Overall evidence is inconclusive - "The evidence on extracorporeal shockwave therapy (ESWT) for refractory plantar fasciitis raises no major safety concerns; however, current evidence on its efficacy is inconsistent." "Local anaesthesia may be used because high-energy ESWT can be painful. Different energies can be used and there is evidence that local anaesthesia may influence the outcome of ESWT." "The Committee found interpretation of the data difficult because of the diversity of treatment protocols and comparators used, varying reported end points, and inconsistencies in terms of the use of local anaesthesia and energy type. The results of studies conflicted and there was evidence of a substantial placebo response. Previous guidance on this procedure published in 2005 had found the evidence on efficacy inadequate, and new evidence has not been published to alter that view. "	(51)
Rompe (2007)	Editorial letter	.	Concluded that ESWT was effective	(328)
Rompe (2007)	Review	Identified 17 articles, involving 2100 patients	Possibly effective – but conflicting results from published works Specifically highlighted the heterogeneity from published research, including the type, frequency and dose of ESWT administered, the period of time between ESWT sessions, and the follow-up arrangements	(301)
Crawford (2003)	(Cochrane) Review	Identified 5 RCT studies – with different doses of energy including (323, 324) plus 3 earlier studies	Inconclusive - Evaluated results from 5RCTs and found the results are equivocal. There was some evidence from two studies that suggest a higher dose may be better, but a further study did not reach the same conclusion. Highlighted that one study showing improvement over placebo only demonstrated only a 6% improvement over placebo- (324)	(81)
Ogden (2002)	Meta-analysis	Meta-analysis of 8 studies, (results from 322 patients) – from 22 identified studies / 1601 patients	Concluded that ESWT is "shown to be safe and effective" Considered that ESWT should be considered prior to surgery, and may be preferable to steroid injections …	(329)
Boddeker (2001)	Review	Identified 21 articles, but none fulfilled the methodological robustness criteria	Efficacy is unclear due to limited robust evidence	(330)

Key: rESWT = radial extra-corporeal shockwave therapy, F-ESWT = Focal / Focussed extra-corporeal shockwave therapy

In addition to plantar fasciitis, ESWT is used in a range of other conditions, including various tendinopathy conditions. These have a variable evidence-base, but this is outside the remit of this thesis which examines interventions for patients with plantar fasciitis. In the United Kingdom, the National Institute for Health & Clinical Excellence (NICE) have given guidance on the use of ESWT for a range of conditions including plantar fasciitis (IPG 311 – Aug 2009)(51), and also for a range of other tendinopathy conditions, including: calcific rotator cuff tendinopathy (IPG21 – Nov 2003)(331), Achilles tendinopathy (IPG312 - Aug2009)(332) which has now been superseded by (IPG571 – Dec 2016)(333), Tennis elbow (IPG 313 – Aug 2009)(334) and Trochanteric pain (IPG 376 – Jan 2011)(295) In addition ESWT has had permission from the USA FDA for its use in plantar fasciitis from 2000, and also for its use in treating tennis elbow in 2002.(261)

Although there is now a good evidence base showing benefit for patients with plantar fasciitis with ESWT there remain many areas of uncertainty, and in the United Kingdom NICE have called for more research to support clinical practice.(51) The effectiveness, dose, frequency, type, and number of ESWT treatment sessions all remains unclear for patients with plantar fasciitis. Additionally, the different primary studies have used specific devices, and there remain no direct comparison studies looking at the effectiveness of different ESWT devices. Additionally, several studies have treated patients with symptoms of “acute” plantar fasciitis (i.e. <6weeks), (278, 311) or have included patients with “chronic” symptoms, but often of far shorter duration that that seen in routine NHS secondary care clinics, or used only a short-term follow-up.(277, 286, 288, 305) Therefore it is not clear how directly transferable results may be to the population typically seen in NHS hospital clinics with longer-duration of symptoms and any longer-term benefits that may be expected.

Whilst there is evidence of benefit following treatment with ESWT for patients with plantar fasciitis, uncertainties remain about the magnitude of the therapeutic benefit, particularly in patients with chronic symptoms, and the impact that any reduction in pain may have on global markers of well-being or function.

These issues are investigated further in this thesis, initially through the use of a prospective case series using a single ESWT device with multiple outcome measures assessing aspects of both local and global functioning. The information from this was then used to construct a double-blinded randomised control trial to investigate this area more robustly in a population with chronic plantar fascia pain. These studies are presented in Chapter 6.

2.2.3 - Treatment option: Autologous Blood Injection (ABI)

Injections of blood products have been used to treat plantar fasciitis and a range of other tendinopathies. In general terms, this covers two main types of procedures, that of injection of a small quantity of unfractionated / whole blood (called Autologous Blood Injections or ABI), or an injection of a fractionated portion of blood (called Platelet-Rich Plasma or PRP). For the purposes of this literature review, both injection modalities are considered. In the ABI procedure, typically 3-4mls of whole blood is obtained by venepuncture from the patient and then injected under ultrasound guidance into the area of damage of the tissue/tendon. A variation on this injection is to take a larger amount of blood, typically 30-40mls of blood, and to centrifuge this sample to separate its contents. A small proportion of this (the plasma which contains a range of growth factors and platelets) is then injected into the area of damage seen. The underlying concept behind this approach, is that this centrifugation increases the concentration of different growth factors that may be involved in tissue healing.(335) This procedure is called a Platelet-Rich Plasma (PRP) injection. The PRP intervention is not necessarily the same across all studies as there are a number of different commercial products available in the UK with varying concentrations of injectate, from 1.6-times to at least 6-times the concentration in circulating whole blood.(32-35) There are no studies directly comparing outcomes using different PRP solutions, and there is very limited evidence directly comparing PRP injections with ABI in any tendinopathy condition.(336-338)

Proposed mechanisms of actions of the injection of blood products, include the effects of various growth factors from within the injectate, many of which are potentially involved in tendon repair. These include different Platelet-Derived Growth-Factors (PDGF), Vascular Endothelial Growth Factor (VEGF), and Transforming Growth Factor-B (TGF-B).(335, 339, 340) However, the evidence for these mechanisms remains unproven. Whilst the concentration in whole blood (ABI) may be known, most studies that involve the use of PRP have made no attempt to assess the concentration in their injectate of any of these factors, even though they often describe their view of the importance of the increased concentration of the growth factors in PRP.(341, 342)

In 2010 the IOC published a consensus paper on the use of PRP in sports medicine which reviewed the basic science and any potential role of PRP in tendon injuries.(35) This drew upon nine studies that had been published to that point, including four randomised studies although the IOC review group considered that only three studies had adequate methodological rigour for them to be able to draw any reliable conclusions. This review concluded that the results seen did not demonstrate any significant benefit from PRP injections.(35) However, this review considered PRP injections in sports medicine practice in general, including any possible roles in muscle injury, tendon injury, and cartilage injury, but did not include any studies that specifically focussed on the use of PRP injections for treating patients with chronic plantar fasciitis. There have been multiple other publications since that time of varying quality that are reviewed below which have looked at any possible role in the management of patients with plantar fasciitis or tendinopathy.

In 2013, the National Institute for Health & Care Excellence (NICE) issued updated guidance on the use of autologous blood injections for plantar fasciitis(52) and also for other tendinopathy conditions.(343) These two documents supersede the previous 2009 NICE guidance & audit support documents (IPG279).(344, 345)
The first paragraph from the 2013 NICE guidance for the use of autologous blood injection for plantar fasciitis (NICE IPG 437 - Jan 2013) highlights the ongoing uncertainties and the need for further research, it reads as follows:

> "*The evidence on autologous blood injection for plantar fasciitis raises no major safety concerns. The evidence on efficacy is inadequate in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research."* (52)

From the available evidence, PRP injections do not appear to be any safer and has not been shown to be any more effective than ABI.(336-338) The PRP injection takes longer to perform due to need to centrifuge the blood before injection that is required as a part of the procedure, and is significantly more expensive to perform, with some manufacturers charging in excess of £200 per patient treated for the consumables required. From the published work available it is not yet clear that this additional cost and time is of clinical benefit.(336-338)

Whilst the precise mechanism of action of blood injections remains unclear, both ABI and PRP injections are thought to promote a healing response in the damaged structures and these two injection treatments are grouped together in this literature review for simplicity, although it is recognised that there may be differences between these two procedures and their outcomes. To examine if differences may exist between outcomes following ABI and PRP in patients with plantar fasciitis, one prospective cohort study compared 34 patients with plantar fasciitis who had received either ABI or PRP and showed that both groups had significant improvements in pain, function, and plantar fascia thickness but found no between-group differences identified at the final 3-month follow up.(336) However the lack of randomisation in this study may have introduced bias, thereby affecting the results, and the relatively short duration of follow-up gives uncertainty as to longer term outcomes.

Two further studies have directly compared the outcomes following either Autologous Blood Injection (ABI) or Platelet-Rich Plasma (PRP) injections for patients with tennis elbow / lateral elbow tendinopathy using a randomised control trial design. However, whilst there may be some equivalence between tennis elbow and plantar fasciitis as conditions, any direct implications for patients with chronic plantar fasciitis remains unclear. The first study, which involved 28 patients with tennis elbow, compared the outcomes following ABI to those seen following PRP injections, with a 6-month follow-up, and found that although improvements in levels of self-reported pain were better with the PRP group, this did not correlate to a change in functional outcome as recorded by the Liverpool elbow score.(337) A separate, and much larger, study which involved 150 patients with tennis elbow compared the outcomes following PRP or ABI, and found no significant difference in reported success rates between the two groups over a 6-month follow-up period, but found a higher rate of conversion to surgical treatment in the ABI group compared to the PRP group (20% v 10%), the clinical significance of which was unclear to the authors.(338) These two studies leave some uncertainty about any possible differences between different specific injection therapies with blood and blood products.

When considering the evidence for the use of the injection of blood products in patients with plantar fasciitis (including both ABI and PRP injections) there may be some evidence of benefit, and a summary of the primary research studies identified in this review is displayed in table 2.4. Many of the published studies have utilised a case series approach, without the use of a comparator group. (346-349) This means that results are less reliable than when a direct comparison group is used and any benefit that is seen cannot be reliably ascribed to the injection therapy itself. In addition, many of the RCTs that have been undertaken were unblinded, which may allow bias to influence results.(342, 350) There were however some RCTs that took specific steps for blinding of participants and observers with two double-blinded RCTs, thought to be the “gold standard” for clinical trials, identified in the literature which have examined the use of injected blood products versus a comparison treatment.(351, 352)

In addition to blinding, there were also a number of other limitations in methodology that can be identified from the published RCTs. In some RCTs the randomisation processes were of poor rigour, with at least one RCT utilising a sequential numbering systems i.e. odd number patient = Group A / even = Group B.(353) Whilst these are simple to run, this process may be considered inadequate as this does not allow reliable blinding and may potentially allow unconscious bias regarding patient selection. Other RCTs have described the use of sealed envelopes to perform group allocation, significantly improving the rigour of this part of the study.(351) The inclusion criteria of different studies were also variable with many studies involving patients with a very short duration of symptoms, some with only 6-8 weeks(354) or 3-months duration(355-357). This is a period of time in which natural resolution may reasonably be expected to influence recovery thereby giving an artificially positive response following treatment.(2, 4, 40) This short duration of symptoms may not be representative of the patients seen in the NHS secondary care sector, who often have much more chronic symptoms.(346, 358) Follow-up periods for many studies were often of short-duration, often only 3-months, giving no information as to longer term outcomes.(336, 355, 359) Lastly, the choice of outcome measures were heterogenous between different studies, with many often using only a simple 0-10 pain score, rather than validated PROMs, and with very few considering anything other than local foot function with no wider measurement of patient global health or

function.(349, 357, 359-361) Due to these limitations, there remains uncertain evidence to draw upon to best advise patients who suffer with chronic plantar fasciitis and who may be considering an injection of blood products.

Typically, injection comparison studies have shown improvements in each of the treatment groups studied, with no significant differences seen between different treatment modalities. However, limitations often exist in approaches undertaken in different studies. For example, one study has sought to compare outcomes from PRP injections with corticosteroid injections in patients with chronic plantar fasciitis symptoms of at least 6-months, and suggested a superiority in the longer-term with PRP, with all participants receiving a total of three injections of either modality, performed on a weekly basis.(362) However there remain a number of uncertainties from the methodology of this manuscript; it is not clear if participants were randomised or not, the nature of any blinding (if any) of the study, and what medication/dose the participant in the steroid injection group received. Additionally, the use of 3 corticosteroid injections performed at weekly intervals does not replicate routine UK clinical practice, and although this potentially facilitated participant blinding, it is not clear that this is an adequate comparator group. One further RCT, involving 60 patients with plantar fasciitis and which had a 12-month follow-up period, compared PRP with steroid injections, found that whilst the two treatments were equivalent in outcome at the short-term time points (3- and 6-months), there were improved outcomes in the PRP group compared to the steroid injection group at 12-months follow-up.(350)

The design of injection studies and choice of comparison procedure is also an important consideration. An injection of saline has been used as a comparison procedure in a couple of studies as a proposed “placebo” injection. However, in a small double-blinded RCT investigating the effects of PRP injections, the saline injection group has been found to have improvements in pain at six-months and twelve-months when compared to baseline figures,(363) although the small numbers and up to 50% loss to follow-up make formal conclusions unreliable. These benefits could potentially have arisen from the injection technique, the saline, the rehabilitation or the effect of time itself. In a larger three-arm study which used PRP and corticosteroid injections in active treatment arms, and a saline injection in a third

(control group) arm, no significant changes from baseline were seen in this control group unlike those benefits seen in the other two groups of the study.(352) This issue remains an important consideration when developing research studies and also assessing the results of any injection study.

In addition to work comparing blood injection treatments against steroid injections or presumed placebo injections, there have been several individual studies that have compared injection of blood products with other treatment modalities which have often shown broad equivalence in outcomes. These include studies comparing against options such as rehab alone or Extra-Corporeal Shockwave Therapy (ESWT)(287), dextrose prolotherapy injections(364), surgery (in the form of endoscopic surgical fasciotomy)(365), or even low dose radiotherapy.(366) This latter study compared PRP with low-dose radiotherapy in 40 sportspeople with an average of at least 6-months plantar fasciitis and this showed that both groups improved in measures of pain, AOFAS score, and plantar fascia thickness, but that there were no statistically significant differences in outcomes between the two groups.(366) Whilst PRP is a treatment that is in use in the UK, due to the tight regulations concerning the use of ionising radiation it is unlikely that radiotherapy, even at “low-dose” will be available in the NHS for patients with chronic plantar fasciitis at this current time. (For the sake of completeness, this modality is briefly discussed in section 2.2.4 of this thesis) However very few of these studies that have compared two different interventions were double-blinded in design, potentially allowing investigator or participant bias to influence outcomes.

A small study involving patients with symptoms of plantar fasciitis randomised 54 participants to receive either autologous conditioned plasma (ACP - which is a less concentrated form of PRP), radial-Extra-corporeal Shockwave Therapy (ESWT), or rehabilitation exercises alone.(287) At six-months with observers blinded to treatment allocation, the study found that both the ACP and ESWT groups were doing better than the rehab-only group, but the only difference between the two interventional groups was that the ACP group had a greater reduction in plantar fascia thickness. This was a small study, which sought to examine effectiveness of two specific interventions in addition to rehabilitation, and although the small participant numbers make reliable conclusions difficult, the question as to whether

one intervention has superior results to another is the question that is often posed by patients to their treating clinicians. This topic is investigated further in Chapter 8.

Table 2.4 gives a brief summary of some of the evidence from primary research studies for the use of the injection of blood products, both Autologous Blood Injections (ABI) and Platelet-Rich Plasma (PRP), for patients with plantar fasciitis.

Table 2.4: Summary of published evidence for the use of injected blood products (ABI / PRP) for the treatment of plantar fasciitis – primary research studies

1st Author (Year)	Design	Intervention	number	Age in years (range)	Symptom duration In months	Follow-up period	Notes / Outcomes	Ref
Garhwal (2018)	RCT	PRP v CSI	63	Mean 39.7	Not stated	24 weeks	Outcome measures: VAS, AOFAS Results favoured steroid injection at 12wks and PRP at 24wks	(353)
Jain (2018)	Unblinded RCT	PRP v CSI	80	Mean 38 (range 23-65)	Min 3M Mean 7.5M (range 3-11)	6 months	Outcome measures: VAS, Roles & Maudsley score, AAOS Foot & Ankle Outcome Instrument, AOFAS, US thickness Statistically significant decrease in VAS, & AOFAS score in both groups – no differences between groups	(342)
Johnson-Lynn (2018)	Double-blinded RCT	PRP v saline	28	Mean 50.0 (range 32-74)	Min 6M	12 months	Outcome measures: VAS, painDETECT Titled a "feasibility study" - had >25% loss to follow-up at 6M / 50% at 12M Improvements in VAS, and painDETECT in both groups – but authors state study was under-powered No differences seen between groups	(363)
Kirmani (2018)	Case series	ABI	55	Average 44 (range 30-65)	Min 6 months (range 6-22M)	Mean 8 months (range 6-12M)	Outcome measures: VAS Statistically significant improvement	(367)
Mahesh (2018)	Case series	PRP	100	Mean 39.4 (range 21-60)	Min 6 weeks	6 months	Outcome measures: VAS, AOFAS Significant improvements in both outcome measures at all time-points	(368)
Rastegar (2018)	Single-blinded RCT	Dry needling (30sec) v corticosteroid	66	Mean 40.9	Min 3M	12 months	Outcome measures: VAS Corticosteroid greater effect than dry needling at 3 and 6-weeks No difference at 3-months and 6-months Dry needling greater effect than steroid at 12-months (included patients with symptoms of 3months+)	(341)
Thora (2018)	RCT	PRP v CSI	60	.	.	12 months	Outcome measures: VAS, AOFAS At 6weeks steroid group performing better than PRP group, but at 12 months PRP showed improvements greater than steroid group	(369)
Acosta-Olivo (2017)	Double-blind RCT	PRP v CSI	28	Mean 44.8 (range 24-61)	Min 3M	16 weeks	Outcome measures: VAS, AOFAS, FADI No significant differences between groups at baseline, interim and final follow-up with any measures used	(351)
Baz (2017)	Case series	PRP	44	Mean 46.5 (range 14-58)	Min 6M	4 months	Outcome measures: VAS, Roles & Maudsley score, US thickness Improved VAS from 8.14 at baseline to 2.59 at 4M Reduced PF thickness at 2M and 4M post injections	(370)
Bhat (2017)	Case series	ABI	32	Mean 42.4	Min 6M (range 6-20)	6 months	(published in IJRMS) - Of uncertain quality Outcome measures: VAS - reduced from 6.9 to 4.28 at 3-months	(371)

Kadam (2017)	Case series	PRP	40	Mean 45.8 (range 25-75)	Min 6M	3 months	Outcome measures: VAS “promising short-term results” – 3 months Mean VAS at baseline - 7.15, 1-week 6.2, 6-week was 5.62, 3-month was 3.2, but no p-values included to quantify significance	(359)
Karimzadeh (2017)	RCT	ABI v CSI v rehab	36	Mean 47.5	Min 8 weeks (mean 8.9 months)	12 weeks	Outcome measures: VAS, Plantar fasciitis pain/disability scale (PFPS), pressure-pain threshold At 4 weeks steroid group faring best At 12 weeks both steroid and ABI group doing better than rehab only	(354)
Kukreja (2017)	Unclear ?RCT	PRP v CS (3 weekly injections both groups)	40	Mean 51	Min 6M	12 months	Outcome measures: VAS, AOFAS, Roles & Maudsley score Unclear methodology - unclear if an RCT or prospective cohort Significant better outcome PRP than steroid injection at 3, 6 and 12 months (published in Med Journal of Dr D.Y Patil University) -poor quality, unclear steroid or dose, unclear if randomised or blinded	(362)
Gogna (2016)	RCT	PRP v low-dose radiotherapy	40	Mean 27.6	Min 6M Range unknown	6 months	Outcome measures: VAS, AOFAS, PF thickness on US 40 “sportspeople”, unknown level Both groups improved, no differences in outcomes of pain, AOFAS score and plantar fascia thickness between groups	(366)
Mahindra (2016)	Double-blind RCT	PRP v CSI v saline	75	?	Min 3M	3 months	Outcome measures: VAS, AOFAS Significant improvements in VAS & AOFAS in PRP & CSI group, but not the placebo group No between-group comparisons	(352)
Sherpy (2016)	Single-blinded RCT	PRP v CS injection	50	Mean 38.0	Min 3M Mean 7.25 / 7.58 months	3 months	Outcome measures: VAS, SF36 Significant improvement in VAS and SF36 in both groups at 3months, but not at 1.5 months PRP group significantly better than CS injection at 1.5months for VAS Improved echogenicity, but no significant change in PF thickness in either group	(355)
Vahdatpour (2016)	Single-blinded RCT (observer-blinded)	PRP v ABI	34	Mean 46.5	Mean 29M	3 months	Outcome measures: VAS (“overall”, “morning”, “walking”) Roles & Maudsley score, US thickness (some differences in baseline data between groups) Significant improvements in pain, function, PF thickness seen in both groups – no differences between groups	(336)
Afsar (2015)	Single-blinded RCT	ABI v corticosteroid	130	Mean 21.8 (range 18-50)	Min 3M	24 weeks	Outcome measures: VAS? No difference between injections at follow-up of up to 24 weeks (included patients with 3-month duration of symptoms)	(357)
van Egmond (2015)	Case series	PRP	61	Mean 48. Outcome measures: VAS,7	Min 3M	Mean 16.2 months	Outcome measures: FFI, satisfaction 4-part Likert scale Mean FFI improved from 69.4 to 31.8	(372)

Jain (2015)	RCT	PRP v CSI	60	Mean 55.6 (range 31-79)	Min 12M	12 months	Outcome measures: VAS, AOFAS, Roles & Maudsley score At 3M & 6M – PRP equivalent to CSI At 12M – PRP significantly better than CSI	(350)
Othman (2015)	RCT? (unclear)	Endoscopic plantar fasciotomy (EPF) v PRP	50	"Average": 39.1 / 36.0 (range 22-51)	Min 6M "average" 11.0 / 11.6	Average 18.2 / 17.5 months (range 6-42)	Outcome measures: VAS, AOFAS, Roles & Maudsley score – only pre & final scores reported Unclear randomisation process (if any) At final f/u VAS improved in EPF group from 8.28 to 2.35, in PRP group from 8.22 to 2.90, both were significant, but no significant difference between groups AOFAS score improved significantly in both, but no significant differences between groups	(365)
Wheeler (2015)	*Case series*	*ABI*	*62*	*Mean 52.5 (range 25.6-80.4)*	*Min 4M* *Mean 50months (range 4-360months)*	*Mean 21 months*	*Outcome measures: VAS, FFI-r* *Average reduction in VAS of 84%* *55% patients reported as pain-free (VAS=0), and 68% as virtually pain-free (VAS=0-1) at average follow-up of 631 days*	(346)
Kim (2014)	Single-blinded RCT	PRP v dextrose injections	21	Mean 37.0 (range 19-57)	Min 6M Mean 2.8/2.9yrs (range:1-6yrs)	6 months	Outcome measures: FFI 2 injections of either PRP or 2ml dextrose/lidocaine at 2-weekly interval Statistically significant improvements in FFI total & subcategory scores for both groups, no statistically significant difference between groups at any follow-up	(364)
Monto (2014)	Single-blinded RCT	PRP v CSI	40	Average 59 (range 24-74)	Min 4M	24 months	Outcome measures: AOFAS, Clinically and statistically improved outcomes favouring PRP at 3, 6, 12 and 24-month Steroid injection group improved only at 3M, then worsened PRP group improved at all time-points	(373)
Say (2014)	Non-randomised cohort study	PRP v CSI	50	Mean 47.5	Min 3M	6 months	Outcome measures: VAS, AFAS Significantly improved improvements in VAS and AFAS scores in PRP v CSI groups	(374)
Shetty (2014)	Non-randomised cohort study	ABI v CSI	60	Mean 36.6	Min 3M	3 months	Outcome measures: VAS, FADI, AFAS Improved outcomes with PRP with all outcome measures	(356)
Wilson (2014)	Case series	PRP	24	Mean 44 (range 21-60)	Min 3M	32 weeks	Outcome measures: FAAM, Foot-SANE, SF-12v2 Improvement in outcomes at 32w (75% response rate)	(347)
Chew (2013)	RCT	ACP v ESWT v rehab alone	54	Mean 46.1 (range 29-71)	Min 4M (range 6-24M)	6 months	Outcome measures: VAS, AOFAS, PF thickness on US Treatment with either ACP or ESWT better than rehab alone, although no differences between ACT & ESWT except PF thickness (greater reduction in ACP group)	(287)
Kumar (2013)	Case series	PRP	50	Mean 51 (range 25-79)	Min 12M	6 months	Outcome measures: VAS, AOFAS, Roles & Maudsley score Significant improvement at 3M & 6M ion	(348)

Martinelli (2013)	Case series	PRP	14	Mean 49.2	Mean 9.9±2.2M	12 months	Outcome measures: VAS, Roles & Maudsley score VAS improved from 7.1±1.1 to 1.9±1.5	(349)
O'Malley (2013)	Retrospective case series	PRP	23	Mean 47 (range 25-63)	Min 6M Average 9 months (range 6-12)	Average 6 months (range 6-10M)	Outcome measures: VAS, SF-12, FAOS 5 patients had 2 injections, 1 month apart Mean VAS significantly improved 5/23 required surgical release for ongoing symptoms	(375)
Tiwari (2013)	Cohort	PRP v CSI	60	(range 30-85)	Median 6M (range 1-120)	6 months	Outcome measures: VAS PRP better outcomes than CSI at 1, 3 and 6-months	(360)
Wheeler (2013)	*Case series*	*ABI*	*35*	*Mean 52 (range 26-74)*	*Min 4M* *Mean 48months (range 4-360months)*	*Mean 6 months*	*Outcome measures: VAS* *average reduction of VAS of more than 85% post-ABI for all enrolled patients, increasing to nearly 90% in patients with at least 2-months follow-up data.* *At the latest F/U 53% of all patients were pain-free, increasing to 71% of patients with at least 2 months of follow-up data.*	(358)
Aksahin (2012)	Non-randomised cohort study	PRP v CSI	60	Mean 46.0	Min 3M	6 months	Outcome measures: VAS, Roles & Maudsley score Both groups improved, no significant difference between groups	(376)
Omar (2012)	RCT	PRP v CSI	30	Mean 43.5	Not reported	6 weeks	Outcome measures: VAS, FHSQ Both groups improved, no significant difference between groups	(377)
Rabag (2012)	Case series	PRP	25	Mean 44	Min 6M	Mean 10M (range 9-13)	Outcome measures: VAS, US appearance & thickness VAS decreased from 9.1 to 1.6/10 Significant changes in US thickness and intensity	(378)
Lopex-Gavito (2011)	Case series (mixed group)	PRP	(10)*	Mean 43 (range 23-56)	Min 12M	12 months	*(case series involved patients with Achilles insertional tendinopathy and plantar fasciitis, heterogenous group) Outcome measures: VAS, AOFAS	(379)
Scioli (2011)	Case series	PRP	30	Not stated	Not stated	12 weeks	Outcome measures not specified Follow-up specified as 6w and 12w Reported "benefit in all but 2 patients"	(380)
Kalaci (2009)	Multicentre RCT	CSI v ABI v peppering	100	.	.	6 months	4 groups: ABI v peppering v CSI v CSI + peppering Improvements in all 4 groups / most improved in CSI + peppering	(381)
Lee (2007)	Single-blinded RCT	ABI versus CS	64	Mean 48.3 / 49.2 (range 28-66)	Min 6 weeks Mean 7.2 / 8.3 months (range 2-24M)	6 months	Outcome measures: VAS, "tenderness threshold" The reduction in VAS for both groups was significant ($p < 0.0001$). At 6 weeks and 3 months, the corticosteroid group had significantly lower VAS than the autologous blood group ($p < 0.011$ and $p < 0.005$, respectively), No significant difference between groups at 6 months.	(361)
Kiter (2006)	RCT	ABI v LA v CSI	44	.	.	6 months	Outcome measures: VAS, AOFAS Improvements seen from baseline, but no significant differences between the groups	(382)

Key: "ABI" = Autologous Blood Injection, "ACP" = Autologous Conditioned Plasma (a "weaker strength" concentrate than "true" PRP), "CS" = Corticosteroid, "LA" = Local Anaesthetic, "PRP" = Platelet-Rich Plasma Injections, Outcome: "AOFAS" = American Orthopaedic Foot & Ankle Society Ankle-Hindfoot score (a combination clinician- and patient-rated score)

In addition to the primary research studies, there have been a number of systematic reviews published in the last few years which have looked at the injection of blood products as a treatment for a range of conditions (including plantar fasciitis) to try to draw conclusions about the effectiveness of this treatment. All but one of these systematic reviews have focussed on the evidence for PRP injections (using centrifuged and fractionated blood) rather than ABI (using whole blood constituents.)

The different systematic reviews have identified studies based on their published dates and the different inclusion criteria. Some of these reviews have examined a range of different tendinopathy conditions or injection therapies generally, whereas others have focussed purely on injections of blood products for patients with plantar fasciitis. The largest of these systematic reviews included twelve studies,(383) whereas the smallest reviewed only two studies.(384) One systematic review (383) has specifically highlighted the heterogeneity of different studies and the challenges that this creates when reviewing the evidence base. As highlighted in the previous section, different studies have used different interventions, have treated potentially different patient populations with different minimum duration of symptoms, have used different outcome measures, and undertook different follow-up periods.

The following table (table 2.5) gives a very brief summary of the findings from these different systematic reviews for the use of the injection of blood products, both Autologous Blood Injections (ABI) and Platelet-Rich Plasma (PRP), for patients with plantar fasciitis

Table 2.5: Summary of published evidence for the use of injected blood products (ABI / PRP) for the treatment of plantar fasciitis – systematic reviews / meta-analyses

1st Author (Year)	Design	Intervention	Notes / Outcomes	Ref
Singh (2017)	Systematic review and meta-analysis	PRP v CSI	10 studies, involving 517 patients included - 7 randomised studies (351) (355) (350) (352) (373) (360) (377) & 3 non-randomised (374) (356) (376) Outcome measures: VAS, AOFAS, FADI score VAS & AOFAS scores – no difference between groups at 1-month, improved outcomes in PRP v CSI group at 3M, no difference at 6M	(385)
Chiew (2016)	Systematic review	PRP	12 studies included: 4 RCTs (355) (350) (364) (373), plus 7 prospective and 1 retrospective cohort studies (374) (356) (347) (348) (349) (375) (376) (378) Heterogeneity noted from included studies Concluded that PRP "*may provide an effective alternative*" with no obvious complications and "*The onset of action depended on the degree of degeneration*"	(383)
Tsikopoulos (2016)	Systematic review and meta-analysis	All injections	Systematic review injection therapy in plantar fasciitis, included 22 trials overall across a range of injection therapies, including 7 studies for injection of blood products (360) (382) (361) (364) (373) (377) (381) Concluded: "*for PRP injections, the quality of the existing RCTs did not allow us to create safe conclusions about the efficacy of this therapy*." And "*Pooled results showed that platelet-rich plasma injections were effective for the treatment of plantar fasciopathy at 0– 6 months. However, conclusions about this therapy were limited by the quality of the included head-to-head comparisons on platelet-rich plasma.* "	(21)
Tsikopoulos (2016)	Systematic review and meta-analysis	ABI v CSI (plantar fasciitis & epicondylitis)	Included a total of 9 RCTs for plantar fasciitis and epicondylitis – n=3 for plantar fasciitis (381) (361) (382) Conclusions of the review were limited due to bias present in the primary research studies Steroids were marginally superior to ABI for plantar fasciitis s at 2-6 weeks, no significant differences following this	(386)
Hsiao (2015)	Network Meta-analysis	"Blood products"	"conflicting results" in chronic plantar fasciitis (>3M duration) Included 5 studies of blood products v CSI, including - (381) (361) (377) (356, 360) & 1 study blood products v ESWT - (287) Trend favouring blood products over CSI for pain reduction at 3M, and statistically significant difference with PRP as sub-group Comparing blood v ESWT v CSI: 78.3% chance blood products being best for pain relief at 3M, but at 6M dropped to 41%, with odds slightly favouring ESWT	(387)
Franceschi (2014)	Systematic review	PRP	Included 8 of 164 initially identified articles – only 3RCTs identified (373) (364) (377), plus 5 case series/cohort studies (347) (348) (349) (378) (376) All papers reported significant improvement at outcomes No paper reported major complications	(388)
Kaux (2013)	Systematic review	PRP (in tendinopathy)	Reviewed evidence for a range of tendinopathies – included 2 studies involving patients with plantar fasciitis (376) (378) Describes results from these two studies, with 1 being positive, the other showing no difference between PRP & CSI	(384)
de Vos (2010)	Systematic review	Autologous growth factors (in tendinopathy)	Reviewed evidence for a range of tendinopathies - included 3 studies for patients with plantar fasciitis (361) (381) (382) Limited evidence of benefit, but lack of good quality evidence. Most reviewed studies had poor methodological quality; no studies shown benefit for autologous growth factor when compared to a control group	(389)

Key: "ABI" = Autologous Blood Injection, "ACP" = Autologous Conditioned Plasma (a "weaker strength" concentrate than "true" PRP), "CS" = Corticosteroid, "LA" = Local Anaesthetic, "PRP" = Platelet-Rich Plasma Injections, Outcome: "AOFAS" = American Orthopaedic Foot & Ankle Society Ankle-Hindfoot score (a combination clinician- and patient-rated score)

The earliest of the systematic reviews investigating any effect of injection of blood products to treat patients with plantar fasciitis was published by de Vos et al in 2010.(389) This identified three studies involving patients with plantar fasciitis, and concluded that there was some evidence of benefit, however that the lack of good quality evidence made conclusions unreliable. Subsequent reviews involving patients with plantar fasciitis have found significant improvements in outcome measure following injections at both 3-month and 6-month follow-up periods, and with no major safety concerns identified.(383, 388) However these have also found limited or no differences identified when blood product injections are compared with other injection modalities.(383, 388) The most recent systematic review and meta-analysis, which used both a 0-10 numerical pain score and the validated AOFAS ankle/hindfoot score, has found that when comparing PRP and corticosteroid injections in patients with plantar fasciitis, there were no differences between groups at 1-month, with results favouring the PRP group at 3-months, and again no difference between groups at 6-months following injection procedure.(385) This differed slightly from a previous systematic review that demonstrated improved outcomes in a steroid injection group compared to a PRP injection group at 2-6 weeks, but that at other time points studied (up to 6-months) there were no differences between the two groups.(386)

One meta-analysis has compared the injection of blood products with other treatment options in patients with plantar fasciitis of more than 3-months duration, and has highlighted the conflicting evidence between different primary studies.(387) This review has concluded that there was a trend favouring steroid injections over other treatment options at 3-month follow-up periods, with comparisons between blood injections, steroid injections, or shockwave showing a 78% chance that blood injections are the best single option at 3-months, with this dropping to 41% at 6-months, favouring shockwave therapy.

In summary, the evidence from the systematic reviews has shown no significant safety concerns from the injection of blood products in the treatment of plantar fasciitis. These reviews have shown that there are significant improvements in some aspects of recorded pain or foot function following blood injections, but there are

uncertainties that remain as to any differences when comparing PRP to steroid injections or when comparing against other treatments for patients with plantar fasciitis.

In addition to plantar fasciitis, the injection of blood products is also used in a range of other tendinopathy conditions with a conflicting evidence base of benefits. Recent systematic review level evidence has questioned the apparent benefit that was seen in earlier studies, and for tennis elbow has concluded there is an strong evidence of the absence of any benefit.(390) An earlier systematic review found only pilot-level evidence to support the use of autologous blood injections (as well as other treatments) in patients with tennis elbow.(113) In patients with patella tendinopathy a systematic review of PRP injections identified 11 studies, however only 2 were RCTs, and from this the only conclusions that could be drawn was that this treatment appeared to be safe, but the efficacy remained unproven.(391) Conflicting evidence for benefit was found in a systematic review of injectable therapies for Achilles tendinopathy.(392) One recent systematic review showed no benefit over placebo for blood product injections in patients with Achilles tendinopathy.(393) Overall, the initial positive findings from early publications are being tempered by subsequent research highlighting uncertainties of benefits following the use of blood injections across a broad range of tendinopathy conditions.

Given the uncertainties that surround the use of the injection of blood products, and their continued use in clinical treatment, this treatment was investigated further during this research. This was undertaken initially as a case series with longer-term follow-up. The information from this was then used to create a double-blinded randomised controlled trial to examine this treatment option more robustly. These two studies are presented in Chapter 7.

2.2.4 - Treatment option: Other novel therapeutic modalities

It is beyond the scope of this thesis to cover in depth all of the range of treatments for patients with plantar fasciitis. Treatment options such as “therapeutic ultrasound” and acupuncture/trigger-point myofascial release have been shown to be ineffective in most, but not all, studies in the treatment of patients with chronic plantar fasciitis (394-396) and as a result lie outside the remit of this thesis.

Other areas of novel or less commonly used treatments in patients with chronic tendinopathies or plantar fasciitis that may be worth consideration include various supplements, injections of hyaluronic acid / hyaluronans,(397) topical nitric oxide,(398) either Low-Level or High-Intensity Laser therapy (LLLT / HILT),(399) percutaneous needle electrolysis(400) or even radiotherapy.(366) None of these have been specifically studied in the experimental studies within this thesis but several are briefly described here for completeness and as further options that may be worth consideration for the future.

- **Hyaluronic acid injections**

Hyaluronic acid is a naturally occurring high molecular weight un-branched polysaccharide, which is found in a range of tissues including ligaments, cartilage and synovium.(401) Its primary role appears to maintain the viscoelastic structural and functional characteristics of a range of tissues.

Intra-articular injections of hyaluronate have been performed for more than 20 years, with a number of different preparations available but with few direct comparative studies. The injections into joints are thought to not only aid lubrication, but can be protective for articular cartilage and decrease local inflammatory pathways.(402, 403) Early studies and products most commonly used 2-3 injections on a weekly basis,(404) whereas in recent years single injection products and formulations have been developed to facilitate administration. Whilst there are a number of positive individual studies, recent systematic reviews in the last 10 years or so have shown mixed results, with different study methodologies, outcome data and publication bias making conclusions challenging and calling for better quality research.(405-407)

More recent review work has shown that after 2 months following administration, hyaluronic acid injections are superior to corticosteroid injections for patients with knee osteoarthritis.(408) However in the 2008 NICE Osteoarthritis Guidelines, section 1.4.4.2 specifically stated that intra-articular hyaluronan injections are not recommended for the treatment of osteoarthritis,(409) and this guidance comes from uncertainties about their clinical effectiveness and cost-effectiveness compared to other treatments. The more recent review of this, published in 2014, re-affirms the same conclusion of not recommending hyaluronan injections for intra-articular use in section 1.5.13 of the updated document.(410)

Further developments in preparations have happened and these are now proposed as alternative injections to corticosteroids in patients with chronic tendinopathy and plantar fasciitis. In animal tendon studies, hyalurons have been found to improve the healing of rat Achilles tendons,(411) improve the gliding properties of canine FDP tendons,(412) and are effective in restoring both the biomechanical and morphological properties of lacerated rabbit tendons.(413) Hyaluronan injections have been found to be safe over the longer-term when performed as periarticular injections in a range of tissues including ankle sprain injuries.(414) Human cadaveric studies have found high concentrations of hyaluronan in the plantar fascia, and one study suggests this may be a possible treatment avenue.(54)

There is a shortage of published evidence on the use of hyaluronan injections so far in tendon conditions in humans. One RCT compared the effect of two 1.2ml 1% hyaluronate injections performed a week apart for patients with tennis elbow versus a similar volume injection of saline as a placebo, this study found that there was a significant improvement in pain favouring hyaluronate injections which lasted up to the final study assessment point at just under 12 months follow-up.(415) This study used a large number of participants, but compared a weaker strength product than others that are also on the market. Another case series study investigated ultrasound-guided injection specifically of Ostenil tendon for several different tendon conditions including 19 patients with Achilles tendinopathy, 14 with tennis elbow (lateral epicondyle pain), and 2 with peroneal tendon pain.(416) This case series study reported a reduction in pain as assessed by a visual analogue scale, however the small participant numbers for specific tendons and the case-series design with

no control group prevents robust conclusions regarding efficacy being made. Further to this a multicentre prospective double-blind trial enrolled people with plantar fasciitis symptoms of at least 12 weeks, and compared the results from a high-molecular-weight hyaluronic acid, a low-molecular-weight hyaluronic acid and a control group.(397) This study showed that following a total of 5 injections, performed on a weekly basis, that the high-molecular-weight hyaluronic acid injection was the most effective, although this study only used a 5-week follow-up period, involved patients with very early plantar fasciitis symptoms who may have improved anyway, and did not compare against other standard treatment such as a corticosteroid injection.(397)

- **Topical Nitric Oxide (GTN patch)**

Nitric oxide has been shown to enhance collagen synthesis in human tendon cells in vitro, giving a possible mechanism as to the clinical benefits seen in vitro.(417) The application of topical glyceryl trinitrate (GTN) has been shown in some studies to significantly improve pain and function outcomes in patients with a range of tendinopathies including tennis elbow, mid-substance Achilles tendinopathy and supraspinatus tendinopathy.(418-420) However later work failed to show benefit of topical GTN in clinical populations and found no histological or immunohistochemical changes compared to standard conservative therapies in patients with Achilles tendinopathy.(421) An evidence-based-review report has shown that for patients with Achilles tendinopathy there are small improvements at 12-weeks in various measures studied, and at 3 years approximately 20% more patients are asymptomatic compared to those without GTN, but for patients with patella tendinopathy GTN was found to have no effect on pain, however these findings for these two tendon conditions were derived from only two small RCTs.(422) A recent systematic review which included 10 RCTs and involving patients with 4 different tendinopathy conditions has concluded that this treatment leads to significant benefits in the medium term compared to placebo with improvements in measures of pain and function, although a side-effect of headache remain common.(398)

There is no work yet looking specifically to see if benefits seen in other tendons are also seen in patients with chronic plantar fasciitis. Further work in this area lies

outside the scope of this thesis but is included as a possible further avenue to explore.

- **Low-dose radiotherapy**

A case series study was published of the treatment of patients over the age of 65 with plantar fasciitis with low-dose radiotherapy, and found that more than two-thirds of patients at 3 months had either no or mild pain, and at the median of 54 month follow-up this figure was 61.4%; the authors suggested that the minimal side-effects of this treatment and its low cost made it an effective alternative to other conservative therapies or surgery.(423) One recent RCT compared the use of PRP with low-dose radiotherapy in patients with chronic plantar fasciitis, and found that patients in both groups improved using measures of pain, function and plantar fascia thickening with no differences between groups seen.(366) In addition to work in patients with plantar fasciitis, low-dose radiotherapy may have benefits in other tendon conditions. Historical use of ionising radiation was reviewed going back many decades in the USA involving over 3500 participants and with more than 30 publications showing that radiation could be an effective treatment for shoulder tendon conditions, however this historical evidence from the 1930s-1970s had low awareness amongst members of the currently practicing medical community.(424)

Given the concerns about the risk of ionising radiation, it is unlikely that this would be considered as a suitable treatment within the United Kingdom by the healthcare regulators in the current healthcare climate. This treatment therefore lies outside the scope of this review

- **Supplements**

Various supplements including green tea extract, fish oils, essential fatty acids or antioxidants have been proposed to assist in tendinopathy management, although with an uncertain evidence base.(425-427) Given the potential breadth of this topic the use of supplements lies outside of the scope of this review, but is an area that may be worthy of further study.

2.3 -

Outcome measures

Regardless of the treatment options undertaken, there are a wide range of different measures of pain and function that have been reported in the literature for patients with different foot & ankle problems. However there has been a lack of consistency in the approach taken between different studies. All methods have advantages and disadvantages, however solely recording changes in self-reported pain levels are likely to be insufficient, as this does not consider the functional impact of symptoms on a patient's life, and is only validated in the use in assessing levels of acute pain, rather than that of a chronic musculoskeletal condition such as plantar fasciitis.(31)

Specific guidance from one of the "Initiative on Methods, Measurements and Pain Assessment in Clinical Trials" (IMMPACT) consensus meetings to explore the use of outcome measures in chronic pain trials has highlighted a need to include wider measures of outcome than simply a pain score itself, and has recommended the use of different validated measures of physical functioning, emotional functioning, and participant self-rating of improvement.(428) Similar approaches may have value in assessing outcomes following intervention of patients with chronic musculoskeletal pain, including the patients with plantar fasciitis that are investigated in the different experimental chapters in this thesis.

For the purposes of this review, outcome measures can be broadly divided into either Patient Reported Outcome Measures (PROMs) or Observer-Rated Outcome Measures (OROMs) depending on the nature of the outcome measure and who is primarily doing the assessing. However, one specific questionnaire, the American Orthopaedic Foot & Ankle Society (AOFAS) Ankle-Hindfoot Scale(429, 430) uses a combined score made up from a self-reported score, and an observer reported score, covering both of these categories.

Patient Reported Outcome Measures (PROMs) include markers for specific conditions or regions, global measures of function, and activity questionnaires. These measures all seek to better understand the impact on functioning of

symptoms of individual patients, and whilst they can drive improvements in healthcare, PROMs have also been used by commissioners in some situations to rationalise access to specific health interventions which may be more controversial, and not necessarily supported by evidence.(431-433) PROMs, which are self-rated by the patient have been shown to be the most important judge of whether changes are important or meaningful to them, with less chance of introducing observer-bias. (31, 434, 435)

In addition to PROMs, observer-rated outcome measures, which are assessed by an external assessor of the patient, can also be used to identify a range of features in the outcome for individual patients. These can include physical measurements and parameters such as markers of flexibility, or formalised investigation modalities. These measures tend to increase the time required for patient-contact and may have increased financial cost, which may limit their usability on a larger scale, although can bring some benefits as discussed later.

2.3.1 - Patient Reported Outcome Measures (PROMs)

An editorial in the British Medical Journal supported the wider-spread use of PROMs in clinical medicine both to assess performance and to act as the basis for research.(433) Nationally there is a requirement for providers to collect specific PROM data for several surgical procedures, such as arthroplasty surgery, but there is no such requirement in the medical management of tendinopathies.(436)

A range of outcome measures are considered from the published literature and these are used to examine the clinical outcomes from specified interventions assessing the impact of symptoms pre/post-treatment. There are a wide range of different PROMs in use in published literature in different settings. One part of this review process sought to identify appropriate and feasible outcome measures to be used in this specific clinical research setting to identify levels of function / dysfunction and any changes following intervention.

A range of different PROMs are used in the different experimental studies that follow to investigate local effects and aspects of wider physical and emotional function; these are specified in each study. These patient reported outcome measures are categorised in table 2.6 and are discussed in the following sections of this review.

Table 2.6: Summary of different categories and examples of Patient Reported Outcome Measures (PROMs)

Category	Example measures
Simple measures of pain / stiffness *(validated in acute pain, possibly un-validated in chronic pain)*	• "Visual Analogue Scale" (VAS) or often simply a "Numerical Rating Scale" (NRS) (30, 31, 36-38, 437-439) *at its simplest this is a self-reported value on a 0-10 scale. As pain often fluctuates depending ion activity / time of day, and to make this more meaningful sub-questions can be asked, including "average pain", "pain at its best", "pain at its worst", "pain first thing in the morning" and "pain in the evening" etc. (this is discussed further in specific experimental chapters)* • Stiffness numerical rating scale (0-10)
Measures of chronic pain / neuropathic pain *(validated)*	• Central Sensitisation Inventory (CSI) (149, 440, 441) • PainDETECT Questionnaire (442-444)
Measure of pain/disability *(validated)*	• Oswestry Disability Index (ODI) (445, 446)
Foot region specific PROMs *(validated)*	• Foot & Ankle Ability Measure (FAAM) (447) • (Revised)-Foot Function Index (FFI-r) (448-451) • Manchester-Oxford Foot Questionnaire (MOXFQ) (452-454)

Global function questionnaires, including general function, mood, and sleep
(validated)
	• Global health functioning
	  ○ EQ-5D-5L (455, 456)
	• Mental Health functioning
	  ○ Hospital Anxiety-Depression Scale (HADS) (457-461)
	  ○ Patient Health Questionnaires
	  ▪ (PHQ-9) (462, 463)
	  ▪ (PHQ-4) (464)
	  ○ Generalised Anxiety Disorder (GAD-7) (465)
	• Sleep
	  ○ Pittsburgh Sleep Quality Index (PSQI) (466, 467)

Global outcome measures *(un-validated)*	• Overall level of function question (single question – choose from 4 available options) • Roles & Maudsley Score (single question – choose from 4 available options) • "Return to normal activity" question (single question – choose from 4 available options) • "Friend & family test" - Would the patient recommend the intervention to friend / family? (single question – choose from 4 available options) • Overall satisfaction (single question – choose from 5 available options)
Physical Activity questionnaires *(validated & un-validated)*	• Short-form International Physical Activity Questionnaire (IPAQ) (468) • Physical Activity "Vital Signs" Questions (469)

- **Pain / Stiffness**

A subjective level of pain can be measured using a visual analogue scale (VAS).(36) This is formally recorded by drawing a 10cm line, with “No pain” indicated at one end and the “Worst pain” at the other, the participant then indicates their level of pain by making a mark on the line.(30) This line can be drawn either horizontally or vertically, however research has shown that although there was a high correlation between the two orientations ($r=0.99$, $p<0.001$) the scores on the horizontal line tended to be lower than the vertical scale , therefore the same orientation is required across a study population for validity.(29, 470) The mark made by the participant is measured in mm with the value indicating their current pain level, and this value is either reported as /100 or converted to /10.

However, the VAS is somewhat cumbersome to use, and may be less reliable in older populations due to cognitive or motor impairments.(30) As the VAS relies on a patient making a mark on a line it must be done in person, therefore a verbal numerical rating system (NRS) for pain using a 0-10 scale is often used instead, which is quicker to administer, can be administered by telephone, and is preferred by some authors.(30) The numerical rating system has been shown to have a very close association with the VAS, and both of which are superior to an alternative brief method of assessing pain, that of a four-point verbal rating scale.(29, 31) Work to categorise levels of pain has suggested that a score of 3/10 or less relates to “mild pain”, more than 3/10 and less than 7/10 as “moderate pain”, and 7/10 or more as “severe pain” on the four-point categorical scale.(37, 38)

When assessing impact of interventions using this 0-10 pain scale (VAS or NRS), the minimally clinically important difference (MCID) is reported as between 0.9 and 1.4 points.(38, 439, 451) However, in patients with chronic musculoskeletal pain this figure has been reported as either 2.0 points on a 0-10 scale, or alternatively a 33% change.(438) In addition, patients with more severe pain may require a greater numerical change to report clinically significant improvements.(437)

Much of the work using a 0-10 scale has been done in acute pain, measuring pain at that point in time, however this may not reliably apply to patients with pain from

chronic musculoskeletal conditions such as plantar fasciitis and more detailed measures may be required for reliable responses.(31, 428) A simple numerical pain score may not be robust enough in this setting as patients may answer for their pain at either that specific point in time, or their worst time, giving a bias to the answers. However, the numerical pain scale (or equivalent) is still commonly used both in clinical practice and continues to be reported in research reports. As plantar fascia pain typically waxes and wanes, and often varies depending on activity and daily patterns, there may be more value gained by asking about pain during certain times/activities. To attempt to get a more reliable indication of pain levels, the following questions are specifically asked by the author using the 0-10 pain numerical rating system:

Q. ***Please can you rate the pain that you have on a 0-10 scale, with 0 being no pain, and 10 being the worst pain that you can imagine***

- *The pain as an average, or overall figure, across a normal day recently*
- *The pain at its worst recently & when was this / what were you doing?*
- *The pain at its best recently & when was this / what were you doing?*
- *The pain first thing in the morning, when you first get out of bed*
- *The pain in the evening*
- *The pain that you get at rest as an average, or overall figure*
- *The pain that you get on walking as an average, or overall figure*

In addition, the same 0-10 scale can be used to assess the self-reported stiffness that patients may be suffering from. The following specific questions can be used:

Q. ***Please can you rate any stiffness that you have recently had first thing in the morning, on a 0-10 scale, (with 0 being no stiffness, and 10 being the worst stiffness imagined)***

- *The overall or average stiffness during the day*
- *The stiffness first thing in the morning, when you first get out of bed*

It is hoped that by using these questions in this manner, then a more reliable assessment of the pain and stiffness suffered by the individual can be assessed but still using this simple 0-10 scale which is simple and easy to understand.

- **Chronic Pain / Neuropathic Pain / Disability**

In addition to classical nociceptive pain, patients with chronic pain can also develop features of what is categorised as neuropathic pain. This is typically reported as pain greater than expected from the rest of the physical findings, which can often be associated with areas of hypersensitivity to touch, and sometimes associated with tingling or pins and needles. The reason for the development of this is unclear, but is thought to arise from aggravation of local sensory nerve ending.(471)

The painDETECT questionnaire sets out to identify whether a given patient's pain may be neuropathic in nature. This questionnaire was designed originally for the assessment of patients with chronic low back pain and was found to have high sensitivity, specificity, and positive predictive value for the presence of neuropathic pain in a prospective multicentre trial.(442) Following this the questionnaire has been used in a wide range of setting with differing clinical problems.(443, 444) This simple questionnaire has 9 questions with a total score on a scale 0-38. A score of 0-12 suggests that a neuropathic pain component is unlikely (<15%), scoring 13-18 suggests an ambiguous result where neuropathic pain can be present, and a score of 19-38 correlates to a 90% likelihood of a neuropathic pain component to a patient's symptoms.(442) Identification of those patients with a previously unknown neuropathic pain component may allow alternative treatments, or treatments alongside that for the nociceptive component of pain. Published work has suggested that up to a quarter of patients with chronic tendinopathies, including those with chronic plantar fasciitis, score highly enough on the painDETECT questionnaire to be considered as likely to have a neuropathic component to their pain.(147)

Whilst subject to ongoing clinical debate, the "Central Sensitisation Syndrome" has been proposed as a condition in where the central nervous system (CNS) become hypersensitive to both noxious and non-noxious stimulation, where specific organic cause cannot be found to attribute to specific symptoms, and which may be caused by neuroinflammation in the peripheral and central nervous systems.(472-475) This

syndrome may be very important consideration in patients with chronic pain, including those with chronic musculoskeletal pain to best guide treatment and correct identification is important.(476-479) The Central Sensitisation Inventory (CSI) is a questionnaire with high reliability and validity in identifying patients thought to have this phenomenon and a score of more than 40 best distinguishes patients with/without Central Sensitisation.(440, 441, 480) Further work has suggested that the CSI has a high false positive rate in patients with complex pain and medical conditions, with a sensitivity of 83% and a specificity of 55%, but was still found to be a useful and valid instrument in screening patients for the possibility of Central Sensitisation.(149) Published work has shown that up to a quarter of patients with chronic plantar fasciitis and other tendinopathies, may score highly enough on the CSI questionnaire to suggest the presence of central sensitisation to their pain.(148) The implications for this for guiding treatment are not yet known.

In addition to pain and central sensitisation, is the concept of the burden of disability that pain places on the individual patient as a result of their symptoms. In an attempt to quantify this a questionnaire called the Oswestry Disability Index (ODI) was developed and this has been in use for more than 20 years, with has more than 200 publications for its use, predominantly in patients with spinal disorders including chronic low back pain and patients following spinal surgery.(445) This is a simple 10-item questionnaire completed by the patient, with each question having a choice from five possible responses covering aspects of function including activity, social life, and sleeping. Work has shown that the minimum clinically important difference (MCID) in patients following spinal surgery was 12.8 points.(446) However, the questions in the ODI do not solely related to spinal function, and this questionnaire may have some validity in the assessment of function/disability in other conditions, although has not yet been validated for this purpose, and if this is valid in conditions such as plantar fasciitis a specific MCID has not yet been calculated.

- **Foot functioning**

Validated measures for foot pain from a wide range of sources include the various forms of the Foot Function Index / Revised Foot Function Index (FFI / FFI-r)(448-451), the Foot and Ankle Ability Measures (FAAM)(447), the Foot Health Status

Questionnaire (FHSQ)(451, 481), and the Manchester-Oxford Foot Questionnaire (MOXFQ).(452-454)

The revised Foot Function Index (FFI-r) is a self-rating questionnaire, with high test-retest reliability and internal consistency.(448) This questionnaire gives a total score summed from 5 sub-domains with a total range of 34-136 and with a lower score indicating fewer symptoms. The FFI-r has been found to have moderate to high levels of correlation with the SF-36, most notably in the disability and activity sub-domains.(449) The minimal clinically important difference for the total score is reported as 7 points for patients with plantar fasciitis.(451)

The 16-item MOXFQ has been validated for patients receiving surgery for a wide range of foot & ankle problems against both the SF-36 and the American Orthopaedic Foot & Ankle Score (AOFAS) questionnaires.(452, 453, 482-484) Work has identified a minimal important clinical difference of between 8-11 points for the MOXFQ walking/standing scale, 8-12 points for the pain scale, and 12-16 for the social interaction scales of the MOXFQ.(452, 485) These MCID figures relate to changes seen following surgery for a range of foot and ankle conditions and MCIDs have not yet been identified for non-surgical interventions, but may be similar values. Subsequent work has shown the validity and reliability of a single combined MOXFQ score when compared to the SF-36, facilitating statistical analysis.(454) This single score totals the 1-5 score for each of the 16 questions, giving a potential range of 16-80, with a lower score indicating superior function.

An alternative ankle/foot-specific questionnaire is the Foot and Ankle Ability Measure (FAAM) which uses a total of 21 items of activities of daily living, and a sub-scale of 8 items of sport function, to assess foot function. The FAAM has found to be valid, with a high correlation with the SF-36 physical function subscale, and has a minimal clinically important difference of 8 points for the ADL-scale, and 9 points for the sport sub-scale respectively.(447)

A further measure that is used in some publications is the American Orthopaedic Foot & Ankle Society (AOFAS) Ankle-Hindfoot Scale.(429, 430) This questionnaire contains both self-rated (“subjective”) and observer rated (“objective”) components to

the total score. One review has highlighted that the observer-rated section has not been demonstrated to have reliability, and also makes the practical use more limited than a self-rated only scoring system.(486) Separate work has demonstrated poor correlations between the AOFAS clinical rating systems, which included the ankle-hindfoot score, and the SF-36 questionnaire as a global marker of health and function.(487) As such this specific questionnaire has not been included as an outcome measure in the experimental studies, but is included here for completeness as it is used in some publications.

- **Global measures of function**

Global measures of health perception in use include the 36-Item Short Form Survey (SF-36).(488) A shorted form, the SF-12, has also been found to be as valid and less burdensome to use, although still time-consuming to complete and requires a commercial licence for use.(489-491)

An alternative questionnaire is the EuroQol five-dimensions questionnaire (EQ-5D), which has a free to use licence and is an equivalent measure of global functioning, and which has been validated across populations in multiple countries and many different disease states.(492-494) The newer version of this questionnaire is the EQ-5D-5L, which contains 5 health questions with 5 options per question (as opposed to 3 options in the previous version) which improves the ceiling effect seen in the original version, as well as a percentage self-rated global health score.(455, 456) This has been shown to be both quick and simple for patients to use, and it has been found to give a reliable indicator of global function.(455, 456)

- **Mental health functioning**

Chronic pain, including pain from chronic tendinopathies, can have a direct impact on a patient's mood state, and which can in turn have a negative impact on the ability to manage pain.(495, 496) There are several different PROMs which can quantify anxiety and depressive features of a patient's mental health state.

The Hospital Anxiety & Depression Score (HADS) is a fourteen item self-rated questionnaire, which can be used to give an understanding of psychological

functioning, and has 85% sensitivity and 76% specificity for major affective disorder.(460) The fourteen questions include seven questions each for depression and anxiety symptoms. Each question is answered with a 0-3 Likert scale, giving a maximal score of 21 for depression and anxiety symptoms; with symptom severity graded as 0–7 = normal, 8–10 = mild, 11–15 = moderate, and ≥16 = severe.(458, 461)

Alternative questions for in use for assessing anxiety and depression symptoms include the Generalised Anxiety Disorder 7-item scale (GAD-7) (465) and Patient Health Questionnaire (PHQ-9) (462, 463) respectively, which are self-completed by patients and can be used to diagnose disorders against the specific DSM-IV (Diagnostic and Statistical Manual of mental Disorders) criteria. A ultra-brief tool, the PHQ-4, with just 4 questions has been developed from these to give a rapid screening for both anxiety and depression symptoms, which has been found with a sub-score of 3 or more to have a sensitivity of more than 80% for different anxiety and depression disorders.(464)

- **Sleep**

Patients with chronic pain can also have impaired quality of sleep,(497, 498) and certain treatments such as a Tension Night Splint can also potentially adversely impact on sleep.(258) Furthermore, it may be hypothesised that as pain may improve following treatments, sleep quality should also improve.

The Pittsburgh Sleep Quality Index (PSQI) is a well-recognised and validated tool across a range of settings and conditions for measuring the quality and nature of sleep, with domains including sleep quality, sleep latency and duration, sleep efficiency, sleep disturbances and a global sleep score.(466, 467, 499-502)

- **Activity questionnaires**

Physical inactivity is the fourth leading cause of death worldwide, and increases the risk of a range of health conditions including coronary heart disease, Type 2 diabetes, breast cancer, colon cancer, and many others leading to very high direct and indirect health and societal costs.(503-506) It is anticipated that those whose

physical activity may be limited by the problems caused by their plantar fasciitis may increase their activity once more following effective treatment, however many individuals who reduce or cease activity post-injury may never restart their activity for a variety of reasons,(507-509) and this may lead to the many health problems previously mentioned. Physical activity levels may therefore be a very important aspect of health to measure when investigating treatment outcome as it is an important independent predictor of longer-term health.(510-512)

There are more than 100 different physical activity questions reported in use from published literature, although very few have good reliability and validity.(513) One of the questionnaires with widespread use is the International Physical Activity Question (IPAQ), typically the short-form seven-day recall question version which is self-completed by a patient and is validated and recommended for monitoring and research requiring detailed assessment.(468) Subsequent work however has suggested that the short-form IPAQ may overestimate physical activity by 36%-173%, when compared to other measures such as accelerometers, or double-labelled water (514), but is more practical to use in clinical practice. The use of technological devices such as accelerometers to record physical activity may be a more reliable measurement of physical activity than questionnaires, although uncertainties remain of the validity of many specific devices.(515) Furthermore the costs of devices may act as a barrier in areas of practice and research. However, as the short-form IPAQ may over-estimate the activity level that an individual is doing, if a given participant does not meet minimum recommended levels of activity on the short-form IPAQ then this would be very suggestive that this represents an accurate representation of those most at risk from low levels of habitual activity.

An alternative approach is the use of much shorter questions, and bring physical activity into one of the regularly recorded “vital signs” by asking about the number of days in a typical week an individually is at least moderately active, asking about how many minutes during that day they are active, and multiplying the two levels to give a rough approximation of the number of active minutes in a typical week to best identify those most at risk for sedentary habits.(469) Initial work suggests that this approach may be of use and have reasonable validity although provide more

conservative estimates of physical activity when compared to more detailed questionnaires in large surveys.(516)

- **Other measures**

There are a number of other non-validated methods of assessing outcome pre/post intervention. A common method in the literature is the use of the Roles & Maudsley scoring questions.(280, 308, 336, 342) These are typically undertaken with a patient self-rating from a choice of four possible options about their symptoms at that time point compared to a previous point in time prior to a given intervention. The following gives one version of the wording used for the Roles & Maudsley score.

Q. How do you rate your symptoms recently, compared to your previous symptoms?

1 – I have **no symptoms or minimal symptoms** now
2 – I have some symptoms, but these are **significantly improved** from before the treatment
3 – I have some on-going symptoms, but these are **somewhat better** from before the treatment
4 – **My symptoms are no better, or are worse** than before the treatment

In a similar manner, patients can be asked whether they feel that they have been able to return to their normal level of activity following procedures, whether they would recommend the intervention that they have had to a friend or family member (akin to a "friends & family test"), and how satisfied they are with the outcome of a given procedure. Examples of these semi-structured questions (and the answer options) are given below.

Q. Have you returned to your "normal" level of activity following the procedure that you have received?

A - Yes, I have been able to return to everything that I want to do
B - I have not returned to my previous level, but not primarily because of my foot symptoms
C - I have been able to return to most things, but with some limitations due to my foot symptoms
D - No, I have been unable to return to my previous level due to limitations from my foot symptoms

Q: From your experience so far, would you recommend the procedure to a friend or family member with the same symptoms?

A – Yes, definitely
B – Yes, probably
C – Maybe
D – No

Q: So far, how satisfied are you with the outcome of the treatments you have received?

A – Very satisfied

B – Satisfied

C – Neutral

D – Dissatisfied

E – Very dissatisfied

All of these non-validated outcome questions can be used to give an overall impression of an individual patient's response, although the reliability of all of these measures remains unproven and so may at best support, rather than replace, other validated measures of recording outcome.

2.3.2 - Observer-Rated Outcome Measures (OROMS)

In addition to the wide range of Patient Reported Outcome Measures, a number of direct measurements by an observer can be used. These have the benefit of being able to assess a range of physical and biomechanical parameters that PROMS may struggle to do, although do require time, money and facilities which may limit their utilisations and may have limitations in ensuring adequate inter-observer and intra-observer reliability of any measurements recorded.

- **Physical parameters**

A range of physical markers can be used as methods of assessing physical improvement, and these include simple measures of flexibility, as well as foot loading pressures, tendon stiffness and power generation or force transmission.

One of the common findings in patients with plantar fasciitis is that of subjective "stiffness", with reduced ranges of movement typically at the ankle (calf flexibility), or knee (hamstring flexibility). It is unclear if these are a cause or an effect of the plantar fasciitis, or possibly both. It has been reported that increasing tension in the Achilles tendon increases the strain through the plantar fascia, and this could be one of the contributing factors to the development of plantar fasciitis.(60) Therefore one of the goals of rehabilitation of patients with plantar fasciitis is to improve the flexibility through the calf-Achilles complex, and this measure of flexibility is routinely

assessed in clinical practice using a range of assessment methods and this can be used to record outcome. However, it is not clear if there is a direct correlation between improved range of flexibility and reduction in pain, and this is the focus of further work in the experimental chapter which utilises a tension night splint (TNS) device.

Power generation or force transmission can also be reduced in patients with established tendinopathy, and one of the goals of rehabilitation is increasing loading through the tendon thereby stimulating a regeneration and also stimulating strength gains. Eccentric strength training has been a standard component of tendinopathy rehabilitation since the seminal work by Alfredson on Achilles tendons.(517) More recently a systematic review has demonstrated a reduction in pain and an improvement in strength in lower limb tendinopathies following an eccentric strength programme, however this review has commented on the low quality of many of the published studies and has highlighted that in many studies there was no increased reduction in pain of patients in intervention groups compared to controls.(518) Different aspects of strength can be assessed as a part of recoding outcomes including maximal force generation, as well as markers of stamina, however the correlation between these markers and functional outcome in populations with tendinopathy remain unclear and lies outside of the scope of the experimental chapters in this thesis, but could be the focus of further works.

2.3.3 – Imaging / Investigation modalities

Whilst not truly outcome measures per se, a range of different imaging modalities can be used to directly visualise the plantar fascia, which are routinely used to aid diagnosis, and could potentially be used for assessing structural change as a part of measuring clinical outcomes. For the purposes of this review, MRI and ultrasound imaging provide the best candidates as potential outcome measurements in patients with chronic plantar fasciitis with advantages and disadvantages to both modalities.

- **MRI**

The use of MRI to document the appearance of a range of different tendons has been well researched, showing increased tendon cross-sectional area and typically

focal intratendinous signal present in established degenerative tendinopathy.(12) Due to its reliability, MRI has often been used as gold-standard investigation of choice for a wide-range of tendinopathies and other conditions.(519, 520) When examining Achilles tendons MRI was very reliably able to identify normal tendons, and was found to be relatively good at identifying symptomatic tendons, with lower grades of abnormality at baseline associated with better outcomes at twelve months.(521) However, whilst MRI has been found to have significant inter-observer and intra-observer reliability for grade of tendinosis in patients with chronic lateral epicondylitis, the severity of MRI grading did not correlate with patient symptoms as recorded with QuickDASH results, pain scores, or grip strength.(522) MRI has been found to have high intra-rater reliability for full-thickness supraspinatus central tendon tears, although this was lower with partial thickness tears(523) and whether the same is the case in plantar fasciitis remains unclear.

Specifically in patients with plantar fasciitis, MRI has an important role in the diagnosis of plantar fasciitis, as well as ruling out a range of other pathologies, including plantar fibromatosis and plantar fascia tears.(524-526) MRI has been able to reliably identify abnormal thickening of the plantar fascia in patients with plantar fasciitis as well as increased signal intensity consistent with pathology.(527-529) Although one study which reviewed nearly 150 patients with a clinical diagnosis of plantar fasciitis, found that the MRI was reported to be normal in more than 20% of cases and highlighted the importance of a diagnosis based on history and examination findings.(530)

Relating specific MRI findings to outcome following treatment may be less clear. One study has shown that patients who were demonstrated to have focal high-intensity areas of the plantar fascia on MRI were more likely to respond well to ESWT.(275) However earlier research which identified further specific MRI findings such as oedema and partial tears, found that these did not correlate to outcomes following treatment compared to those with more minor MRI changes.(531) This evidence base indicates that MRI can be useful in establishing a specific diagnosis most of the time, and in ruling out other differential diagnoses, but may be normal in up to one-fifth of cases of plantar fasciitis, and any role in predicting outcome may be unclear.

- **Ultrasound**

Diagnostic ultrasound is commonly used to asses a range of different tendon structures. Normal tendons are described as having a homogenous pattern of tightly aligned parallel fascicles of fibres with an echogenic nature, whereas appearances in tendinopathy may include focal thickening of the tendon, blunting or partial interruption of the parallel fascicle appearance normally seen, which often have increased numbers of surrounding blood vessels which may penetrate the tendon, described as “neovascularisation”.(532-537) In patients with plantar fasciitis, common ultrasound findings are of increased plantar fascia thickness and reduced echogenicity (hypoechogenicity) of the plantar fascia structure.(182, 538-541) Any ultrasound changes tend to be long-lasting with a study showing that only 24% of asymptomatic patients with previous plantar fasciitis had a normal ultrasound scan appearance, when re-assessed at an average of more than 2 years.(6)

In patients with chronic heel pain, ultrasound has been shown to be of great value in diagnosis, with 13 studies identified in a published systematic review.(541) This review demonstrated that patients with chronic plantar aspect heel pain were 100 times more likely than controls to have a plantar fascia thickness of 4mm or greater, providing a reliable cut-off value. Further work has been published demonstrating a high intra-rater and inter-rater reliability of ultrasound in the assessment of plantar fascia thickness(542) and the ability of ultrasound to detect relatively small differences in plantar fascia thickness measurements.(543) However the amount of plantar fascia thickness has been shown to not corelate with levels of pain, function, or prognosis following treatment, and at least one paper has highlighted that the extent of thickening should not be used to determine treatment.(47, 544) Furthermore, one longitudinal study has shown that even in patients with plantar fasciitis whose symptoms have improved, the abnormal thickening and echotexture often persists, with only 24% of patients whose symptoms had settled had returning to a normal ultrasound appearance at long-term follow-up (545) and any clinical significance of this remains unclear.

Ultrasound is known to be highly operator dependent, with lower inter-observer reliability when compared to imaging modalities such as MRI.(546, 547) Furthermore

whilst ultrasound can give very good visualisation of tendon or plantar fascia architecture, the correlation between the ultrasound appearance and a patient's symptoms remains unclear and the ability of ultrasound to predict future symptoms or outcomes is uncertain. One study of 141 athletes found that the presence of hypoechoic areas in an asymptomatic patella tendon was strongly predictive of subsequent development of patellar tendinopathy with an average follow-up of more than 18 months.(548) Another study in professional footballers demonstrated that a thicker baseline mid-Achilles tendon thickness was a strong predictor for the subsequent development of tendinopathy symptoms.(549) These findings contrast with previous work that showed that ultrasound did not correlate with clinical outcome in patients with Achilles tendinopathy.(521) This difference could potentially have arisen from improvements in technology, more sensitive measurements, or different patient populations. Similar work has not been published in patients with plantar fasciitis to assess the future significance of abnormal findings in asymptomatic populations.

Neovascularity is often present in many patients with tendinopathy which can be reliably assessed on ultrasound.(550) This neovascularity has been thought to correlate with pain and is a potential target for therapies as it is proposed that the ingrowth of new blood vessels brings with it neural structures associated with pain sensation that a range of therapies can target to facilitate recovery.(112) Neovessels have been shown to associate with pain and chronicity of tendinopathy.(551) One study has demonstrated a high inter-rater reliability and the extent of the neovessels were thought to be able to be used to track changes by clinicians,(550) and these neovessels have been the target for treatments such as injection of polidocanol to sclerose these abnormal vessels.(113, 552) However subsequent work has found that the whilst values for inter-observer reliability exists for presence of neovessels, these did not correlate to the extent of pain or limitation of activity, and only weakly correlated to the impairment of function domain in the VISA-A questionnaire in patients with established Achilles tendinopathy, and as such it remains unclear whether the presence of neovessels has any clinically important diagnostic or prognostic value.(114, 553, 554) Furthermore as neovascularity is not reported in patients with plantar fasciitis, this has only been included in this background review for completeness.

- Ultrasound modality: shear-wave elastography

A relatively new ultrasound modality is that of shear-wave elastography, in which the viscoelastic properties of soft-tissue structures can be assessed through measurement of shear-wave velocity (SWV) generated by an ultrasound pulse.(555) This has been in use in assessment of liver conditions previously,(556, 557) with recent work also assessed this parameter in patients with Achilles tendinopathy or patella tendinopathy.(134, 558, 559) Information is very limited currently, but one study has shown differences between Achilles and Patella tendinopathy, with patients with Achilles tendinopathy having a lower elastic modulus than healthy controls, but with conflicting evidence for those with patella tendinopathy, with some studies suggesting patella tendinopathy has a higher elastic modulus than control populations.(560) Very limited work is published currently using shear-wave elastography to investigate the plantar fascia, with a small study of ten healthy subject reporting values of Young's modulus in a healthy male population.(561) However work has not yet been conducted in patients with plantar fasciitis, to examine how any interventions may influence the measured elastic modulus of tendons and how this could correlate with changes in symptoms. Given the costs associated with this modality, and the lack of clarity in this area, this lies outside the remit of this thesis, but is included for completeness.

- Ultrasound modality: Ultrasound Tissue Characterisation (UTC)

UTC is a new imaging modality that analyses the dynamics of the ultrasound echotexture of a tendon, which relate closely to the three-dimensional physical structure of the tendon, and can be used to identify damage or change to collagen tendon bundles in both animal and human subjects.(562-564) UTC imaging has shown that in healthy Achilles tendons there is a 80-85% content of echo-type I collagen, 10-15% echo-type II, and only 2-5% echo-type III and IV, however these proportions change in tendinopathy with increasing proportions of echo-type II collagen which is thought to be representative of remodelling or fibrosis, or echo-type III collagen thought to represent fibrillar or cellular degeneration.(563) These changes can be used to track changes in tendon microarchitecture, however the cost and availability of UTC imaging currently limits greater utilisation of this as an outcome modality. In addition, this may be less useful in assessing structures such

as the plantar fascia, as this modality requires a structure to be parallel to the ultrasound probe. As the plantar fascia arising in the deep portion of the calcaneus and becomes more superficial as it spreads distally, this impairs the reliability of this modality for this tissue type.

- Ultrasound - summary

Overall, the evidence base demonstrates the high reliability and accuracy of ultrasound in the diagnosis of plantar fasciitis, and the availability to undertake this during a consultation can be a useful clinical adjunct, with ultrasound considered by some authors to be the first-line investigation of choice.(565) There remain unanswered questions about the usefulness of newer ultrasound-based technologies such as UTC and shear-wave elastography in the diagnosis and monitoring improvements in patients with plantar fasciitis.

- **Comparing Ultrasound and MRI findings**

Ultrasound has certain advantages over MRI in the assessment of patients with tendinopathy as it is cheaper and potentially more accessible, and can be used to scan a patient dynamically attempting to replicate provocative movements rather than statically as is the case in an MRI. Furthermore, ultrasound may be more accurate than MRI in certain conditions, including in the diagnosis of patients with patella tendinopathy with a sensitivity of 83% compared to 70% for MRI (566) and has also been shown to be sensitive but not highly specific for rotator cuff pathology when compared to MRI or surgical findings.(567) When investigating other tendon conditions including Achilles tendinopathy or tennis elbow the comparisons of the results were more equivocal between Ultrasound and MRI investigations.(536) A small study involving 17 patients with plantar fasciitis (23 symptomatic heels) compared to 11 healthy volunteers (22 heels) and which compared ultrasound and MRI findings, concluded that ultrasound and MRI had similar diagnostic accuracy, and that MRI may be best reserved for cases where complex pathology is suspected.(568)

Outcome measures - summary

In summary, this section introduces some of the many different outcome measures that can be used to assess a wide-range of domains in which improvement or change can be tracked. It is recognised that no system of recording outcome is perfect, and all have flaws and limitations. In addition to these measures described here, many other alternative forms of assessment and scoring can be found in published literature, and a balance has to be struck between tools that are reliable, reproducible, sensitive to change, practical, and not overly burdensome for the patient or the treating clinician.

In the experimental chapters of this thesis that follow this introduction, several different outcome measures are used in different studies depending on the nature of the intervention, and these will be specified within each section.

Chapter 3 –

Introduction to the Department of Sport & Exercise Medicine, University Hospitals of Leicester NHS Trust

The department of Sport & Exercise Medicine at the University Hospitals of Leicester (UHL) NHS Trust has been running since 1993, and is one of the oldest, and the largest NHS Sports Medicine Depts in the UK. It receives referrals for patients with a wide range of different, and predominantly musculoskeletal, conditions from General Practitioners and other Secondary Care Consultants, averaging about 2000 new referrals to this clinic each year.

- **New referrals**

Information was available from ongoing clinic records for a total of 7361 new referrals seen in the 4-year period from April 2014 – April 2018. Of this total, there were 542 new patients that had been referred for symptoms of chronic plantar fasciitis, accounting for 7.4% of new referrals. 89% of these new referrals were referred by their registered General Practitioner, 6% from an orthopaedic surgeon within UHL, 3.1% from a rheumatologist, and 1.5% came from another consultant working outside UHL.

- **Patient demographics**

Of the new referrals, 37% were male and 63% were female (a 1:1.7 ratio.) There was a mean age of the patients referred with symptoms of plantar fasciitis of 51.1 ± 11.3 years (range: 17 - 90 years.) Ethnicity was not recorded in this data set. Figure 3.1 displays the ages of new patients seen for symptoms of chronic plantar fasciitis at different age bands.

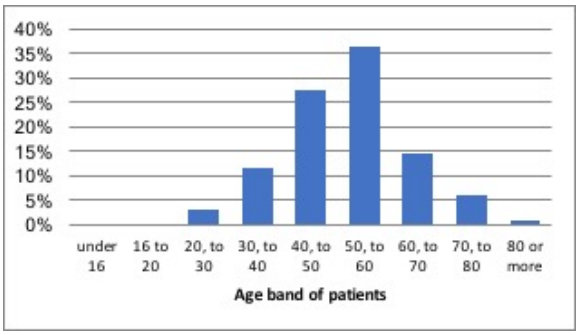


Figure 3.1: Age bands of patients with plantar fasciitis referred to the UHL Sports Medicine Department

The patients had a self-reported median duration of symptoms of 12 months with a positively skewed mean of 23.9 ± 33.7 months, (range: three months to forty years.)

- **Levels of pain and physical activity**

Using a 0-10 pain scale, patients who were referred for plantar fasciitis self-reported their values of “average pain” at a mean of 7.38 ± 1.83 (median = 8.0/10)

Using the “Vital Signs” questions that are described in Chapter 2, patients reported their levels of physical activity both in the week immediately preceding the hospital appointment, and also for their “normal week” prior to the onset of their symptoms. This showed that patients with plantar fasciitis symptoms had greatly reduced levels of activity in the week prior to their appointment at the hospital (median 15 minutes of physical activity per week), compared to their self-reported pre-morbid levels (median 135 minutes of physical activity per week), although this manner of self-reporting has inherent recall bias which is recognised as a limitation. The values obtained are displayed in table 3.1, with median values shown.

Table 3.1: Physical activity rates for both a normal week prior to symptoms, and the week preceding the hospital appointment, using the “vital signs” questions

	"normal week" *(n=390)*	**week before 1st appt** *(n=399)*
Days per week of activity	3	1
Mins/day of activity	45	15
total mins/week	135	15

Key: data are median values

- **Investigations**

At the time of their first appointment in the Sports Medicine Dept, 25.3% of patients (n=137) had an ultrasound performed during the time of their clinical consultation. In total, 33% (n=180) were referred formally for an ultrasound investigation and 5.7% for an MRI (n=31), most typically for pre-interventional planning, and 3.1% (n=17) received blood tests, mainly to rule out other medical problems.

- **Interventions**

During their first consultation in the Sports Medicine department, 88.2% of the 542 patients (n=478) referred with symptoms of plantar fasciitis received a specific structured home exercise programme for rehabilitation, and 17.2% (n=93) were also given specific graded return to activity advice. To support their rehabilitation programme, 21.0% (n=114) were referred formally to physiotherapists at their first appointment. In addition, 56.1% (n=304) were referred to podiatry for custom-made insoles, and 12.4% (n=67) were either provided with an off-the-shelf tension night splint or referred to the Occupational Therapy service to provide/manufacture a night splint. Only 0.2% of new referrals for patients with plantar fasciitis (n=1) underwent a corticosteroid injection at their first appointment. Figures were not available of how many patients had previously received a corticosteroid injection prior to their referral to the department.

- **Follow-up**

Following the initial consultation 79.9% of patients referred with plantar fasciitis were booked a further appointment to continue their clinical care, and 20.1% were left with an open appointment which they could use to contact the department again in the future should further care be required. Figures were not readily available about how many of these patients were subsequently seen again in the Sports Medicine dept for the same problem.

Chapter 4 – Introduction to experimental studies

The literature review has given a general overview of the nature of plantar fasciitis, the various management options that are available for treatment, and the methods of assessing pain and function in patients with plantar fasciitis. Using the concepts used in the management of chronic tendinopathies, this thesis examines three specific treatment options in the medical management of patients with chronic plantar fasciitis. These interventions are a Tension Night Splint (TNS) device, the use of Extra-Corporeal Shockwave Therapy (ESWT) and the use of Autologous Blood Injections (ABI). Each of the subsequent chapters presents data from a case series study and a randomised-controlled trial which have sought to investigate outcomes from these interventions. These studies are listed below using a "medical treatment model", from the least invasive treatments to the most invasive for single intervention modalities, concluding with a comparison study between two different modalities at the end.

Intervention	Chapter /section	Experimental study and design	Participant numbers
Tension Night Splint (TNS)	5.2	Study A: Retrospective case series	17/20 identified
	5.3	Study B: Single-blinded randomised controlled trial	40
Extra-Corporeal Shockwave Therapy (ESWT)	6.2	Study C: Prospective case series	35
	6.3	Study D: Double-blinded randomised controlled trial	72
Autologous Blood Injection (ABI)	7.2	Study E: Prospective case series	70
	7.3	Study F: Double-blinded randomised controlled trial	69
Comparison between ESWT & ABI as "novel interventions"	8	Prospective cohort study	74 total (ESWT n=38, ABI n=36),

** These clinical studies all took place in the Department of Sport & Exercise Medicine, University Hospitals of Leicester (UHL) NHS Trust*

Chapter 5 -

Intervention:
Tension Night Splint (TNS)
for patients with chronic plantar fasciitis

Figure 5.1: Tension Night Splint device

5.1 – Introduction

Tension Night Splints (TNS) are devices that hold the foot in a dorsiflexed position, applying passive stretch to the calf musculature.(250, 253) This approach aims to improve ankle dorsiflexion by improving calf flexibility, which is one of the leading risk factors for plantar fasciitis.(62, 191, 192) These devices are typically worn throughout the night for a period of six-weeks or longer, and potentially facilitate recovery by improving calf flexibility with prolonged periods in this elongated position.(247)

In chapter 2, a number of studies investigating the effectiveness of the addition of a tension night splint (TNS) in patients with plantar fasciitis were examined. Overall, there is a lack of consistent evidence, with several of the published studies demonstrating a lack of benefit in either pain or function.(250, 253, 256) There is some evidence of benefit from the use of a TNS from several studies, including two small RCTs with follow-up period of 8-12 weeks.(249, 250, 252) However, the larger studies, those with longer duration of symptoms pre-intervention, and those with a with more robust study design, such as using observer blinding or longer follow-up periods, have often failed to show any improvements with the use of a TNS.(254, 255) Although the hypothesis for their use in treating patients with plantar fasciitis relates to improving calf flexibility, the range of movement has only been specifically studied in one small study which found that due to intra-observer error no firm conclusions could be drawn.(249) In addition, most studies use only relatively crude outcome measures such as a simple numerical pain score and so reliably quantifying any benefit, if any, remains unclear.

The majority of published studies to date have taken place using participants from private clinics, where patients typically present for treatment at an earlier stage in the disease process than those seen in NHS hospital clinics. This body of evidence includes studies that have recruited patients with symptoms of only 2-6 months on average, which for the majority of patients is well-within within the expected time for symptoms to resolve spontaneously.(252, 254, 255) The short-duration of symptoms in many patients enrolled in these published trials may directly influence the results found, although this remains unclear.(40) It is not certain if the results seen in

populations with a relatively short duration of symptoms may be directly comparable to those patients seen in a routine NHS clinical practice in a secondary care setting. These patients often present with more chronic or recalcitrant symptoms, and with other co-existing medical co-morbidities.(257, 258) To date, there are no other published works examining the effectiveness, or lack thereof, of TNS devices in this NHS population group with chronic symptoms of plantar fasciitis.

There remains uncertainty of benefit of the use of TNS in patients with chronic plantar fasciitis symptoms. Given the ongoing use of these devices in routine care which may not be supported by evidence, this treatment is specifically investigated in this thesis chapter which describes the findings from two linked studies which investigated the effects of a TNS device provided to patients with chronic plantar fasciitis who were being treated at an NHS hospital clinic, utilising two complimentary study designs. The first was a retrospective case series, and the second was a single-blinded randomised controlled trial.

The initial study used a retrospective design and examined the use of the TNS in routine clinical care and any effect on simple, self-reported, pain and function outcome measures. This also sought to quantify treatment adherence and tolerability of the TNS device. This pragmatically-designed study, identified a possible beneficial effect reported by patients on their levels of pain following the use of a TNS device. Data from this initial study was then used to estimate an effect size, which was subsequently used for an a priori power calculation for the RCT to investigate this treatment more robustly.

The second study formally investigated any effects on pain, function, or flexibility of the provision of a TNS device in patients with chronic plantar fasciitis using a single-blinded RCT design. The primary outcome measure for this study was a change in self-reported levels of pain using a simple pain numerical rating system. Additional secondary outcome measures were physical parameters of flexibility and plantar fascia thickness, as well a number of validated measures of local foot function, and wider global measures of function including activity levels, mood and sleep quality as these measures can be affected by the foot pain or the TNS device itself.

5.2 -

Experimental study A: The effectiveness and tolerability of Tension Night Splints for the treatment of patients with chronic plantar fasciitis – a case-series study

Specific study aim(s)

The aim of this case series study was to assess self-reported changes in pain and function following the use of tension night splint (TNS) in routine NHS practice for patients with chronic plantar fasciitis. Secondary outcomes sought to quantify treatment adherence / compliance and tolerability to the TNS device.

Methods

- Study design

This study used a retrospective case series design. The Department of Sport & Exercise Medicine at University Hospitals of Leicester NHS Trust maintains detailed procedure logs and service reports detailing patients treated. These records were examined by the researcher to identify patients with a clinical diagnosis of plantar fasciitis, who had been prescribed a Tension Night Splint (TNS) between 1st January and 31st December 2013.

The identified patients (n=20) were initially contacted by letter which was sent to their registered home address inviting them to participate in this study. The covering letter advised patients that their participation was optional and that that they were being contacted to seek a better understanding of the effects of the treatment that they had previously received. A bespoke questionnaire was also included for patients to complete and return in a pre-paid envelope included. There were no validated questionnaires in use and so the development of this questionnaire was guided by clinical expertise, with reference to published literature where available. Question wordings were piloted with patients in clinic for comprehension prior to use and the final specific questions are detailed in table 5.1 below. These questions sought to

understand any changes in pain, function and levels of tolerability, adherence and patient satisfaction with the use of the TNS.

Table 5.1: Research instrument - Questionnaire

1. **In total, how long did you wear the tension night splint?**
    a. Less than 1 week
    b. More than 1 week, but less than 1 month
    c. Up to 2 months
    d. More than 2 months
2. **For each night, how long on average did you wear the tension night splint?**
    a. Less than 1 hour
    b. More than 1 hour, but less than half the night
    c. About half the night or more
    d. Most or all of each night
3. *What are the reasons for wearing the splint the amount that you have done? (instructions, comfort, life, other problems etc.) – free text answer*
4. **How comfortable would you rate the tension night splint that you had?** *(Using a scale of 0-10, with 0 being very uncomfortable, and 10 being very comfortable)*
5. **If you found the night splint uncomfortable initially, did this get better?**
    a. Yes; it became comfortable / tolerable
    b. Maybe; it became somewhat more comfortable, although was still uncomfortable
    c. No
    d. N/A
6. **Which of the following best describes any effect that the tension night splint had on your sleep?**
    a. I don't think the tension night splint affected my sleep to any significant amount
    b. The tension night splint affected my sleep by not greatly
    c. The tension night splint affected my sleep greatly
    d. I was unable to sleep wearing the tension night splint
7. **What of the following other treatments were you using <u>at the same time</u> as you were trying the tension night splint? (please tick all that apply)**
    a. Home exercise programme / physiotherapy
    b. Orthotics
    c. Different shoes – such as rocker bottom shoes
    d. Painkillers
    e. Steroid injection
8. **How would you rate your pain as an overall figure, and first thing in the morning, before you had the tension night splint?** *(Using a scale of 0-10, with 0 being no pain at all, and 10 being the worst pain you can imagine)*
9. **How would you rate your pain as an overall figure, and first thing in the morning, after you had been using the tension night splint?**
10. **How would you rate your current level of function during your <u>usual activities of daily living</u> from 0 to 100,** (with 100 being your level of function prior to your foot problem and 0 being the inability to perform any of your usual daily activities) – before / after wearing the splint
11. **If you just consider the effect that the tension night splint had, rather than any other treatment, do you think that the tension night splint helped your symptoms?**
    a. I think that the tension night splint helped a lot, or cured my symptoms
    b. I think that the tension night splint helped a reasonable amount
    c. I think the tension night splint helped only a little

d. I don't think I got any help from the tension night splint

12. **How do you rate your symptoms following the use of the night splint, compared to your symptoms before?**
    a. I have **no symptoms or minimal symptoms** following the use of the tension night splint
    b. I have some symptoms, but these are **significantly improved** from before the use of the tension night splint
    c. I have some on-going symptoms, but these are **somewhat better** from before the tension night splint
    d. My symptoms are **no better, or are worse** than before the tension night splint
13. **From your experience with the tension night splint, would you recommend this to a friend or family member with the same symptoms?**
    a. Yes, definitely
    b. Yes, probably
    c. Maybe
    d. No
14. **If you had the same symptoms again, would you wear the tension night splint again?**
    a. Yes, definitely
    b. Yes, probably
    c. Maybe
    d. No
15. **So far, how satisfied are you with the outcome of the tension night splint you have received?**
    a. Very satisfied
    b. Satisfied
    c. Neutral
    d. Dissatisfied
    e. Very dissatisfied

A confidential record was kept of the patients contacted and those that responded. Patients were given the choice at all stages to opt out of this research. Patients who failed to respond to the initial letter within 4 weeks were sent a further reminder letter. A single attempt was made to contact those who failed to respond to this reminder letter by telephone after a further 4 weeks. No further attempts were made to contact patients who failed to respond to the first two letters and who could not be reached by one telephone call.

- Participants

Participant recruitment was directed by the inclusion criteria which were: patients who had been referred for the provision of a TNS device, with a clinical diagnosis of plantar fasciitis, either with or without supporting imaging, and with a minimum duration of 6 months since the TNS was prescribed. Patients were excluded if the medical records documented that they required a translator as finance was not available to provide translations of the questionnaire, or to validate the questionnaire

for consistency between different languages. All patients contacted had a minimum of 6 months and maximum of 18 months since the TNS was prescribed. In total, 17/20 patients responded, providing a response rate of 85%. There were no identified differences in the biographical data for the respondents and the non-respondents, although the small numbers limit this analysis.

- Intervention(s)

A bespoke TNS for each patient was manufactured from thermoplastic by a senior Occupational Therapist at the University Hospitals of Leicester NHS Trust. When worn, the TNS held the patient's in a fixed, dorsiflexed position with the angle achieved based on their baseline flexibility and the individual tolerability of the device. All patients were given standard instructions about the application of the TNS device when they first got into bed at night and were advised to take the splint off before getting up in the morning, wearing the TNS throughout each night for a period of at least 6 weeks.

In addition to the TNS device, all patients had been given a physical rehabilitation programme based on routine clinical care. This included stretching the posterior chain muscles of gastrocnemius, soleus, hamstrings & Flexor Hallucis Longus (FHL), passive stretching of the plantar fascia itself, intrinsic foot muscle strengthening, and proprioception training exercises, all of which are recommended to be performed twice or three times per day. (An example of this home exercise programme is included in Appendix 2 of this thesis.)

- Statistical analysis

Participants' responses were entered into a spreadsheet (MS Excel 2010) for calculation of descriptive data, including means and standard deviations. Further analysis was conducted using IBM SPSS Statistics (version 21). Scale data were shown to be normally distributed using the Shapiro-Wilk test, and analysis was performed with paired T-tests for comparison of pre and post values. Results are displayed predominantly as mean ±SD, with ranges also given where specified. Statistical significance was set at $p<0.05$, with statistically significant results being indicated by an asterisk (*)

- Ethical considerations

This study was classified as a service analysis within the Department of Sport & Exercise Medicine at University Hospitals of Leicester NHS Trust. It was registered as such with the CASE Team at the hospital, and the results reported via the normal hospital audit mechanism. NHS ethics permissions were not required. In keeping with similar protocols, patient response to the contact was taken as evidence of their informed consent.

Results

The mean age of the respondents was 51.6 ±12.2 years (range 28.5 to 76.6 years) of age, and 47% were male. Ethnicity was not recorded in this data set. The mean duration of symptoms before the TNS was tried was 30 ± 34.7 months (range: 6 months, to >12 years.) 53% of patients had been prescribed the TNS at their first appointment at the Sports Medicine Department, the remainder at their first or subsequent follow-up appointments after initial treatments had proven unsuccessful. In addition to the TNS device, half of the patients were trying orthotics at the time of the tension night splint, and half reported that they were using regular analgesia.

- Adherence to treatment

From the 17 responses received, nearly one-third of participants (n=5/17) reported that they wore the TNS for less than a month, and one-third wore it for more than two months (n=6/17). Approximately half (n=9/17) reported that they wore it for what they reported was “most, or all, of each night.” The most common reason reported for not wearing the TNS for as long, or as much, as had been requested was due to discomfort felt with the TNS.

Respondents self-reported a mean comfort score of 5.3/10 ±2.4, (range 1-9/10). For the patients who reported that they found the night splint uncomfortable (n=14/17), 29% thought that the tension night splint became comfortable to wear, 57% thought that it became more comfortable but was still uncomfortable, and 14% reported that it remained uncomfortable throughout the period that it was tried.

- Pain and function

There was an improvement of 1.9 ±2.1 points on a 0-10 pain numerical rating scale in overall levels of pain, and 2.8 ±2.4 for pain specifically felt first thing in the morning, when comparing pre/post values. Both of these changes reached statistical significance and this information is detailed in table 5.2. There were no differences in outcomes identified between male and female patients.

Table 5.2: Pain scores pre/post tension night splint

	Immediately before you started wearing the tension night splint? (n=17)	After you had been wearing the tension night splint? (n=17)	*p-value*
Overall pain levels (/10)	6.9 ± 2.7 (range: 1-10)	5.1 ± 2.6 (range: 0-9)	** *0.001*
Pain felt first thing in the morning (/10)	7.8 ± 2.6 (range: 0-10)	5.0 ± 2.4 (range: 0-9)	* *0.020*

*Key: data shown are mean ± SD (range) Significance of change from baseline shown using paired t-tests, * = p<0.05, ** p<0.01*

Self-reported function altered from 55% ±17% (range 20-80%) before the TNS, to 73% ±18% (range 50-100%) after the TNS was worn, however this difference was not statistically significant using paired T-tests (p=0.121).

More than 70% of patients (n=12/17) reported that they believed the tension night splint helped their symptoms to at least a “reasonable amount” or greater, one-quarter of patients (n=4/16, with 1 non-response to this question) had “no or minimal symptoms” following their use of the splint. Nearly 60% were either “satisfied” (n=4/17) or “very satisfied” (n=6/17) with the results that they had obtained, although 12% (n=2/17) patients rated themselves as dissatisfied.

- Sleep quality

Patients were asked about any effect that the TNS had on their sleep whilst it was being worn. Only 2/17 (12%) did not think that the TNS affected their sleep, with 59% reporting some but not great adverse impact on their sleep, 18% reported that sleep was greatly affected, and 12% reported that they could not sleep whilst wearing the TNS.

- Patient “recommendations”

When patients were asked if they would wear the TNS should they suffer the same pain again: 59% responded that they “definitely would”, 12% “probably would”, compared to 12% who were “unsure”, and 18% who “would not”. Likewise, when patients were asked from their experience if they would recommend the TNS to a friend or family member: 65% “definitely would recommend”, 6% (1/17) “probably would recommend”, 12% (2/17) were “unsure”, and 18% (3/17) “would not recommend” the TNS.

Initial conclusions

This retrospective study found that the majority of respondents tolerated the TNS device and would recommend the TNS device to other patients with similar symptoms. There was found to be a mean improvement in “overall pain” of 1.9 ±2.1 points on a 0-10 scale, and an improvement of 2.8 ±2.4 points for the pain felt first thing in the morning. However, the nature of the study design, including the lack of a comparison group and potential recall bias, means that any reported benefits cannot be ascribed solely to the use of the TNS and these limitations are discussed formally in the discussion section of this chapter.

The results from this study and the previously published work discussed in the literature review, suggest that this is an area worthy of further study. Data from this study were used to construct a formal randomised control trial to more robustly investigate the effectiveness of the use of a TNS for treating patients with chronic plantar fasciitis.

5.3 -

Experimental study B:

"The addition of a Tension Night Splint to a structured home rehabilitation programme in patients with chronic plantar fasciitis does not lead to significant additional benefits in either pain, function, or flexibility – a single-blinded randomised controlled trial"

Specific study aim(s), and hypothesis to be tested

The aim of this RCT was to assess the effectiveness of the addition of a Tension Night Splint (TNS) device, compared to those receiving a rehabilitation programme only, in patients with chronic plantar fasciitis,. The study hypothesis was that there would be significantly greater improvements in outcome of altering pain, function, or flexibility in a group that received the TNS plus rehabilitation, compared to a group that received the same rehabilitation programme alone.

Methods

- Study design

This single-blinded randomised controlled trial recruited patients that were being treated by the researcher in their clinic for symptoms of plantar fasciitis, and who had not benefitted from a home exercise programme already. In this study, participants were randomly assigned to one of two groups, who received either a structured home exercise programme alone, or the same home exercise programme and the addition of a TNS device. Follow-up duration was three-months, with interim data also recorded at six-weeks. Patients were encouraged to continue with their allocated treatment throughout the whole duration of their study inclusion.

- Participants

A total of 40 participants were recruited between September 2014 and June 2016. These were split evenly between the two treatment groups. Inclusion criteria were: >18 years of age at time of enrolment, with unilateral plantar fasciitis symptoms only, symptoms of at least four months duration, with pain reproduced on palpation of the

medial calcaneal tubercle at the plantar fascia attachment, and / or with pain on loading (heel-stand test), and to have had the diagnosis confirmed on either ultrasound (plantar fascia thickening of >4mm, without full/partial thickness tear) or MRI.(540)

Exclusion criteria included previous or current partial or full thickness tears of the Achilles or Plantar Fascia (to avoid risk of further injury), lower limb sensorimotor or vascular problems (as these could be adversely affected by the use of the TNS), those with other known causes for their pain (such as referred pain, or inflammatory / connective tissue disorders), or those that could not adequately apply the TNS device.

Using G*Power 3.1, an *a priori* sample size calculation was performed with power set at 0.8 and α set at 0.05, using the data for improvements in self-reported pain from the preliminary study and other published research. Using a mean ± SD improvement following the use of a TNS in the measure of self-reported average pain of 1.9 ± 2.1 /10, and estimating a projected improvement of 25-50% of this value in a control population who were not provided with a TNS (i.e. an improvement in pain of no more than 0.95 ± 1.2 /10), gave an effect size of 0.67-0.9 i.e. a medium to large effect size. This calculation indicated that a range of between 15-25 participants in total were needed. Allowing for possible attrition, permissions were granted to recruit a total of 40 participants, split evenly between the intervention and control groups. This compares to other published RCTs examining the effectiveness of TNS which have used 16-85 participants per treatment arm studied.(249, 250, 255)

- Consent, randomisation and masking

Suitable patients that met the inclusion criteria met with the researcher during their routine clinical care and had the study outline and aims discussed with them. They were provided written information about the study, and advised that the study was designed to assess any benefits with the addition of a TNS device. Following this discussion, if they wished to participate in the study, they were booked in to commence formal enrolment. In keeping with NHS research guidance, all patients were given a minimum period of 24 hours between the study being discussed with

them and being formally consented to enter the study using signed written consent forms.

At enrolment, after consent was taken, participants were randomised by a study nurse practitioner who remained independent from the rest of the study. Participants were allocated equally to either an “intervention” group (who received a home exercise programme & TNS device) or a “control” group (who received a home exercise programme only) using the “Sealed Envelope” software (www.sealedenvelope.com , ©Sealed Envelope Ltd). Participants and the study nurse practitioner were aware of group allocation, but the researcher that reviewed the patient in clinic at follow-up remained blinded to group allocation throughout their involvement and no accidental un-blinding occurred during the study period.

- Interventions

Both groups of participants were given a standardised structured Home Exercise Programme (HEP) which included static stretches of the plantar fascia, the calf (selectively involving both gastrocnemius and soleus for different stretches), plus Flexor Hallucis Longus (FHL) and hamstrings, as well as calf and intrinsic foot muscle strengthening and balance training exercises. At baseline, after initial measurements were taken, all participants were taught how to perform and progress, their home exercise programme, gradually lengthening the time static stretches were held for, and increasing the number of repetitions of strengthening exercises as able. Their technique was checked at the interim (six-week) appointment by their treating clinician, and any necessary corrections to the technique were made to optimise rehabilitation. All patients were also given written material to support the use of this home exercise programme and to progress the rehabilitation as symptoms allowed. (This material is included as Appendix 2 of this thesis as this is a common method across multiple studies, this information includes the specific rehabilitation guidance given to patients.)

In addition to the home exercise programme, participants that were randomised to the “intervention” group (n=20) were also provided with a commercially available TNS device (“LA Brace ® Plantar Fasciitis Night Splint”) which was bought from a medical supply company before the study commenced. Patients were taught how to

apply the device by the study nurse practitioner and had her contact details should any further assistance about the device be required. They were instructed how to alter the tension within the splint device over time both for comfort, and to maintain a dorsiflexion force during the intervention period.

- Outcome measures

Patients completed a structured questionnaire about their symptoms up to 24 hours before their treatment commenced, and at the six-week and three-month follow-up visits. This questionnaire contained a series of different outcome measures, including questions about pain including the pain felt by the patient “on average”, “at its best” and “at its worst” using a 0-10 numerical rating scale. In addition, this questionnaire contained a number of validated PROMs including those investigating local foot/ankle function (revised-Foot Function Index (FFI-r) and Manchester-Oxford Foot Questionnaire (MOXFQ), as well as measures of global function (EQ-5D-5L). PROMs were also used to examine the impact of symptoms of other areas of patient functioning including measures of anxiety and depression symptoms (Hospital Anxiety and Depression Scale – HADS) and sleep quality (Pittsburgh Sleep Quality Index – PSQI). Measures to quantify levels of physical activity included the short-form (7-day recall) version of the International Physical Activity Questionnaire (IPAQ), and two “vital signs” physical activity questions. These different outcome measures are all discussed and evaluated in Chapter 2.

A range of physical measurements were also recorded by the researcher at the same time points as the questionnaire. Measurements of physical flexibility included ankle dorsiflexion range, popliteal angle, and knee to wall distance. Additionally, ultrasonographic assessment of the plantar fascia thickness was recorded.

The ranges of passive ankle dorsiflexion were assessed using a hand-held goniometer with the participant in a prone position with the knee both extended and flexed to 90°. The popliteal angle was assessed with the patient lying supine, with the hip flexed to 90°, and the range of knee extension measured using a hand-held goniometer (with 180° being fully extended). The “knee to wall” distance in mm was recorded as a measure of flexibility in a more functional position, measuring the distance a participant could move their foot back from the wall and still just touch the

knee to the wall without their heel lifting. The plantar fascia thickness was assessed using a musculoskeletal ultrasound (GE LogiqE) with the participant lying prone with their foot suspended over the end of an examination couch. An average of three recordings was taken to reduce intra-observer error between measures, with previous work showing a reduction in plantar fascia thickness correlating to improvement in symptoms.(569)

The primary outcome measure studied was the self-reported “average pain” (as recorded on a 0-10 numerical scale) assessing any change between values recorded at baseline and at three-months, with the remainder of the outcome measures being secondary to this.

Those participants who were in the control group and who had not improved significantly at three-months were offered a TNS after the final study follow-up.

- Statistical analysis

Data were collated prospectively into an Excel spreadsheet (MS Excel from MS Office 2011, version 14.5.7) and analysed in SPSS (IBM SPSS Statistics, version 23). Comparisons were made between the baseline data and data from the six-week, and the three-month follow-up appointments, with most of the outcome measures in this dataset being scale data. All data were analysed on an intention to treat basis, deliberately not taking the amount of time patients wore the device into account, mimicking the use of the TNS in the real-world.

As the sample sizes were small, the Shapiro-Wilk test was used to assess normality and as data were found to be normally distributed, analysis was predominantly performed with parametric testing, aside from exceptions such as gender (categorical data) which was analysed with chi-square testing. A two-way ANOVA (time x treatment group allocation) was performed primarily to assess if a time x group interaction effect occurred between baseline and both the final (3-month) and also the interim (6-week) time points. Additional paired-samples T-tests were used for specific within groups comparisons at the two specified time-points vs. baseline. Unpaired T-tests were used to compare data at baseline to ensure groups were comparable. Statistical significance was set at $p<0.05$.

- Ethical considerations

This study had all necessary permissions and was registered on a publicly accessible database (ClinicalTrials.Gov identifier NCT02546115). The study was given a favourable opinion from an NHS Research Ethics Committee (REC ref 14/WS/1069) and had all required local site approvals.

Results

A total of 41 participants with chronic plantar fasciitis were initially identified as being potentially suitable for inclusion based on inclusion/exclusion criteria. One patient was initially put forward to enter the study, but after baseline assessment chose not to continue for personal reasons, leaving the total of 40 patients who were recruited.

All patients completed the study with final data collection at three-months, however two patients did not attend for the interim / six-week appointment giving 38/40 responses at this point (one was due to an administrative error, the other due to patient availability) and both of these participants were in the control group. Information for this recruitment is detailed in the included CONSORT 2010 Flow Diagram (Figure 5.2)

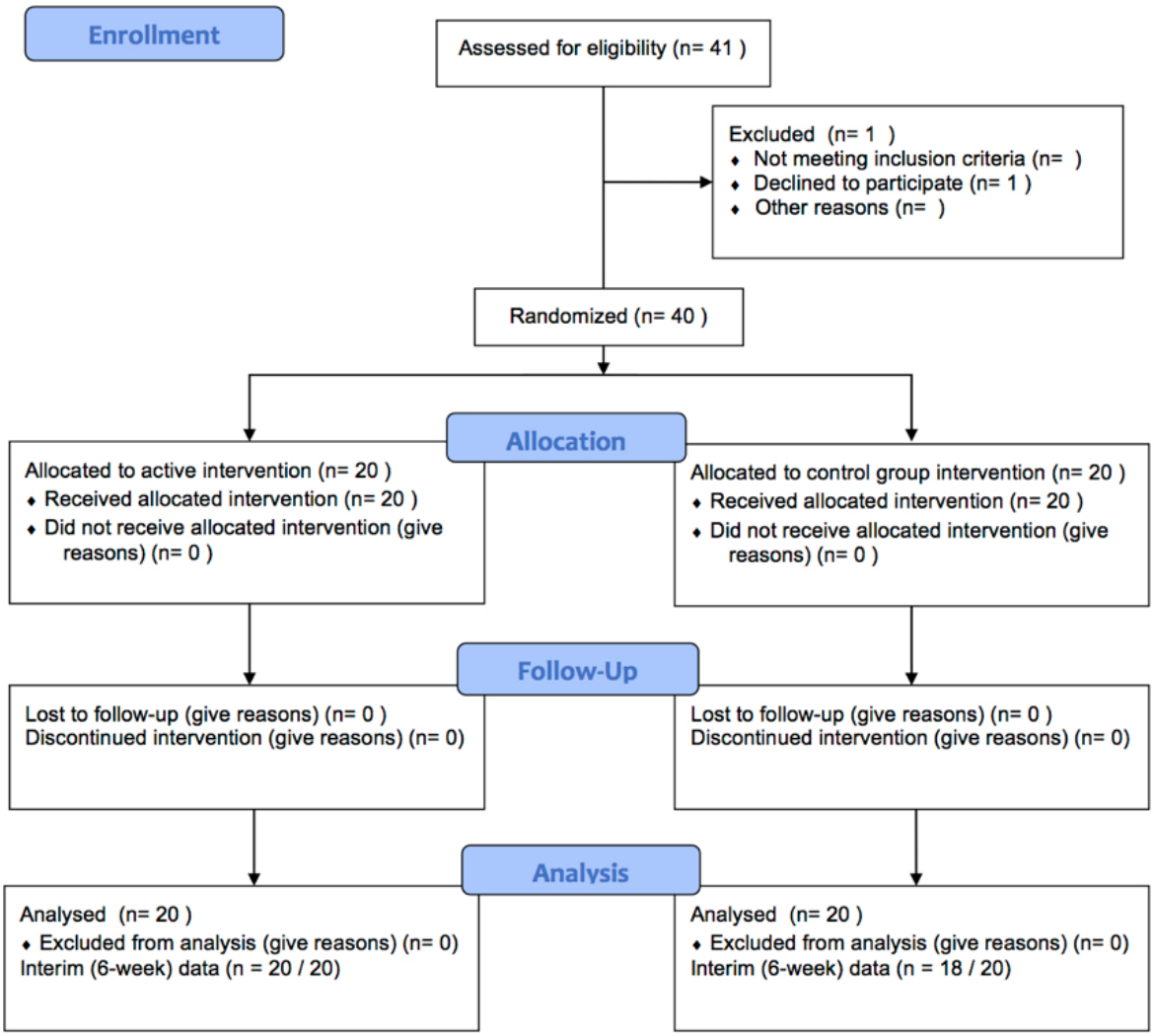


Figure 5.2: CONSORT Flowchart for TNS RCT (Study B)

The mean age of the participants was 52.1 ±10.3 years, 70% (n=28/40) were female and the participants had a mean BMI of 30.8 ±5.2kg/m^2. At entry into the study, the participants' mean duration of symptoms was 25.2 ±24.5 months, (range 5 months – 10 years) and with 2 participants reporting symptoms of 10 years or more. The participants in the intervention group had a mean duration of symptoms of 30.3±33.2 months, compared to the control group of 20.1±9.2, but this difference was not found to be significant (p=0.204). This information is displayed in Table 5.3. All participants reported the prior to inclusion in this study they undertook a home exercise programme without success. There were no significant differences in any of the demographics recorded between participants in the intervention and control groups (Table 5.3, with figures displayed as mean ±SD)

Table 5.3: Demographic information for participants

	"Intervention Group" HEP + TNS (n=20)	**"Control Group"** HEP alone (n=20)	***p-value***
Age	53.4 ± 8.9	50.9 ± 11.7	*0.444*
Gender (male/female)	5M / 15F (75% female)	7M / 13F (65% female)	*0.503*
BMI (kg/m^2)	32.6 ± 5.0	29.0 ± 4.9	*0.071*
Symptom duration (months)	30.3 ± 33.2	20.1 ± 9.2	*0.204*

Key: Data shown are mean ± SD. p-value compares data between different groups using Unpaired T-tests (normally-distributed data), or Chi-square testing (gender - categorical data).

- Patient Reported Outcome Measures (PROMs)

There were no differences in any of the baseline PROMs between the two groups, except for the self-reported "worst pain" which did differ significantly at baseline (Intervention Group 8.0 ±1.7/10, Control Group 9.0 ±1.0 /10, p=0.032).

The baseline and follow-up variables for both groups are displayed in table 5.4 for pain/stiffness and in table 5.5 for the validated PROMs data.

Table 5.4: Numerical pain/stiffness scores (/10) at baseline and follow-up

		Baseline	6-weeks		3-months	
		X ± SD	**X ± SD**	***2*2 p=***	**X ± SD**	***2*2 p=***
"average pain"	I	6.8 ± 2.2	5.6 ± 2.8 *	*0.819*	5.3 ± 2.6 **	*0.944*
	C	7.1 ± 1.7	6.2 ± 2.6		5.6 ± 2.9 *	
"pain at its worst"	I	8.0 ± 1.7	6.6 ± 2.6 **	*0.622*	5.9 ± 2.9 ***	*0.870*
	C	9.0 ± 1.0	7.1 ± 2.6 **		6.7 ± 3.2 **	
"pain at its best"	I	5.2 ± 2.4	4.2 ± 2.5 *	*0.952*	3.7 ± 2.2 **	*0.738*
	C	5.5 ± 2.4	4.4 ± 3.0		4.4 ± 3.0	
"pain in the morning"	I	7.3 ± 2.2	5.8 ± 2.6 **	*0.995*	5.2 ± 2.7 **	*0.790*
	C	8.3 ± 1.3	6.8 ± 2.9 **		5.8 ± 3.4 ***	
"pain in the evening"	I	6.9 ± 2.1	6.1 ± 2.9	*0.397*	5.5 ± 2.8 *	*0.767*
	C	7.7 ± 1.4	5.9 ± 3.2 *		6.0 ± 3.1 **	
"pain at rest"	I	5.4 ± 2.7	4.3 ± 2.9 *	*0.780*	4.3 ± 2.4 *	*0.983*
	C	6.0 ± 2.2	5.2 ± 2.7		4.9 ± 3.0	
"pain when walking"	I	7.1 ± 2.3	5.7 ± 2.8 **	*0.629*	5.5 ± 2.8 **	*0.663*
	C	7.5 ± 1.8	5.6 ± 3.2 *		5.5 ± 3.1 **	
"average stiffness"	I	6.0 ± 3.2	4.9 ± 2.9	*0.583*	4.3 ± 2.9 *	*0.899*
	C	6.5 ± 3.0	6.1 ± 2.6		4.6 ± 3.2 *	
"stiffness in the morning"	I	6.7 ± 3.0	5.3 ± 2.9	*0.377*	4.9 ± 3.0	*0.721*
	C	5.7 ± 3.2	6.3 ± 3.2		4.6 ± 3.6	

Key:

Figures shown are mean ±SD. I = "intervention group" (n=20, n=20/20 at 6w, n=20/20 at 3M), C = "Control Group" (n=20, n=18/20 at 6w, n=20/20 at 3M). Group x time interaction effects between baseline and the either the six-week or three-month follow-up time-points were assessed using 2-way (Time*Group) ANOVA (value displayed). Within group effects were assessed using paired t-tests; an asterisk at the 6-week or 3-month period indicates a statistically significant change from baseline values for the variable studied. *(* = p<0.05, ** p<0.01, *** p<0.001)*

Statistically significant improvements in a number of the validated PROMs were observed in both groups between baseline and both the interim / 6-week) and final / 3-month time-points (Table 5.5). These improvements included measures of pain, and specific local foot function. However, there were no time*group interaction effects identified for any of the measures studied.

Table 5.5: Patient Reported Outcome Measures (PROMs) at baseline and follow-up

		Baseline	6-weeks		3-months	
		X ± SD	**X ± SD**	***2*2 p=***	**X ± SD**	***2*2 p=***
painDETECT *(0-38, lower score indicates lower likelihood of neuropathic pain)*	I	13.4 ± 8.6	11.4 ± 7.3	*0.938*	11.9 ± 8.0	*0.568*
	C	15.4 ± 7.3	13.6 ± 7.5		11.9 ± 5.2 *	
MOXFQ (total score) *(range 16-80, with lower score indicating better function)*	I	56.2 ± 14.5	50.3 ± 16.0 *	*0.969*	49.2 ± 16.2	*0.411*
	C	64.5 ± 12.0	58.4 ± 16.7		51.8 ± 17.2 **	
FFI-r (total) *(range 34-136, with lower score indicating better function)*	I	88.3 ±24.5	81.4 ±24.0	*0.851*	77.6 ± 25.4 *	*0.492*
	C	95.5 ± 22.9	86.6 ± 22.5		77.0 ± 27.4 **	
FAAM - %score *(higher score indicating better function)*	I	56% ± 23%	58% ± 23%	*0.651*	67% ± 22% **	*0.983*
	C	55% ± 20%	61% ± 19% *		66% ± 23% *	
FAAM - %function *(higher score indicating better function)*	I	56% ± 28%	61% ± 25%	*0.940*	53% ± 27%	*0.374*
	C	61% ± 13%	65% ± 26%		68% ± 22% *	
FAAM - %sport score *(higher score indicating better function)*	I	36% ± 27%	39% ± 29%	*0.670*	44% ± 31%	*0.951*
	C	34% ± 22%	43% ± 20%		44% ± 31%	
FAAM - %sport function *(higher score indicating better function)*	I	34% ± 32%	31% ± 25%	*0.698*	37% ± 27%	*0.339*
	C	51% ± 28%	53% ± 30%		67% ± 28%	
HAD - anxiety subscale *(range 0-21, with lower score indicating fewer symptoms)*	I	6.5 ± 4.7	6.1 ± 3.5	*0.681*	5.5 ± 4.0	*0.800*
	C	7.2 ± 5.0	8.1 ± 4.6		6.7 ± 4.9	
HAD - depression subscale *(range 0-21, with lower score indicating fewer symptoms)*	I	5.7 ± 4.6	6.6 ± 5.1	*0.531*	5.6 ± 4.6	*0.666*
	C	6.1 ± 4.7	5.8 ± 4.2		5.1 ± 4.7	
PSQI (total score) *(range 0-21, with lower score indicating fewer symptoms)*	I	8.7 ± 5.3	10.4 ± 5.1	*0.686*	8.8 ± 4.7	*0.978*
	C	10.1 ± 4.9	10.7 ± 5.3		10.2 ± 4.7	

Key: Figures shown are mean ±SD. I = “intervention group” (n=20, n=20/20 at 6w, n=20/20 at 3M), C = “Control Group” (n=20, n=18/20 at 6w, n=20/20 at 3M). Group * time interaction effects between baseline and the either the six-week or three-month follow-up time-points were assessed using 2-way (Time*Group) ANOVA (value displayed.) Within group effects were assessed using paired t-tests; an asterisk at the 6-week or 3-month period indicates a statistically significant change from baseline values for the variable studied. *(* = p<0.05, ** p<0.01, *** p<0.001)*

- Physical parameters

Although some measures of pain and function improved in both of the two groups, there were fewer changes from baseline changes in the physical parameters studied that reached statistical significance in either group. In the intervention group, there were significant improvements in the knee-to-wall flexibility test at six-weeks only, and the popliteal angle at three-months only, using within-group testing. There were no significant changes in flexibility in the control group at any time-points. However, the time*group ANOVA testing demonstrated no time-group interaction effects, indicating no additional benefit seen from the TNS for any of the flexibility measures recorded. (Table 5.6)

In the members of the control group only, there was a statistically significant decrease in the plantar fascia thickness between baselines and both the 6-week and 3-month time-points, but the changes did not reach statistical significance in the intervention group, both assessed using within-group testing. However, the time*group ANOVA testing showed no interaction effect for this variable, and in view of this, and as the levels of pain did not differ significantly between the two groups, any clinical significance of this remains of uncertain significance.

Table 5.6: Physical measurements at baseline and at follow-up

		Baseline	6-weeks		3-months	
		X ± SD	**X ± SD**	***2*2 p=***	**X ± SD**	***2*2 p=***
knee to wall distance (mm)	I	89.0 ± 36.5	100.3 ± 33.2 *	*0.611*	93.4 ± 37.0	*0.725*
	C	86.8 ± 41.5	89.4 ± 35.9		97.3 ± 39.1	
ankle dorsiflexion angle - with knee straight (°)	I	93.7 ± 5.5	94.5 ± 5.0	*0.513*	95.1 ± 5.9	*0.708*
	C	94.4 ±5.5	96.8 ± 4.5		94.9 ± 5.8	
ankle dorsiflexion angle – with knee bent (°)	I	99.2 ± 7.0	101.2 ± 6.4	*0.951*	99.5 ± 5.3	*0.714*
	C	98.6 ±5.1	100.7 ± 5.7		99.8 ± 5.5	
popliteal angle (°)	I	145.9 ± 10.3	145.7 ± 21.1	*0.470*	150.8 ± 11.0 *	*0.564*
	C	145.8 ±10.7	150.2 ± 9.7		147.8 ± 12.7	
plantar fascia thickness (mm)	I	6.1 ± 1.4	5.7 ± 1.5	*0.815*	6.0 ± 1.9	*0.486*
	C	6.3 ±1.2	5.8 ± 1.1 **		5.7 ± 1.2 *	

Key:

Figures shown are mean ±SD. I = “intervention group” (n=20, n=20/20 at 6w, n=20/20 at 3M), C = “Control Group” (n=20, n=18/20 at 6w, n=20/20 at 3M). The group * time interaction effects between baseline and the either the six-week or three-month follow-up time-points were assessed using 2-way (Time*Group) ANOVA (value displayed.) Within group effects were assessed using paired t-tests; an asterisk at the 6-week or 3-month period indicates a statistically significant change from baseline values for the variable studied. *(* = p<0.05, ** p<0.01, *** p<0.001)*

5.4 -

Tension Night Splint (TNS) Interventions Discussion

The initial retrospective cohort study (study A) suggested that the majority of patients were able to tolerate the Tension Night Splint (TNS), and that the TNS became more comfortable to wear as patients continued with the treatment. However, a minority of participants struggled to tolerate the device, and sleep was reported to be affected in a just under a third of patients to a great extent. Overall in this initial study, there was a reduction of pain first thing in the morning by nearly 3 points on a 0-10 numerical pain rating scale, and an improvement in self-reported function by 17 percentage points, after wearing the TNS. These changes, taking note of the limitations from the study design, were found to be significant. There were no differences found in treatment effectiveness comparing male and female patients, although small numbers make assessment of this unreliable. However, not all patients benefited from the tension night splint, and a broad range of responses in self-reported measures of pain were reported from the TNS. Whilst the findings from Study A suggest benefit from the TNS, they must be interpreted with caution. This study only involved 20 patients, with 17 responses, and this small sample size, and the retrospective nature of the study cause some hesitation in extrapolating these results to a wider population. As this was a retrospective study, true causation of benefit cannot be reliably determined from this study design. There is inherent bias in this design, most notably recall bias, which was likely to have affected the results from the study. However, the high response rate of 85% may have reduced many of the other problems commonly associated with study designs such as this, including the uncertainties caused by non-response bias.

The case series study acted as preliminary work and allowed an estimate of a possible treatment effect size in this specific population, thereby guiding the development of the RCT (study B). This second study used a range of outcome measurements in a clinical population with chronic plantar fasciitis, including a

number of validated PROMs. This RCT used a single-blinded design. Consideration was given prior to the study as to whether sham devices could be used to give a double-blinded design, but the technical challenges and costs associated meant that this was not feasible although this could be a consideration for the future.

In the RCT (study B), there were no significant changes in any of the measures studied between the two groups at either the interim (6-week) or final (3-month) outcome point. This indicates that the addition of the TNS had no measurable difference in any of the outcome measures studied in addition to the home exercise programme. The benefits seen in both groups cannot be reliably ascribed to the HEP alone without the inclusion of an additional comparison group who did not have this intervention.

Study B, the RCT, has demonstrated improvements in several domains of pain and self-reported function in patients who were given a home exercise programme (HEP), both with and without the TNS. Benefits in pain/function were seen in patients with very chronic symptoms, for an average of 2 years, which is a far longer duration of symptoms than many other previously published works.(250, 252, 254, 255) It is possible that these benefits were a simply as a consequence of the natural resolution of the condition. However, as the average duration of symptoms in the participants in this group was in excess of 18 months, it is not clear whether the benefits seen over a further 3-month period could be solely attributable to this, and the mechanisms of benefits seen remains unclear. The specific results from this RCT are discussed in the following sub-headings for clarity.

- Pain / PROMs results (Study B)

Both groups within the RCT had statistically significant improvements in the primary outcome measure of the self-reported levels of “average pain” of ~1.5 points on a 0-10 pain scale at 3-months, which exceeded the minimally clinically important difference of the equivalent of 0.9 points found in previous research.(451) However, there were no statistically significant differences between the two groups at any time point, using either pain scores or PROMs, thereby demonstrating no additional benefit from the TNS to the structured home exercise programme (HEP) in patients with chronic plantar fasciitis.

Statistically significant improvements were seen in both groups across self-reported levels of “average pain”, “pain at its worst”, “pain in the morning”, “pain in the evening”, and “pain walking, indicating benefits throughout the day, rather than just first thing in the morning. However, it is noted that the majority of participants in both groups had improvements in, rather than resolution of, their levels of pain, and realistic advice needs to be given to patients with chronic symptoms about expectations from treatment.

Improvements were seen in both groups using different validated PROMs with the in-group analysis, although as previously highlighted no statistical significances were seen with the ANOVA analysis comparing between-group changes. There were improvements in the MOXFQ score reaching statistical significance in the intervention group at 6-weeks, but not at 3-months, and only at 3-months in the control group. This improvement was different from that seen for the FAAM questionnaire score which showed statistically significant improvements in the intervention group at 3-months, but at the 6-week and also the 3-month point for the control group. The FFI-r score changed to a statistically significant amount in both groups at the 3-month time point, although did not differ significantly between the groups, and the magnitude of the improvements seen are greater than the 7 points found to be the minimum clinically significant change in previous work.(451) Overall regarding specific foot-function PROMs, although all three of these different foot questionnaires are validated in patient groups such as this, the differences seen between different questionnaires raises further questions about which may be the most suitable in this population to assess benefits.

The control group within the RCT achieved significant improvements in a range of measures studied. This was despite them having only the same interventions (e.g. rehabilitation exercises) within the study as they had before entry and the reasons for this benefit remain unclear. It is possible that benefits were gained as patients had better compliance with the exercise programme within the study (the so-called “Hawthorne effect”), however this cannot be reliably determined from this data.

There was no significant improvement in mental health functioning for either anxiety or depressive symptoms as assessed by the HAD questionnaire. Anecdotally patients may report impaired sleep quality from the use of the TNS devices, which was also reported in the initial pilot cohort study. In the RCT here was no statistically significant worsening of sleep quality as formally assessed by the Pittsburgh Sleep Quality Index (PSQI), in members of the intervention group at either of the follow-up time-periods studied. Any self-reported worsening of sleep may not be of sufficient magnitude to be measured with the PSQI. Conversely it may be that that patients who found their sleep to be greatly disturbed by the TNS may have simply taken this off, as compliance was shown to be a possible issue in study A.

- Physical parameters (Study B)

Despite the improvements in pain seen, less definite benefits were seen in either group across the domains of physical flexibility within the randomised control trial. Improvements were found in two of the different recorded measures of flexibility in the intervention group, but no significant differences were seen between different groups at the different time points, and neither group showed consistent improvements in flexibility. This differs from previous work showing a close correlation between the two variables of pain and flexibility,(193) suggesting that variables other than flexibility account for the reduction in pain reported in this study.

Previously published works have shown an association between reduction in plantar fascia thickening and improvements in pain, but this was not seen specifically in this study.(569) Within the RCT study, the plantar fascia thickness improved to a statistically significant extent in the control group, but not the intervention group. The reasons for this, and any clinical significance for the changes seen, remain unclear, particularly as the ANOVA analysis did not show any significant difference in the between-groups effect over time and the within-groups may simply be a statistical anomaly.

- Comparisons between treatment groups in Study B

The two groups within the RCT were demonstrated to be similar across a range of measurements at baseline, and whilst patients in the intervention group were slightly

older, slightly more overweight and with a longer duration of symptoms, none of the differences in these variables reached statistical significance between groups at baseline. These parameters appear to be typical for those patients presenting in the secondary care clinic in which this was based, with patients with chronic symptoms that had not already resolved. Of the pain/function variables, the participants in the control group of the RCT did have a statistically higher self-reported “worst pain” at baseline, although the other variables were the same as the intervention group, and it is not clear if this could have had an influence on subsequent outcome results. Given the lack of differences seen between groups, co-variate analysis to investigate this was not performed.

- Possible limitations, and considerations for the future

Although both groups in study B had improvements across several of the outcome measures studied, there were no statistical differences identified between the groups. A larger study population may be better able to explore this area of research in patients with chronic plantar fasciitis, and this could be the focus of further study. This may identify if a smaller than expected treatment effect was seen, and one which this study may have been underpowered to detect. This was a single-blinded study, in which the participants, but not the investigator, knew which group they had been allocated to. This was chosen for pragmatic purposes, but this could have had an influence on the outcome. Further work could be done with sham devices should funding be available to study this as an intervention.

The data were all analysed on an intention to treat basis, meaning that all data were analysed based on treatment allocation, without weighting given to compliance with treatment. This could have reduced any positive or negative effects of the TNS, but this better represents the effects seen in the real world with some patients having limited compliance to the use of the device for a variety of factors including comfort.

Inter-observer error is well recognised as a limitation for both the goniometer and ultrasound measures, which was avoided with a single investigator taking all of the measurements.(570, 571) Intra-observer error was minimised with familiarity with the techniques used and by taking an average of three ultrasound readings,(571) but

could not be eliminated completely. This issue remains a recognised limitation of this study.

Improvements in pain occurred in both groups in study B without necessarily seeing statistically significant differences seen in measures of physical flexibility. Inflexibility of the posterior chain muscles of the calf and hamstrings are believed to be one of the risk factors for the development and chronicity of plantar fasciitis.(62, 151, 191, 193) It is possible that the study was underpowered to detect small changes in flexibility reliably, and either larger groups or more robust methods are needed. Alternatively, it may be that the improvements seen represent changes other than that directly from changes in flexibility, such as improvements in the load tolerability of tissue, or desensitisation of tissue, and exploring these areas could be the focus of further work.

- Comparison between two studies

The initial study used a bespoke TNS device, and the later RCT used a standard commercially available splint for reasons of cost, and also to standardise the device/intervention to avoid further confounders. It is not known if different designs of tension night splint are tolerated to a greater or lesser extent, or have differing effects, and this could be the focus of further work.

- Overall summary

Overall, these studies have demonstrated improvements in pain and function, but not necessarily physical parameters, in patients even with very chronic symptoms following a home exercise programme alone (i.e. Study B – control group). However, the absence of a group that did not have the HEP means that benefits cannot be ascribed to the HEP alone and could be from natural resolution over time, or other possible confounding factors. From the data seen here in Study B, the addition of a Tension Night Splint does not have any identified benefit in measurements of pain or functioning beyond those seen from the rehabilitation programme alone in the treatment of this population, which is in keeping with two of the larger previously published randomised controlled trials.(254, 255)

Chapter 6 -

Intervention:
Extra-Corporeal Shockwave Therapy (ESWT)
for patients with chronic plantar fasciitis

Figure 6.1: Example illustration of ESWT for plantar fasciitis

6.1 – Introduction

Another treatment option for patients with recalcitrant plantar fasciitis is that of Extra-Corporeal Shockwave Therapy (ESWT). This involves the use of high-energy sound waves, most typically performed alongside a structured rehabilitation programme of exercises, to promote tissue healing and reduce pain. The precise mechanism of action of ESWT is not yet fully understood, with a number of animal and human-cell studies demonstrating that ESWT has a wide range of biological effects in tendon tissue, including the release of angiogenetic factors and a subsequent increase in neovascularisation, and a reduction in inflammatory mediators including various interleukins and MMPs.(268, 270) How these specific biological factors relate to improvements in pain and function remain as yet unclear.

A number of systematic review and primary research studies, involving the use of ESWT in patients with plantar fasciitis were examined in chapter 2 / section 2.2.2. These studies have shown ESWT to be a safe and an effective treatment in patients with chronic plantar fasciitis recalcitrant to other conservative treatments.(263, 282, 303, 325) This evidence-base includes studies that have used focal-ESWT (F-ESWT),(288, 297, 312, 314) those that have used radial-ESWT (rESWT), (273, 279, 308) and those that have used a combination of both.(307, 309)

Many of the early studies used focal-ESWT which was performed under local or regional anaesthesia (297, 315, 324) however with the use of radial shockwave this is no longer required. In addition, there are some risks and challenges associated with the use of local anaesthesia to numb the treated area, as this means that the patient cannot give feedback about how they are tolerating the ESWT, and potentially either under- or over-dosing could occur. There are differences between different types of ESWT, and attempting to extrapolate information from studies with different ESWT regimes and machines has significant limitations.(22, 260, 301) Currently there is only a single study published which has used the specific rESWT machine that is in use in the department in which this research has been undertaken (“Intelect” RPW ESWT machine - DJO Global Chattanooga), and which found no difference in outcomes comparing rESWT performed under ultrasound guidance against rESWT without guidance.(300) However there are currently no published

studies investigating the effectiveness that this specific rESWT device has with patients with chronic plantar fasciitis comparing either against placebo or another active treatment. In addition there are no published studies directly comparing outcomes between different ESWT machines, although a meta-analysis has suggested that rESWT is an appropriate alternative to F-ESWT and may have improved effectiveness.(303) Current guidance from the manufacturer (DJO Chattanooga) of the specific radial shockwave (rESWT) machine is to use three ESWT treatment sessions (performed at weekly intervals) with the optimal energy dose of shockwave being the “highest comfortably tolerated dose” by the patient. However the basis for this advice is unclear as this device is a radial-ESWT machine and any potential dose-effect has only been reported convincingly from studies involving focal-ESWT.(263)

Research has demonstrated improved outcomes in patients with plantar fasciitis undertaking ESWT alongside a rehabilitation programme compared to those receiving ESWT alone,(273) and most published studies have used a rehabilitation programme delivered alongside the ESWT treatment.(20, 263, 326) However, the heterogeneity of different studies, with different treatment regimens and outcome measures, as well as different patient cohorts with different duration of symptoms and different ages, means that any direct comparison of outcomes between different studies remains difficult.(301)

Many of the published studies have involved patients with a shorter-duration of symptoms (typically circa 6 months) than those often encountered in routine NHS secondary care clinics who, as described in Chapter 3, have often had symptoms for a far longer period of time.(275-277, 279) The duration of symptoms may influence outcomes following ESWT (either radial or focal), with some evidence suggesting there may be an optimal time period of symptoms in which ESWT may be most effective, but the detail about when this is remains unclear and the evidence is of weak strength, or may arise from methodological issues in some studies.(22) Two studies have specifically investigated the effects of ESWT in patients with acute symptoms of plantar fasciitis, (i.e. symptoms of 6-weeks or less) and these found greater improvements in those given stretches only, or a steroid injection, rather than those given ESWT indicating this treatment modality may not be as useful as other

treatments in those with very early symptoms.(278, 311) One further study investigated the impact of symptom duration on treatment outcomes following rESWT, comparing those with symptoms less than 3-months compared to those with symptoms of more than 6-months and found that both groups improved.(308) Although there was a suggestion of greater improvements in those with shorter-duration symptoms (<3M compared to >6M), this difference did not reach statistical significance in this small pilot study which only involved 28 patients.(308)

The current guidance from NICE calls for further research to be undertaken in NHS patients with chronic symptoms with validated outcome measures to ensure that safe and effective care is undertaken.(51) Many of the published studies have attempted to assess the impact that ESWT has only on levels of foot pain,(298, 304, 309) or on local foot function with one of several PROMs.(20, 280, 305) However there have been few attempts to assess whether there have been any improvements in validated measures of global function of the patients.(276, 284, 285) This is one of the areas that are explored in the two studies in this experimental chapter.

Given the heterogeneity of intervention, outcome measures and follow-up, in the published research to date, and the lack of evidence from this specific rESWT machine, it is necessary to study the outcomes following ESWT using this specific device that is in clinical use in this department in this clinical population. This chapter describes the findings from two linked studies which have investigated the effects of rESWT for patients with chronic plantar fasciitis who had been referred to a single hospital outpatient department. The first study (C) was a prospective case series, and the second study (D) was a double-blinded randomised controlled trial. Both have been undertaken in line with the published NICE guidance around the use of rESWT for patients with plantar fasciitis.(51) Both studies aim to identify any improvements in pain or functioning following rESWT.

The first study (C) used a prospective case series design and examined outcomes following the use of rESWT in patients with chronic plantar fasciitis in routine clinical care. Outcome measures recorded at baseline and subsequent follow-up included simple self-reported measures of pain, plus a number of validated PROMs which assessed foot function as well as markers of global function and wellbeing. These

are detailed in the study methodology (section 6.2). Data from Study C were used to estimate a treatment effect size which was then used in an a priori power calculation for the RCT study (D) to investigate this treatment more robustly.

The second study (D) formally investigated the effect of rESWT on pain and function in patients with chronic plantar fasciitis. To reduce the influence of bias, this was undertaken as a double-blinded RCT design. The comparator arm of the study received “minimal-dose” rESWT as a control intervention, with all patients receiving the same advice and the same structured rehabilitation programme. “Minimal-dose” rESWT was chosen as a comparator group as an attempt to blind the participants about treatment allocation. There may have been a therapeutic effect even from the lowest level of rESWT that the machine was able to generate, and the limitations of this approach are discussed in section 6.4. The primary outcome measure for study D was a change in self-rated levels of “average pain” reported by the participants using a simple pain numerical rating system. A wide range of validated PROMs were used as secondary outcome measures to better understand any improvement in markers of global wellbeing and functioning that any improvement in the patients’ foot symptoms may have, as this is a notable gap in the published literature.

6.2 -

Experimental study C:

Extra-Corporal Shockwave Therapy plus rehabilitation for patients with chronic plantar fasciitis. A prospective case-series study with multiple outcome measures."

Specific study aim(s)

The aim of this case series study was to assess self-reported changes in pain and function following the use of radial-Extra-Corporeal Shockwave Therapy (rESWT) and a structured home exercise programme (HEP) in routine NHS practice for patients with chronic plantar fasciitis.

Methods

- Study design

A prospective case-series study design was used, which included all patients from a single clinic who undertook radial-Extra-Corporeal Shockwave Therapy (rESWT) between April 2014 and July 2016. This study compared self-reported data at baseline and 3-months following the last session of rESWT treatment.

- Participants

The results for all consecutive patients who had undergone ESWT treatment from a single clinic were included in this case series study. The ESWT treatment was offered as a part of routine clinical care to patients aged 18 and over, who had symptoms of plantar fasciitis of at least 4 months of duration that were having a significant impact on their quality of life.

Prior to being offered ESWT, patients were required to have already tried a rehabilitation programme for a minimum period of 3-months. Patients could not have received a steroid injection in the 3-months prior to ESWT being performed, and could not be on anticoagulation therapy. All patients had received either an ultrasound or MRI scan of their foot prior to treatment with ESWT. This was done to confirm the clinical diagnosis, and to exclude the presence of a partial thickness tear

which is a contra-indication to shockwave therapy as this may predispose to full-thickness tear. All patients received written patient information about ESWT (published by NICE) prior to rESWT being conducted.(51) Written consent forms were used to record patient consent before the first session of rESWT was undertaken, and verbal consent re-confirmed at the two subsequent treatment sessions.

- Intervention

Patients had three sessions of rESWT, which was performed by one of two clinicians, who had undergone the same training in the use of ESWT and followed a standardised protocol. All individual patients had all sessions of ESWT delivered by the same practitioner. The rESWT was performed once per week for three weeks using an “Intelect” RPW ESWT machine (DJO Global Chattanooga). The treatment protocol from the manufacturer for patients with plantar fasciitis was ESWT delivered at a frequency of 10 Hz with 2000 shocks per treatment session. Manufacturer instructions were that the “energy dose” from the generated pressure wave, (measured in bar) should be controlled by the operator to use a “maximal comfortably-tolerated” level, rather than a single specified pressure setting. This level was individual for different patients, and varied between sessions depending on comfort. In this study group the mean value of the pressure waves generated was 2.44±0.32 bar over the three treatment sessions.

The patients were given a standardised home exercise programme to undertake and informed as to how to progress this. This included stretches for the posterior kinetic chain, involving the plantar fascia, gastrocnemius, soleus, Flexor Hallucis Longus (FHL), and the hamstrings muscle groups. In addition to the stretches, the patient progressed onto calf muscle strengthening, balance/ proprioception, and intrinsic foot muscle strengthening exercises. Patients were advised to undertake these exercises twice or three times per day and that this programme was to be re-started the day after each ESWT procedure. An example of this rehabilitation plan is included in Appendix 2. Patients were advised that these exercises could be uncomfortable, particularly to begin with, and were taught how to manage and progress the exercise programme. Patients were advised to continue these rehabilitation exercises throughout the period that the shockwave therapy was being

conducted and throughout the whole follow-up period. Following rESWT, patients were also given standardised post-procedural advice and reminded what to expect (early expected side-effects include transient mild increase of pain, redness, bruising, or tingling) and in keeping with manufacturer representative advice patients were advised to avoid NSAIDs for the day of, and for a few days following, each session of rESWT.

- Outcome measures

Specific outcome measures used in this study were numerical (0-10) scores for self-reported values of “average pain”, “pain at its worst”, and “average stiffness”. Additional measures included validated Patient Reported Outcome Measures (PROMs) assessing foot function (revised-Foot Function Index (FFI-r)(448-451), the Manchester-Oxford Foot Questionnaire (MOXFQ)(452-454) and assessing global function (EQ-5D-5L).(455, 456) Questionnaires examining the impact of symptoms of other areas of functioning, including measures of anxiety and depression symptoms (Hospital Anxiety and Depression Scale – HADS)(457-461) and sleep quality (Pittsburgh Sleep Quality Index – PSQI)(466, 467) were used. In addition, questionnaires to quantify levels of physical activity including the short-form (7-day recall) version of the International Physical Activity Questionnaire - IPAQ,(468) and two “vital signs” physical activity questions (469) were included.

- Statistical analysis

Data were recorded prospectively and transcribed into a spreadsheet (MS Excel 2016) for calculation of descriptive data. Demographic and baseline data for patient groups at different time-points were also tabulated to allow comparison of patient characteristics between different follow-up time points for clarity.

Further analysis was conducted using IBM SPSS Statistics (version 24). The majority of the scale data were shown to be normally distributed using the Shapiro-Wilk test, and statistical analysis was performed with parametric tests, using Paired-Samples T-test comparing pre/post values, with Wilcoxon Signed-Rank Test to look at pre/post differences for data that were not normally distributed, mainly the sub-scales of the IPAQ. Simple sub-group analysis, including unpaired-group

(Independent Samples Mann-Whitney U Test) and correlation analysis (Spearman's rank correlation coefficient), were conducted to assess any impact that variables such as severity of patient age, gender, length of symptoms of severity of baseline pain may have had on subsequent outcomes. Results are displayed predominantly as mean ± SD, and specified where other data are presented. Statistical significance was set at $p<0.05$ with statistically significant results being highlighted by an asterisk (*) The primary outcome measure was a change in the self-reported level of 'average pain" between baseline and follow-up, with other measures being secondary to this.

- Ethical considerations

The ESWT procedure was registered with the hospital's New Intervention Procedure Group (NIPAG) in keeping with local policies. Data are recorded here in the format of a service evaluation project and was registered as such with the CASE Team at the hospital. Formal NHS ethics permissions were not required.

Results

Results were available for 31 patients who had received radial-Extra-Corporeal Shockwave Therapy for chronic plantar fasciitis. There was a mean age of 49.4 ± 9.1 years (range 33.1-71.7 years), 68% were female, and ethnicity was not recorded. The mean duration of symptoms prior to ESWT was 30.8 ± 42.0 months (range: 6-months to 20-years.)

All patients had undertaken a structured rehabilitation programme for a minimum of three months prior to starting shockwave therapy treatments, with the exercises routinely being given to patients by a treating physiotherapist. In addition, 60% of patients had been given at least one steroid injection prior to ESWT (median 1, range 0-4 injections) with a mean self-reported /self-recalled duration of benefit of 1.3 ± 6.1 weeks (range 0-24 weeks) from their most recent injection.

No significant side-effects were reported following rESWT. Two of the thirty-one patients (6.5%) reported minor bruising at the time of their third session of shockwave, but this did not prevent them receiving all of the sessions of shockwave,

and all bruising had settled within a couple of weeks. No significant numbness, or any tissue injury was reported by any of the patients at any of the time-points.

The values for the primary outcome measure, self-reported “average” pain, improved significantly from a mean value of 6.8 ± 1.8 at baseline, to 4.5 ± 2.7 at 3-months (p=0.032) using the 0-10 pain scale. Statistically and clinically significant improvements between baseline and follow-up were seen in many of the local foot & ankle PROMs, but were not seen for the more global measures of health/function or the markers of physical activity that were used. The different PROMs at baseline and at three-month follow-up are displayed in table 6.1

Table 6.1: Patient Reported Outcome Measures (PROMs) at baseline and follow-up

Local foot/ankle PROM	**Baseline (n=31)**	**3-month follow-up (n=31)**	***p-value***
"Average pain" (0-10)	6.8 ± 1.8	4.5 ± 2.7	*0.032 **
"Worst pain" (0-10)	8.3 ± 1.8	5.9 ± 2.6	*0.021 **
"Average stiffness"(0-10)	5.8 ± 2.9	4.0 ± 2.9	*<0.001 ****
MOXFQ	58.4 ± 10.7	45.5 ± 14.4	*0.005 ***
total FFI-r score	87.7 ± 25.4	67.2 ± 21.6	*0.024 **
FAAM – ADL	57% ± 18%	76% ± 17%	*0.006 ***
FAAM – level of function	53% ± 25%	63% ± 23%	*0.223*
FAAM – Sport	33% ± 18%	52% ± 27%	*0.743*
FAAM – Sport level of function	31% ± 26%	50% ± 28%	*0.900*
Global PROMs			
painDETECT	11.9 ± 7.0	8.2 ± 6.4	*0.015 **
EQ-5D-5L (%overall health score)	69% ± 20%	72% ± 20%	*0.021*
PSQI (total score)	8.7 ± 4.6	7.6 ± 4.1	*0.132*
HAD-Anxiety	5.5 ± 4.1	5.8 ± 4.3	*0.985*
HAD-Depression	5.3 ± 4.0	4.8 ± 4.0	*0.264*

Key: data shown are mean ± SD. Significance of change from baseline shown using paired samples T-tests / Related-samples Wilcoxon Signed Rank tests, (= p<0.05, ** p<0.01, *** p<0.001)*

Physical activity rates were also assessed at baseline and follow-up to investigate if any improvements in pain may also be associated with an increase in activity. Overall there were no statistically significant changes seen in activity rates pre/post treatment as recorded with the different sub-scales of the short-form International Physical Activity Questionnaire (IPAQ), or through the use of the "vital signs" questions. The baseline and follow-up values for each of these parameters are displayed in table 6.2.

Table 6.2: Levels of physical activity at baseline and at follow-up

PROM	Baseline (n=31)	3-month follow-up (n=31)	*p-value*
IPAQ – amount of time in "vigorous-level physical activity" (minutes / week)	30 ± 66	98.0 ± 208	*0.168*
IPAQ – amount of time in "moderate-level physical activity" (minutes / week)	42 ± 105	99.9 ± 207	*0.074*
IPAQ – amount of time spent walking per week (minutes/week)	511 ± 808	370 ± 636	*0.687*
IPAQ – sitting on a week day (hours/day)	5.3 ± 4.7	4.0 ± 2.1	*0.386*
"Vital signs" – number of "at least moderately active minutes" per week	55 ± 100	114 ± 169	*0.102*

Key: data shown are mean ± SD. Significance of change from baseline shown using paired samples T-tests / Related-samples Wilcoxon Signed Rank tests, (= p<0.05, ** p<0.01, *** p<0.001)*

There were no significant correlations between the duration of symptoms and any of the baseline data recorded regarding pain or function. There were no differences between the baseline data for male (n=10) and female (n=21) patients for any of the parameters studied. There were no significant correlations found in this study between the duration of symptoms prior to rESWT, or the age of the patient, and the changes in outcomes measured. There were no differences in outcome between male and female patients.

Initial conclusions

No significant side-effects were reported. Significant improvements in pain and certain aspects of local foot function were seen at the three-month time-point following three sessions of rESWT for patients with chronic plantar fasciitis using a "Intelect" RPW ESWT machine performed on a weekly basis with the manufacturer recommended guidance. These benefits were seen in a cohort of patients with a long duration of symptoms, averaging two and half years and recalcitrant to other treatments prior to rESWT. However, these benefits were seen in the absence of a control group and as such it is not possible to ascribe the benefits seen from the use of rESWT, as benefits could potentially have arisen from other factors such as the impact of time.

The results from this study, and the previously published works in both patients with plantar fasciitis and other tendinopathies, suggest that this is a treatment option that is worthy of further research study. This may be particularly important as this particular rESWT machine ("Intelect" RPW ESWT machine - DJO Global Chattanooga) has not been used in previously published studies, and so any evidence for benefit is extrapolated from other rESWT devices only. In addition, this clinic often treats patients with very chronic symptoms of plantar fasciitis who may be under-represented in previously published studies.(275-277, 279)

Data from this study were used to inform the *a priori* power calculation in the development of a formal double-blinded randomised controlled trial (Study D), which investigated the effectiveness of treatment with Extra-Corporeal Shockwave Therapy for patients with chronic plantar fasciitis more robustly.

6.3 -

Experimental study D:
Extra-Corporal Shockwave Therapy for patients with chronic plantar fasciitis: a double-blinded randomised controlled trial.

Specific study aim(s), and hypothesis to be tested

The aim of this RCT was to assess the effectiveness of treatment for patients with chronic plantar fasciitis using radial Extra-Corporeal Shockwave Therapy (generated from an “Intelect” RPW ESWT machine, DJO Global Chattanooga) with outcome measures of self-reported pain and function. This study compared outcomes following three treatment sessions with rESWT performed at the “recommended-dose”, in comparison to a group that received three treatments with a “minimal-dose” rESWT, with all patients also receiving identical rehabililitation programmes and post-procedural advice. The study hypothesis was that there would be significantly greater improvements in outcome in a group that received rESWT at the “recommended-dose” compared to a group that received “minimal-dose” rESWT.

Methods

- Study design

This double-blinded randomised controlled trial recruited patients that were being treated by the researcher in their clinic for symptoms of chronic plantar fasciitis, and who had not received sufficient benefit a home exercise programme. In this study, participants were randomised evenly to one of two groups. The first (intervention) group received three rESWT treatment sessions performed at weekly intervals using a DJO Chattanooga radial ESWT machine (identical treatment as Study C, with the strength of the radial pressure wave controlled by the operator to the “maximally comfortably tolerated dose” for the individual patient), this is referred hereafter as the “recommended-dose” rESWT treatment. The second (control) group received three sessions with a “minimal-dose” of radial ESWT using the lowest possible wave pressure setting from this rESWT machine. The randomisation processes, and interventional procedures are described in the relevant sub-sections below.

In addition to the ESWT treatment, members of both groups received an identical structured home exercise programme, this is the same programme to that previously described in the case series (Study C). Patients were encouraged to continue with their home exercise programme throughout the whole duration of their study inclusion.

Baseline assessments were conducted before the procedure using a range of patient reported outcome measures investigating aspects of local foot pain/function, global function, mental health, sleep quality and physical activity; these are described below. The study follow-up duration was six-months, with interim data recorded at six-weeks, and three-months, with all time-points measured from the date of the last/3rd ESWT session. All patients were reviewed by investigators blinded to treatment group.

- Participants

Patients were required to meet the following inclusion criteria: aged over the age of 18 at time of enrolment, plantar fascia pain for at least six months duration, with their pain reproduced on palpation of the medial calcaneal tubercle at the plantar fascia attachment, and / or with pain on loading (heel-stand test), who had failed to improve sufficiently with a structured rehabilitation programme over a minimum of 3-months, and to have had the diagnosis confirmed on either ultrasound or MRI investigation (plantar fascia thickening of >4mm).(540)

Exclusion criteria included previous or current partial or full thickness tears of the Plantar Fascia (to avoid risk of further injury), those with other known causes for their pain (such as referred pain, or inflammatory / connective tissue disorders), those unable or unwilling to do the structured rehabilitation programme alongside the injection, those who had received a corticosteroid injection within 3 months, and those on anticoagulation.

Sample size calculations were performed using G*Power 3.1, using data for improvements in self-reported pain using the results from the preliminary study (mean ± SD reduction in pain of 2.3/10 ± 1.8), and allowing an estimate that the

“minimal-dose” rESWT (believed to be equivalent to “sham” therapy) plus rehab may have one-third to one-half of the reduction in pain of the “recommended-dose” rESWT (i.e. mean reduction of pain of no more than 1.15/10 ± 1.8) giving an effect size of 0.6 (i.e. a “medium” effect size.) Multiple calculations were performed with power set between 0.8-0.9 and α set at 0.05. These calculations indicated that a minimum number of 52-60 participants in total were needed to show a measurable effect. Allowing for attrition, initial permissions were granted to recruit a total of 60 participants, split evenly between the intervention and control groups. An in-study power calculation, performed after 2 years with data to that point, suggested a smaller than expected difference between groups. Following this, ethical and Sponsor permissions were obtained to increase recruitment to a total of up to 120 participants, submitted through a formal study amendment (IRAS ref 159000.R2) This sample size, of up to 60 participants in each group, compares to previously published RCTs that have investigated the effectiveness of ESWT in patients with plantar fasciitis which have used 25-36 participants per treatment arm investigated.(20, 280, 288, 300, 305)

- Consent, randomisation and masking

Suitable patients who met the inclusion criteria met with the researcher during their routine clinical care and had the study outline and aims discussed with them. Patients were provided with written information about the study, as well as the NICE patient information leaflet about ESWT for plantar fasciitis (included in appendix 1). They were advised that the study was designed to assess any benefits from Extra-Corporeal Shockwave Therapy, by comparing two different ESWT doses, a “higher-dose” and a “lower-dose”. Following this discussion, if they wished to participate in the study, they were booked in to commence formal enrolment. In keeping with NHS research guidance, all study participants were given a minimum period of 24 hours between the study being discussed with them and being formally consented to enter the study which was done using signed written consent forms. As this study was open to patients seen in routine clinics by the researcher who assessed potential suitability based on inclusion and exclusion criteria a formal screening log was not kept for this study.

At enrolment, after consent was taken, participants were randomised to intervention/control groups by a study nurse practitioner who also conducted the rESWT treatment sessions and afterwards remained independent from the rest of the study. Participants were allocated equally to either an “intervention” group (who received 3 treatment sessions of “recommended-dose” rESWT) or a “control” group (who received 3 treatment sessions of “minimal-dose” rESWT) using the “Sealed Envelope” software (www.sealedenvelope.com , ©Sealed Envelope Ltd).

Steps were taken during the rESWT procedure to blind participants to treatment group allocation, and these are discussed in the following section. Only the administering clinician (study nurse practitioner) was aware of group allocation, with study participants being reviewed subsequently, where follow-up data were recorded, by clinicians who were blinded to group allocation throughout their involvement in the study.

Participants completed final data at the six-month point and the completion of this final data set marked their individual completion of the study. They consulted with Dr Wheeler after this data were collected, their progress was assessed, and patient unblinding occurred. No accidental un-blinding occurred during the study period.

- Interventions

Members of both groups received three sessions of rESWT which was performed once per week for three weeks using an “Intelect” RPW ESWT machine (DJO Global Chattanooga). The intervention group had ESWT performed in the same manner as previously described in the case series (study C) using a frequency of 10 Hz, with 2000 shocks per treatment, and with the strength of the ESWT (bar pressure) directed by the patient’s maximally comfortably tolerated dose. The mean strength of the rESWT delivered in the intervention group was 2.4±0.2, 3.0±0.3, 3.6±0.3 bar for the three rESWT sessions respectively. The participants in the control group received a “minimal-dose” rESWT, using the lowest settings from this commercially available ESWT machine. This minimal-dose rESWT used a frequency of 10 Hz (same as intervention group), with 500 shocks per treatment (one-quarter of the intervention group), and a 1.4 bar pressure for all three sessions (approximately half

that received by the intervention group.) Thus, the participants in the control group received approximately one-eighth of the total “dose” of rESWT compared to the intervention group.

Participants were blinded in both groups as to the strength of the rESWT that they received. Prior to rESWT, participants were advised that the sensation felt during rESWT treatment by individuals was very variable. In both groups, the study participants’ observation of the rESWT device were obscured by patient positioning and efforts were made by the administrator (nurse practitioner) to obscure the strength of the ESWT treatment delivered by asking the patients throughout about comfort levels and altering / appearing to alter the settings on the ESWT machine throughout treatment based on patient responses.

The after-care following each of the rESWT treatment sessions for members of both groups, including initial advice and the home exercise programme given was identical to that previously described in the case series (Study C). At baseline, before rESWT was carried out, all participants were taught how to perform and progress, their home exercise programme by the lead clinician. This included static stretches of the plantar fascia, the calf (selectively involving both gastrocnemius and soleus for different stretches), plus Flexor Hallucis Longus (FHL) and hamstrings, as well as calf and intrinsic foot muscle strengthening and balance training exercises. Their technique was checked at the interim appointments by their treating clinicians, and any necessary corrections to the technique were made to optimise rehabilitation. All study participants were also given written material to support the use of this home exercise programme and to progress the rehabilitation as symptoms allowed. In the same manner as the case series (Study C), participants were instructed to re-commence the structured Home Exercise Programme (HEP) from the evening each ESWT session, and to continue this throughout the whole duration of the study. (This written material is included as Appendix 2.)

- Outcome measures

All study participants completed a structured questionnaire about their symptoms at baseline (up to 24 hours before their treatment commenced), and at the six-week, three-month and the final/six-month follow-up visits after their final (3rd) ESWT

treatment procedure. This questionnaire contained a series of different outcome measures, including questions about pain including the pain felt by the patient “on average”, “at its best” and “at its worst” using a 0-10 numerical rating scale. In addition, this questionnaire contained a number of validated PROMs covering a wide range of aspects of function. These included PROMs investigating local foot/ankle function (the revised-Foot Function Index (FFI-r)(448-451) and the Manchester-Oxford Foot Questionnaire (MOXFQ)(452-454) as well as measures of global function (EQ-5D-5L).(455, 456) PROMs were also used to examine the impact of symptoms of other areas of patient functioning including measures of anxiety and depression symptoms (Hospital Anxiety and Depression Scale – HADS)(458, 461) and sleep quality (Pittsburgh Sleep Quality Index – PSQI).(466, 467, 499-502) Physical activity was assessed with the short-form (7-day recall) version of the International Physical Activity Questionnaire (IPAQ),(468) and two “vital signs” physical activity questions.(469) These outcome measures are reviewed in Chapter 2.

The primary outcome measure was the self-reported “average pain” (as recorded on a 0-10 numerical scale) with between-groups analysis comparing changes in values between baseline and six-months, with the remainder of the outcome measures being secondary to this.

Those participants who believed that they had not improved sufficiently (self-rated) at the six-month point, were offered further treatment if they wished after the final study follow-up. These included choices between “higher-dose” rESWT (for those who were in the control group) or other options such as Autologous Blood Injections, depending on patient preferences.

- Statistical analysis

Data were collated prospectively into an Excel spreadsheet (MS Excel from MS Office 2011, version 14.5.7) and analysed using SPSS (IBM SPSS Statistics, version 24). Most of the outcome measures in this dataset are scale data. All data were analysed on an intention to treat basis, regardless of how well the participants had reported that they had conducted their rehabilitation programme alongside the

specific ESWT administered. Data are presented as mean ± SD, unless otherwise specified. Missing Value Analysis (MVA) was not undertaken.

As the sample sizes were small, the Shapiro-Wilk test was used to assess normality. To ensure that the groups were comparable, baseline data were compared between-groups using either Unpaired T-tests (for normally-distributed data), Mann-Whitney U-tests (data that did not conform to normal distribution) or Chi-square testing (for gender which is categorical data).

Primary statistical analysis was conducted through a two-way repeated measures ANOVA (time x treatment group) to assess if a significant time x group interaction effect occurred between baseline and the final (6-month) point. This test is widely considered to be robust to manage data that does not conform to normal distribution. Two-way repeated measures ANOVA were also used to the data at different interim time points each compared to baseline. As secondary analyses, additional tests (either paired-samples T-tests for normally distributed data or related-samples Wilcoxon Signed Rank tests for data that did not conform to a normal distribution) were used for specific within-groups comparisons at specific follow-up time-points vs. baseline. Statistical significance was set at $p<0.05$.

- Ethical considerations

This study had all necessary permissions and was registered on a publicly accessible database (ClinicalTrials.Gov identifier NCT02546128.) The study was given a favourable opinion from an NHS Research Ethics Committee (REC ref 15/EM/0122) and had all required local site approvals. Ongoing reporting to, and monitoring by, the host Sponsor (UHL NHS Trust) was undertaken. (UHL study id 11401 / EDGE ref 41336)

Results

A total of 72 participants with chronic plantar fasciitis participated in this study having met the formal inclusion/exclusion criteria. 70/72 participants completed the final 6-month follow-up as planned. One patient in the control group contacted the department after their 6-week appointment to advise that due to external life pressures they no longer wanted further follow-up in clinic, and despite attempts to

persuade them to stay within the study they ceased attending and did not complete further questionnaires. One further patient in the intervention group failed to attend for their 6-month appointment, having attended at 3-months when they were doing well. Despite multiple attempts to rebook the patient they did not attend for this final appointment. Both patients were withdrawn from data analysis after the latest set of follow-up data for them. A small number of interim appointments were missed due to participant availability, staff availability including unexpected staff absence due to sickness, or administrative errors. Participant numbers were: baseline n=72, 6-week n=68/72 (94%), 3-month n=68/72 (94%), and 6-month n=70/72 (97%) Information for study recruitment is detailed in the included CONSORT 2010 Flow Diagram (Figure 6.2)

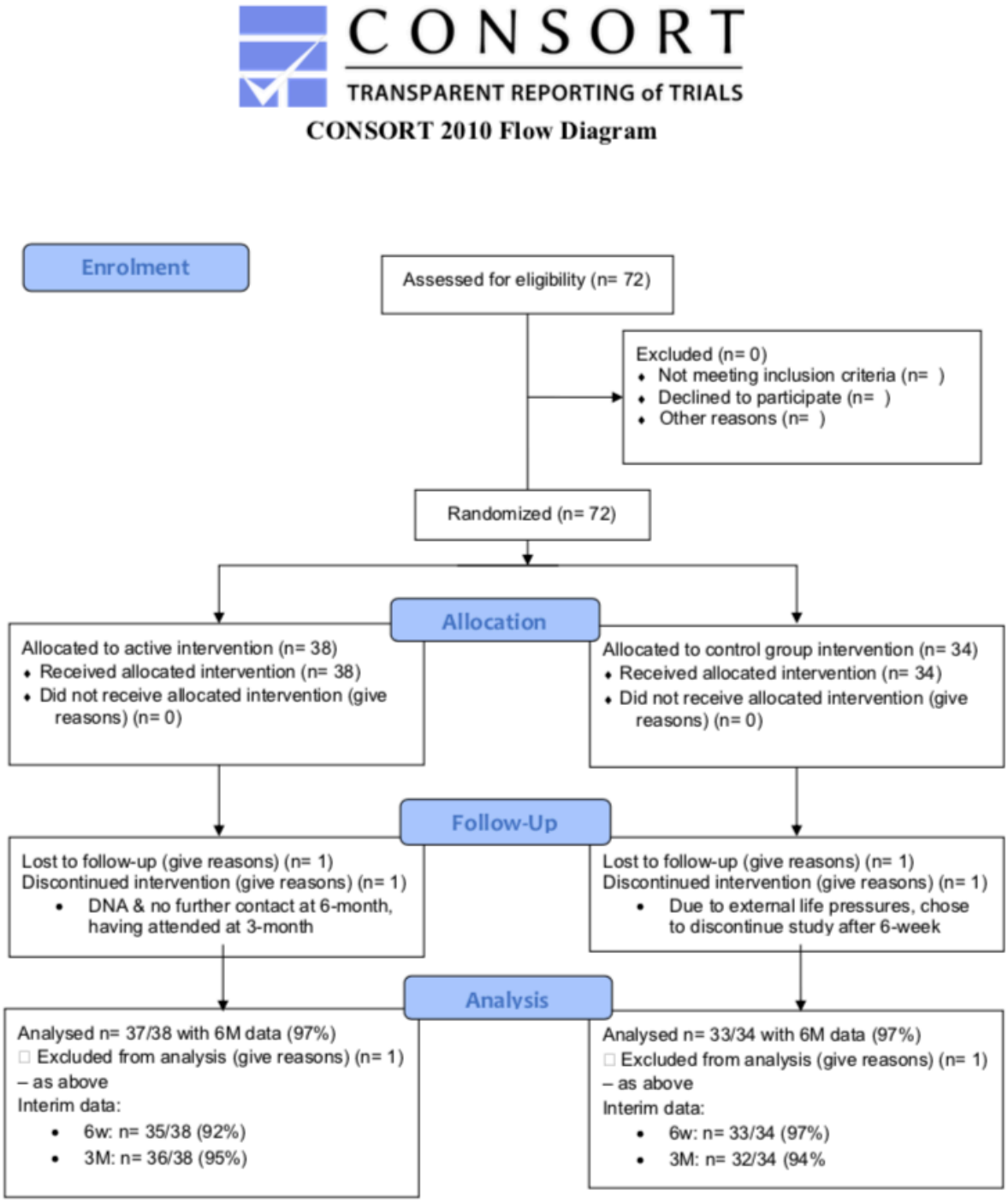


Figure 6.2: CONSORT Flowchart for ESWT RCT study

The mean age of the participants at baseline was 51.2 ± 9.9 years; 64% of participants were female. The participants had a mean duration of symptoms of 30.2 ± 34.1 months; (median duration: 24 months), with 9/72 (13%) participants having had symptoms for ≥5 years, and 3/72 (4.2%) participants having symptoms of ≥10

years. There were no significant differences in any of the demographics between participants in the intervention and control groups. (Table 6.3)

Table 6.3: Demographic information for study participants

	Intervention Group (“recommended-dose” rESWT) (n=38)	**Control Group** (“minimal-dose” rESWT) (n=34)	***p-value***
Age (years)	50.1 ± 9.1	52.5 ± 10.7	*0.291*
Gender (male/female)	16M / 22F (58% female)	10M / 24F (71% female)	*0.267*
Symptom duration (months)	32.1 ± 42.0	28.1 ± 22.8	*0.626*

Key: Data shown are mean ± SD. p-value compares data between different groups using Unpaired T-tests (normally-distributed data), Mann-Whitney U-tests (data that did not conform to normal distribution) or Chi-square testing (gender - categorical data).

Prior to inclusion, all patients had previously undertaken a home exercise programme, and all had tried regular analgesia. Prior to inclusion 85% (n=61) of the participants had tried orthotics / insoles, and 17% (n=12) had tried a tension night splint. Participants had received a mean of 0.65 ± 0.97 steroid injections prior to ESWT (range 0-4 injections), with a mean of 2.63 ± 4.96 weeks of benefit reported from their last injection (range 0-24 weeks benefit). All participants had undergone an ultrasound assessment prior to ESWT (including clinic-based ultrasound scans performed by the investigator) and in addition 7% of participants had also received an x-ray (n=5), and 15% (n=11) an MRI.

- Self-reported markers of pain / stiffness (0-10 scale)

There were no differences in any of the baseline pain/stiffness scores or baseline PROMs studied between the two groups.

There were no statistically significant time*group interaction effects identified between the two groups at any time-points for any of the measures of pain or stiffness. This included self-reported values for measure of “average pain” (repeated measures 2*2 (time*group) ANOVA p>0.4), or the self-reported “worst pain”

($p>0.18$). There was found to be a significant effect of time as a variable ($p<0.001$) across multiple outcome measures studied.

Significant within-group improvements were seen in both the intervention and control groups for various measures of pain/stiffness studied at different time-points compared to baseline values. These were assessed as secondary measures using specific within-group analyses.

The baseline and follow-up values for the different parameters studied for the participants in the intervention and control groups are displayed in table 6.4 for the primary outcome measure of the self-reported values for “average level of pain” as well as other sub-scores of aspects of pain/stiffness using the same 0-10 numerical self-rating scale.

Table 6.4: Numerical pain/stiffness scores (0-10) at baseline and follow-up

			6-weeks		3-months		6-months	
		Baseline	**X ± SD**	***2*2 p=***	**X ± SD**	***2*2 p=***	**X ± SD**	***2*2 p=***
"average pain"	I	6.9 ± 1.6	4.3 ± 2.2 **	*0.400*	4.6 ± 2.5 **	*0.831*	3.7 ± 2.6 *	*0.680*
	C	6.6 ± 1.7	4.5 ± 2.5 ***		4.1 ± 2.7 ***		3.7 ± 2.6 ***	
"pain at its worst"	I	8.3 ± 1.4	6.4 ± 2.5 *	*0.694*	4.4 ± 2.5 *	*0.182*	5.2 ± 3.2	*0.914*
	C	8.1 ± 1.6	5.8 ± 2.9 ***		5.1 ± 3.0 ***		4.8 ± 3.1 ***	
"pain at its best"	I	4.0 ± 2.3	2.5 ± 2.2 **	*0.742*	2.5 ± 2.7 **	*0.506*	1.8 ± 1.9 ***	*0.983*
	C	4.5 ± 2.5	2.8 ± 2.1 **		2.5 ± 2.3 ***		2.3 ± 2.4 ***	
"pain in the morning"	I	6.4 ± 2.6	4.1 ± 2.5 ***	*0.927*	4.4 ± 2.9 ***	*0.448*	3.4 ± 2.6 ***	*0.918*
	C	6.5 ± 2.8	4.3 ± 3.0 ***		3.8 ± 3.1 ***		3.4 ± 3.0 ***	
"pain in the evening"	I	6.8 ± 2.2	4.7 ± 2.7 ***	*0.635*	4.8 ± 3.0 ***	*0.344*	3.8 ± 3.0 ***	*0.757*
	C	7.0 ± 2.2	4.5 ± 2.7 ***		4.1 ± 3.0 ***		3.7 ± 2.8 ***	
"pain at rest"	I	5.1 ± 2.3	3.2 ± 2.3 ***	*0.600*	3.1 ± 2.7 ***	*0.919*	2.4 ± 2.4 ***	*0.644*
	C	5.0 ± 2.2	3.4 ± 2.5 **		2.8 ± 2.5 ***		2.6 ± 2.3 ***	
"pain when walking"	I	6.7 ± 1.9	4.7 ± 2.4 *	*0.672*	4.9 ± 2.8 **	*0.132*	3.6 ± 2.6	*0.960*
	C	6.9 ± 2.0	4.6 ± 2.9 ***		3.9 ± 2.7 ***		3.8 ± 2.7 ***	
"average stiffness"	I	5.3 ± 2.6	3.9 ± 2.8 ***	*0.585*	4.0 ± 2.9 ***	*0.319*	3.0 ± 2.5 **	*0.830*
	C	5.8 ± 2.4	3.8 ± 2.7 ***		3.5 ± 2.4 ***		3.2 ± 2.5 ***	
"stiffness in the morning"	I	6.0 ± 2.6	4.0 ± 2.7 **	*0.661*	4.2 ± 2.9 **	*0.862*	3.2 ± 2.3 *	*0.585*
	C	5.8 ± 2.7	4.2 ± 3.0 *		3.8 ± 2.9 **		3.4 ± 2.8 ***	

Key:

*Figures shown are mean ± SD "Intervention group" (i.e. "recommended-dose" rESWT, n=38, n=35/38 at 6w, n=36/38 at 3M, n=37/38 at 6M) "C" = "control group" (i.e. "minimal-dose" rESWT, n=34, n=33/34 at 6w, n=32/34 at 3M, n=33/34 at 6M). Statistical significance was calculated between data at baseline and the different follow-up time-points respectively, comparing intervention and control groups using 2x2 (time*group) ANOVA testing (p-value displayed.) Within-group comparisons between baseline and follow-up time points was undertaken using either paired t-tests or Wilcoxon tests, and statistical significance is denoted by the use of asterisks within that row. (* = p<0.05, ** p<0.01, *** p<0.001)*

- Patient Reported Outcome Measures (PROMs)

A number of secondary outcomes were studied examining aspects of foot/ankle function, global function, mental health function, sleep and levels of physical activity. There were no statistically significant time*group interaction effects identified for any of the foot-specific outcome measures studied. These included the results at 6-months for the MOXFQ (p=0.732) the total score of the FFI-r (p=0.973), or the FAAM %ADL or %function score (p=0.326 / p=0.876 respectively.) However, the within-group analyses demonstrated significant changes from baseline for a number of foot-specific outcome measures in both groups studied. These include significant improvements in scores with the MOXFQ and total FFI-r score at all time points for both groups, and improvements in the ADL and %function sub-scores of FAAM at all time points for both groups, but not the specific %sport sub-score. (Data displayed in Table 6.5)

The PROMS assessing aspects of neuropathic pain, central sensitisation, mental health or global function, showed inconsistent within-group improvements in some scores, in some groups, at some time-points, with a greater number of significant findings at 6-months than earlier periods. (Table 6.6) However, there were no significant time*group interaction effects for any follow-up time point.

Despite the improvements in pain seen in both groups using the within-group analyses, there were no significant changes in levels of moderate- or vigorous-level physical activity for either group as assessed by the short-form IPAQ, or overall active minutes as assessed by the “Vital signs” questions. There was a statistically significant increase in the amount of walking undertaken at 6-months compared to baseline in the intervention group (414 ± 614 v 314 ± 606 minutes) but no difference in the control group. The analysis showed there were no significant time*group interaction effects for any follow-up time point for any of these measures studied. (Table 6.7)

Table 6.5: Foot-region-specific Patient Reported Outcome Measures (PROMs) at baseline and follow-up

		Baseline	6-weeks		3-months		6-months	
			X ± SD	***2*2 p=***	**X ± SD**	***2*2 p=***	**X ± SD**	***2*2 p=***
MOXFQ total score	I	55.7 ± 11.8	44.5 ± 13.7 ***	*0.994*	42.4 ± 14.9 ***	*0.859*	38.8 ± 14.2 ***	*0.732*
	C	56.6 ± 14.0	45.3 ± 16.4 ***		42.4 ± 16.5 ***		41.3 ± 16.8 ***	
FFI-r total score	I	82.3 ± 22.2	66.3 ± 18.0 **	*0.812*	63.6 ± 18.0 ***	*0.661*	59.4 ± 18.0 ***	*0.973*
	C	83.6 ± 23.3	61.5 ± 25.9 **		61.5 ± 25.9 ***		60.9 ± 24.3 ***	
FAAM %ADL score	I	57% ± 18%	69% ± 19% ***	*0.824*	75% ± 19% ***	*0.771*	80% ± 17% ***	*0.326*
	C	61% ± 20%	72% ± 21% **		77% ± 19% ***		78% ± 20% ***	
FAAM %function	I	57% ± 22%	64% ± 22% *	*0.438*	70% ± 20% **	*0.896*	71% ± 25% **	*0.876*
	C	53% ± 25%	66% ± 24% *		66% ± 25% *		66% ± 25% **	
FAAM %sport score	I	32% ± 19%	48% ± 22% ***	*0.636*	54% ± 28% ***	*0.906*	60% ± 33% ***	*0.753*
	C	37% ± 24%	57% ± 30% ***		58% ± 32% ***		62% ± 31% ***	
FAAM %sport function	I	39% ± 29%	50% ± 27% *	*0.399*	56% ± 27% *	*0.304*	62% ± 30% **	*0.163*
	C	44% ± 30%	48% ± 32%		51% ± 29%		53% ± 32%	

Key:

*Figures shown are mean ± SD "Intervention group" ("recommended-dose" rESWT, n=38, n=35/38 at 6w, n=36/38 at 3M, n=37/38 at 6M) "C" = "control group" (i.e. "minimal-dose" rESWT, n=34, n=33/34 at 6w, n=32/34 at 3M, n=33/34 at 6M). Statistical significance was calculated between data at baseline and the different follow-up time-points respectively, comparing intervention and control groups using 2x2 (time*group) ANOVA testing (p-value displayed.) Within-group comparisons between baseline and follow-up time points was undertaken using either paired t-tests or Wilcoxon tests, and statistical significance is denoted by the use of asterisks within that row. (* = p<0.05, ** p<0.01, *** p<0.001)*

MOXFQ total score - range 16-80, with lower score indicating better function

FFI-r total score - range 34-136, with lower score indicating better function

FAAM sub-scores - %scale, with higher score indicating better function

Table 6.6 Patient Reported Outcome Measures (PROMs) at baseline and follow-up assessing wider aspects of functioning

		Baseline	6-weeks		3-months		6-months	
			X ± SD	*2*2 p=*	X ± SD	*2*2 p=*	X ± SD	*2*2 p=*
painDETECT	I	12.4 ± 8.1	11.7 ± 8.3	*0.328*	10.3 ± 7.9	*0.254*	8.4 ± 5.9 **	*0.871*
	C	13.6 ± 7.7	10.2 ± 7.5 **		8.5 ± 6.8 ***		9.2 ± 7.0 ***	
CSI	I	25% ± 16%	25% ± 19%	*0.591*	24% ± 18%	*0.681*	23% ± 17% *	*0.861*
	C	28% ± 16%	25% ± 17%		25% ± 18%		27% ± 18%	
ODI	I	25% ± 16%	20% ± 19% *	*0.958*	19% ± 18% **	*0.956*	19% ± 17% ***	*0.778*
	C	26% ± 16%	21% ± 15% ***		20% ± 15% **		18% ± 19% ***	
EQ-5L %health	I	73% ± 20%	78% ± 17% *	*0.450*	76% ± 19%	*0.963*	74% ± 22%	*0.752*
	C	73% ± 18%	72% ± 21%		76% ± 20%		75% ± 17%	
HAD - anxiety subscale	I	5.7 ± 4.2	4.9 ± 3.9	*0.907*	5.5 ± 4.0	*0.459*	5.1 ± 4.3	*0.671*
	C	6.9 ± 4.4	6.3 ± 5.3		5.6 ± 4.7 *		5.7 ± 5.3	
HAD - depression subscale	I	5.5 ± 3.8	4.6 ± 3.9	*0.976*	4.3 ± 3.7	*0.856*	4.5 ± 4.2	*0.817*
	C	6.0 ± 4.0	5.1 ± 4.0 *		4.6 ± 3.8 **		4.8 ± 3.9 *	
PHQ-4	I	1.9 ± 2.8	1.9 ± 2.7	*0.651*	2.1 ± 2.9	*0.690*	1.9 ± 2.8	*0.776*
	C	2.6 ± 3.5	2.1 ± 3.5 *		2.4 ± 3.4		2.3 ± 4.0	
GAD-7	I	3.9 ± 4.8	3.5 ± 4.2	*0.984*	3.8 ± 4.4	*0.920*	3.7 ± 4.9	*0.916*
	C	4.6 ± 5.8	4.1 ± 5.5		4.3 ± 5.5		4.2 ± 6.4	
PHQ-9	I	5.1 ± 5.1	4.5 ± 4.6	*0.731*	4.8 ± 5.3	*0.456*	4.5 ± 5.5	*0.483*
	C	6.9 ± 7.1	5.6 ± 6.4 *		5.0 ± 6.1 **		4.8 ± 6.3 **	
PSQI (total score)	I	8.8 ± 3.9	8.3 ± 3.7	*0.785*	7.9 ± 4.0	*0.966*	8.2 ± 4.4	*0.679*
	C	9.0 ± 3.6	8.1 ± 4.2		8.1 ± 4.2		7.8 ± 4.0 *	
Roles & Maudsley Score	I	.	2.8 ± 0.8 ***	*0.762*	2.7 ± 0.8 ***	*0.326*	2.4 ± 1.1 ***	*0.743*
	C	.	2.8 ± 0.9 ***		2.5 ± 0.9 ***		2.5 ± 1.1 ***	

Table 6.6 key:

*Figures shown are mean ± SD "Intervention group" (i.e. "recommended-dose" rESWT, n=38, n=35/38 at 6w, n=36/38 at 3M, n=37/38 at 6M) "C" = "control group" (i.e. "minimal-dose" rESWT, n=34, n=33/34 at 6w, n=32/34 at 3M, n=33/34 at 6M). Statistical significance was calculated between data at baseline and the different follow-up time-points respectively, comparing intervention and control groups using 2x2 (time*group) ANOVA testing (p-value displayed.) Within-group comparisons between baseline and follow-up time points was undertaken using either paired t-tests or Wilcoxon tests, and statistical significance is denoted by the use of asterisks within that row. (* = p<0.05, ** p<0.01, *** p<0.001)*

Specific questionnaires:

painDETECT – range 0-38, with lower score indicating lower likelihood of neuropathic pain)

CSI - %scale, lower score indicates lower likelihood of central pain component)

ODI - (%scale, lower score indicates less self-rated disability pain

EQ-5D – health %scale, higher score indicates better self-rated global health)

HAD - anxiety / depression sub-scales, each range 0-21, with lower score indicating fewer symptoms

PHQ-4 - (range 0-12, with lower score indicating fewer symptoms)

GAD-7 – (range 0-21, with lower score indicating fewer anxiety symptoms)

PHQ-9 – (range 0-27, with lower score indicating fewer depressive symptoms)

PSQI - (range 0-21, with lower score indicating fewer symptoms of sleep disturbance

Roles & Maudsley Score – converted to 1-4 score, with higher score being better function/fewer symptoms

Table 6.7 Patient Reported Outcome Measures (PROMs) at baseline and follow-up assessing levels of physical activity

		Baseline	6-weeks		3-months		6-months	
			X ± SD	*2*2 p=*	X ± SD	*2*2 p=*	X ± SD	*2*2 p=*
IPAQ - Number of vigorous-level activity mins/week	I	260 ± 624	210 ± 365	*0.642*	310 ± 511	*0.669*	197 ± 373	*0.978*
	C	166 ± 517	209 ± 737		303 ± 190		108 ± 190	
IPAQ - Number of moderate-level activity mins/week	I	236 ± 521	222 ± 407	*0.472*	240 ± 413	*0.533*	321 ± 553	*0.414*
	C	142 ± 505	264 ± 720		260 ± 674		97 ± 180	
IPAQ - Number of walking mins/week	I	314 ± 606	417 ± 580 *	*0.913*	405 ± 564 *	*0.685*	414 ± 614 *	*0.603*
	C	392 ± 928	466 ± 818		589 ± 896		368 ± 630	
IPAQ - number of hours sitting on a weekday	I	4.8 ± 4.6	4.3 ± 2.3	*0.984*	3.9 ± 2.3	*0.620*	4.6 ± 3.6	*0.267*
	C	5.9 ± 4.4	5.5 ± 4.2		4.4 ± 3.4 *		4.2 ± 2.5	
"Vital signs" – active minutes per week	I	251 ± 566	233 ± 309	*0.832*	209 ± 331	*0.580*	222 ± 371	*0.921*
	C	167 ± 564	187 ± 593		227 ± 630		122 ± 266	

Key:

Figures shown are mean ± SD "Intervention group" (i.e. "recommended-dose" rESWT, n=38, n=35/38 at 6w, n=36/38 at 3M, n=37/38 at 6M) "C" = "control group" (i.e. "minimal-dose" rESWT, n=34, n=33/34 at 6w, n=32/34 at 3M, n=33/34 at 6M). Statistical significance was calculated between data at baseline and the different follow-up time-points respectively, comparing intervention and control groups using 2x2 ANOVA testing (p-value displayed.) Additional within-group testing between the data at baseline at follow-up period for each group using either paired t-tests or Wilcoxon tests is displayed with the use of asterisks when statistically significant within the row. An asterisk at the follow-up period indicates a statistically significant change from baseline values for the specific variable studied. (= p<0.05, ** p<0.01, *** p<0.001)*

6.4 - Extra-Corporeal Shockwave Therapy Intervention Discussion

The results from these two studies have shown improvements in measures of pain and function following three sessions of rESWT, comparing data at baseline with follow-up time points. However, the lack of any time*group interaction effect between the intervention and control groups in the RCT (Study D) seen at any of the assessed time points, means that the improvements are not arising from the level of energy delivered by the rESWT. As a result, the hypothesis that a difference in outcome between the two groups would be identified was not proven and the null hypothesis (that there is no difference) remains in place. These results are counter to other published systematic review and meta-analysis level evidence that has shown significant improvements for patients with plantar fasciitis following focal or radial ESWT(263, 282, 303, 325) and the reason for this difference is unclear at this time.

The initial ESWT prospective case series (Study C) demonstrated significant improvements in levels of self-reported pain and some of the markers of foot function that were studied. These findings were consistent with benefits seen in other previous case series studies examining ESWT for patients with plantar fasciitis. (274, 275, 284, 285) However, the benefits seen in study C were in the absence of a control group, and as such benefits seen cannot be ascribed to the ESWT intervention itself, and could be from other factors such as the rehabilitation or a natural resolution of symptoms over time.

Although there were some significant improvements seen in the double-blinded RCT (Study D) for the within-group analyses, there were no time*group interaction effects found between the groups at any of the follow-up periods, for any of the outcome measures studied. This indicates that three sessions of shockwave therapy, performed at weekly intervals at the “recommended dose”, with an “Intelect” RPW ESWT machine (DJO Global Chattanooga) had no measurable benefit over a “minimal-dose” ESWT treatment protocol which used one-quarter of the number of shocks at about half of the pressure (approximately one-eighth of the “dose”) for patients with chronic plantar fasciitis.

These results from the RCT (Study D) differ from other robust evidence showing benefit from ESWT in patients with chronic plantar fasciitis(263, 282, 303, 325), including evidence from randomised controlled trials comparing rESWT with placebo(283) or other treatment options such as corticosteroid injections.(279) The findings presented here raise important questions about the lack of effectiveness of this specific rESWT machine/ treatment regime in this population of patients. The reasons for the lack of differences in outcomes following either three sessions of rESWT at “recommend dose” or “minimal dose” are not clear at this time. Possibilities could include: that this population of patients with plantar fasciitis were in some way different to those involved in other studies, that radial-ESWT is not effective in patients with chronic plantar fasciitis, that this specific rESWT machine is ineffective, that the “minimal dose” rESWT was sufficient to create the improvement seen with ESWT treatment, or that three sessions of rESWT is insufficient and that further treatment sessions are required. Each of these possibilities are discussed below.

- Symptom duration

The duration of symptoms prior to ESWT of the participants in both the case series study (study C – mean duration of symptoms: 30.8 ± 42.0 months) and the RCT (study D – mean duration of symptoms: 30.2 ± 34.1 months) were much greater than that in many other published studies which typically include patients with symptoms of 6-months. As previously highlighted there may be greater success reported in patients with a shorter duration of symptoms, although the evidence for this is relatively weak in strength, coming from a single small study involving 28 patients with plantar fasciitis with analysis possibly favouring early treatment, but the differences in improvements seen between groups did not reach statistical significance.(308) However the sub-group analysis in the case series study (C) did not show any correlation between the duration of symptoms before treatment, and the outcome seen, although due to the small numbers the validity of this finding remains unknown. Based on these findings, the symptom duration itself is not necessarily thought to be the sole cause of the lack of differences in outcomes seen in Study D between the two study groups.

- rESWT and plantar fasciitis

As discussed in section 2.2.2 there are some differences between specific types of ESWT-technology including focal-shockwave (F-ESWT) versus radial-shockwave (rESWT). There are currently no published comparative studies directly assessing whether there may be differences seen in results between different types of ESWT or even between different ESWT machines. One meta-analysis has attempted to compare results following F-ESWT and rESWT for patients with plantar fasciitis and concluded that rESWT was an "*appropriate alternative* (to F-ESWT) *because of its lower price and probably better effectiveness*".(303) rESWT was chosen as the intervention studied here and other previous research involving patients with plantar fasciitis has shown benefits in levels of pain and function lasting at least up to 6-12 months from radial shockwave therapy including studies comparing rESWT to either sham-ESWT or other active treatments.(263, 325). Based on these previous findings radial ESWT as a treatment modality has been found to be an effective treatment for patients with plantar fasciitis.

- rESWT with Intelect" RPW ESWT machine (DJO Global Chattanooga)

This is the first study to have published results comparing active treatment with this specific rESWT machine compared to another treatment, and given the lack of positive findings in study D, it is at least theoretically possible that this machine is less effective than other rESWT machines that have been used in other studies. However, given that this is a medical device, that is licenced for this indication, and the necessary steps that the manufacturer has undertaken to obtain these required licences it is unclear if this is likely. A robust comparative study between two different rESWT machines may however seek to address this consideration.

- "minimal-dose" rESWT

A possibility is that the "minimal-dose" ESWT that was chosen as a comparator was itself of a therapeutic effect. There were a number of within-group improvements seen in the control group when comparing baseline and follow-up data. The "minimal-dose" regime used the lowest possible settings from this commercially available rESWT machine as a pragmatic comparison group that facilitated patient blinding of treatment group allocation. It is possible that this still had a therapeutic

effect, although this cannot be confirmed from this study design. Overall the treatment used in the control group used one quarter of the number of shocks administered in the intervention group, performed at about half of the strength of pressure wave. A previous study has demonstrated a significant placebo-effect from low-dose ESWT compared to sham ESWT(293) and the placebo-effect itself may have had an influence on the results seen in the RCT (study D). Should funding permit, a true placebo ESWT machine could be constructed that sounds and feels like a “real” ESWT machine but does not generate any transmitted energy to the participants, and this approach has been undertaken for a couple of other studies previously published.(289, 313) The funding was not available for this device in this study, but this methodology could be the focus of further works. An alternative study methodology could be to compare outcomes following rESWT plus rehabilitation in this clinical population with chronic symptoms to a group receiving rehabilitation only, and run a study as a single-blind (observer blinded) study only.

- rESWT treatment sessions

An alternative possibility for the lack of effectiveness seen in the RCT (study D) was the specific treatment regime itself. The advice received from the manufacturer was that the treatment was a total of 3 sessions, performed on a weekly basis, at the patient’s “maximal comfortably tolerated dose.” However, the evidence behind these specific recommendations is unclear. At least one review has highlighted the great heterogeneity in study intervention in published studies, with these studies that were included in reviews using different numbers of treatment sessions.(263, 325) Some studies demonstrating positive results have used a 3-treatment session protocol,(273, 280, 291, 308) but others have used treatment regimens involving 4-6 treatment sessions.(274, 279, 317), and others only used one or two treatment sessions.(287, 288) Although a dose-effect has been demonstrated for focal-ESWT (F-ESWT) with higher level energy doses leading to improved outcomes compared to lower energy F-ESWT,(263) there are no currently published direct comparative studies looking at number of treatment sessions and how this may influence outcome. It may be that between-group differences may have been found if an increased number of treatment sessions were used in the RCT (study D). However, this cannot be answered from this study design, and this would need to be the focus of further works to explore this issue.

Summary of the research

A strength of the ESWT RCT (study D) was the number participants (n=72) recruited, with numbers greater than many of the other published studies that have previously investigated ESWT in patients with plantar fasciitis.(20, 279, 280, 286-290) A further significant strength of the RCT (Study D) was the small number of patients that were lost to follow-up, with only a single participant in each group failing to complete the study, and more than 90% of data from interim appointments collected as well. This improves the robustness of the data that was obtained from this study.

The two studies in this chapter had a maximal duration of follow-up of only 6-months, although this is as long or longer than many other published ESWT studies.(20, 275, 280) A study design with longer duration of follow-up could be considered to give more clarity about any possible longer term outcomes, and whether benefits seen are maintained, which is an area which has limited evidence.(282) Longer-term follow-up has proven a challenge to do, with difficulties contacting patients over prolonged periods after routine care may have finished, and also that patients may seek to undertake further interventions for ongoing symptoms if they are remaining troubled, which adds confounding factors for any symptom changes that may be seen. At least one RCT and one case series study however has managed to account for these issues and have showed ongoing improvements from baseline following shockwave therapy with published follow-up data of up to 24month duration.(283-285) Longer term outcomes could be studied as a further project, with appropriate permissions, but this project would lie outside this chapter.

In conclusion, statistically significant improvements over time in measurements of pain and local foot function were seen in both the ESWT prospective case series (Study C) and the RCT (Study D) comparing baseline and follow-up values. However, the lack of any differences identified between the intervention and control groups in the RCT (Study D) means that the benefits seen cannot be solely ascribed to the “energy level” (i.e. pressure wave bar strength) of the radial-ESWT that was administered.

Chapter 7 -

Intervention:

Autologous Blood Injection (ABI)

for patients with chronic plantar fasciitis

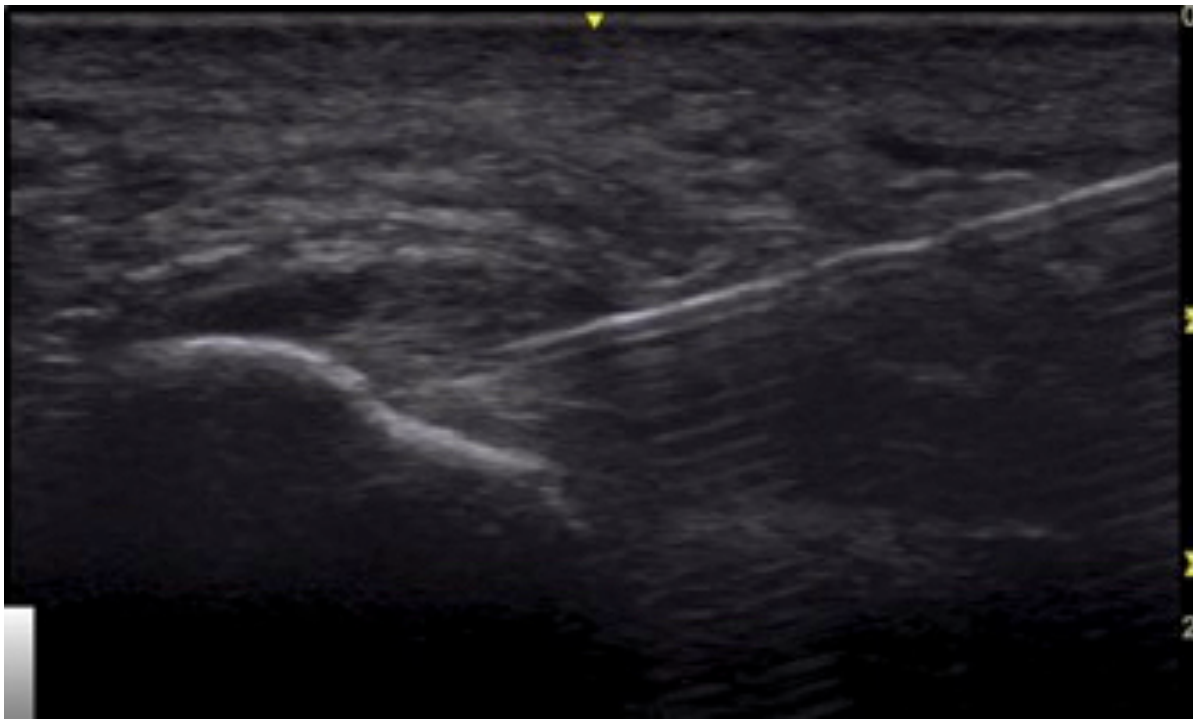


Figure 7.1: Image of ultrasound-guided Autologous Blood Injection, with long-axis view of plantar fascia insertion at calcaneus, and needle in-plane

7.1 - Introduction

A further treatment option in the management of patients with plantar fasciitis, is the use of an injection of blood or blood products. This use of blood injections, including whole autologous blood injections (ABI) and platelet-rich plasma (PRP) injections for patients with a number of different tendinopathy conditions has been increasing in popularity in recent years, with a growing, albeit variable quality, evidence base.(21, 35, 384) There is also a growing awareness amongst the general public about this treatment modality, and it has featured in at least one national newspaper article as a possible treatment for patients with plantar fasciitis.(572)

In chapter 2, a number of studies involving the use of blood injections to patients with plantar fasciitis were reviewed and these have concluded that blood injections have been found to be safe with no major safety concerns raised. The higher-level evidence including a number of systematic reviews and meta-analyses have highlighted a great heterogeneity in intervention, follow-up and outcome measures used in different primary research studies and robust conclusions have been further hampered by often poor methodological quality of much of the published research.(21, 383-389)

The evidence from the better designed RCT-studies suggests a significant improvement in pain following blood injections for patients with plantar fasciitis. However studies have often only shown equivalent benefit to other treatment options such as steroid injections (341, 342, 351) or endoscopic surgery.(365) Two studies have also compared a PRP injection against a saline injection and found limited, if any between-group differences raising questions about effectiveness of the PRP injection.(352, 363)

Many of the RCT and case series studies only report results at 3- or 6-months post intervention, giving uncertainty as to longer-term outcomes and whether any benefits that may be seen early-on following intervention are maintained.(351, 354, 359, 370) To seek to address this deficit, several recent RCTs have attempted to follow patients up for longer including several with a 12-month period of follow-up, with results at longer-term follow failing to show consistent superiority of blood injections

(most commonly in the form of PRP) over steroid injections for patients with plantar fasciitis.(341, 363). However, one of these studies had a 50% loss to follow-up at 12M (and 25% loss to follow-up at 6M) and the authors comment that with the follow-up numbers available the study became under-powered to detect between-group differences.(363) Another noted limitation is that studies have often included patients with relatively short-duration of symptoms, with least two RCTs including patients who only had symptoms of 3 months duration or less.(342, 355) In these two studies both the intervention and control groups improved to a similar extent, and the natural resolution of symptoms, which could be expected in a cohort with a relatively short duration of symptoms, may have influenced results greatly due to the expected improvements in both groups from natural resolution.(2, 40) Any effect that ABI may have in patients with chronic symptoms of plantar fasciitis remains unknown.

Other evidence concerning blood injections for the treatment of patients with plantar fasciitis is available from a number of case series studies.(346, 358, 359, 371, 372) However, the lack of a direct comparison group in case series studies means that any benefits seen cannot be reliably ascribed to the injection of the blood product itself, and could be from other factors including the injection procedure or technique, the rehabilitation that is often undertaken concurrently with the injection, or simply as a result of a natural resolution over time.

An additional limitation of the published research is the choice of outcome measures. Several of the studies, including many recent publications, (341, 357, 359, 371) have utilised a simple numerical pain score rather than any of the more reliable measures of foot function that may provide greater validity (31, 428) and which were reviewed in chapter 2. Other studies have used a single foot and ankle Patient Reported Outcome Measure (PROM),(353, 368) with several studies also examining ultrasound parameters before and after treatment.(342, 370) Only a single study has attempted to quantify any wider aspects of global functioning, utilising the SF36 questionnaire, however this study only had a 3-month follow up giving no indication about any longer-term outcomes.(355) Therefore there remains ongoing uncertainty as to the effectiveness of blood injections for treating patients with plantar fasciitis, including how foot pain/symptoms should be reliably assessed and reported, and

any changes in wider aspects of the patients' functioning in the short-, medium-, and longer-term using validated outcome measures.

In the UK, the National Institute of Health and Care Excellence (NICE) has issued specific guidance for the use of blood injections in patients with plantar fasciitis in the NHS.(52) These recommendations, which were published in 2013 and remain current state that "the evidence on efficacy (of blood injections) is inadequate in quantity and quality" and that "outcomes should include specific measures of pain and function".(52) NICE has encouraged further robust research for the use of Autologous Blood Injections (ABI) in the management of patients with plantar fasciitis.

This chapter describes the findings from two linked studies which investigated the effects of an ABI for patients with chronic plantar fasciitis who had been referred to a single hospital outpatient department. The first study (E) was a prospective case series, and the second study (F) was a double-blinded randomised controlled trial. Both have been undertaken in line with the published NICE guidance around the use of blood injections for patients with plantar fasciitis.(52) Both studies have sought to identify any improvements in pain or functioning following an ABI.

The first study (E) used a prospective case series design to examine outcomes following the use of ABI in patients with chronic plantar fasciitis in routine clinical care. Outcome measures recorded at baseline and subsequent follow-up were a simple self-reported measure of pain, and a measure of foot function using a validated patient reported outcome measure, the revised Foot Function Index (FFI-r). Data from this case-series study (E) were used to estimate a treatment effect size which was then used in an a priori power calculation for the RCT study (F) to investigate this treatment more robustly.

The second study, (F) formally investigated the effect on aspects of pain and function following either an autologous blood injection or dry-needling procedure in patients with chronic plantar fasciitis within a double-blinded randomised controlled trial with a six-month follow-up period. A dry-needling injection (needle fenestration procedure) was chosen as an active comparator for this study as traditionally ABI

procedures involve a dry-needling component, therefore comparison with tendon dry-needling only group would allow the effect of the injection of the small quantity of blood to be directly assessed. (These procedures are described in more detail in the experimental methods in section 7.3). A previous systematic review has identified 4 clinical trials in tendinopathy conditions which overall suggest a benefit from dry-needle with a trend to additional benefit with the co-administration of autologous blood,(19) however this review did not identify any studies involving patients with plantar fasciitis. The primary outcome measure for study F was a change in self-rated levels of “average pain” reported by the participants using a simple pain numerical rating scale (NRS). A wide range of validated PROMs were used as secondary outcome measures to better understand any improvement in markers of global wellbeing and functioning that any improvement in the patients’ foot symptoms may have, as this is a notable gap in the published literature.

7.2 -

Experimental study E:
The effectiveness of Autologous Blood Injections for the treatment of patients with chronic plantar fasciitis – a prospective case-series study

Specific study aim(s)

The aim of this case series study was to assess self-reported changes in pain and function following the use of an Autologous Blood Injection (ABI) and a structured home exercise programme (HEP) in routine NHS practice for patients with chronic plantar fasciitis.

Methods

- Study design

A prospective case-series study design was used, which included all patients from a single clinic who undertook an Autologous Blood Injection procedure for symptoms of chronic plantar fasciitis from April 2010 to December 2017.

Self-reported data was obtained from patients at the time of the ABI procedure (baseline) and any follow-up appointments, when patients were typically seen at 2-weeks, 6-weeks, 3-months and 6-months post-ABI. However, the times of all of these appointments were booked according to patient and appointment availability and as can be seen from the results some patients missed at least one of these routine follow-up appointment times. Additional data was obtained beyond the 6-month routine period opportunistically with any subsequent patient contact, and all available results from all follow-up periods are included (for example at 12- and 18-months), with results categorised into different periods of time post-procedure.

- Participants

The results for all consecutive patients who had undergone an ABI procedure by the author were included in this case series study. The ABI procedure was offered as a part of routine clinical care to patients aged 18 and over, who had symptoms of plantar fasciitis of at least 4 months of duration that were having significant impact on their quality of life. Patients were required to have either ultrasound or MRI evidence of plantar fascia thickening, and to have already tried a rehabilitation programme for at least 3-months prior to ABI. Patients could not have received a steroid injection in the 3-months prior to ABI being performed and could not be on anticoagulation therapy.

- Intervention

The ABI procedure was performed with the patient lying supine on a couch with their hip and knee extended, and the ankle in a comfortably dorsiflexed position. The site of maximal pain was indicated by the patient and marked. The area around the injection site was cleaned using skin preparation and the injection was performed under a sterile no-touch technique by the administering clinician (Dr Wheeler.) Ultrasound confirmation using sterile gel was performed to locate the area of maximal thickening. In order to anaesthetise the foot, 1-2 mL of either 1% or 2% lidocaine was injected to the skin layers of the sole of the foot, distal to the site of pain. Following this, and under direct ultrasound guidance, a 21-gauge needle was introduced in line with the plantar fascia through the subcutaneous planes to the plantar fascia attachment to the calcaneus, where the site of thickening was localised. A dry-needling (fenestration) technique was performed under direct ultrasound observation using multiple (15-20) needle passes through the thickened area over a 30-second period. During this time, venepuncture at the antecubital fossa was performed by a nurse assistant, with 5 mL of blood obtained and passed to the clinician performing the ABI procedure. A total of 3-4 mL of this whole blood was then injected using a luer-lock syringe with a peppering technique to the area of damage evident on the ultrasound machine. The whole procedure was performed under real-time direct ultrasound visualisation.

Figure 7.2 demonstrates the standard view obtained at the time of the procedure with a longitudinal view of the plantar fascia and its calcaneal attachment, with the ultrasound probe in line with the needle for adequate visualisation throughout the injection procedure. This demonstrates the position of the needle within the plantar fascia near the calcaneal attachment.

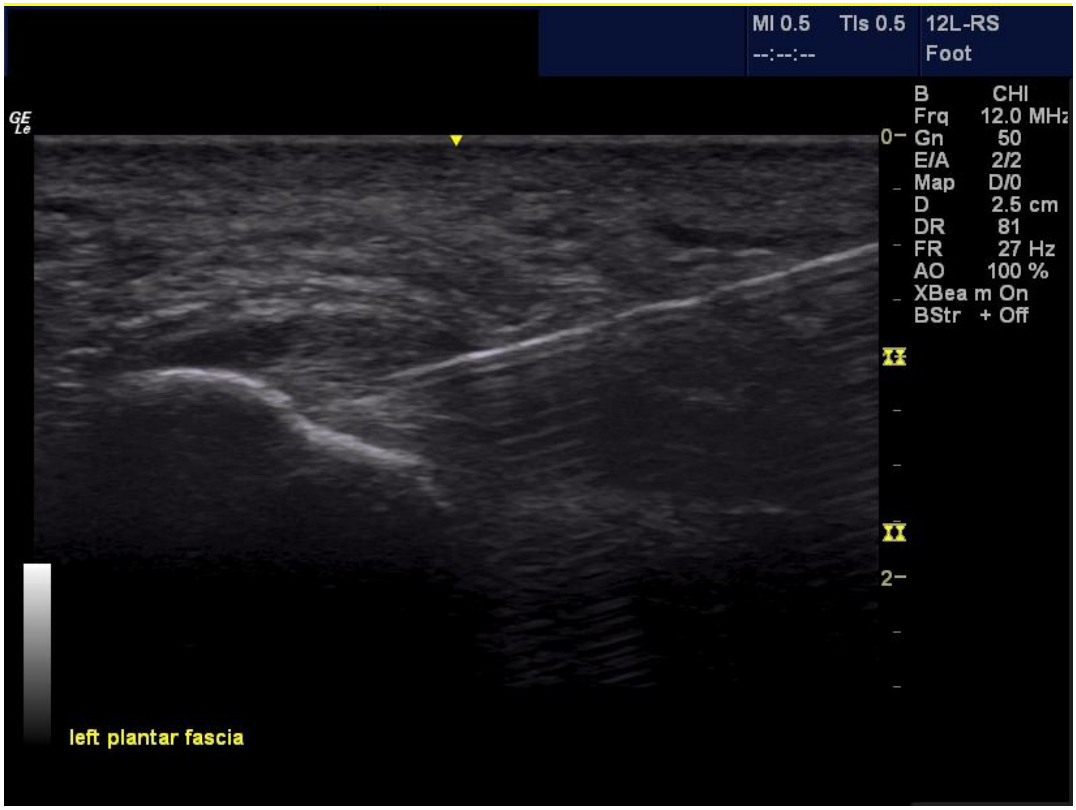


Figure 7.2: Image of ultrasound-guided Autologous Blood Injection, with long-axis view of plantar fascia insertion at calcaneus, and needle in-plane

After the procedure, the needle was withdrawn, and a small adhesive plaster applied. Patients were given standardised post-procedure information. They were advised that they could walk short-distances immediately but were instructed to limit their physical activity for the first 48-72 hours post-procedure, and then progress cautiously as pain allowed. The patients were advised to avoid non-steroidal anti-inflammatories (NSAIDs) for a minimum of 72 hours post-procedure but could use simple analgesia or ice if required for pain.

The patients were given a standardised home exercise programme to undertake and informed as to how to progress this. This included stretches for the posterior kinetic

chain, involving the plantar fascia, gastrocnemius, soleus, Flexor Hallucis Longus (FHL), and the hamstrings muscle groups. In addition to the stretches, the patient progressed onto calf muscle strengthening, balance/ proprioception, and intrinsic foot muscle strengthening exercises. Patients were advised to undertake these exercises twice or three times per day and which was to be (re-)started the day after the ABI procedure. An example of this rehabilitation plan is included in Appendix 2.

- Outcome measures

Specific outcome measures used in this study included a self-reported “average pain” score (using a 0-10 numerical rating scale, and hereafter abbreviated as “NRS”), and a specific validated Patient Reported Outcome Measure (PROM), the total score of the revised Foot Function Index (FFI-r) questionnaire.(448-451)

- Statistical analysis

Data were recorded prospectively and transcribed into a spreadsheet (MS Excel 2016) for calculation of descriptive data. Demographic and baseline data for patient groups at different time-points were also tabulated to allow comparison of patient characteristics between different follow-up time points for clarity.

Further analysis was conducted using IBM SPSS Statistics (version 24). Scale data were shown not to be normally distributed using the Shapiro-Wilk test, and non-parametric analysis was performed, predominantly with Wilcoxon Signed Rank Test comparing pre/post values. Results are displayed predominantly as median (IQR). Statistical significance was set at $p<0.05$, with significant results below being highlighted by an asterisk (*)

All analyses were conducted with results that were available at each time point. There was no statistical correction conducted for any missing data to avoid introducing statistical bias. In statistical terms, missing data is believed to be missing completely at random (MCAR). Missing value analysis and data substitution processes such as multiple imputation or other techniques that were available within SPSS were considered. However, as the missing data exceeded the 25% level often set as a threshold, it was considered that was less appropriate as this would

potentially introduce fictitious relationships and artificially linearize data. Consideration was given to using a multilevel modelling statistical approach to this data set as this is believed to be robust and can potentially account for missing values and analyse data sets with unbalanced data. However, as the data studied was not truly continuous in nature, using a pain NRS and the FFI-r scale, this approach was also rejected in favour of the simpler analysis approach comparing baseline to different timepoints.

Simple sub-group analysis, including unpaired-group (Independent Samples Mann-Whitney U Test) and correlation analysis (Spearman's rank correlation coefficient), were conducted to assess any impact that variables such as severity of patient age, gender, length of symptoms of severity of baseline pain may have had on subsequent outcomes.

- Ethical considerations

This study was classified as a service analysis within the Department of Sport & Exercise Medicine at University Hospitals of Leicester NHS Trust. It was registered as such with the CASE Team at the hospital, and the results reported via the normal hospital audit mechanism. NHS ethics permissions were therefore not required.

Results

Results were available for a total of 70 patients who had received an autologous blood injection for plantar fasciitis. There was a median age of 52.1 years (IQR: 43.3-62.0, range 25.6 - 80.4 years), 53% were female, and ethnicity was not recorded in this data set. The median duration of symptoms prior to the ABI was 30 months (IQR: 24.0-52.5), with a positively skewed mean (49.4 months) and a maximum duration of 30 years. Seven patients (10%) reported having symptoms for ten years or longer prior to the ABI procedure.

Patients with chronic plantar fasciitis were offered an ABI after trying a range of other treatments. All patients had previously tried analgesia and a rehabilitation programme for their symptoms, all but one patient (98.6%) had previously tried orthotics, and 55/70 (79%) had previously tried a Tension Night Splint device. Prior to the ABI being offered, patients had received a mean of 1.6 ± 1.6 steroid injections

(range 0-7) with an average self-reported duration of benefit of 1.9 ± 3.1 weeks (range 0-12).

The first procedure was undertaken in April 2010. From the data available, there was a median follow-up of 556 days duration (range 46-1211) after the ABI procedure. 69/70 patients (99%) had at least 3-month follow-up data, 64/70 patients (91%) had at least 6-month follow-up data, and 46/70 (66%) had at least 12-month follow-up data.

To assess the different patient sub-groups at each follow-up time-point, the patient demographics and baseline data for the overall group, and at the different follow-up periods are displayed in table 7.1. This demonstrates that the sub-groups at each of the follow-up time-points had similar characteristics to the overall group.

Table 7.1: Baseline demographic data and PROM data for patient cohorts in study.

	Overall group at baseline	*Cohort at 2-weeks follow-up*	*Cohort at 6-weeks follow-up*	*Cohort at 3-months follow-up*	*Cohort at 6-months follow-up*	*Cohort at 12-months follow-up*	*Cohort at 18-months+ follow-up*
n=	70	*42*	*52*	*53*	*46*	*27*	*39*
Age (years)	52.1 (43.3-62.0)	52.2 (44.3-62.3)	50.5 (43.7-61.0)	52.3 (44.4-62.2)	52.1 (43.3-43.3)	52.3 (44.6-62.2)	52.3 (44.1-62.0)
Gender (male/ female)	47%/ 53%	45%/ 55%	52%/ 48%	47%/ 53%	43%/ 57%	52%/ 48%	46%/ 54%
Duration of symptoms (months)	30 (24-53)	30 (24-48)	33 (24-50)	30 (24-48)	33 (24-48)	30 (24-48)	30 (24-48)
Baseline pain NRS (0-10)	8.0 (7.0-9.0)	8.0 (7.0-9.0)	8.0 (7.0-10.0)	8.0 (7.0-9.0)	8.0 (7.0-9.0)	8.0 (7.0-9.0)	8.0 (7.0-9.0)
Baseline FFI-r total score	89.0 (70.5-106.5)	91.0 (67.5-108.0)	91.0 (72.5-106.5)	81.5 (68.5-103.8)	89.0 (70.5-107.0)	95.0 (73.0-110.0)	88.0 (70.5-94.5)

Key: data shown are median (and interquartile range)

- Patient Reported Outcome (PROMS) - Self-reported pain (0-10 scale)

There was a statistically significant improvement in levels of self-reported pain, using a 0-10 numerical pain scale (NRS) from 8.0 (IQR:7.0-9.0) at baseline compared to all subsequent time-points. There was an improvement in the median pain score of 6.0 points on the 0-10 scale from the follow-up periods of 6-weeks onwards, exceeding the proposed minimum clinically important difference of 0.9-2.0 points reported in the literature.(438, 451)

Statistical analysis showed a significant improvement in pain from baseline to 2-weeks (p<0.001) and then from 2-weeks to 6-weeks (p=0.002), but after that there were no further significant differences between adjacent time-points, although all time-points showed significantly lower values for pain than baseline values. However, this finding may have been influenced by the issue of missing data previously described. These figures are displayed in Table 7.2 and Figure 7.3 respectively.

Table 7.2: Self-reported 0-10 Pain Scores (NRS) at baseline and follow-up

	Baseline (n=70)	**2-weeks (n=42)**	**6-weeks (n=52)**	**3-months (n=53)**	**6-months (n=46)**	**12-months (n=27)**	**18-months+ (n=39)**
Pain NRS Median (IQR)	8.0 (7.0-9.0)	4.5 (3.0-6.0)	3.0 (2.0-4.0)	2.0 (0-4.0)	1.5 (0-3.0)	1.0 (0-3.5)	0.0 (0-1.8)
Significance of difference from baseline		*** *p<0.001*	*** *p<0.001*	*** *p<0.001*	*** *p<0.001*	*** *p<0.001*	*** *p<0.001*
Significance of difference from previous time-point (number of participants with paired data tested)			** *p=0.002 (n=30)*	*p=0.458 (n=39)*	*p=0.321 (n=34)*	*p=0.645 (n=21)*	*p=0.845 (n=27)*

Key: data shown are median (IQR) with lower score indicating fewer symptoms. The significance of any change from baseline is shown, and separately any statistical significance of change from the previous time point (and the number of participants with this paired data set for comparison) using Related-Samples Wilcoxon Signed Rank Test. (= p<0.05, ** p<0.01, *** p<0.001)*

Figure 7.3 displays the 0-10 pain score (NRS) at baseline and at each follow-up period for which data were available. This plots the trend of improvement in pain seen over the different follow-up periods studied.

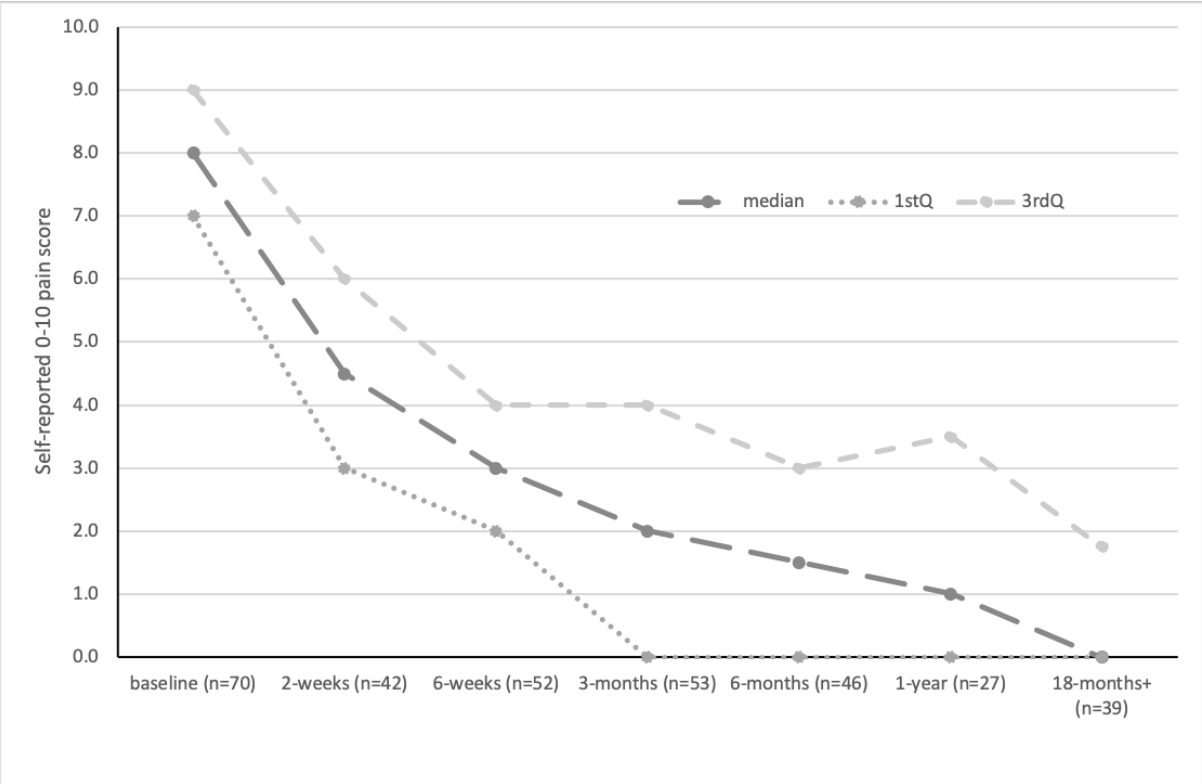


Figure 7.3: Self-reported 0-10 pain numerical rating scale ("NRS") score at baseline and follow-up (data shown are median and interquartile ranges: 1stQ and 3rdQ)

At two-weeks post injection, 7% of patients self-reported themselves as pain-free (NRS=0) and a total of 21% had either no or minimal pain (defined as an NRS 0-2). The figures at 6-weeks were 12% reported as pain-free and 44% with no or minimal pain, at 3-months the figures were 32% and 53% respectively, at 6-months these figures were 39% and 67%, and at 1 year 41% of patients rated themselves as pain-free, and 59% had no or minimal pain.

- Patient Reported Outcome (PROMS) - Revised Foot Function Index (FFI-r) scores

There was a statistically significant improvement in function, as assessed by the FFI-r total score and the different sub-scales at all of the follow-up periods compared to

baseline readings. This total score is made up of the sum of the individual sub-scores, a higher value indicates greater burden from symptoms, with the possible range of scores being 34 (least) to 134 (greatest impact of symptoms) and are displayed in Table 7.3 and Figure 7.4.

The FFI-r questionnaire was used in routine clinical practice in this clinic for this intervention from July 2012 onwards, and this accounts for the smaller numbers compared to NRS results. It is noted that there were limited number of participants with FFI-r data at many of the specific time periods, limiting statistical interpretation particularly between adjacent follow-up time points.

Table 7.3: Total FFI-r scores at baseline and follow-up

	Baseline (n=51)	**2-weeks (n=23)**	**6-weeks (n=52)**	**3-months (n=37)**	**6-months (n=28)**	**12-months (n=13)**	**18-months+ (n=32)**
Total FFI-r score median (IQR)	89.0 (70.5 – 106.5)	63.0 (45.5 – 90.0)	68.0 (47.0 – 76.0)	49.5 (42.0 – 75.8)	44.0 (39.5 – 65.3)	62.0 (40.0 – 77.0)	37.0 (34.0 – 50.3)
Significance of change from baseline		*** *p<0.001*	*** *p<0.001*	*** *p<0.001*	*** *p<0.001*	* *p=0.046*	*** *p<0.001*
Significance of difference from previous time-point (number of participants with paired data tested)			*p=0.382 (n=13)*	* *p=0.027 (n=27)*	*p=0.055 (n=19)*	*p=0.237 (n=8)*	*p=0.109 (n=3)*

Key: data shown are median (IQR) with lower score indicating fewer symptoms. The significance of any change from baseline is shown, and separately any statistical significance of change from the previous time point (and the number of participants with this paired data set for comparison) using Related-Samples Wilcoxon Signed Rank Test. (= p<0.05, ** p<0.01, *** p<0.001)*

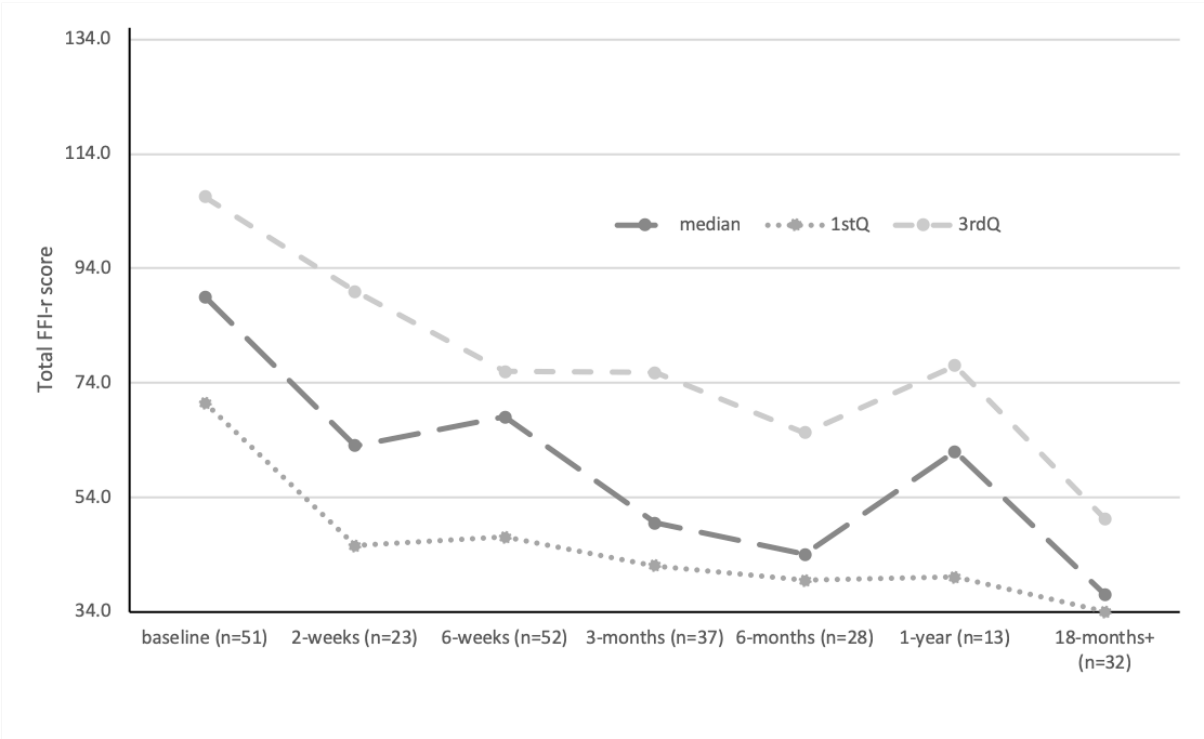


Figure 7.4: Total FFI-r score at baseline and follow-up (data shown are median and interquartile ranges: 1stQ and 3rdQ)

Sub-group analysis / possible predictors of response

Statistical analyses were performed to assess any differences between gender of patients, patient ages, or different lengths of symptoms prior to the ABI procedure, to assess any impact that these factors may potentially have had on outcome.

There was a statistically significant difference between the age of male and female patients in this study. Male patients had a median age of 58.9 (IQR:47.0 - 63.9) and female patients a median age of 49.8 (IQR:41.9 - 53.4), (p=0.024). However, none of the measures recorded at baseline, nor any of the outcome measures at any of the outcome points, differed significantly between male and female patients. Any clinical significance of this difference in the patient age at baseline remain uncertain and there were no statistically significant correlations between the age of patient and any of the outcome scores recorded at baseline, nor at any of the follow-up periods studied.

Spearman's rank-order correlation showed no significant correlation between duration of symptoms before the ABI procedure and baseline level of pain as recorded by the 0-10 NRS (r_s = -0.127, p=0.294). Nor was there one between the duration of symptoms and the FFI-r total score at baseline (r_s = -0.339, p=0.15).

There were no statistically significant correlations between the duration of symptoms, and the outcome measures of pain studied at the different follow-up periods, except for the NRS recorded at 12M (r_s = 0.429, p=0.025) and 18-months or more (r_s = 0.451, p=0.004). Using the validated FFI-r score the only statistically significant correlation was found between duration of symptoms and the score at different outcomes was again at the 18-months+ follow-up period (r_s = 0.359, p=0.044), but not at the 12-month point. The clinical significance, if any, for these correlations at these longer-term follow-up periods remains unclear and may have been a statistical anomaly due to the low numbers of data points at each time period.

The baseline FFI-r total score had statistically significant correlations with the FFI-r scores recorded at 2-weeks (r_s = 0.647, p=0.01), 6-weeks (r_s = 0.620, p<0.01) and 3-months (r_s = 0.527, p=0.002). There were no statistically significant correlations for data at the 6-month and 12-month period, but again the correlation at 18months+ was statistically significant. (r_s = 0.441, p=0.040). This indicates that the severity of symptoms may influence early outcomes, with more uncertainty seen at longer-term follow-up periods. The equivalent analysis for the baseline levels of pain (NRS) score did not reach statistical significance for any of the time periods studied except the data at 2-weeks (r_s = 0.469, p=0.02). The clinical relevance of the differences seen between the validated FFI-r and the NRS remains unclear.

Initial conclusions

This prospective case series has demonstrated a significant improvement in pain and self-reported function in patients who have undertaken an Autologous Blood Injection procedure for chronic plantar fasciitis, and thus this procedure is worthy of further research attention. Within the limitations of this experimental design, there was a reduction in median levels of pain of 75% after 6-weeks as assessed by 0-10 numerical rating scale (NRS), with half to three-quarters of patients at different time points having no or minimal pain using a NRS self-reporting system.

Data from this study were used to inform the development of a formal double-blinded randomised controlled trial (Study F) to investigate the effectiveness of an Autologous Blood Injection procedure for patients with chronic plantar fasciitis more robustly. Additionally, to investigate global aspects of function as well as local foot pain, a range of different outcome measures were studied more formally in the RCT (Study F).

7.3 -

Experimental study F:
Autologous blood injections versus dry-needling alone for chronic plantar fasciitis: a double-blind randomised controlled trial

Specific study aim(s), and hypothesis to be tested

The aim of this RCT was to assess the effectiveness of treatment for patients with chronic plantar fasciitis using Autologous Blood Injection (ABI) with outcome measures of self-reported pain and function. This study compared outcomes following the co-administration of a small quantity of autologous blood to a dry-needling injection (needle fenestration technique) procedure in comparison to a group that received a dry-needling injection procedure without blood, with all patients also receiving identical rehabililitation programmes and post-procedural advice. The study hypothesis was that there would be significantly greater improvements in outcome in a group that received the co-administration of autologous blood, compared to a group that did not.

Methods

- Study design

This double-blinded randomised controlled trial recruited patients that were being treated by the researcher in their clinic for symptoms of chronic plantar fasciitis, and who had not received sufficient benefit a home exercise programme. In this study, participants were randomised evenly to one of two groups, the first (intervention) group received an ultrasound-guided autologous blood injection including dry-needling procedure, the second (control) group received an identical dry-needling injection only but did not receive an injection of autologous blood. The randomisation processes, and interventional procedures are described in the relevant sub-sections below.

In addition to the injections, members of both groups received an identical structured home exercise programme. Patients were encouraged to continue with their home exercise programme throughout the whole duration of their study inclusion.

Baseline assessments were conducted before the procedure using a range of patient reported outcome measures (described below) investigating aspects of local foot pain/function, global function, mental health, sleep quality and physical activity. The study follow-up duration was six-months, with interim data recorded at two-weeks, six-weeks, and three-months. All patients were reviewed by investigators blinded to treatment group.

- Participants

Patients were required to meet the following inclusion criteria: aged over the age of 18 at time of enrolment, plantar fascia pain for at least six months duration, with their pain reproduced on palpation of the medial calcaneal tubercle at the plantar fascia attachment, and / or with pain on loading (heel-stand test), who had failed to improve sufficiently with a structured rehabilitation programme over a minimum of 3-months, and to have had the diagnosis confirmed on either ultrasound or MRI investigation (plantar fascia thickening of >4mm).(540)

Exclusion criteria included previous or current partial or full thickness tears of the Plantar Fascia (to avoid risk of further injury), those with other known causes for their pain (such as referred pain, or inflammatory / connective tissue disorders), those unable or unwilling to do the structured rehabilitation programme alongside the injection, those who had received a corticosteroid injection within 3 months, and those on anticoagulation.

An *a priori* sample size calculation was undertaken using G*Power 3.1, using data from the preliminary study (mean reduction in VAS at 6w: 4.9 ± 2.7, at 3M: 5.2 ± 2.9, at 6M 5.6 ± 3.1). As evidence about the efficacy of a needle-fenestration procedure alone was not available to make reliable calculations from, a clinically-driven estimate of a possible improvement following the dry-needle fenestration itself at half that of the ABI was used (i.e. an improvement of no more than 2.45-2.8 ± 2.7 / 10), resulting in an effect size 0.7-0.9 (a “medium” to “large” effect size.) Power was set at 0.95 with α set at 0.05. Using these parameters, calculations indicated 26-56 participants in total were required. To ensure the risk of study under-powering was reduced, the more conservative values were used. Allowing for an estimated 10%

attrition, initial permissions were sought and were granted to recruit a total of 60 participants, split evenly between the intervention and control groups. An in-study power calculation, performed after 2 years with data to that point, suggested a smaller than expected difference between groups. Following this, ethical and Sponsor permissions were obtained to increase recruitment to a total of up to 90 participants, submitted through a formal study amendment (IRAS ref 157824.R1) Limited other evidence exists for comparisons, but previously published RCTs examining the effectiveness of injections of blood products (ABI or PRP) have typically used between 12 and 30 participants in each intervention arm studied, (336, 350-352, 354, 355, 369), with a single study identified that involved a total of 130 participants split between two intervention groups.(357)

- Consent, randomisation and masking

Suitable patients who met the inclusion criteria met with the researcher during their routine clinical care and had the study outline and aims discussed with them. Patients were provided with written information about the study (included in Appendix 1) and were advised that the study was designed to assess any benefits from an Autologous Blood Injection compared to the dry-needling technique alone. Following this discussion, if they wished to participate in the study, they were booked in to commence formal enrolment. In keeping with NHS research guidance, all study participants were given a minimum period of 24 hours between the study being discussed with them and being formally consented to enter the study which was done using signed written consent forms. As this study was open to patients seen in routine clinics by the researcher, who assessed potential suitability based on inclusion and exclusion criteria, a formal screening log was not kept for this study.

At enrolment, after consent was obtained, participants were randomised to intervention/control group by a study nurse practitioner who remained independent from the rest of the study. Participants were allocated equally to either an “intervention” group (who received a home exercise programme & ABI including dry-needling technique) or a “control” group (who received a home exercise programme and dry-needling injection only) using the “Sealed Envelope” software (www.sealedenvelope.com , ©Sealed Envelope Ltd).

Steps were taken during the injection procedure to blind the participant to treatment group allocation, and these are discussed in the following section. The administering clinician (Dr Wheeler) and the study nurse practitioner were aware of group allocation, but study participants were reviewed subsequently by consultant colleagues in clinics, where follow-up data were recorded, and who were blinded to group allocation throughout their involvement in the study.

Participants completed final data at the six-month point and the completion of this final data set marked their individual completion of the study. They consulted with Dr Wheeler after this data were collected, their progress was assessed, and patient unblinding occurred. No accidental un-blinding occurred during the study period.

- Interventions

The intervention group had an ABI procedure, which included ultrasound-guided dry-needling / fenestration of the damaged plantar fascia. This injection procedure was performed in an identical technical manner as the injection in the previous study (Study E – ABI case series), and all injections in both studies were performed by the same clinician. The control group (dry-needling only) received a similar injection as the intervention group and received an ultrasound-guided dry-needling procedure of the plantar fascia with a 21-gauge needle, but without co-injection of autologous blood. The dry-needling intervention was conducted in an identical manner as received by members of the intervention (ABI) group in this study: using a local anaesthetic injection to the foot, 5 mL of blood obtained by venepuncture at the antecubital fossa, the site of plantar fascia damage localised on ultrasound, a dry-needling injection was performed with the blood obtained by venepuncture attached to the needle, but this was not injected. The after-care following the injection procedure including initial advice and the home exercise programme (HEP) given was identical to that previously described in the case series (Study E).

Participants in both groups were blinded as to the injection that they received. In both groups, the study participants' views of the injection were obscured by patient positioning and syringes were discarded into sharps bins out of sight of the participants, so that they could not see how much blood remained in the syringe after the injection.

At baseline, before the injection was carried out, all participants were taught how to perform and progress, their home exercise programme by the lead clinician. This included static stretches of the plantar fascia, the calf (with separate stretches targeting gastrocnemius and soleus), plus Flexor Hallucis Longus (FHL) and hamstrings, as well as calf and intrinsic foot muscle strengthening and balance training exercises. These exercises were demonstrated to the participants in the clinic at the time of the procedure and their technique was checked at the interim appointments by their treating clinician, and any necessary corrections to the technique were made to optimise rehabilitation. All study participants were also given written material to support the use of this home exercise programme and to progress the rehabilitation as symptoms allowed. In the same manner as the case series (Study E), participants were instructed to commence the structured Home Exercise Programme (HEP) as tolerated from that evening onwards following the injection, and to continue this throughout the duration of the study period. (This written material is included in Appendix 2.)

- Outcome measures

All study participants completed a structured questionnaire about their symptoms at baseline (up to 24 hours before their treatment commenced), and at the two-week, six-week, three-month and the final/six-month follow-up visits after their injection procedures. This questionnaire contained a series of different outcome measures, including questions about pain including the pain felt by the patient “on average”, “at its best” and “at its worst” using a 0-10 numerical rating scale (“NRS”) In addition, this questionnaire contained a number of validated PROMs covering a wide range of aspects of function. These included PROMs investigating local foot/ankle function (the revised-Foot Function Index (FFI-r)(448-451) and the Manchester-Oxford Foot Questionnaire (MOXFQ)(452-454) as well as measures of global function (EQ-5D-5L).(455, 456) PROMs were also used to examine the impact of symptoms of other areas of patient functioning including measures of anxiety and depression symptoms (Hospital Anxiety and Depression Scale – HADS)(458, 461) and sleep quality (Pittsburgh Sleep Quality Index – PSQI).(466, 467, 499-502) Physical activity was assessed with the short-form (7-day recall) version of the International Physical

Activity Questionnaire (IPAQ),(468) and two “vital signs” physical activity questions.(469) These outcome measures are reviewed in Chapter 2.

The primary outcome measure was the self-reported “average pain” (as recorded on a 0-10 numerical scale) between baseline and six-months, with the remainder of the outcome measures being secondary to this.

Those participants who were in the control group and who believed that they had not improved sufficiently (self-rated) at the six-month point, were offered the ABI procedure if they wished after the final study follow-up.

- Statistical analysis

Data are presented as mean ± SD. Data were collated prospectively into an Excel spreadsheet (MS Excel from MS Office 2011, version 14.5.7) and analysed using SPSS (IBM SPSS Statistics, version 24). Comparisons were made between data at baseline and each of the post-treatment time points. Most of the outcome measures in this dataset are scale data. All data were analysed on an intention to treat basis, regardless of how well the participants had reported that they had conducted their rehabilitation programme alongside the specific injection therapy administered.

As the sample sizes were small, the Shapiro-Wilk test was used to assess normality. Parametric testing was undertaken for data that were found to be normally distributed, including patient age, two sections of the pain NRS (“pain at its best”, and “pain at rest”) as well as the specific PROMS. As the remainder of the NRS data were not found to be normally distributed, non-parametric testing was undertaken for these data. Either Unpaired T-tests or Mann-Whitney U-tests were used to compare data at baseline to ensure groups were comparable. Additional Chi-square testing was performed for categorical data. The primary analysis was performed using a two-way repeated measures ANOVA (time*treatment group allocation) to assess if a significant time*group interaction effect occurred between baseline and the final (6-month) and also at the different interim time points, which is widely considered to be robust to manage data that does not conform to normal distribution. As secondary outcome measures, additional tests (either paired-samples T-tests or related-samples Wilcoxon Signed Rank tests) were used for specific within-groups

comparisons at specific follow-up time-points vs. baseline. Statistical significance was set at $p<0.05$. Missing Value Analysis (MVA) was not undertaken.

- Ethical considerations

This study had all necessary permissions and was registered on a publicly accessible database (ClinicalTrials.Gov identifier NCT02546089). The study was given a favourable opinion from an NHS Research Ethics Committee (REC ref 14/EM/1061) and had all required local site approvals. Ongoing reporting to, and monitoring by, the host Sponsor (UHL NHS Trust) was undertaken. (UHL study id 11334 / EDGE ref 34528)

Results

A total of 69 participants with chronic plantar fasciitis completed this study having met the formal inclusion/exclusion criteria, and all but one completed their final 6-month follow-up as expected. A single participant suffered an unrelated ankle fracture at 4.5 months which required time immobilised in plaster and so were unable to mobilise freely or continue the rehabilitation required for this study and so they were therefore withdrawn from the study after the 3-month data were collected. A small number of interim appointments were missed due to participant availability, staff availability including unexpected staff absence due to sickness, or administrative errors, thus participants numbers were: baseline n=69, 2-week n=65/69 (94%), 6-week n=65/69 (94%), 3-month n=66/69 (96%), and 6-month n=68/69 (99%). Information for study recruitment is detailed in the included CONSORT 2010 Flow Diagram (Figure 7.5)

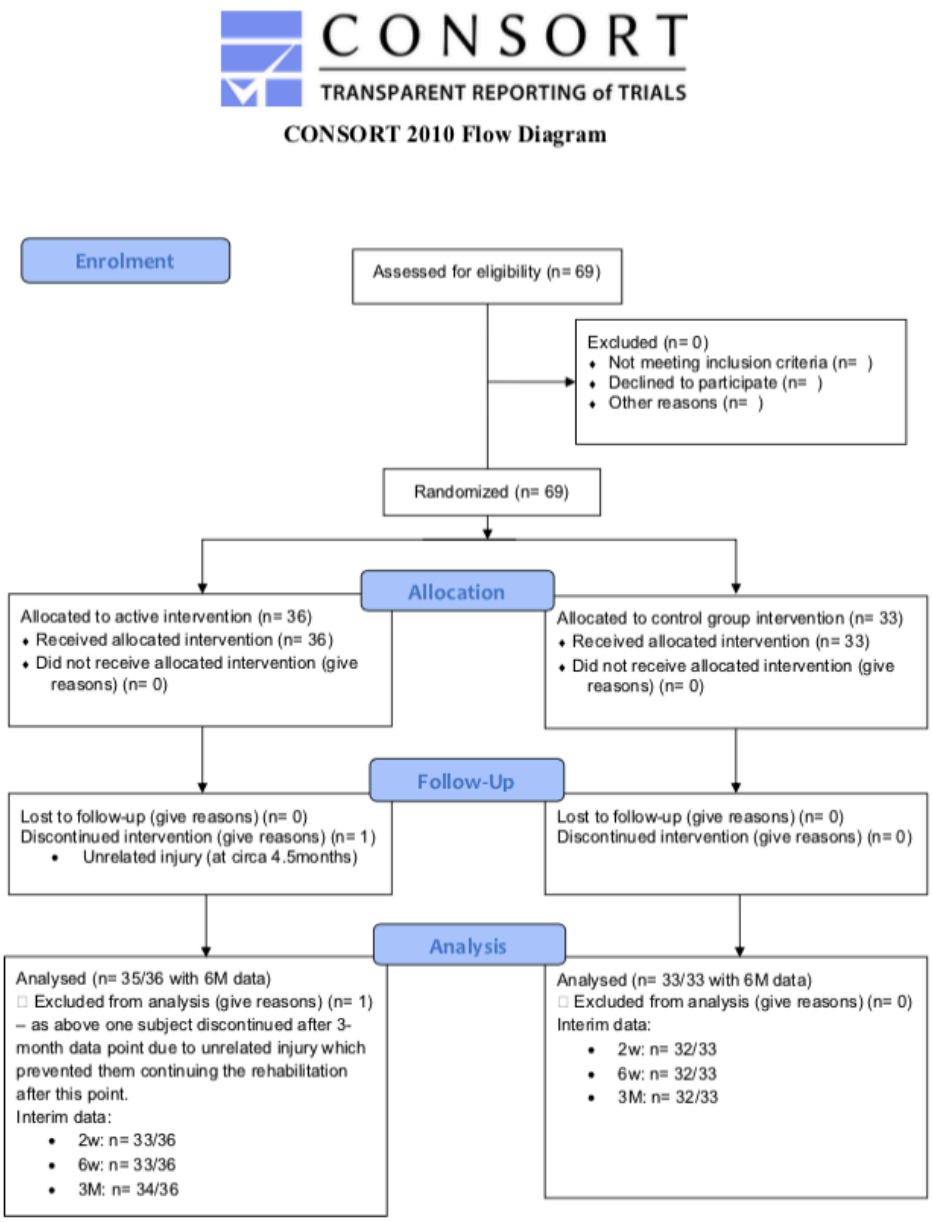


Figure 7.5: CONSORT Flowchart for ABI RCT study

The mean age of the participants at baseline was 49.1 ± 9.4 years; 62% were female. The participants had a mean duration of symptoms of 39.4 ± 25.8 months; there was a median symptom duration of 36 months, with 14/69 (20%) participants having had symptoms for 5 years or longer, and 2/69 (2.9%) participants having symptoms of ≥10 years. There were no significant differences in any of the demographics recorded between participants in the intervention and control groups. These data are displayed in Table 7.4

Table 7.4: Demographic information for study participants

	"Intervention Group" dry-needling + ABI (n=36)	**"Control Group"** Dry-needling alone (n=33)	***p-value***
Age (years)	48.0 ± 9.2	50.3 ± 9.6	*0.306*
Gender (male/female)	16M / 20F (56% female)	10M / 23F (70% female)	*0.336*
Symptom duration (months)	43.3 ± 27.3	35.2 ± 23.7	*0.178*
Height (m)	1.68 ± 0.11	1.70 ± 0.09	*0.720*
Weight (kg)	85.9 ± 19.6	90.5 ± 13.8	*0.350*
BMI (m/kg^2)	30.2 ± 5.6	31.7 ± 6.1	*0.519*

Key: Data shown are mean ± SD. p-value compares data between different groups using independent samples t-testing / independent samples Mann-Whitney U Test

Prior to inclusion all participants had previously undertaken a home exercise programme, all had tried regular analgesia, 93% (n=64) had tried orthotics / insoles, and 51% (n=35) had tried a tension night splint. Participants had received a mean of 1.0 ± 1.2 steroid injections prior to ABI (range 0-5 injections), with a mean of 4.6 ± 6.4 weeks of benefit reported from their last injection (range 0-20 weeks benefit). All participants had undergone an ultrasound assessment (including clinic-based ultrasound scans performed by the investigator) prior to ABI administration and in addition 36% of participants (n=25) had also received an x-ray, and 28% (n=19) an MRI.

- Self-reported markers of pain / stiffness (0-10 scale)

There were no differences found in any of the baseline pain/stiffness scores or baseline PROMs studied between the two groups.

There were no statistically significant time*group interaction effects identified between the two groups at any time-points for any of the measures of pain or stiffness. This included measures of self-reported "average pain" (repeated measures 2*2 (time*group) ANOVA p>0.45), or the self-reported "worst pain" (p>0.34). There was found to be a significant effect of time as a variable (p<0.001)

for the self-reported measures of “average” and “worst” pains, but no significant time*group differences were identified.

Significant within-group improvements were seen in both the intervention and control groups for various measures of pain/stiffness studied at different time-points compared to baseline values. These were assessed as secondary measures using specific within-group analyses.

The baseline and follow-up values for the different parameters studied for the participants in the intervention and control groups are displayed in table 7.5 for the primary outcome measure of the self-reported “average level of pain” and well as other sub-scores of aspects of pain/stiffness using the same 0-10 numerical self-rating scale.

Table 7.5: Numerical rating scale (NRS) for pain/stiffness scores (0-10) at baseline and follow-up

		Baseline	2-weeks		6-weeks		3-months		6-months	
		X ± SD	**X ± SD**	***2*2 p=***	**X ± SD**	***2*2 p=***	**X ± SD**	***2*2 p=***	**X ± SD**	***2*2 p=***
"average pain"	I	7.2 ± 1.5	5.8 ± 2.3 ***	*0.800*	5.2 ± 2.5 ***	*0.998*	4.7 ± 2.7 ***	*0.795*	4.1 ± 2.7 ***	*0.455*
	C	7.2 ± 1.9	5.9 ± 2.0 ***		5.2 ± 2.0 ***		4.8 ± 2.3 ***		3.4 ± 2.4 ***	
"pain at its worst"	I	8.6 ± 1.1	7.1 ± 2.3 **	*0.828*	6.3 ± 2.9 ***	*0.510*	6.1 ± 2.9 ***	*0.776*	5.4 ± 3.0 ***	*0.347*
	C	8.5 ± 1.6	7.2 ± 2.1 ***		6.7 ± 2.5 ***		6.2 ± 2.4 ***		4.6 ± 2.7 ***	
"pain at its best"	I	5.1 ± 2.2	4.2 ± 2.8	*0.646*	3.9 ± 2.5 **	*0.706*	3.1 ± 2.6 ***	*0.679*	3.1 ± 2.5 ***	*0.288*
	C	4.6 ± 2.6	3.3 ± 2.4 **		3.1 ± 2.2 **		2.9 ± 2.4 **		1.7 ± 1.8 ***	
"pain in the morning"	I	7.0 ± 2.5	6.0 ± 2.8	*0.922*	5.6 ± 3.1 **	*0.647*	5.1 ± 2.9 **	*0.410*	4.4 ± 3.2 ***	*0.174*
	C	7.0 ± 2.7	5.9 ± 2.8 ***		5.2 ± 2.3 ***		4.4 ± 2.6 ***		3.1 ± 2.7 ***	
"pain in the evening"	I	7.5 ± 1.8	5.9 ± 2.7 **	*0.720*	5.6 ± 3.1 **	*0.784*	5.0 ± 3.0 ***	*0.739*	4.4 ± 3.2 ***	*0.350*
	C	7.3 ± 2.0	5.9 ± 2.1 **		5.7 ± 2.1 ***		5.1 ± 2.3 ***		3.4 ± 2.6 ***	
"pain at rest"	I	5.5 ± 2.5	4.8 ± 2.3	*0.414*	4.4 ± 2.6 *	*0.422*	3.9 ± 2.9 **	*0.762*	3.4 ± 2.7 ***	*0.201*
	C	5.4 ± 2.4	4.1 ± 2.3 **		3.7 ± 2.2 ***		3.6 ± 2.2 **		2.3 ± 2.2 ***	
"pain when walking"	I	7.0 ± 1.9	5.9 ± 2.9 *	*0.934*	5.4 ± 2.9 ***	*0.584*	4.9 ± 2.9 ***	*0.610*	4.1 ± 3.1 ***	*0.249*
	C	7.3 ± 1.7	6.1 ± 2.2 **		5.3 ± 2.2 ***		4.7 ± 2.3 ***		3.4 ± 2.5 ***	
"average stiffness"	I	5.7 ± 2.6	4.8 ± 3.0	*0.480*	4.8 ± 3.1 *	*0.841*	4.3 ± 2.8 **	*0.777*	3.8 ± 3.0 **	*0.769*
	C	5.2 ± 2.6	5.1 ± 2.4		4.6 ± 2.1 *		4.2 ± 2.2		3.1 ± 2.4 **	
"stiffness in the morning"	I	6.2 ± 2.9	5.4 ± 3.4	*0.472*	5.2 ± 3.0 *	*0.898*	4.7 ± 3.1 **	*0.983*	4.5 ± 3.3 *	*0.266*
	C	6.1 ± 3.2	6.1 ± 2.6		5.2 ± 2.5 *		4.5 ± 2.5 **		3.2 ± 2.6 **	

Key:

*Data shown are mean ± SD. "I" = "Intervention group" (n=36, n=33/36 at 2w, n=33/36 at 6w, n=34/36 at 3M, n=35/36 at 6M), "C" = "control group" (n=33, n=32/33 at 2w, n=32/33 at 6w, n=32/33 at 3M, n=33/36 at 6M.) Statistical significance was calculated between data at baseline and the different follow-up time-points respectively, comparing intervention and control groups using 2x2 (time*group) ANOVA testing (p-value displayed.) Within-group comparisons between baseline and follow-up time points was undertaken using either paired t-tests or Wilcoxon tests, and statistical significance is denoted by the use of asterisks within that row. (* = p<0.05, ** p<0.01, *** p<0.001)*

- Patient Reported Outcome Measures (PROMs)

There were no statistically significant time*group interaction effects identified for any of the outcome measures studied. These included results from a number of validated foot PROMs including the MOXFQ (p=0.723) the total score of the FFI-r (p=0.821), or the FAAM %ADL or %function score (p=0.968 and p=0.930 respectively.) These values are all displayed in table 7.6 This lack of differences between the groups as shown by the time*group 2*2 ANOVA at the different timepoints has shown that the co-administration of a small quantity of the patients' own blood made no difference to a dry-needling fenestration procedure alone.

The within-group analyses demonstrated changes from baseline for a number of outcome measures in both groups studied. The self-reported level of pain improved to a statistically significant degree in the intervention group from baseline to 2-weeks (p<0.001), 6-weeks(p<0.001), 3-months (p<0.001), and 6-months (p<0.001) with similar findings also found in the control group. Additionally, the different validated foot PROMs improved in members of both the intervention group and the control group at different time points, with these values displayed in table 7.6

Despite the improvements seen in aspects of both self-reported pain and local function, this did not necessarily result in consistent benefits in wider aspects of function. The %health sub-scale of EQ-5D significantly improved from baseline for the intervention group at 3-months and at 6-months, but not at 6-weeks, whereas in the control group this improved only at 6-weeks compared to baseline, but not at other time points. PROMs assessing aspects of anxiety and depressive features (HADS, PHQ4, GAD7, PHQ9) showed inconsistent results, with limited statistically significant changes in either group. A measure of sleep quality (PSQI) showed improvements in the intervention group that were statistically significant at 6-weeks and 3-month, but not at 6-months. Additionally, the reductions in levels of pain did not lead to any increased levels of physical activity in members of either group at the follow-up periods studied. However, the tools used (short-form IPAQ and "Vital Signs") have more validity as screening tools rather than being necessarily robust enough to detect individual changes.

The specific values for members of the intervention and control groups are displayed in Table 7.6 (foot-specific PROMS), Table 7.7 (PROMs assessing wider aspects of function), and Table 7.8 (PROMs measuring aspects of physical activity). These tables give baseline and follow-up values for the different PROMS used, as well as displaying the time*group significance value at each time point (2*2 ANOVA p-value displayed) and also highlighting any specific within-group changes of statistical significance.

Table 7.6: Foot-region-specific Patient Reported Outcome Measures (PROMs) at baseline and follow-up

		Baseline	2-weeks		6-weeks		3-months		6-months	
		X ± SD	X ± SD	*2*2 p=*	X ± SD	*2*2 p=*	X ± SD	*2*2 p=*	X ± SD	*2*2 p=*
MOXFQ total score	I	60.8 ± 12.5	53.5 ± 15.2	*0.702*	52.1 ± 16.8 **	*0.850*	48.2 ± 16.1 ***	*0.815*	46.7 ± 18.8 ***	*0.354*
	C	59.2 ± 10.7	53.7 ± 12.0 *		51.4 ± 12.1 **		47.7 ± 13.9 ***		40.3 ± 16.0 ***	
FFI-r total score	I	92.9 ± 19.8	83.7 ± 24.1 **	*0.985*	78.3 ± 22.7 ***	*0.945*	72.5 ± 23.6 ***	*0.736*	70.0 ± 26.0 ***	*0.410*
	C	89.3 ± 20.2	80.2 ± 18.8 ***		75.2 ± 17.4 ***		71.4 ± 20.7 ***		60.2 ± 21.1 ***	
FAAM %ADL score	I	51% ± 21%	60% ± 25%	*0.860*	62% ± 22% **	*0.775*	69% ± 21% ***	*0.463*	74% ± 21% ***	*0.696*
	C	58%± 19%	65% ± 18% **		67% ± 20% **		71% ± 19% **		79% ± 20% ***	
FAAM %function	I	49% ± 26%	66% ± 24%	*0.606*	65% ± 22% **	*0.837*	65% ± 22% **	*0.723*	71% ± 24% **	*0.897*
	C	48% ± 24%	60% ± 18% **		62% ± 20% ***		67% ± 19% ***		72% ± 23% ***	
FAAM %sport score	I	22% ± 16%	32% ± 19%	*0.450*	41% ± 27% **	*0.139*	45% ± 31% ***	*0.185*	49% ± 33% ***	*0.778*
	C	29% ± 22%	33% ± 26%		35% ± 26%		41% ± 24% *		54% ± 31% ***	
FAAM %sport function	I	27% ± 29%	42% ± 31%	*0.354*	48% ± 35% **	*0.175*	49% ± 32% **	*0.155*	53% ± 38% **	*0.718*
	C	35% ± 29%	40% ± 25%		41% ± 30%		42% ± 30%		57% ± 30% ***	

Key:

*Data shown are mean ± SD. "I" = "Intervention group" (n=36, n=33/36 at 2w, n=33/36 at 6w, n=34/36 at 3M, n=35/36 at 6M), "C" = "control group" (n=33, n=32/33 at 2w, n=32/33 at 6w, n=32/33 at 3M, n=33/36 at 6M.) Statistical significance was calculated between data at baseline and the different follow-up time-points respectively, comparing intervention and control groups using 2x2 (time*group) ANOVA testing (p-value displayed.) Within-group comparisons between baseline and follow-up time points was undertaken using either paired t-tests or Wilcoxon tests, and statistical significance is denoted by the use of asterisks within that row. (* = p<0.05, ** p<0.01, *** p<0.001)*

MOXFQ total score - range 16-80, with lower score indicating better function

FFI-r total score - range 34-136, with lower score indicating better function

FAAM sub-scores - %scale, with higher score indicating better function

Table 7.7: Patient Reported Outcome Measures (PROMs) at baseline and follow-up assessing wider aspects of functioning

		Baseline	2-weeks		6-weeks		3-months		6-months	
		X ± SD	X ± SD	*2*2 p=*	X ± SD	*2*2 p=*	X ± SD	*2*2 p=*	X ± SD	*2*2 p=*
painDETECT	I	15.6 ± 7.3	11.9 ± 7.3**	*0.540*	12.4 ± 7.4 **	*0.989*	10.0 ± 6.7 ***	*0.358*	11.9 ± 8.8 **	*0.289*
	C	14.4 ± 7.1	12.3 ± 6.0		11.2 ± 6.3 **		11.0 ± 6.2 **		8.1 ± 5.7 ***	
CSI	I	30% ± 13%	27% ± 15%	*0.974*	25% ± 15% **	*0.554*	23% ± 14% **	*0.535*	23% ± 17% **	*0.653*
	C	29% ± 15%	26% ± 15%		29% ± 19%		26% ± 17%		25% ± 19%	
ODI	I	27% ± 13%	27% ± 16%	*0.429*	27% ± 15%	*0.625*	27% ± 15%	*0.298*	24% ± 14%	*0.235*
	C	31% ± 16%	26% ± 16% *		28% ± 17%		25% ± 16% **		21% ± 19% **	
EQ-5L %health	I	62% ± 19%	68% ± 20%	*0.531*	65% ± 21%	*0.608*	68% ± 19% *	*0.807*	72% ± 21% *	*0.601*
	C	64% ± 19%	66% ± 20%		71% ± 18% *		69% ± 18%		71% ± 20%	
HAD - anxiety subscale	I	6.2 ± 4.9	5.1 ± 4.0	*0.950*	4.6 ± 4.0 *	*0.614*	4.8 ± 4.4 *	*0.844*	4.8 ± 4.7 **	*0.780*
	C	5.6 ± 3.9	4.6 ± 3.5 *		4.8 ± 3.9		4.5 ± 3.6 *		4.6 ± 3.9	
HAD - depression subscale	I	6.4 ± 4.9	4.9 ± 5.0	*0.788*	5.0 ± 4.7 *	*0.933*	4.8 ± 4.4 *	*0.626*	5.4 ± 5.2	*0.679*
	C	6.1 ± 3.6	5.1 ± 3.3		4.9 ± 3.9 *		5.3 ± 4.6		4.5 ± 4.3 **	
PHQ-4	I	1.5 ± 1.9	0.7 ± 1.1	*0.297*	1.4 ± 2.4	*0.905*	0.5 ± 1.0	*0.184*	1.2 ± 1.9	*0.955*
	C	1.4 ± 2.3	1.6 ± 2.2		1.3 ± 2.0		1.9 ± 3.2		1.1 ± 1.8	
GAD-7	I	3.7 ± 3.8	2.6 ± 3.2	*0.513*	2.7 ± 2.8	*0.927*	2.1 ± 2.3	*0.334*	3.1 ± 4.4	*0.872*
	C	2.8 ± 3.6	2.8 ± 3.1		2.0 ± 2.9		2.9 ± 4.8		2.0 ± 2.9	
PHQ-9	I	5.2 ± 4.5	3.3 ± 2.7	*0.381*	4.8 ± 5.6	*0.572*	3.6 ± 3.6 *	*0.515*	3.7 ± 4.8 *	*0.825*
	C	4.6 ± 4.1	4.4 ± 5.0		3.0 ± 3.7		4.3 ± 5.4		3.5 ± 3.8 **	
PSQI (total score)	I	9.6 ± 4.2	8.1 ± 4.3	*0.636*	8.4 ± 4.7 *	*0.712*	8.2 ± 4.2 *	*0.529*	8.2 ± 4.3	*0.832*
	C	8.6 ± 4.8	7.9 ± 4.4 *		8.0 ± 4.7		8.2 ± 4.7		6.9 ± 4.0 **	
Roles & Maudsley Score	I	.	3.3 ± 0.7	*>0.99*	3.2 ± 0.8 ***	*0.125*	2.8 ± 0.9 ***	*0.485*	2.7 ± 1.1 ***	*0.058*
	C	.	3.4 ± 0.8		2.9 ± 0.8 ***		2.8 ± 0.8 ***		2.2 ± 1.1 ***	

Table 7.7 key:

*Data shown are mean ± SD. "I" = "Intervention group" (n=36, n=33/36 at 2w, n=33/36 at 6w, n=34/36 at 3M, n=35/36 at 6M), "C" = "control group" (n=33, n=32/33 at 2w, n=32/33 at 6w, n=32/33 at 3M, n=33/36 at 6M.) Statistical significance was calculated between data at baseline and the different follow-up time-points respectively, comparing intervention and control groups using 2x2 (time*group) ANOVA testing (p-value displayed.) Within-group comparisons between baseline and follow-up time points was undertaken using either paired t-tests or Wilcoxon tests, and statistical significance is denoted by the use of asterisks within that row. (* = p<0.05, ** p<0.01, *** p<0.001)*

Specific questionnaires:

painDETECT – range 0-38, with lower score indicating lower likelihood of neuropathic pain)

CSI - %scale, lower score indicates lower likelihood of central pain component)

ODI - (%scale, lower score indicates less self-rated disability pain

EQ-5D – health %scale, higher score indicates better self-rated global health)

HAD - anxiety / depression sub-scales, each range 0-21, with lower score indicating fewer symptoms

PHQ-4 - (range 0-12, with lower score indicating fewer symptoms)

GAD-7 – (range 0-21, with lower score indicating fewer anxiety symptoms)

PHQ-9 – (range 0-27, with lower score indicating fewer depressive symptoms)

PSQI - (range 0-21, with lower score indicating fewer symptoms of sleep disturbance

Roles & Maudsley Score – converted to 1-4 score, with higher score being better function/fewer symptoms

Table 7.8 Patient Reported Outcome Measures (PROMs) at baseline and follow-up assessing levels of physical activity

		Baseline	2-weeks		6-weeks		3-months		6-months	
		X ± SD	**X ± SD**	***2*2 p=***	**X ± SD**	***2*2 p=***	**X ± SD**	***2*2 p=***	**X ± SD**	***2*2 p=***
IPAQ - Number of vigorous-level activity mins/week	I	202 ± 537	49 ± 127	*0.547*	161 ± 345	*0.729*	105 ± 278	*0.652*	170 ± 329	*0.765*
	C	160 ± 488	96 ± 248		179 ± 505		128 ± 212		86 ± 161	
IPAQ - Number of moderate-level activity mins/week	I	163 ± 440	160 ± 320	*0.772*	54 ± 95	*0.380*	111 ± 252	*0.693*	92 ± 226	*0.685*
	C	114 ± 419	73 ± 159		113 ± 219		111 ± 231		92 ± 242	
IPAQ - Number of walking mins/week	I	466 ± 949	295 ± 624	*0.951*	471 ± 805	*0.350*	456 ± 729	*0.987*	418 ± 582	*0.909*
	C	323 ± 663	168 ± 266		604± 798 *		318 ± 480		304 ± 478	
IPAQ - number of hours sitting on a weekday	I	5.3 ± 4.2	3.5 ± 3.9	* *0.049*	5.0 ± 3.4	*0.897*	5.1 ± 3.7	*0.894*	3.8 ± 2.5	*0.498*
	C	5.0 ± 3.7	6.0 ± 2.8		4.5 ± 2.9		4.6 ± 2.1		4.4 ± 3.5	
"Vital signs" – active minutes per week	I	155 ± 708	69 ± 120	*0.806*	129 ± 400	*0.977*	181 ± 332	*0.815*	108 ± 244	*0.980*
	C	137 ± 438	92 ± 200		116 ± 234 *		123 ± 186		86 ± 139	
Hours spend standing on a typical normal day	I	4.8 ± 3.2	4.2 ± 2.7	*0.164*	4.5 ± 2.6	*0.614*	4.8 ± 2.4	*0.780*	5.0 ± 3.4	*0.602*
	C	5.7 ± 2.6	6.6 ± 2.8		4.9 ± 2.3		5.4 ± 2.5		5.4 ± 2.1	
Hours spend standing on a busy day	I	6.5 ± 3.7	6.5 ± 4.2	*0.661*	6.3 ± 4.0	*0.496*	6.6 ± 3.8	*0.696*	6.6 ± 3.9	*0.562*
	C	7.5 ± 3.1	8.1 ± 3.2		6.5 ± 3.1		7.1 ± 3.0		7.0 ± 2.7	

Key:

*Data shown are mean ± SD. "I" = "Intervention group" (n=36, n=33/36 at 2w, n=33/36 at 6w, n=34/36 at 3M, n=35/36 at 6M), "C" = "control group" (n=33, n=32/33 at 2w, n=32/33 at 6w, n=32/33 at 3M, n=33/36 at 6M.) Statistical significance was calculated between data at baseline and the different follow-up time-points respectively, comparing intervention and control groups using 2x2 (time*group) ANOVA testing (p-value displayed.) Additional within-group testing between the data at baseline at follow-up period for each group using either paired t-tests or Wilcoxon tests is displayed with the use of asterisks when statistically significant within the row. An asterisk at the follow-up period indicates a statistically significant change from baseline values for the specific variable studied. (* = p<0.05, ** p<0.01, *** p<0.001)*

7.4 - Autologous Blood Injection (ABI) procedure interventions Discussion

The results from these two studies have shown benefits in measures of pain and function following dry-needling ± ABI procedures, but the lack of any differences between the intervention and control groups in the RCT (Study F) seen at any of the time points studied, indicates that the benefits seen are not as a result of the co-administration of a small quantity of the patient's own blood.

The initial ABI prospective case series (Study E) demonstrated improvements in pain and also in foot function (using the validated FFI-r score) following ABI, and these findings are in keeping with other published case series studies.(348, 349, 371, 378) The improvements that were seen in Study E occurred within a few weeks of the ABI procedure and continued with both statistically and clinically significant improvements over the whole duration of follow-up. This follow-up period had a mean of 18 months, which is longer than many other previously published works which have most commonly used a maximum of 6-month follow-up and often shorter periods of time.(347, 348, 359, 376) The case series study acted as preliminary work and allowed an estimation of the ABI treatment effect size in this clinical population, with a high incidence of chronic and treatment-resistant symptoms, facilitating the development of the subsequent DB-RCT (Study F).

Robust statistical analysis of the ABI case series (Study E) was limited by the variation in the numbers patients that were assessed at each of the time-points. Due to the issues with missing data i.e. most patients only having follow-up data from some of the timepoints studied, repeated-measures tests could not be undertaken without data modification. The multiple sub-analyses that have been conducted have potentially increased the risk of either a Type I or Type II error occurring, which is noted. Furthermore, this case series is limited in approach, particularly with the longer-term follow-up, in that patients who were not doing well at the 6-month time point may then have undertaken further treatments and so were excluded from later results giving a possible positive reporting bias, which was not specifically accounted for in this study design.

The benefits seen in Study E were in the absence of a control group, therefore any improvements cannot be reliably ascribed to the ABI procedure. It is possible that the benefits seen could have been accrued from other sources, including the structured rehabilitation programme or the natural resolution of symptoms over time. However, as patients, prior to the ABI procedure, had already tried a rehabilitation programme for at least 3-months and had a median duration of symptoms 30 months prior to the ABI procedure it is not clear how much benefit could be attributed to these factors, but these cannot be excluded from the results seen in Study E, and this limitation also influences interpretation of results from other published case series studies.(367, 368, 370, 371) It is at least theoretically possible the act of the dry-needling (plantar fascia fenestration) part of the procedure, rather than the injection of the blood itself, was the underlying mechanism of any benefits seen and this consideration was the main driver for the study design of the randomised controlled trial (Study F) which sought to explore this with a robust approach utilising a double-blinded randomised controlled trial design.

In the ABI versus dry-needling randomised controlled trial (Study F), a wide range of outcome measures which assessed aspects of local pain, validated measures of foot function, and validated measures of wider function and activity were used. Previous studies have demonstrated improvements following blood injections in measures foot pain and function through the use of specific foot-related PROMs (353, 366, 369), but with only a couple of studies including any wider measures of functioning leaving a significant knowledge gap in this area. (355, 375) The RCT study (Study F) has attempted to address this deficit by including a wide range of outcome measures with results as previously described.

There were significant within-group improvements seen in both the intervention and control groups for many of the outcome measures that were recorded at different time-points. However, there were no significant time*group interaction effects or differences at any of the time points between the group that received the ABI + dry-needle fenestration procedure compared to the group that received the dry-needle fenestration procedure alone. This demonstrates that the addition of a small quantity of the patients' own blood did not show any additional benefit compared to dry-

needle fenestration of the plantar fascia in this cohort of patients. The results from this study raise an important question of whether the autologous blood injection component of this procedure should be offered to patients, as this has not been shown to give any additional benefit compared to dry-needle fenestration alone. This potentially differs from the results found in a systematic review which has examined the effects of tendon dry-needling for tendinopathy, and which identified a trend to greater improvements with the co-administration of autologous blood,(19) however this review only included four clinical trials and none of which involved patients with plantar fasciitis which may suggest that differences may exist between conditions,

It is unclear if it is the act of plantar fascia dry-needle fenestration or another factor, such as the rehabilitation programme undertaken or the influence of time itself, that has produced the benefits seen across different outcome measures. There is no previously published work that specifically examines a dry-needle fenestration procedure against a placebo intervention alone for patients with plantar fasciitis. One RCT has compared ABI with local anaesthetic and “peppering” and corticosteroid ± “peppering” and shown superior results in those who received a steroid-containing injection than those without.(381) However there were only 25 participants per intervention arm, and the study used only a NRS and “modified Roles and Maudsley score” as outcome measures. In contrast, one previous RCT which compared PRP with corticosteroid injections failed to show any between-group differences, although this involved only 28 participants and had only a 16-week follow-up period but did use validated PROMs as outcome measures in the form of Foot and Ankle Disability Index (FADI) and American Orthopaedic Foot and Ankle Scale (AOFAS).(351)

Previous research has often involved patients with far-shorter duration of symptoms, which could potentially influence results as those with a shorter-duration of symptoms could reasonably expect greater benefit from natural resolution of symptoms over time.(342, 351, 354, 365) Improvements in the outcome measures studied were observed in patients with long average duration of symptoms in both experimental studies, demonstrating that the dry-needle fenestration ± ABI procedure may be worth considering even in with those with very recalcitrant symptoms whose quality of life is adversely affected. However, without a control group that did not receive a dry-needling injection, the evidence for this (from the

“control group” in Study F) is effectively a case series, with the uncertainties that this brings.

No significant adverse events were reported in either study, which have involved a total of more than 140 patients, and this is in keeping with the safety of this both dry-needling and ABI procedures described in previous systematic reviews.(388)

- Comparison between participants in case series (Study E) & RCT (Study F)

As described in the study methods sections, the participants in the case series (Study E) and those in the intervention group in the RCT (Study F) received the same injection procedure, that of ultrasound-guided dry-needling and co-administration of an Autologous Blood Injection. In both of these populations there were significant improvements in levels of self-reported pain and the FFI-r score comparing baseline with follow-up periods studied. Those in the intervention group in study F were on average 4 years younger than Study E and this difference was found to be significant ($p=0.030$). The baseline self-reported “average pain” was also slightly lower in the intervention group in Study F, and again this was significant statistically ($p=0.010$). Using a time*group ANOVA, there were significant differences between these two cohorts for the changes seen in self-reported average pain at follow-up ($p<0.001$) favouring those in Study E (case series) over Study F (RCT), but not for the FFI-r score ($p=0.140$). The underlying reasons for this difference remain unknown and may be a statistical anomaly could represent the greater reliability of the FFI-r as a tool, or could potentially represent the placebo effect that was seen when patients were not blinded to the injection modality that they received.

- Possible limitations, and considerations for the future

It is recognised that there was no “true placebo” group in the RCT (Study F). At the onset of study design a deliberate decision was taken for an active intervention group, to see if it was possible to measure any additional benefit that the administration of a small quantity of blood had in addition to the dry-needle fenestration of the plantar fascia. The decision for a potentially active-intervention comparator rather than placebo was undertaken noting the lack of differences seen

between intervention groups in several published studies comparing results following injection of blood products and several other injection therapies, including steroid injections. (385, 386, 389) The RCT (Study F) has sought to explore this area further to investigate potential sources of any benefit seen.

For future research, it is worth considering issues of a placebo intervention as a comparator. Recruitment to a trial involving a placebo intervention may be more difficult, and ethical considerations may also limit the use of a sham procedure in this population, and may influence how the intervention can be delivered within an NHS setting. Consideration has been made as to further research studies, which could potentially use a placebo injection such as a local anaesthetic injection to the skin only, as this could potentially allow a double-blinded study design as a more robust approach than an unblinded or single-blinded study. An alternative may be to use a comparison of a “delayed treatment” approach in which patients were randomised to receive the injection straight away or delayed by a set time-period, although this could only be undertaken with a single-blinded approach. Either of these could attempt to determine the origin of the within-group changes found in these two studies, to potentially assess if benefits from baseline seen were as a result of the dry-needling fenestration intervention or another source. However, these would lie outside the timescale and remit of this thesis.

Additionally, these two experiments have used whole blood (ABI), rather than fractionated blood (PRP).(21, 387) This was chosen at the start of the study for pragmatic reasons, chiefly the cost of PRP, the potential differences between different PRP substrates causing additional confounding problems, and limited availability of PRP through the NHS at this time. It is recognised that subsequent to the study design there have been multiple publications of varying quality and the majority have utilised PRP, although often supported by funding from device manufacturers which could potentially create a conflict of interest. (These studies are reviewed formally in Chapter 2 of this thesis.) There has been a single non-randomised study comparing ABI and PRP in patients with plantar fasciitis (336) and also two other studies that have involved patients with tennis elbow (337, 338), none of which have shown any consistent differences between the two interventions. It is not clear therefore that the additional material costs and additional time required for

PRP compared to ABI procedures is of clinical benefit. However, the differences in procedure type from the two studies presented here (ABI as opposed to PRP injection) and those in some of the other published literature is noted.

- Overall summary

The RCT (Study F) has demonstrated no significant additional benefits of co-administration of a small quantity of the patients' own blood, compared to a dry-needle fenestration procedure alone. As a result, the hypothesis that a difference in outcome between the two groups would be identified was not proven and the null hypothesis (that there is no difference) stands.

Clinically and statistically significant within-group improvements were seen in some measures of pain/function following the use of an injection procedure which used a dry-needle fenestration technique ± ABI to the plantar fascia, when comparing baseline and follow-up data. However, it remains unclear if these arise solely from the procedure undertaken. Given the lack of between-group differences in the RCT (Study F) it is accepted that the underlying reasons for benefit seen following dry-needling ± ABI cannot be reliably determined from these studies at this time. It may be that the benefit arises from the rehabilitation procedure itself, the dry-needle fenestration technique, or even the natural resolution of symptoms over time. However, the duration of symptoms prior to intervention and the failure of other previously-tried treatment approaches including a structured rehabilitation procedure may make this latter factor less likely. It may be therefore that the benefits seen are as a direct result of the dry-needling fenestration of the plantar fascia itself, but without a direct comparison group that did not receive this intervention, this cannot be proven from these studies, and will need to be the focus of further works.

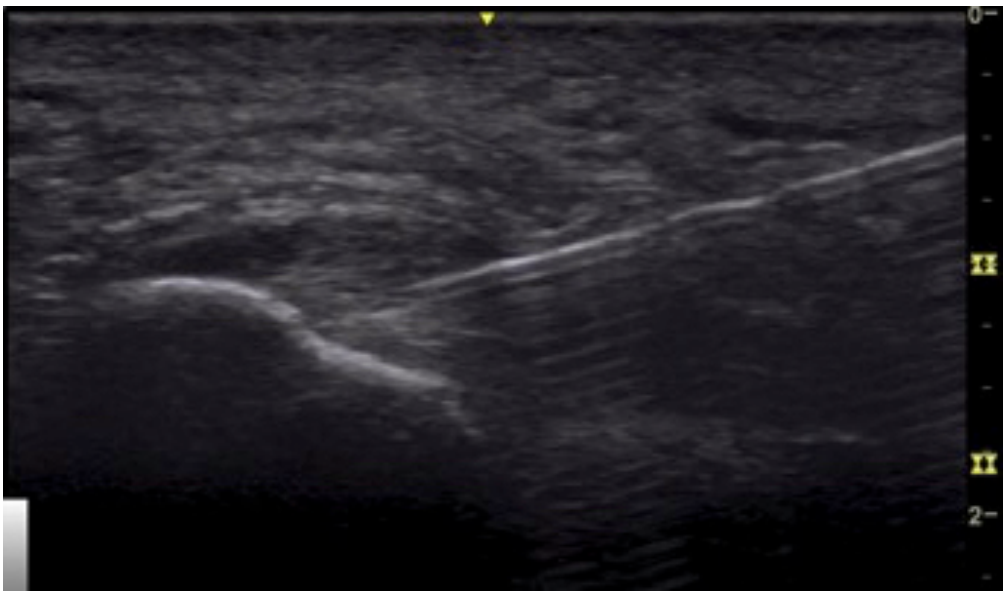
Chapter 8 -

Comparing interventions:

Extra-Corporeal Shockwave Therapy (ESWT)

v

Autologous Blood Injection (ABI)



Interventions:
Comparing ESWT v ABI

8.1 - Introduction

With the trend potentially moving away from surgery for patients with recalcitrant plantar fasciitis symptoms in recent years, there are two relatively new treatments for patients who may be struggling with symptoms of plantar fasciitis. These treatments are Extra-Corporeal Shockwave Therapy (ESWT) and Autologous Blood Injections (ABI). Both of these two procedures have NICE approval for the treatment of plantar fasciitis,(51, 52) but to date little comparative work has been done seeking to identify which of these two treatment may have better outcomes. A single small RCT has compared the results following comparing ESWT with PRP injections which demonstrated no differences in measurements of pain between the two procedures.(287) A further RCT compared the outcomes following ESWT or dry needling alone for patients with plantar fasciitis and identified similar levels of improvement from baseline in both groups at four-weeks, but superior results in the dry-needling group compared to the ESWT group at the end of the study at eight-weeks,(20) but no information as to any longer-term outcomes. Injections of blood products (either ABI or PRP) were not included within a recent systematic review of treatments for plantar fasciitis.(189)

From the available evidence it is therefore difficult to know how best to advise patients with chronic plantar fasciitis who ask the question “which treatment is best?” in clinic. To start to address this question, a prospective cohort study analysis has been performed using the data presented here from Chapters 6 and 7 using the results from the intervention groups of Study D (ESWT RCT) and Study F (ABI RCT). It is anticipated that this will identify any differences in outcomes for these two interventions that may be offered in clinical practice for patients with chronic plantar fasciitis.

Methods

- Study design

This prospective cohort study compares the findings from the ESWT RCT (Study D – REC ref 15/EM/0122) and the ABI RCT (Study F – REC ref 14/EM/1061) in relation to participants who were randomised to receive the specific “active intervention” in either study.

As discussed in the specific study sections for Study D (section 6.3) and Study F (section 7.3), in addition to the ESWT or ABI, members of both groups received an identical structured home exercise programme. Patients were encouraged to continue with their home exercise programme throughout the whole duration of their study inclusion.

Baseline assessments were conducted before the procedure using a range of patient reported outcome measures (described below) investigating aspects of local foot pain/function, global function, mental health, sleep quality and physical activity. The maximum follow-up duration was six-months, with interim data also recorded at six-weeks, and three-months. All patients were reviewed by investigators blinded to treatment group in the two RCT studies.

- Participants

The specific inclusion and exclusion criteria are specified in section 6.3 for the ESWT RCT and in section 7.3 for the ABI RCT. All patients had their diagnosis confirmed with imaging (US or MRI) prior to intervention.

- Interventions

Patients received either three sessions of radial Extra-Corporeal Shockwave Therapy which was performed once per week for three weeks using an “Intelect” RPW ESWT machine (DJO Global Chattanooga), or a single ultrasound-guided dry needle fenestration procedure with an Autologous Blood Injection using 3ml of whole autologous blood. Specific information about the two interventions is detailed in section 6.3 for the ESWT procedure and in section 7.3 for the ABI procedure.

- Outcome measures

All participants completed a structured questionnaire about their symptoms at baseline (up to 24 hours before their treatment commenced), and at the six-week, three-month and the final/six-month follow-up visits after their treatment. This questionnaire contained a series of different outcome measures, including questions about pain including the pain felt by the patient “on average”, “at its best” and “at its worst” using a 0-10 numerical rating scale (NRS). In addition, this questionnaire contained a number of validated PROMs covering a wide range of aspects of function. These included PROMs investigating local foot/ankle function (the revised-Foot Function Index (FFI-r)(448-451) and the Manchester-Oxford Foot Questionnaire (MOXFQ)(452-454) as well as measures of global function (EQ-5D-5L).(455, 456) PROMs were also used to examine the impact of symptoms of other areas of patient functioning including measures of anxiety and depression symptoms (Hospital Anxiety and Depression Scale – HADS)(458, 461) and sleep quality (Pittsburgh Sleep Quality Index – PSQI).(466, 467, 499-502) Physical activity was assessed with the short-form (7-day recall) version of the International Physical Activity Questionnaire (IPAQ),(468) and two “vital signs” physical activity questions.(469) These outcome measures are reviewed in Chapter 2.

The primary outcome measure was the self-reported “average pain” (as recorded on a 0-10 numerical scale) between baseline and six-months, with the remainder of the outcome measures being secondary to this.

- Statistical analysis

Data are presented as mean ± SD. Data were collated prospectively into an Excel spreadsheet (MS Excel from MS Office 2011, version 14.5.7) and analysed using SPSS (IBM SPSS Statistics, version 24). The primary analysis was performed using a two-way repeated measures ANOVA (time*treatment group allocation) to assess if a significant time*group interaction effect occurred between baseline and the final (6-month) time-point, as well as comparing baseline data to the different interim time points. This analysis is widely considered to be robust to manage data that does not conform to normal distribution. As secondary analyses, additional tests (either

paired-samples T-tests or related-samples Wilcoxon Signed Rank tests) were used for specific within-groups comparisons at specific follow-up time-points vs. baseline. Statistical significance was set at $p<0.05$. Missing Value Analysis (MVA) was not undertaken.

- Ethical considerations

These two studies from which this data was extracted had all necessary permissions and are both registered on a publicly accessible database. Full details about registration, ethical permissions and sponsor monitoring is described in section 6.3 for the ESWT RCT and in section 7.3 for the ABI RCT.

Results

Results for 38 patients who received radial ESWT and 36 patients who received ABI were compared. Final (6-month) data were available for 37/38 (97%) patients in the ESWT group and 35/36 (97%) patients in the ABI group. There were no significant differences in the demographic information of the participants in the two intervention groups, and these data (and the respective p-values) are displayed in table 8.1

Table 8.1: Demographic information for participants

	ESWT (“recommended-dose” ESWT) (n=38)	**ABI** (dry-needling + ABI) (n=36)	***p-value***
Age (years)	50.1 ± 9.1	48.0 ± 9.2	*0.337*
Gender (male/female)	16M / 22F (58% female)	16M / 20F (56% female)	*0.842*
Symptom duration (months)	32.1 ± 42.0	43.3 ± 27.3	*0.185*

Key: Data shown are mean ± SD. p-value compares data between different intervention groups using independent samples testing

- Self-reported markers of pain / stiffness (0-10 scale)

There were no differences found in any of the baseline pain/stiffness scores or baseline PROMs studied between the two groups.

Significant within-group improvements were seen in both the rESWT and the ABI treatment groups for various measures of pain/stiffness studied at different time-points and these are discussed previously in Chapter 6 (ESWT) and Chapter 7 (ABI). These within-group improvements in the rESWT group includes the values of the primary outcome measure (0-10 self-reported numerical rating of “average pain”) which improved from 6.9 ± 1.6 at baseline to 4.6 ± 2.5 at three-months ($p<0.001$), and 3.7 ± 2.6 at six-months ($p<0.001$). In the ABI-group these values improved from 7.2 ± 1.5 at baseline to 4.7 ± 2.7 at three-months ($p<0.001$) and 4.1 ± 2.7 at six-months ($p<0.001$). However, when comparing the data from the two different interventions, there were no statistically significant time*group interaction effects seen at the final, or at any of the interim, time-points. This included the primary outcome measurement of self-reported “average pain” (repeated measures time*group 2*2 ANOVA $p = 0.969$ at 6-months), as well as the different secondary outcome measures studied.

The baseline and follow-up values for the different parameters studied for the participants in the rESWT and ABI groups are displayed in table 8.2 for the primary outcome measure of the self-reported “average level of pain” and well as other sub-scores of aspects of pain/stiffness using the same 0-10 numerical self-rating scale. Specific values for the two studied groups with significance of changes between groups at different time points (using 2x2 (time*group) ANOVA) are displayed, and within-group changes are highlighted with asterisks in Table 8.2

Table 8.2: Numerical pain/stiffness scores (/10) at baseline and follow-up

		Baseline	6-weeks		3-months		6-months	
		X ± SD	**X ± SD**	***2*2 p=***	**X ± SD**	***2*2 p=***	**X ± SD**	***2*2 p=***
"average pain"	ESWT	6.9 ± 1.6	4.3 ± 2.2 **	*0.357*	4.6 ± 2.5 **	*0.804*	3.7 ± 2.6 *	*0.969*
	ABI	7.2 ± 1.5	5.2 ± 2.5 ***		4.7 ± 2.7 ***		4.1 ± 2.7 ***	
"pain at its worst"	ESWT	8.3 ± 1.4	6.4 ± 2.5 *	*0.589*	4.4 ± 2.5 *	*0.487*	5.2 ± 3.2	*0.989*
	ABI	8.6 ± 1.1	6.3 ± 2.9 ***		6.1 ± 2.9 ***		5.4 ± 3.0 ***	
"pain at its best"	ESWT	4.0 ± 2.3	2.5 ± 2.2 **	*0.712*	2.5 ± 2.7 **	*0.541*	1.8 ± 1.9 ***	*0.742*
	ABI	5.1 ± 2.2	3.9 ± 2.5 **		3.1 ± 2.6 ***		3.1 ± 2.5 ***	
"pain in the morning"	ESWT	6.4 ± 2.6	4.1 ± 2.5 ***	*0.273*	4.4 ± 2.9 ***	*0.841*	3.4 ± 2.6 ***	*0.591*
	ABI	7.0 ± 2.5	5.6 ± 3.1 **		5.1 ± 2.9 **		4.4 ± 3.2 ***	
"pain in the evening"	ESWT	6.8 ± 2.2	4.7 ± 2.7 ***	*0.759*	4.8 ± 3.0 ***	*0.589*	3.8 ± 3.0 ***	*0.939*
	ABI	7.5 ± 1.8	5.6 ± 3.1 **		5.0 ± 3.0 ***		4.4 ± 3.2 ***	
"pain at rest"	ESWT	5.1 ± 2.3	3.2 ± 2.3 ***	*0.298*	3.1 ± 2.7 ***	*0.591*	2.4 ± 2.4 ***	*0.404*
	ABI	5.5 ± 2.5	4.4 ± 2.6 *		3.9 ± 2.9 **		3.4 ± 2.7 ***	
"pain when walking"	ESWT	6.7 ± 1.9	4.7 ± 2.4 *	*0.603*	4.9 ± 2.8 **	*0.679*	3.6 ± 2.6	*0.827*
	ABI	7.0 ± 1.9	5.4 ± 2.9 ***		4.9 ± 2.9 ***		4.1 ± 3.1 ***	
"average stiffness"	ESWT	5.3 ± 2.6	3.9 ± 2.8 ***	*0.534*	4.0 ± 2.9 ***	*0.989*	3.0 ± 2.5 **	*0.580*
	ABI	5.7 ± 2.6	4.8 ± 3.1 *		4.3 ± 2.8 **		3.8 ± 3.0 **	
"stiffness in the morning"	ESWT	6.0 ± 2.6	4.0 ± 2.7 **	*0.328*	4.2 ± 2.9 **	*0.802*	3.2 ± 2.3 *	*0.247*
	ABI	6.2 ± 2.9	5.2 ± 3.0 *		4.7 ± 3.1 **		4.5 ± 3.3 *	

*Key: Data shown are mean ± SD. "ESWT"/ "ABI" = treatment group. (rESWT n=38, n=35/38 at 6w, n=36/38 at 3M, n=37/38 at 6M, ABI n=36, n=33/36 at 6w, n=34/36 at 3M, n=35/36 at 6M),Statistical significance was calculated between data at baseline and the different follow-up time-points respectively, comparing intervention and control groups using 2x2 (time*group) ANOVA testing (p-value displayed.) Within-group comparisons between baseline and follow-up time points was undertaken using either paired t-tests or Wilcoxon tests, and statistical significance is denoted by the use of asterisks within that row. (* = p<0.05, ** p<0.01, *** p<0.001)*

- Patient Reported Outcome Measures (PROMs)

There were a number of within-group changes from both of these two interventions comparing baseline to follow-up data, and these were previously discussed in Chapter 6 (ESWT) and Chapter 7 (ABI). However, when comparing the two interventions in this cohort study there were no statistically significant time*group interaction effects for any of the outcome measures studied. This included results from a number of validated foot PROMs including the MOXFQ (p=0.569) the total score of the FFI-r (p=0.999), or the FAAM %ADL or %function score (p=0.977 and p=0.339 respectively)

The specific values for the ESWT and ABI groups are displayed in Table 8.3 (foot-specific PROMS), Table 8.4 (PROMs assessing wider aspects of function), and Table 8.5 (PROMs measuring aspects of physical activity). These tables give baseline and follow-up values for the different PROMS used, as well as displaying the time*group significance value at each time point (2*2 ANOVA p-value displayed) and also highlighting any specific within-group changes of statistical significance.

Table 8.3: Foot-region-specific Patient Reported Outcome Measures (PROMs) at baseline and follow-up

		Baseline	6-weeks		3-months		6-months	
		X ± SD	**X ± SD**	***2*2 p=***	**X ± SD**	***2*2 p=***	**X ± SD**	***2*2 p=***
MOXFQ total score	ESWT	55.7 ± 11.8	44.5 ± 13.7 ***	*0.589*	42.4 ± 14.9 ***	*0.881*	38.8 ± 14.2 ***	*0.569*
	ABI	60.8 ± 12.5	52.1 ± 16.8 **		48.2 ± 16.1 ***		46.7 ± 18.8 ***	
FFI-r total score	ESWT	82.3 ± 22.2	66.3 ± 18.0 **	*0.840*	63.6 ± 18.0 ***	*0.804*	59.4 ± 18.0 ***	*0.999*
	ABI	92.9 ± 19.8	78.3 ± 22.7 ***		72.5 ± 23.6 ***		70.0 ± 26.0 ***	
FAAM %ADL score	ESWT	57% ± 18%	69% ± 19% ***	*0.836*	75% ± 19% ***	*0.950*	80% ± 17% ***	*0.977*
	ABI	51% ± 21%	62% ± 22% **		69% ± 21% ***		74% ± 21% ***	
FAAM %function	ESWT	57% ± 22%	64% ± 22% *	*0.279*	70% ± 20% **	*0.703*	71% ± 25% **	*0.339*
	ABI	49% ± 26%	65% ± 22% **		65% ± 22% **		71% ± 24% **	
FAAM %sport score	ESWT	32% ± 19%	48% ± 22% ***	*0.675*	54% ± 28% ***	*0.879*	60% ± 33% ***	*0.948*
	ABI	22% ± 16%	41% ± 27% **		45% ± 31% ***		49% ± 33% ***	
FAAM %sport function	ESWT	39% ± 29%	50% ± 27% *	*0.366*	56% ± 27% *	*0.618*	62% ± 30% **	*0.786*
	ABI	27% ± 29%	48% ± 35% **		49% ± 32% **		53% ± 38% **	

*Key: Data shown are mean ± SD. "ESWT"/ "ABI" = treatment group. (rESWT n=38, n=35/38 at 6w, n=36/38 at 3M, n=37/38 at 6M, ABI n=36, n=33/36 at 6w, n=34/36 at 3M, n=35/36 at 6M) Statistical significance was calculated between data at baseline and the different follow-up time-points respectively, comparing the two groups using 2x2 (time*group)ANOVA testing (p-value displayed.) Within-group comparisons between baseline and follow-up time points was undertaken using either paired t-tests or Wilcoxon tests, and statistical significance is denoted by the use of asterisks within that row. (* = p<0.05, ** p<0.01, *** p<0.001)*

MOXFQ total score - range 16-80, with lower score indicating better function

FFI-r total score - range 34-136, with lower score indicating better function

FAAM sub-scores - %scale, with higher score indicating better function

Table 8.4 Patient Reported Outcome Measures (PROMs) at baseline and follow-up assessing wider aspects of functioning

		Baseline	6-weeks		3-months		6-months	
		X ± SD	**X ± SD**	***2*2 p=***	**X ± SD**	***2*2 p=***	**X ± SD**	***2*2 p=***
painDETECT	ESWT	12.4 ± 8.1	11.7 ± 8.3	*0.362*	10.3 ± 7.9	*0.175*	8.4 ± 5.9 **	*0.894*
	ABI	15.6 ± 7.3	12.4 ± 7.4 **		10.0 ± 6.7 ***		11.9 ± 8.8 **	
CSI	ESWT	25% ± 16%	25% ± 19%	*0.485*	24% ± 18%	*0.297*	23% ± 17% *	*0.419*
	ABI	30% ± 13%	25% ± 15% **		23% ± 14% **		23% ± 17% **	
ODI	ESWT	25% ± 16%	20% ± 19% *	*0.451*	19% ± 18% **	*0.301*	19% ± 17% ***	*0.619*
	ABI	27% ± 13%	27% ± 15%		27% ± 15%		24% ± 14%	
EQ-5L %health	ESWT	73% ± 20%	78% ± 17% *	*0.898*	76% ± 19%	*0.539*	74% ± 22%	*0.150*
	ABI	62% ± 19%	65% ± 21%		68% ± 19% *		72% ± 21% *	
HAD - anxiety subscale	ESWT	5.7 ± 4.2	4.9 ± 3.9	*0.599*	5.5 ± 4.0	*0.413*	5.1 ± 4.3	*0.570*
	ABI	6.2 ± 4.9	4.6 ± 4.0 *		4.8 ± 4.4 *		4.8 ± 4.7 **	
HAD - depression subscale	ESWT	5.5 ± 3.8	4.6 ± 3.9	*0.795*	4.3 ± 3.7	*0.797*	4.5 ± 4.2	*0.999*
	ABI	6.4 ± 4.9	5.0 ± 4.7 *		4.8 ± 4.4 *		5.4 ± 5.2	
PHQ-4	ESWT	1.9 ± 2.8	1.9 ± 2.7	*0.972*	2.1 ± 2.9	*0.236*	1.9 ± 2.8	*0.737*
	ABI	1.5 ± 1.9	1.4 ± 2.4		0.5 ± 1.0		1.2 ± 1.9	
GAD-7	ESWT	3.9 ± 4.8	3.5 ± 4.2	*0.766*	3.8 ± 4.4	*0.395*	3.7 ± 4.9	*0.857*
	ABI	3.7 ± 3.8	2.7 ± 2.8		2.1 ± 2.3		3.1 ± 4.4	
PHQ-9	ESWT	5.1 ± 5.1	4.5 ± 4.6	*0.932*	4.8 ± 5.3	*0.489*	4.5 ± 5.5	*0.628*
	ABI	5.2 ± 4.5	4.8 ± 5.6		3.6 ± 3.6 *		3.7 ± 4.8 *	
PSQI (total score)	ESWT	8.8 ± 3.9	8.3 ± 3.7	*0.611*	7.9 ± 4.0	*0.660*	8.2 ± 4.4	*0.572*
	ABI	9.6 ± 4.2	8.4 ± 4.7 *		8.2 ± 4.2 *		8.2 ± 4.3	

Table 8.4 key:

*Data shown are mean ± SD. "ESWT"/ "ABI" = treatment group. (rESWT n=38, n=35/38 at 6w, n=36/38 at 3M, n=37/38 at 6M, ABI n=36, n=33/36 at 6w, n=34/36 at 3M, n=35/36 at 6M) Statistical significance was calculated between data at baseline and the different follow-up time-points respectively, comparing the two groups using 2x2 (time*group) ANOVA testing (p-value displayed.) Within-group comparisons between baseline and follow-up time points was undertaken using either paired t-tests or Wilcoxon tests, and statistical significance is denoted by the use of asterisks within that row. (* = p<0.05, ** p<0.01, *** p<0.001)*

Specific questionnaires:

painDETECT – range 0-38, with lower score indicating lower likelihood of neuropathic pain)

CSI - %scale, lower score indicates lower likelihood of central pain component)

ODI - (%scale, lower score indicates less self-rated disability pain

EQ-5D – health %scale, higher score indicates better self-rated global health)

HAD - anxiety / depression sub-scales, each range 0-21, with lower score indicating fewer symptoms

PHQ-4 - (range 0-12, with lower score indicating fewer symptoms)

GAD-7 – (range 0-21, with lower score indicating fewer anxiety symptoms)

PHQ-9 – (range 0-27, with lower score indicating fewer depressive symptoms)

PSQI - (range 0-21, with lower score indicating fewer symptoms of sleep disturbance

Roles & Maudsley Score – converted to 1-4 score, with higher score being better function/fewer symptoms

Table 8.5 Patient Reported Outcome Measures (PROMs) at baseline and follow-up assessing levels of physical activity

		Baseline	6-weeks		3-months		6-months	
		X ± SD	**X ± SD**	***2*2 p=***	**X ± SD**	***2*2 p=***	**X ± SD**	***2*2 p=***
IPAQ - Number of vigorous-level activity mins/week	ESWT	260 ± 624	210 ± 365	*0.965*	310 ± 511	*0.401*	197 ± 373	*0.852*
	ABI	202 ± 537	161 ± 345		105 ± 279		170 ± 329	
IPAQ - Number of moderate-level activity mins/week	ESWT	236 ± 521	222 ± 407	*0.515*	240 ± 413	*0.702*	321 ± 553	*0.314*
	ABI	163 ± 440	54 ± 95		111 ± 252		92 ± 226	
IPAQ - Number of walking mins/week	ESWT	314 ± 606	417 ± 580 *	*0.714*	405 ± 564 *	*0.689*	414 ± 614 *	*0.535*
	ABI	466 ± 949	471 ± 805		456 ± 729		418 ± 582	
IPAQ - number of hours sitting on a weekday	ESWT	4.8 ± 4.6	4.3 ± 2.3	*0.905*	3.9 ± 2.3	*0.591*	4.6 ± 3.6	*0.343*
	ABI	5.3 ± 4.2	5.0 ± 3.4		5.1 ± 3.7		3.8 ± 2.5	
"Vital signs" – active minutes per week	ESWT	251 ± 566	233 ± 309	*0.966*	209 ± 331	*0.707*	222 ± 371	*0.915*
	ABI	155 ± 708	129 ± 400		181 ± 332		108 ± 244	

Key:

*Data shown are mean ± SD. "ESWT"/ "ABI" = treatment group. (rESWT n=38, n=35/38 at 6w, n=36/38 at 3M, n=37/38 at 6M, ABI n=36, n=33/36 at 6w, n=34/36 at 3M, n=35/36 at 6M) Statistical significance was calculated between data at baseline and the different follow-up time-points respectively, comparing the two groups using 2x2 (time*group) ANOVA testing (p-value displayed.) Within-group comparisons between baseline and follow-up time points was undertaken using either paired t-tests or Wilcoxon tests, and statistical significance is denoted by the use of asterisks within that row. (* = p<0.05, ** p<0.01, *** p<0.001)*

8.2 -

ESWT v ABI interventions
Discussion

There were no time*group interaction effects between the cohorts receiving the ESWT and ABI treatment interventions for chronic plantar fasciitis for any of the outcome measures studied. These outcome measures included both the primary outcome measure (a change in self-rated levels of “average pain”) and the different secondary measures that were used, which including a number of different validated PROMs. This analysis demonstrates no significant differences in outcomes following the two different interventions for patients with plantar fasciitis over the 6-month time period that was studied.

The cohort study presented here is one of the first direct comparisons of these two different interventions in this clinical population. Previously, one single-blinded randomised clinical trial has sought to compare the results following ESWT and blood injections in patients with plantar fasciitis of at least 4-months duration.(287) The methodology for this published study used a single injection with “Autologous Conditioned Plasma” (ACP) as the blood injection, and two sessions of focal-ESWT as the ESWT intervention, comparing both treatments against “conventional therapy alone” which involved analgesia, a home exercise programme ± orthotics, and which was given to members of all investigated groups.(287) At a maximum follow-up of 6-months, this single-blinded RCT showed that there was no significant differences in either a pain score or the AOFAS ankle-hindfoot score between any of the three intervention groups, but that the group who had received blood injections had a greater reduction in plantar fascia thickness compared to other groups.(287) (This latter outcome measure was not assessed in the two studies specifically described in this experimental thesis (Study D and Study F) and is of uncertain clinical significance given the lack of differences in pain / function scores.) This published study (287) had less than 20 patients in each of the intervention groups, with average symptom duration of 13.7 months (range 6-24months) which is shorter than the studies in this chapter (data from Study D and Study F). There were also differences in the interventions in this published study(287) compared to the studies

presented in this thesis as it used two sessions of focal-ESWT in the ESWT group, rather than three sessions of radial-ESWT investigated in the studies in Chapter 6, and used an injection of centrifuged blood, (Autologous Conditioned Plasma / ACP), rather than the whole autologous blood injections (ABI) described in Chapter 7. (Differences between different types of ESWT and between different types of blood injections are both discussed in Chapter 2.) It is therefore not clear from these differences how transferrable the findings from this study may be to the patients in the NHS clinics in which research presented in this thesis was undertaken.

Separate studies have previously compared the outcomes seen following corticosteroid injections to those seen following either blood injections or shockwave therapy. Several studies comparing blood injections versus corticosteroid injections have given results potentially favouring steroid injections over blood injections at early outcome time periods (up to 3 months), and favouring blood injections at longer-term outcomes, defined as 4-12 months or longer.(350, 353, 354, 369) However a number of other studies have demonstrated no significant differences between these two different injection groups at the different time-points studied. (336, 342, 351, 352, 357, 373) In comparison, two RCTs have compared the outcomes following ESWT versus corticosteroid injections, and neither showed any difference in outcomes between these two interventions, although one study only had an 8-week follow-up period and the other study had a mean follow-up of 20 weeks, therefore no information is available as to longer-term outcomes.(279, 286) However, the heterogeneity in study populations, intervention treatments, outcome measures, and follow-up periods makes direct comparisons between these different studies difficult, and any indirect comparisons between ABI and ESWT cannot reliably be drawn from these previously published studies.

The lack of robust comparative evidence between ESWT and ABI interventions, with only a single small RCT study published (287) and this cohort study data presented here, potentially makes this area worthy of further study, although this would lie outside the remit of this thesis. The available evidence to date has not shown a difference in clinical outcome measures of pain or function between these two interventions in patients with chronic plantar fasciitis, and patients can be advised of this in deciding treatment choices.

Chapter 9 - General discussion

The preceding experimental chapters have presented findings from studies involving three different interventions for patients with chronic plantar fasciitis who were seen within a single NHS secondary care Sport & Exercise Medicine Clinic. These studies have examined outcomes following the use of a Tension Night Splint (TNS) device, radial-Extra-Corporeal Shockwave Therapy (rESWT) and Autologous Blood Injections (ABI), with a case-series study and a randomised controlled clinical trial undertaken for each of these three different treatments. In addition, results from the interventions using rESWT and ABI were compared in a cohort study (Chapter 8) to examine if there was evidence favouring one intervention over the other. Importantly, there were no significant adverse events reported in any of the studies presented here, highlighting the safety in clinical practice of these three interventions.

9.1 – Main study hypotheses explored in thesis

Three main hypotheses were tested in the studies presented in this thesis; these were that there would be significant improvements in outcome (using a range of markers of pain or function) in patients with plantar fasciitis who were all given a structured rehabilitation programme and following interventions:

1. Tension Night Splint (TNS) compared to a group that received the rehabilitation programme alone. (Study B)
2. Radial-Extra-Corporeal Shockwave Therapy (rESWT) at the “recommended-dose” compared to a group that received three treatments with “minimal-dose” rESWT. (Study D)
3. Autologous Blood Injection (ABI) co-administered with a dry-needle fenestration procedure, compared to a dry-needle fenestration procedure alone. (Study F)

There was no evidence to support any of these three hypotheses from the RCT studies presented here, meaning that any benefits of these specific interventions in this population were not identified. These findings are discussed specifically in each of the experimental chapters, and summarised in the following sub-sections.

9.2 – Summary of key findings

The main study findings relating to pain and function are summarised in the following sub-sections for each intervention modality.

- Tension Night Splint (TNS) – Chapter 5 / Studies A & B

There is inconsistent evidence supporting the use of tension night splints with patients with plantar fasciitis, with several small studies with a short-follow-up duration showing positive results (249, 250, 252) although larger studies have often failed to show any benefits from the use of a TNS device.(254, 255)

The TNS retrospective case series (Study A) demonstrated a statistically significant improvement in self-reported levels of pain overall, and also in levels of pain felt first thing in the morning, following the use of a TNS in routine clinical care. However, this study was subject to a number of methodological limitations, including the possibility of recall bias affecting the results, and the lack of a comparator group. A single-blinded RCT (Study B) was subsequently undertaken to investigate this intervention further, and which showed significant within-group improvements across a number of the outcome measures used assessing levels of pain and function. However, there were no time*group interaction effects, indicating that the addition of a TNS made no difference in outcomes compared to a rehabilitation programme alone in patients with plantar fasciitis. In addition, there were no consistent improvements seen in the physical parameters that were studied, including measures of flexibility or plantar fascia thickness, in either group. This suggests that the reduction in pain levels that were seen in members of both groups did arise directly from alterations in levels of flexibility and that other mechanisms, such as the load tolerance of the tissue, may have been underlying the improvements seen from baseline.

- Radial Extra-Corporeal Shockwave Therapy (rESWT) – Chapter 6 / Studies C & D

Both focal-ESWT (F-ESWT) and radial-ESWT (rESWT) have been shown in published research to be of benefit in treating patients with plantar fasciitis.(22, 263,

282, 325) However much of the published research has included patients with a far shorter duration of symptoms than those seen in the NHS clinic in which this research was based.(273, 279, 280) Additionally, there has been only a single study examining the effectiveness of this specific radial-ESWT machine used, which investigated whether ultrasound guidance may improve outcomes following rESWT treatment, rather than demonstrating treatment effectiveness against a control group.(300)

The initial rESWT prospective case series (Study C) compared baseline and follow-up data 3-months after patients received 3 treatment sessions with rESWT, using a range of outcome measures that are described in chapter 6. This case series identified significant improvements in measures of pain and some measures of local foot function using validated PROMS following the use of rESWT but did not find any significant changes in measures of global function, sleep, or mental health functioning. Additionally, it did not demonstrate any statistically significant improvements in levels of physical activity even though pain levels significantly decreased at follow-up compared to baseline values.

The subsequent double-blind randomised controlled trial (Study D) that investigated rESWT performed at “recommended-dose” compared to “minimal-dose” rESWT found no significant time*group interaction effects, indicating that three treatment sessions using rESWT performed at “recommended-dose” levels was no more effective than three sessions of rESWT performed at the lowest level (“minimal-dose”) from this machine. This study did however identify significant improvements in a number of the outcome measures for both the intervention and the control groups, who received the “recommended dose” and the “minimal-dose” rESWT respectively. These within-group improvements included self-rated levels of pain and foot-specific PROMs, as well as the Oswestry Disability Index (ODI). There was however a lack of improvement seen in markers of overall function using the EuroQol EQ-5D-5L questionnaire, in measures of mental health functioning (including HADS and PHQ4), or in levels of physical activity, compared to baseline values.

- Autologous Blood injection (ABI) – Chapter 7 / Studies E & F

There is a varied evidence of benefit to support the use of the injection of blood products to treat a number of conditions, including plantar fasciitis. Many studies are limited by poor methodological quality, or have only a short follow-up period. (21, 383-389)

The prospective case series study (Study E) was performed to investigate outcomes of pain or function in patients with chronic plantar fasciitis in routine clinical practice. This study identified significant improvements in levels of pain reported in patients across multiple time periods compared to baseline values, with a median of 556 days of follow-up (range 46-1211 days). However, the different numbers of patients at each follow-up point in this study made robust analysis difficult.

The double-blind randomised controlled trial compared ABI versus dry-needle fenestration alone (Study F) which utilised a range of different outcome measures over a six-month period. This RCT did not identify any significant time*group interaction effects between the two groups at any of the time points studied, indicating that the addition of 3mL autologous blood had not led to any difference in outcomes compared to a dry-needle fenestration procedure alone. This RCT demonstrated significant within-group improvements in both groups in levels of pain at all follow-up periods. Additionally, this RCT has demonstrated significant improvements in both groups for different foot-specific PROMs most notably at 6-week, 3-month and 6-month periods. There were however few statistically significant improvements in any of the other wider aspects of function that were studied including markers of overall health, mental health functioning, sleep, or levels of physical activity compared to baseline values.

- Comparisons of rESWT v ABI – Chapter 8

Data from the members of the intervention groups in Study D (rESWT RCT) and Study F (ABI RCT) were compared to assess if there were any differences in outcomes between these two different intervention modalities. This was performed in the format of a cohort study and this sought to identify if one intervention had superior results to the other, as this is a question that patients frequently ask in clinic.

Baseline and demographic data were demonstrated to be similar between the two groups, indicating this was a fair comparison. Whilst data from both groups improved significantly from baseline values for a number of the outcome measures studied, there were no significant time*group interaction effects. Therefore, this analysis has not demonstrated any superiority in outcomes from one procedure compared to the other procedure over a six-month follow-up period following the intervention.

- Study outcomes overview

It is not clear why no specific time*group interaction effects were seen in any of the three RCT studies presented here. These findings, or lack thereof, may be due to the use of unexpectedly “active” control interventions in the rESWT and ABI studies that were previously discussed in the experimental chapters, or that the effect of the rehabilitation programme which was undertaken was in some way more effective in the research studies, than it had been prior to enrolment in the studies. Even though the participants in the rESWT and ABI RCT in particular had a very long duration of symptoms preceding study enrolment, it may be that the findings presented here allude to a natural resolution of symptoms over time. These considerations have been discussed briefly in the experimental chapters and will need to be explored in further research that lies outside of the remit of this thesis.

9.3 – Summary of outcome domains studied, including pain and function

This research included RCT studies involving a TNS device (Study B), the use of rESWT (Study D) and the use of ABI (Study F), in the treatment of patients with chronic plantar fasciitis. Improvements were seen in measurements of self-reported pain in both the intervention and control groups across all three RCTs, however, the lack of a time*group interaction effect means that the improvements in pain from baseline seen cannot be directly ascribed to the specific interventions that were studied in each of these studies. Within-group improvements were identified in values of “average pain” and various other pain sub-scales including the “level of pain felt first thing in the morning”, and the “pain felt at rest”. Additional measures of subjective “stiffness” also improved from baseline across these three RCTs in members of both the intervention and the control groups.

The primary outcome measure for the different interventional studies was the self-reported level of “average pain” using a 0-10 numerical rating scale. In the TNS RCT at the 6-week follow-up period was a mean improvement of 1.2 points for the intervention group and 0.9 for the control group, representing a 16% and 13% improvement from baseline value respectively for the two groups. At 3-months there were statistically significant improvements of 1.5 points in both the intervention and control groups, which represented a 22% improvement / 21% improvement respectively. These figures either reached or exceeded the proposed minimum important clinical difference (MCID) for the 0-10 pain scale at 3-months which is reported between 0.9 and 1.4 points.(38, 439, 451) However other research has suggested that patients with chronic musculoskeletal pain the MCID may be either 2.0 points, or a 33% change, (438) in which case these figures were not met in either group at either time-point studied in the TNS study. In the rESWT RCT (Study D) the MCID for self-rated levels of “average pain” was met at all time points for the intervention group who received the higher-dose rESWT (38% improvement at 6-weeks, 33% at 3-months, 46% at 6-months for the members of the intervention groups, compared to 32%, 38% and 44% respectively for the control group. In the ABI RCT (Study F) the MCID values for those in chronic pain of 2.0 points were met

or exceeded in members of both the intervention and control groups at all time periods from 6-weeks onwards. There was a 28% improvement in “average pain” at 6-weeks compared to baseline values in both the intervention and control groups were 28% for both, at 3-months this figure was 35% in the intervention groups and 33% in the control group, and at 6-months this was 43% and 53% respectively. These figures are displayed in Table 9.1 with figures representing a change in the mean 0-10 pain scale from baseline for members of the intervention and control groups in each of the RCTs included in this thesis, with values displayed as improvement in numerical points and also as a percentage change from baseline.

Table 9.1: Change in mean self-reported levels of “average pain” at follow-up time points

Intervention		2-weeks	6-weeks	3-months	6-months
TNS	I	.	1.2 (18%)	1.5 (22%)	.
(Study B)	C	.	0.9 (13%)	1.5 (21%)	.
rESWT	I	.	2.6 (38%)	2.3 (33%)	3.2 (46%)
(Study D)	C	.	2.1 (32%)	2.5 (38%)	2.9 (44%)
ABI	I	1.4 (19%)	2.0 (28%)	2.5 (35%)	3.1 (43%)
(Study F)	C	1.3 (18%)	2.0 (28%)	2.4 (33%)	3.8 (53%)

Key:

Data shown are mean numerical change in 0-10 numerical pain score (and % change) from baseline values “I” = “Intervention group”, “C” = “control group”.

Values for minimum clinically important differences for various of the foot-specific PROM are also reported in the literature. The MCID for the FFI-r score has been identified as 7 points for patients with plantar fasciitis,(451) whereas the FAAM score has a MCID of 8 points for the ADL sub-scale and 9 points for the sport sub-scale respectively.(447) These MCID values have been met at all time points in both intervention and control groups in the ABI RCT (Study F), and the rESWT RCT (Study D), but as discussed in Chapter 5 were met more inconsistently in the

participants in the TNS RCT (Study B). Meeting these MCID values demonstrates that for measures of foot pain and foot function these studies have shown both statistically and clinically significant improvements in members of both groups.

However as highlighted in the individual study results sections, the outcome measures that have assessed aspects of more global function, aspects of mental health functioning, sleep quality, and activity rates have not shown consistently positive results. The lack of benefit comparing baseline and follow-up values for these domains has indicated that any improvements seen are often limited only to domains of local pain and function and have less of an impact on overall markers of health.

9.4 – Critical appraisal of the work

One strength in particular of the research studies that are presented in this thesis is the low drop-out rate within the three different RCT studies. In the TNS RCT (Study B) all 40 enrolled participants (100%) completed their final data collection at 3-months, in the rESWT RCT (Study D) 97% of participants (n=70/72) completed their study inclusion at 6-months, and in the ABI RCT (Study F) this figure was 99% (n=68/69) The large number of participants and the high completion rates strengthen the power of each of the studies and reduces the risk of either a type 1 or type 2 error from occurring.

In addition, the multiple outcome measures used in the RCTs, measuring aspects of pain and using validated measures of foot function, as well as more global markers of patient health and wellbeing, are a strength of this research. Whilst a numerical pain rating score (NRS), or visual analogue scale of pain (VAS) are simple, quick and easy to use, specific patient reported outcome measures (PROMs) such as the FFI-r questionnaire are a more reliable measure than VAS alone.(31, 428) These PROMs have been validated for assessing pain and function in patients with chronic symptoms, whereas the VAS although commonly used in clinical practice is validated in the assessment of current/acute pain only.(31, 428) The use of a range

of PROMs has therefore given a detailed and more robust assessment of any possible benefits from the intervention across multiple aspects of function.

The studies have all involved patients with chronic plantar fasciitis symptoms that have been referred to an NHS hospital Sports Medicine clinic. These patients have often had very chronic symptoms, that had been recalcitrant to previous treatments that had been tried. These may therefore not be indicative of a general population with plantar fasciitis with a shorter duration of symptoms that are more typically encountered in primary care, but may represent a sub-set with more difficult to treat symptoms. It is therefore not clear how generalisable the findings from these studies may be to a general population presenting with symptoms of plantar fasciitis.

9.5 – Limitations

The rESWT RCT (Study D) and the ABI RCT (Study F) were both potentially limited by the lack of a true placebo comparison intervention, and this may have influenced the results seen in these two clinical trials. Neither of these two studies identified any significant differences between the “active” and “control” interventions that were studied and possible explanations for the findings from these experimental studies have been discussed previously in chapters 6 and 7 respectively. These findings differ from previous research which has demonstrated clinical effectiveness in measures of pain and function from these two interventions.(21, 263, 282, 383) However, as discussed in the background section (chapter 2) there is some inconsistent evidence for both interventions in the published literature with ongoing uncertainties about outcomes, particularly in the longer-term.

As with all novel research, certain assumptions have to be made in the sample size calculation, which can have a bearing on the final study data. Evidence from the initial case series was used for the calculation of the expected effect size for the intervention groups in the RCTs, with assumptions made about the level of improvement that were expected to be seen in the control groups. These estimations and values have been stated in the relevant experimental methodology. From the case series data, in the TNS RCT drawing on the results from the case series (A) the

sample size calculation was based on the intervention group achieving a reduction in pain on a 0-10 scale of 1.9 points, and the control group having no more than a 0.95 point improvement, however the improvement in the intervention group was below this level, and the improvements in the control group were at this level at the size-week point, but greater than this at the three-month point (Table 9.1). Similarly in the ESWT RCT (study D) the mean improvement seen in the members of the intervention group at three-months was 2.3 (the same as the figure used in the *a priori* sample size calculation), however the control group achieved a similar level of improvement to the intervention group, whereas the *a priori* power calculation had estimated a mean improvement of 1.15 points. In the ABI RCT (F) the mean improvement seen in the intervention group was lower than that seen in the earlier case series (2.5 to 3.1 points at 3-months and 6-months in the RCT, compared to more than 5 points in the case series) and the mean improvement seen in the control group at 3-months of 2.4 points was similar to the estimated values used in the a prior sample size calculations, however there was a greater than expected improvement in the control group at six-months or 3.8 points. These figures may all have influenced the final study findings. The greater-than-expected improvements in the control groups at some time-points, and the less-than-expected improvement in the intervention group in the ABI, could have left the different studies underpowered to identify small changes. However, if these treatments do have a smaller than expected impact on levels of pain in patients with plantar fasciitis, it is not clear that larger studies would be easily able to identify these reliably without significant increase in sample sizes, and it is unclear how clinically relevant a very small treatment difference would be. In addition, the sample sizes used in the three different RCTs compared favourably with other published research examining the outcomes following these three treatments, with published TNS RCTs using 16-85 participants per treatment arm studied, (249, 250, 255) compared to the 20 per treatment arm in study B, ESWT RCTs involving 25-36 participants per treatment arm investigated,(20, 280, 288, 300, 305) compared to more than 30 in each treatment arm in study D, and blood injection RCTs typically involving between 12 and 30 participants in each intervention arm studied, (336, 350-352, 354, 355, 369), compared to more than 30 in each arm in Study F, these comparisons suggest that the recruitment targets for the RCTs were justifiable, and the reason for a lack of

difference in improvements in the intervention compared to the control groups is unclear, but may not be due to under-powered RCTs.

Another potential limitation of the three RCT studies was the duration of follow-up that was chosen. The TNS RCT used a three-month follow-up for study inclusion, and the rESWT and ABI RCTs both had a six-month follow-up period. Beyond these periods of time patients continued to be treated depending on clinical symptoms, but unblinding of the investigator (and in the case of the rESWT and ABI studies, participant unblinding) had happened, and data was not collected formally beyond this point. The RCTs have demonstrated within-group improvements in measures of pain and function to the final data collection point, but there is no information from these studies as to whether the improvements from baseline continued after this point. As plantar fasciitis may in at least a proportion of patients be a chronic, ongoing condition, the longer-term outcomes following treatment are an important consideration, however data collection in the longer-term is often challenging to accomplish. There was some suggestion from the ABI case series (Study E) that benefits that were seen at different time-point continued, but the different numbers of participants at different time-points made formal analysis unreliable.

As well as assessing any clinical-effectiveness, the cost-effectiveness of treatments needs to be considered. The financial costs of treatment with rESWT or ABI are substantially lower than the financial cost of surgery, and the burden on patients themselves is far less, with far fewer restrictions post-ESWT and post-ABI, than following surgery which can require in-patient hospitalisation, immobilisation, and at times a prolonged period of time off work.(229) The issue of cost-effectiveness however is not an area that these studies have set out to specifically include in their study designs and lies outside the remit of this thesis. It is recognised that a health economics perspective is an important consideration in healthcare design and delivery, and further consideration of this topic may be important to support the work of the National Institute of Health and Care Excellence (NICE), and could be factored in to future works.

9.6 – Implications

The results from the studies presented here have shown that these three interventions, each of which are commonly used in clinical care of patients with chronic plantar fasciitis, may have less benefit than previously thought. Or it may be that benefits seen in practice may not be coming directly from the specific intervention itself. The data from the rESWT RCT (Study D) and the ABI RCT (Study F) have both shown significant improvements from baseline values for a range of outcome measures, but without any differences in outcomes in the “intervention” and “control” groups seen in these two studies, the within-group benefits observed cannot be ascribed to the specific intervention studied.

However as there are significant within-group changes when comparing baseline and follow-up data, including a mean reduction in self-reported values of pain by about 50% at the six- month period following rESWT or ABI, there is evidence that can support a cautiously optimistic outlook being given to patients with chronic plantar fasciitis regarding their prognosis. These patients, who often have had chronic symptoms for many months if not years, can be advised that many patients report clinically important improvements (if not a cure) to their pain following intervention with rESWT or ABI. Additionally, the cohort study (chapter 8) that compared outcomes following rESWT and ABI+dry-needling has not demonstrated the superiority of one procedure over the other, and again patients can be advised of this to help inform their choice of treatment for their symptoms.

9.7 – Future work

Many patients with recalcitrant symptoms have reported improvements in many of the studies presented here, however as with many interventions in medicine this benefit is not uniform, with different patients benefitting to a greater and lesser extent. There is no previously published research that has shown factors that should be measured at baseline to predict outcome following treatment. There is evidence that ultrasound or MRI plantar fascia thickness did not correlate with improvements seen following treatment and so may assist diagnosis but should not dictate treatment.(47, 544) There is some published evidence that patients with a shorter-

duration of symptoms may do better following rESWT than those patients with longer-duration of symptoms.(308) However the evidence for this is from a single, small study which compared outcomes in patients with symptoms of less than three-months, compared to those with symptoms of more than six-months. The symptom duration in the participants in the studies presented here (Study C, Study D) was of much longer duration, and was not found to influence outcomes seen following intervention. The reasons for this difference are not known. The identification of reliable measures that assess prognosis following treatment remain unclear and should be the focus of further works to better inform clinical decision making.

Additional gaps in published research is a lack of comparative prospective clinical trials comparing different types of ESWT. This includes a lack of studies comparing focal-ESWT versus radial-ESWT, or different rESWT devices from different manufacturers, to assess any possible differences in outcomes that may exist between different machines. An analogy to this would be medical trials that have compared different medicines across different classes for patients with hypertension, such as comparing an ACE-inhibitor with a calcium channel antagonist,(573) or comparing two different medicines within the same class, for example two different ACE inhibitors.(574) This comparative research has been done in the treatment of hypertension, but has not yet been undertaken in the management of patients with chronic plantar fasciitis. The cohort study in chapter 8 has attempted to start to address the deficit comparing ESWT and ABI as interventions in this population, but this could also be the focus of a formalised RCT which may better take into consideration any confounders that may influence results seen.

Other research considerations for the future include studies directly comparing the effectiveness of the rehabilitation programme alone in patients with chronic plantar fasciitis, possibly by comparing two different rehabilitation programmes, or different ways in which the rehabilitation could be delivered such as comparing results from face to face rehabilitation to those from a patient-guided rehabilitation strategy after the provision of written material. Other studies that could be considered have been discussed in the experimental chapters, which include the comparison of rESWT or ABI against a placebo-intervention, such as rESWT performed with acoustic shielding, or an injection study which used a local anaesthetic injection to the sole of

the foot only as a comparator, but no intervention to the plantar fascia itself. These future studies could better explore the effectiveness of the use of rESWT or ABI in the treatment of patients with chronic plantar fasciitis but lie outside the remit of this thesis.

9.8 – Final conclusions

In summary the results presented here have shown that there are clinically and statistically significant improvements in a number of measures of pain and function in patients with chronic plantar fasciitis, following different interventions, even in patients with a long duration of symptoms. These improvements in pain and function often relate only to foot-specific measures, and measures of wider function, mood, and activity often remain unchanged even when pain improves. The lack of differences in outcome measures between the members of the intervention and control groups in the rESWT and ABI RCTs means that the underlying mechanism of the improvements that were seen remain unclear.

Acknowledgements

Research, particularly that involving patients in the NHS, is very much a team effort. I fully recognise that the works here would not have been possible without the assistance of many different people in various roles. I would like to take this opportunity to offer my thanks to them for the individual efforts that they have put in, and the support given.

As is customary, I would like to start by offering my sincere thanks to my PhD supervisors at Loughborough University, Professor Jonathan Folland and Dr Hilary McDermott, both of whom work within the School for Sport, Exercise and Health Sciences. They have acted as guides and mentors along the way, trying valiantly to rein me in at times, and encouraging me to take big steps at others. The journey has not always been smooth, but thanks to everyone's diligence and patience we have made progress and their ongoing attention has led the focus of this thesis in which these thanks reside. Thank you for all that you have done to assist me in these endeavours, and for "never being satisfied" – I believe that this is the correct phrase ….. ;-)

I also offer my thanks to Professor Mark Lewis, Dean of the Sport, Exercise and Health Sciences at Loughborough University for the support that he has offered along the way in this journey and the significant assistance that he has given to my research development over these last few years including ultimately undertaking my PhD studies here.

I would also like to offer my thanks to two other people that were instrumental in me commencing my PhD studies at this stage in my career. These are Professor James Bilzon at the University of Bath (http://www.bath.ac.uk/health/staff/james-bilzon/), whose initial discussions all those many years ago led me to consider undertaking a PhD at all, and also to Professor Myra Nimmo, formerly of Loughborough University, who was instrumental in me originally coming to Loughborough University in 2013.

I would like to offer my thanks also to several colleagues at Loughborough University that have offered me informal assistance to me over this period of time in ways both

great and small. To spare blushes, I will list people in alphabetical order and would like to offer thanks specifically to Dr Richard Ferguson, Dr Will Johnson, Dr Emily Petherick, and Dr Keith Tolfrey.

Regarding specific help with the research studies themselves, I will start by offering my thanks to Chloe Dudson (nee Tattersall), who works as a Nurse Practitioner in the Department of Sports Medicine at the University Hospitals of Leicester NHS Trust. She has been a linchpin of the various studies, involved both in managing the randomisation processes for the different randomised controlled trials, as well as the specific consenting for entry into research, administering the shockwave therapy in the ESWT randomised controlled trial (study D), and for administering the shockwave for some of the patients in the initial ESWT case-series (study C). She is named as a co-author on several of the studies that have already been published, and much of the work here could not have been done without her time and assistance.

I would also like to offer my thanks to a number of my colleagues that reviewed patients at the time of their clinical follow-up in two of the studies and who have nagged the patients ceaselessly to complete the study questionnaires for me to analyse. Their work has facilitated both study blinding and also helped manage clinic follow-up appointment capacity issues. These colleagues were Dr Harjinder Singh, and Dr Kim Gregory for their help with the Autologous Blood Injection RCT (study F), and Dr Duncan Goodall and Ms Rachel Calver for their help with some of the participants in the Shockwave Therapy RCT (study D). In addition to these I would also offer my thanks to Mr Kevin Boyd and Ms Mary Shipton for their assistance in the running of the original surgical case series study which started my journey into researching this topic. In addition, I would offer my heartfelt and personal thanks to Mr Mike Allen who set up, and was the former Head of Service of, the Sports Medicine Department at Leicester Hospitals. He was instrumental in bringing me into the Leicester Sports Medicine Department in 2000, and who retired from our department a number of years ago. I would also offer my thanks to all the members of our clinic administrative team who have valiantly tried to make sure that all patients returned for appointments in the right place, at the right time, with the right person, having done the appropriate questions in advance wherever possible….

I will also offer my thanks to the Leicester Arthritis Research Fund, for their small charitable grant that allowed the purchase of the Tension Night Splint devices in the TNS RCT study. I would also offer my thanks to Dr Waji Hassan, a (now retired) Consultant Rheumatologist at Leicester hospitals and a much-valued colleague, who put me in touch with this charity.

In addition, I want to also offer my thanks to Ms. Carolyn Maloney, Head of Research Operations, and the rest of the team in the Research and Innovation Department at University Hospitals of Leicester, who have all helped in various ways over the last few years in the management of the research studies.

I will also offer my thanks to Dr Roger Stone, formally of Loughborough University, who I contracted to develop an electronic scoring system for patients, which has greatly facilitated the data collocation aspect of the research studies, and who I wish I had met some time sooner, as this would have greatly cut down on the use of paper questionnaires, the manual scoring and the time that this takes ….

Penultimately, I will offer thanks to my family for their amazing support during this time. I could not have done this without you. It has not been easy, but we have got there in the end ….

Lastly, and most importantly, I will offer my thanks to the many patients that have chosen to participate in these specific studies, and the other studies that I run, in my NHS clinics. It is recognised that their participation in clinical research is optional and voluntary, but by the decisions that they each take individually, it is hoped that we can move clinical care forwards to help not just themselves, but also the patients of the future as well.

So, thank you, one and all …

Dr Patrick Wheeler

Consultant, Sport & Exercise Medicine, University Hospitals of Leicester NHS Trust

Senior Clinical Academic Fellow, SSEHS, Loughborough University

Appendices

Appendix 1: Patient information

- NICE – ESWT for plantar fasciitis (51)
- NICE – ABI for plantar fasciitis (52)
- Study Participant information leaflets – Studies B, D, F

Appendix 2: Plantar fasciitis sample written patient information leaflet and Home Exercise Programme (HEP) – used within multiple studies

Appendix 3: Summary of patient demographics across different experimental studies

Appendix 4: Summary of patient reported outcome measures (PROMs) used within different experimental studies

Appendix 5: Summary of publications from material included in thesis, and further publication strategy

Appendix 1: Participant information leaflets (PILs)

National Institute of Health and Care Excellence (NICE) patient information leaflets

- ESWT for plantar fasciitis (51)
- ABI for plantar fasciitis (52)

Study participant information leaflets and study consent forms:

- Study B – TNS RCT (NHS REC ref: 14/WS/1069 / UHL study ref: 11335)
- Study D – ESWT RCT (NHS REC ref: 15/EM/0122 / UHL study ref: 11401) *
- Study F – ABI RCT (NHS REC ref: 14/EM/1061 / UHL study ref:11334)

** re: NHS REC ref: 15/EM/0122 / UHL study ref: 11401*
Please note that the results presented here, are a part of a much larger study which has included six different conditions run as separate sub-studies under the same study environment and protocol. The title of the Participant Information Leaflet, refers to "tendons" and "tendon conditions", rather than just "plantar fasciitis".
The condition of plantar fasciitis is one single sub-study within this wider body of research, with specified inclusion and exclusion criteria as discussed in the relevant chapter, and with all necessary approvals. The results relating to plantar fasciitis only are presented here.

NHS
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Understanding NICE guidance

Information for people who use NHS services

Treating chronic plantar fasciitis using shockwave therapy

NICE 'interventional procedures guidance' advises the NHS on when and how new procedures can be used in clinical practice.

This leaflet is about when and how shockwave therapy can be used in the NHS to treat people with plantar fasciitis. It explains guidance (advice) from NICE (the National Institute for Health and Clinical Excellence).

Interventional procedures guidance makes recommendations on the safety of a procedure and how well it works. An interventional procedure is a test, treatment or surgery that involves a cut or puncture of the skin, or an endoscope to look inside the body, or energy sources such as X-rays, heat or ultrasound. The guidance does not cover whether or not the NHS should fund a procedure. Decisions about funding are taken by local NHS bodies (primary care trusts and hospital trusts) after considering how well the procedure works and whether it represents value for money for the NHS.

NICE has produced this guidance because there is not a lot of information yet about how well it works, how safe it is and which patients will benefit most from it.

This leaflet is written to help people who have been offered this procedure to decide whether to agree (consent) to it or not. It does not describe plantar fasciitis or the procedure in detail – a member of your healthcare team should also give you full information and advice about these. The leaflet includes some questions you may want to ask your doctor to help you reach a decision. Some sources of further information and support are on the back page.

Information about NICE interventional procedure guidance 311
Issue date: August 2009

Corporate member of Plain English Campaign. Committed to clearer communication. 197

What has NICE said?

Although there is evidence to say that this procedure is safe, there are still uncertainties about how well it works. If a doctor wants to use shockwave therapy for chronic plantar fasciitis, they should make sure that extra steps are taken to explain the uncertainty about how well the procedure works, as well as the potential risks. This should happen before the patient agrees (or doesn't agree) to the procedure. The patient should be given this leaflet and other written information as part of the discussion. There should also be special arrangements for monitoring what happens to the patient after the procedure.

NICE has encouraged further research into using shockwave therapy for plantar fasciitis, and patients' progress should be assessed for up to a minimum of 1 year after the procedure. NICE may review the procedure if more evidence becomes available.

Other comments from NICE

The Committee found interpreting the data difficult because the studies were very different from each other, the results were inconsistent and the placebo treatments had a large beneficial effect.

If the procedure works in selected patients, it could have a big impact because plantar fasciitis is common and in many patients other treatments don't work. This means that having reliable evidence is particularly important.

Treating plantar fasciitis using shockwave therapy

This procedure may not be the only possible treatment for plantar fasciitis. Your healthcare team should talk to you about whether it is suitable for you and about any other treatment options available.

The medical name for this procedure is 'extracorporeal shockwave therapy for refractory plantar fasciitis'. 'Extracorporeal' means outside the body and 'refractory' means that the condition does not respond to conventional treatments. The 'shock waves' are inaudible, high-energy sound waves. The procedure is not described in detail here – please talk to your specialist for a full description.

Plantar fasciitis occurs when the ligament at the bottom of the foot between the heel and the toes deteriorates and causes foot pain. It often follows injury. Conventional treatments include rest, applying ice, pain-relieving and anti-inflammatory medication, support devices, physiotherapy, physical exercises and corticosteroid injection.

In this procedure shock waves are passed through the skin to the affected area using a special device, and ultrasound guidance may be used. Shockwave therapy can be given in one or more sessions. It may be carried out under local anaesthesia if high-energy shock waves are used because it can be painful. However, local anaesthesia may influence the outcome.

Summary of possible benefits and risks

Some of the benefits and risks seen in the studies considered by NICE are briefly described here. NICE looked at 9 studies on this procedure.

What does this mean for me?

If your doctor has offered you this procedure, he or she should tell you that NICE has decided that although the procedure is safe there are uncertainties about how well it works. This does not mean that it should not be done, but that your doctor should fully explain what is involved in having the procedure and discuss the possible benefits and risks with you. You should only be asked if you want to agree to this procedure after this discussion has taken place. You should be given written information, including this leaflet, and have the opportunity to discuss it with your doctor before making your decision.

NICE has also decided that more information is needed about this procedure. Your doctor may ask you if details of your procedure can be used to help collect more information about this procedure. Your doctor will give you more information about this.

You may want to ask the questions below

- What does the procedure involve?
- What are the benefits I might get?
- How good are my chances of getting those benefits? Could having the procedure make me feel worse?
- Are there alternative procedures?
- What are the risks of the procedure?
- Are the risks minor or serious? How likely are they to happen?
- What care will I need after the procedure?
- What happens if something goes wrong?
- What may happen if I don't have the procedure?

How well does the procedure work?

In a study of 293 patients, in which 144 had the procedure and 141 had a placebo (dummy) procedure, 67 and 42 patients, respectively, had less pain after 3 months and didn't need pain medication.

In a study of 172 patients, the average reduction in pain score at 3 months was greater in patients who had the procedure (112 patients) than in those who had the placebo treatment (56 patients).

In a study of 149 patients, 69% of patients who had the procedure reported an 'excellent' result (no heel pain), whereas all patients who had conventional treatment reported some pain, after an average of 64 months.

As well as looking at these studies, NICE also asked expert advisers for their views. These advisers are clinical specialists in this field of medicine. The advisers said that the main success factor is relief of symptoms.

You might decide to have this procedure, to have a different procedure, or not to have a procedure at all.

Risks and possible problems

In 2 studies, involving a total of 216 patients who had the procedure and 221 who had a placebo treatment, 8 patients who had the procedure had pain during treatment, compared with 3 patients in the placebo group. In another study, 6 out of 61 patients who had the procedure had throbbing pain and skin reddening, and 8 out of 64 patients who had a different treatment (a corticosteroid injection) had pain that needed medication or ice for about a week.

In another study, 16 out of 135 patients who had the procedure had skin reddening, compared with 5 out of 136 patients who had the placebo treatment. In 2 studies involving a total of 250 patients who had the procedure, 4 had swelling around the treatment site.

As well as looking at these studies, NICE also asked expert advisers for their views. These advisers are clinical specialists in this field of medicine. The advisers said that problems include bruising, pain and skin damage around the site of treatment. In theory, problems could include the condition getting worse because of rupture of the ligament at the bottom of the foot, or damage to the soft tissue.

More information about plantar fasciitis

NHS Choices (www.nhs.uk) may be a good place to find out more. Your local patient advice and liaison service (usually known as PALS) may also be able to give you further information and support. For details of all NICE guidance on plantar fasciitis, visit our website at www.nice.org.uk

About NICE

NICE produces guidance (advice) for the NHS about preventing, diagnosing and treating different medical conditions. The guidance is written by independent experts including healthcare professionals and people representing patients and carers. They consider how well an interventional procedure works and how safe it is, and ask the opinions of expert advisers. Interventional procedures guidance applies to the whole of the NHS in England, Wales, Scotland and Northern Ireland. Staff working in the NHS are expected to follow this guidance.

To find out more about NICE, its work and how it reaches decisions, see www.nice.org.uk/aboutguidance

This leaflet is about 'extracorporeal shockwave therapy for refractory plantar fasciitis'. This leaflet and the full guidance aimed at healthcare professionals are available at www.nice.org.uk/IPG311

You can order printed copies of this leaflet from NICE publications (phone 0845 003 7783 or email publications@nice.org.uk and quote reference N1972). The NICE website has a screen reader service called Browsealoud, which allows you to listen to our guidance. Click on the Browsealoud logo on the NICE website to use this service.

We encourage voluntary organisations, NHS organisations and clinicians to use text from this booklet in their own information about this procedure.

National Institute for Health and Clinical Excellence
MidCity Place, 71 High Holborn, London, WC1V 6NA; www.nice.org.uk

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Issue date January 2013

Information for the public

NHS
National Institute for Health and Clinical Excellence

Treating plantar fasciitis by injecting a patient's own blood into the painful area of the foot

NICE 'interventional procedures guidance' advises the NHS on when and how new procedures can be used in clinical practice.

This document is about when and how injecting a patient's own blood into the painful area of the foot can be used in the NHS to treat people with plantar fasciitis. It explains guidance (advice) from NICE (the National Institute for Health and Clinical Excellence).

Interventional procedures guidance makes recommendations on the safety of a procedure and how well it works. An interventional procedure is a test, treatment or surgery that involves a cut or puncture of the skin, or an endoscope to look inside the body, or energy sources such as X-rays, heat or ultrasound. The guidance does not cover whether or not the NHS should fund a procedure. Decisions about funding are taken by local NHS bodies (primary care trusts and hospital trusts) after considering how well the procedure works and whether it represents value for money for the NHS.

NICE has produced this guidance because the procedure when used for people with plantar fasciitis is quite new. This means that there is not a lot of information yet about how well it works and which patients will benefit most from it.

This document is written to help people who have been offered this procedure to decide whether to agree (consent) to it or not. It does not describe plantar fasciitis or the procedure in detail – a member of your healthcare team should give you full information and advice about these. The document includes some questions you may want to ask your doctor to help you reach a decision. Some sources of further information and support are on page 8.

What has NICE said?

Although there is evidence to say that this procedure is safe, there are still uncertainties about how well it works. If a doctor wants to treat plantar fasciitis by injecting a patient's own blood into the painful area of the foot, they should make sure that extra steps are taken to explain the uncertainty about how well it works, as well as the potential risks of the procedure. This should happen before the patient agrees (or doesn't agree) to the procedure. The patient should be given this document and other written information as part of the discussion. There should also be special arrangements for monitoring what happens to the patient after the procedure.

NICE has encouraged doctors to consider asking patients to take part in a research study (called a clinical trial) looking at how well this procedure works compared with other treatments that are already being used for plantar fasciitis. Research should describe which patients are offered the procedure, how long patients have had symptoms and any treatments they have already tried. The research should also look at how well the procedure reduces patients' pain and improves their use of the affected foot.

Other comments from NICE

Plantar fasciitis usually goes away without treatment, and this made it difficult to tell how much the procedure has helped patients. The treatments this procedure was compared with did not help NICE to decide if this procedure worked, and the procedure was often used at the same time as other treatments.

The procedure should only be considered for patients who still have symptoms despite other treatments.

Treating plantar fasciitis by injecting a patient's own blood into the painful area of the foot

This procedure may not be the only possible treatment for plantar fasciitis. Your healthcare team should talk to you about whether it is suitable for you and about any other treatment options available.

The medical name for this procedure is 'autologous blood injection for plantar fasciitis'.

The procedure is not described in detail here – please talk to your doctor for a full description.

Plantar fasciitis occurs when the tissues between the heel and the middle of the foot becomes inflamed. This usually happens because of overuse or injury, and it causes pain underneath the heel and the sole of the foot. Plantar fasciitis usually gets better, either on its own or with the help of rest, pain-relieving and anti-inflammatory medication, orthotics (support devices), physiotherapy and stretching. If these don't work, other treatments may be tried, such as corticosteroid injections, extracorporeal shockwave therapy (in which shockwaves are passed through the skin to the affected area) and sometimes surgery.

In autologous blood injection, a small amount of blood is taken from the patient and 2–3 ml injected into the area around the affected tissue. Sometimes the blood is separated into red blood cells and platelets (cell fragments that produce substances called growth factors) before injecting 2–3 ml of the sample containing mainly platelets. The patient is usually given a local anaesthetic before the procedure. Ultrasound may be used to check the needle is put in the right place.

The aim is to supply the tissues in the foot with growth factors that promote the healing process. Sometimes another procedure called 'dry needling' is done first, in which a needle is passed repeatedly through the tissue to disrupt the fibres and cause bleeding. The injection is sometimes carried out by 'peppering' (inserting the needle, injecting some of the blood, pulling the needle back but not all the way out of the skin, and then pushing the needle back in to inject more blood in a

slightly different place). Patients should be advised to avoid high-impact activities (such as running) for about 2 weeks and to do stretching exercises. The procedure may be repeated if needed.

What does this mean for me?

If your doctor has offered to treat your plantar fasciitis by injecting your own blood into the painful area of the foot, he or she should tell you that NICE has decided that although the procedure is safe there are uncertainties about how well it works. This does not mean that the procedure should not be done, but that your doctor should fully explain what is involved in having the procedure and discuss the possible benefits and risks with you. You should only be asked if you want to agree to this procedure after this discussion has taken place. You should be given written information, including this document, and have the opportunity to discuss it with your doctor before making your decision.

NICE has also decided that more information is needed about this procedure. Your doctor may ask you if details of your procedure can be used to help collect more information about this procedure. Your doctor will give you more information about this.

You may want to ask the questions below

- What does the procedure involve?
- What are the benefits I might get?
- How good are my chances of getting those benefits? Could having the procedure make me feel worse?
- Are there alternative procedures?
- What are the risks of the procedure?
- Are the risks minor or serious? How likely are they to happen?
- What care will I need after the procedure?
- What happens if something goes wrong?
- What may happen if I don't have the procedure?

You might decide to have this procedure, to have a different procedure, or not to have a procedure at all.

Summary of possible benefits and risks

Some of the benefits and risks seen in the studies considered by NICE are briefly described below. NICE looked at 8 studies on this procedure.

How well does the procedure work?

Three studies (involving 64, 45 and 100 patients) reported that the procedure and the other treatments studied all improved foot pain, tenderness or how well the foot worked. In the study of 64 patients, 6 months after patients were treated with injection of their own blood or with corticosteroid injection, pain improved overall in both groups. Three patients in each group had no change in their pain. Foot tenderness also improved in both groups.

In the study of 45 patients, at 6 months after the procedure, patients reported that their pain had improved. Pain reduced in patients treated with injection of their own blood, in patients treated with corticosteroid injection, and in patients treated by peppering. There were also improvements in how well the foot worked in all patients. Ten patients treated by blood injection and 7 patients treated with the peppering procedure needed a third blood injection. Of those treated with corticosteroid injection, none required a third injection.

The study of 100 patients assessed how the foot worked and whether pain improved. Results at 6 months after the procedure were ‘excellent’ or ‘good’ in 15 patients treated with injection of their own blood, in 13 patients treated with a local anaesthetic and peppering, in 20 patients treated with corticosteroid injection, and in 22 patients treated with corticosteroid injection and peppering.

As well as looking at these studies, NICE also asked expert advisers for their views. These advisers are clinical specialists in this field of

medicine. The advisers said that the main aims of the procedure are to reduce heel pain and improve how well the foot works.

Risks and possible problems

The study of 64 patients reported that all patients found the injection painful. After the procedure, 16 of the patients treated with their own blood and 4 of the patients treated with corticosteroid injection needed painkillers, ice or both to help with the pain. On average the pain lasted 7 days for patients treated with their own blood, and 5 days for patients treated with corticosteroid injection.

A study of 60 patients treated with either injection of their own blood or corticosteroid injection and a study of 25 patients treated with injections of their own blood both reported no problems with the procedure.

As well as looking at these studies, NICE also asked expert advisers for their views. These advisers are clinical specialists in this field of medicine. The advisers said that possible problems with the procedure include rupture of the connective tissue, damage to the nerves and blood vessels around the connective tissue, infection, and bruising.

More information about plantar fasciitis

NHS Choices (www.nhs.uk) may be a good place to find out more.

For details of all NICE guidance on plantar fasciitis, visit our website at www.nice.org.uk

About NICE

NICE produces guidance (advice) for the NHS about preventing, diagnosing and treating different medical conditions. The guidance is written by independent experts including healthcare professionals and people representing patients and carers. They consider how well an interventional procedure works and how safe it is, and ask the opinions of expert advisers. Interventional procedures guidance applies to the whole of the NHS in England, Wales, Scotland and Northern Ireland. Staff working in the NHS are expected to follow this guidance.

To find out more about NICE, its work and how it reaches decisions, see www.nice.org.uk/aboutguidance

This document is about 'autologous blood injection for plantar fasciitis'. This document and the full guidance aimed at healthcare professionals are available at guidance.nice.org.uk/IPG437

The NICE website has a screen reader service called Browsealoud, which allows you to listen to our guidance. Click on Accessibility at the bottom of the NICE homepage to use this service.

We encourage voluntary organisations, NHS organisations and clinicians to use text from this document in their own information about this procedure.

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Jan 13

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Participant Information Sheet

Title of Project: Assessing the benefits of the use of a tension night splint in patients with plantar fasciitis *(UHL study number 11335)*
Name of Researcher: Dr Patrick Wheeler

Invitation
We would like to invite you to participate in a research study that we are running which will investigate the effectiveness of a treatment for patients with symptoms from plantar fasciitis This treatment involves wearing a lightweight device called a Tension Night Splint during the night-time to stretch your calf muscles, thereby possibly reducing your foot pain.

What is the purpose of the study?
This study is to see how effective the tension night splint is in improving your symptoms, alongside other treatments, which include a structured rehabilitation plan that you will be shown.

Why have I been invited?
All patients who are treated for symptoms of plantar fasciitis by the Sports Medicine Department in Leicester are being invited to participate in this study. Due to the numbers needed for the study, the recruitment for this study is expected to take about a year to complete.

Do I have to take part?
It is your choice whether or not to participate in this study. We will describe the study and go through this information sheet and if you agree to take part we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This will not affect the care you receive.

What will happen to me if I take part?
Sometimes we don't know which way of treating patients is best and to find out we need to compare different treatments. We put people into groups and give each group a different treatment and the results are compared to see if one is better. To try to make sure the groups are the same to start with, each patient is put into a group by chance ("like tossing a coin"). All patients will receive the structured rehabilitation programme. In addition, half of the patients will receive the tension night splint device to wear at night. The device is easy to put on and take off. Our Nurse Practitioner will show you how to wear the device and will

stay in touch with you if you need any assistance.

What will I have to do?

We will arrange for you to come in to discuss this study with our Nurse Practitioner. She will explain everything that is required and will arrange for half of the people in this study to wear a tension night splint during the night-time. Each night this group will need to put the splint on as they have been shown. In addition all of the study participants will be shown the same rehabilitation exercises which we will need you to do at home each day.

What are the alternatives for treatment?

There are benefits from the structured rehabilitation programme and the podiatry insoles that you will be offered, this study seeks to understand how much additional benefit the tension night splint may bring.

What are the possible disadvantages and risks of taking part? What are the side-effects of any treatment received when taking part?

Tension Night Splints are in widespread use in the NHS both in Leicester and elsewhere in the UK. There will be a need for half of the people in this study to wear a tension night splint during the night which may cause a little disruption to your sleep initially, although this seems to improve within a week or two of wearing it.

What are the possible benefits of taking part?

We hope that the information we get from this study will help improve the treatment of people with plantar fasciitis symptoms, although we cannot give a guarantee of benefit of any particular treatment.

What happens when the research study stops?

When your involvement in the research study stops you will continue to remain an NHS patient under the care of Dr Wheeler or one of the other Consultants here as long as is thought to be clinically appropriate.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you that Dr Wheeler uses and which leaves the hospital will have your name and address removed so that you cannot be identified.

You will be asked for permission to inform your General Practitioner about your involvement in this study, and if permission is granted then this will be within the clinic letter that we normally send to your General Practitioner each time that you are seen in the hospital.

Involvement of the General Practitioner/Family doctor (GP)

As is normal practice Dr Wheeler, or a member of his team, will write to your GP after each and every consultation with you. You will receive a copy of this letter. This letter will detail the clinical care that you receive from Dr Wheeler's clinic, and will inform your General Practitioner that you are assisting in this research project.

Dr Wheeler will ask for specific permission from you that this is acceptable to you on the study consent form.

What will happen to any samples I give? - No samples are taken within this study.

Will any genetic tests be done? - No, these are not carried out within this study.

Expenses and payments - There is no payment available for participation in this study.

What if relevant new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens, your research doctor (Dr Wheeler) will tell you and discuss whether you should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If you decide to continue in the study he may ask you to sign an agreement outlining the discussion.

If the study is stopped for any other reason, we will tell you and arrange your continuing care.

What will happen if I don't want to carry on with the study?

You can withdraw from the study at any time, although we would appreciate it if you keep in contact with us to let us know your progress. Information collected may still be used but this will be kept anonymous.

What will happen to the results of the research study?

The results of this study will be shared with Dr Wheeler's colleagues through means such as publication in scientific journals, and it is possible that a summary of the findings will be published via the hospitals communications team. All the information from this study will be kept anonymous and you will not be able to be personally identified from any results.

If you would like to be informed of the results of the study once they are completed, then please let us know and we can arrange for you to receive a copy of the summary at the end of the study. You will need to give specific consent for us to keep hold of your address for this purpose.

Who is organising and funding the research?

Dr Wheeler, Head of Service and Consultant in Sport & Exercise Medicine at the University Hospitals of Leicester is organising the research, which is being supported from both within the Sports Medicine Department, and within University Hospitals of Leicester. The research has been conducted in such a way

to minimise any costs, and the costs of the research that are needed are being covered by the Sports Medicine Department. No-one is being paid directly by or for this study.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee (REC), to protect your interests. The Research Ethics Committee that reviewed this study are the West of Scotland Research Ethics Committee 5 (WoSREC5).

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. If you have a concern about any aspect of this study, you should ask to speak to Dr Wheeler who will do his best to answer your questions. This can done during the time that you are with him, or this can be via the normal clinic telephone number (0116 2584365). If you remain unhappy and wish to complain formally, you can do this and the hospital Patient Information Liaison Service (PILS) will be able to assist you with this. They can be reached by a Freephone number 0808 178 8337, or emailed at pils@uhl-tr.nhs.uk

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the University Hospitals of Leicester NHS Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Further information and contact details

Please ask one of the staff in the clinic, or Dr Wheeler if you have any other questions about the study that have not been addressed by this information leaflet. The contact details are as at the top of this letter:

Dr Patrick Wheeler, **Consultant in Sport and Exercise Medicine**
Department of Sport & Exercise Medicine
University Hospitals of Leicester NHS Trust,
Leicester General Hospital, LE5 4PW
Secretary: 0116 2588101
Clinic: 0116 2584365

Department of Sport and Exercise Medicine
University Hospitals of Leicester NHS Trust

University Hospitals of Leicester NHS
NHS Trust

Dr Patrick Wheeler
Consultant in Sport and Exercise Medicine
Leicester General Hospital
University Hospitals of Leicester NHS Trust
Gwendolen Road, Leicester, LE5 4PW
Telephone: 0116 258 4365

UHL Study Number: 11335

Patient Identification Number for this trial:

CONSENT FORM

Title of Project: Assessing the benefits of the use of a tension night splint in patients with plantar fasciitis

Name of Researcher: Dr Patrick Wheeler

Please initial boxes below

1. I confirm that I have read and understand the information sheet dated 9th August 2014 (version 2.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by Dr Wheeler, and if necessary from the appropriate regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to my GP being informed of my participation in the study. ☐

5. I agree to take part in the above study. ☐

This last section gives you two options to choose from.

6. If you would like to receive it, a simple copy of the final results of the study can be sent to you after the study concludes, however please be aware that this is likely to be early 2016 at the earliest. Please initial the first of the two boxes below if you would like a copy of the results, in which case the study team will keep a copy of your postal address for this summary to be sent to you, or initial the second box if you do not require a copy to be sent to you.

a) I give consent for the study team to keep a copy of my address so that they can send me a summary of the results at the end of the study ☐

b) I do not wish for a copy of the results to be sent to me ☐

Name of Participant	Date	Signature
Name of Person taking consent.	Date	Signature

Consent form date of issue: 9th August 2014
Consent form version number: 2.0

University Hospitals of Leicester NHS
NHS Trust

Department of Sport and Exercise Medicine

Dr Patrick Wheeler
Consultant in Sport and Exercise Medicine
University Hospitals of Leicester NHS Trust
Leicester General Hospital, Gwendolen Road, Leicester, LE5 4PW
Direct telephone: 0116 258 4365

Participant Information Sheet *(UHL study number 11401)*

Title of Project: Assessing the benefits of the addition of Extra-Corporeal Shockwave Treatment to a structured home-rehabilitation programme for patients with tendinopathy.

(LEICSTES = LEICeSter Tendon Extracorporeal Shockwave Studies)

Name of Researcher: Dr Patrick Wheeler

Invitation

We would like to invite you to participate in a research study that we are running which will investigate the effectiveness of a treatment for patients with symptoms from a range of different tendon problems. This treatment is the use of "Extra-Corporeal Shockwave Therapy" (commonly called shockwave or "ESWT") in addition to a structured rehabilitation programme. This treatment will already have been discussed with you prior to you receiving this leaflet and is described in more detail below. This research study is being conducted by Dr Wheeler as a part of his PhD examining the management options for tendon problems.

What is the purpose of the study?

This study is to see how effective the shockwave treatment is in improving your symptoms.

Why have I been invited?

Patients treated for symptoms of tendinopathy by the Department of Sport & Exercise Medicine at the Leicester Hospitals and whom it is thought shockwave may be an appropriate treatment option are being invited to participate in this study. Due to the numbers needed for the study, the recruitment for this study is expected to take at least a year or more to complete.

Do I have to take part?

It is your choice whether or not to participate in this study. We will describe the study and go through this information sheet and if you agree to take part we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This will not affect the care you receive.

What will happen to me if I take part?

Sometimes we don't know which way of treating patients is best and to find out we need to compare

different treatments. We put people into groups and give each group a different treatment and the results are compared to see if one is better. To try to make sure the groups are the same to start with, each patient is put into a group by chance ("like tossing a coin"). This project uses this method of allocating patients by chance to one of two shockwave treatment programmes.

All patients will receive a similar structured rehabilitation programme. These exercises will be shown to you, are easy to do yourself at home, and you will be taught how to do these effectively and how to progress them to maximise your chances of recovery. In addition half of patients will receive what is thought to be a therapeutic dose of shockwave treatment, the other half of patients initially will be given a much lower dose to assess the benefits of the shockwave. At the end of the study if you have received the lower dose of shockwave and remain with symptoms you will be offered the other dose of shockwave so that no-one will be missing out, but this way we can assess the benefits more reliably.

What will I have to do?

We will arrange for you to discuss this study with our Nurse Practitioner. She will explain everything that is required. As a part of the study you will be given an exercise programme for your pain and you will need to do these exercises regularly at home to get benefit from them. In addition you will be given appointments to come back for the shockwave treatment options, which will be one appointment a week for three consecutive weeks.

You will be asked to fill in a questionnaire about your symptoms at the start of this project, and at several points following, these are 6 weeks after completing shockwave treatment, 3 months after shockwave, and 6 months after shockwave. You will not need to return to the hospital to complete these questionnaires as you can complete these at home and send them back to us.

What are the alternatives for treatment?

The alternative to this study would to be progress with the home exercise programme alone, or it is possible that other treatments such as injections or surgery may be possible for your symptoms. Your treating doctor will discuss these with you.

What are the possible disadvantages and risks of taking part? What are the side-effects of any treatment received when taking part?

Shockwave therapy is thought to be very safe, with few reported serious side-effects reported. These will be discussed with you in detail, but it is not uncommon for the shockwave to be uncomfortable at the time (although not everyone finds that it is.) In addition some people can get some bruising (less than one in ten people), or temporary reddening or irritation of the skin (depending on the site to be treated about one in

every three to five patients), and there is thought to be a very low risk of tendon injury from shockwave therapy (thought to be less than one episode in a thousand).
You will be given a specific information sheet about shockwave for tendons that has been written by the National Institute for Health and Clinical Excellence (NICE), which will discuss the benefits and risks of shockwave in more detail, and you will be able to ask questions of Dr Wheeler or another member of the study team.

What are the possible benefits of taking part?
We hope that the information we get from this study will help improve the treatment of people with tendon symptoms, although we cannot give a guarantee of benefit of any particular treatment.

What happens when the research study stops?
When your involvement in the research study stops you will continue to remain an NHS patient under the care of your doctors for as long as needed currently. If you have on-going symptoms after the end of the study, then further options for treatment as thought to be clinically necessary will be discussed with you.

Will my taking part in the study be kept confidential?
Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you that Dr Wheeler uses and which leaves the hospital will have your name and address removed so that you cannot be identified.
The study questionnaire can be completed electronically, and this information is stored on secure computers at Loughborough University. This is anonymous data, which will only be accessible by Dr Wheeler or his team, and as a matter of routine you will be asked to consent specifically to storing data in this way.
You will be asked for permission to inform your General Practitioner about your involvement in this study.

Involvement of the General Practitioner/Family doctor (GP)
You will be given a letter to give to your General Practitioner informing them that you are taking part in this project as a matter of courtesy, however no specific action is needed from them.

What will happen to any samples I give? - No samples are taken within this study.

Will any genetic tests be done? - No, these are not carried out within this study.

Expenses and payments - There is no payment available for participation in this study.

What if relevant new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens, your research doctor (Dr Wheeler) will tell you and discuss whether you should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If you decide to continue in the study you may be asked to sign a consent form to indicated on-going participation.

If the study is stopped for any other reason, we will tell you and arrange your continuing care.

What will happen if I don't want to carry on with the study?

You can withdraw from the study at any time, although we would appreciate it if you keep in contact with us to let us know your progress. Information collected may still be used but this will be kept anonymous.

What will happen to the results of the research study?

All the information from this study will be kept anonymous and you will not be able to be personally identified from any results.

The results of this study will be shared with Dr Wheeler's colleagues through means such as publication in scientific journals, and it is possible that a summary of the findings will be published via the hospitals communications team. In addition a lay summary of the results will be produced once the study is completed which if you are interested will be available for you to read via the Sports Medicine department website.

Who is organising and funding the research?

Dr Wheeler, Head of Service and Consultant in Sport & Exercise Medicine at the University Hospitals of Leicester is organising the research, which is being supported from both within the Sports Medicine Department, and within University Hospitals of Leicester. The research has been conducted in such a way to minimise any costs, and the costs of the research that are needed are being covered by the Sports Medicine Department. No-one is being paid directly by or for this study.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee (REC), to protect your interests. The Research Ethics Committee that reviewed this study is the Northampton REC, and this was given the REC identification number of 15/EM/0122.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. If you have a concern about any aspect of this study, you should ask to speak to the team who are looking after you who will do their best to answer your questions. This can be done during the time that you are with them or this can be via the normal telephone number on your appointment letter.

If you remain unhappy and wish to complain formally, you can do this and the hospital Patient Information Liaison Service (PILS) will be able to assist you with this. They can be reached by a Freephone number 0808 178 8337, or emailed at pils@uhl-tr.nhs.uk

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the University Hospitals of Leicester NHS Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Further information and contact details

Please ask one of the staff in the department, or a member of Dr Wheeler's research team, if you have any other questions about the study that have not been addressed by this information leaflet. You can contact them via the details that are at the top of this letter:

Dr Patrick Wheeler, **Consultant in Sport and Exercise Medicine**
Department of Sport & Exercise Medicine,
University Hospitals of Leicester NHS Trust,
Leicester General Hospital,
LE5 4PW

Department of Sport and Exercise Medicine
University Hospitals of Leicester NHS Trust

University Hospitals of Leicester NHS Trust

Dr Patrick Wheeler
Consultant in Sport and Exercise Medicine
Leicester General Hospital
University Hospitals of Leicester NHS Trust
Gwendolen Road, Leicester, LE5 4PW
Telephone: 0116 258 4365

UHL Study Number: 11401

Patient Identification Number for this trial:

CONSENT FORM

Title of Project: Assessing the benefits of the addition of Extra-Corporeal Shockwave Treatment to a structured home-rehabilitation programme for patients with tendinopathy.
(LEICSTES = LEICeSter Tendon Extracorporeal Shockwave Studies)

Name of Researcher: Dr Patrick Wheeler

Please initial boxes below

1.	I confirm that I have read and understand the information sheet dated 2nd February 2015 (version 1.1) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2.	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	☐
3.	I understand that relevant sections of my medical notes and data collected during the study may be looked at by Dr Wheeler, and if necessary from the appropriate regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
4.	I agree that Dr Wheeler may hold securely at Loughborough University, some of the anonymised data recorded during this study.	☐
5.	I agree to my GP being informed of my participation in the study.	☐
6.	I agree to take part in the above study.	☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

Consent form date of issue: 1st April 2015
Consent form version number: 1.2

Page 1 of 1

University Hospitals of Leicester NHS
NHS Trust

Department of Sport and Exercise Medicine

Dr Patrick Wheeler
Consultant in Sport and Exercise Medicine
University Hospitals of Leicester NHS Trust
Leicester General Hospital, Gwendolen Road, Leicester, LE5 4PW
Direct telephone: 0116 258 4365

Patient Information Sheet

Title of Project: Investigating the effects of ultrasound guided autologous blood injection for chronic plantar fasciitis versus ultrasound guided dry-needling alone

Name of Researcher: Dr Patrick Wheeler

Invitation

We would like to invite you to participate in a research study that we are running which will investigate the effectiveness of two different treatments for patients with chronic symptoms from plantar fasciitis that have not benefited from previous treatments.

One treatment option is an ultrasound-guided injection of a small quantity of a patient's own blood (Autologous Blood Injection, often called ABI) into the area of damage of the plantar fascia. This is compared with another treatment option called ultrasound-guided dry needling. Both these procedures are explained in detail below.

What is the purpose of the study?

This study is to see if both treatment options are equally effective in the treatment of chronic plantar fasciitis, or if one is superior to the other.

Why have I been invited?

All patients who are treated with chronic plantar fasciitis by the Sports Medicine Department in Leicester whose symptoms have not improved with other treatments are being invited to participate in this study. Due to the numbers needed for the study, the recruitment for this study is expected to take several years to complete.

Do I have to take part?

It is your choice whether or not to participate in this study. We will describe the study and go through this information sheet and if you agree to take part we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This will not affect the care you receive.

What will happen to me if I take part?

Sometimes we don't know which way of treating patients is best and to find out we need to compare different treatments. We put people into groups and give each group a different treatment and the results are compared to see if one is better. To try to make sure the groups are the same to start with, each patient is put into a group by chance ("like tossing a coin"). Half of the patients will receive the ultrasound guided dry needling procedure alone, and half of the patients will also receive the autologous blood injection at the same time. Neither you, nor the doctors who follow you up in clinic, will know which treatment that you have received, although they will be able to find out if needed.

Each procedure will involve a blood sample taking 5ml (a teaspoon) of blood from a vein. All patients will have this

blood sample taken so that it is not easy to determine which of the two treatment groups they have been allocated to and all unused blood is discarded at the end of the procedure. An ultrasound machine will be used to localise the area of damage (scarring/thickening) of your plantar fascia. You will have an injection of local anaesthetic to the sole of your foot, and a dry needling technique will be used to open up channels in the plantar fascia and hopefully stimulate a healing response. Half of the patients in this study will also have an injection of 3-4mls (less than a teaspoon) of their own blood using a peppering injection where small drops are injected in a number of areas around the damage that can be seen in the plantar fascia. Following the procedures, all patients will undertake the same rehabilitation exercises at home, and these will be shown to you.

What will I have to do?

The procedure will be done during a hospital outpatient visit where you see Dr Wheeler. Following this procedure you will be required to undertake a series of rehabilitation exercises at home every day; these will be shown to you and you will receive a set of written information to facilitate your ability to do these.

Following the procedure you will be invited back to routine clinic follow-up appointments with a member of the team, these will normally be at 2 weeks, 6 weeks, 3 months and 6 months. These follow-up appointments provide an opportunity to check how you are getting on, and support the rehabilitation exercises that you are doing.

At each hospital visit you will be given a written questionnaire to complete, which attempts to better understand your symptoms at that point, and a member of the clinical team will assess you.

At the end of your involvement in this study (6 months following the procedure) if your symptoms have failed to improve we will find out what treatment group you were in and discuss further treatment options with you, which will include the Autologous Blood Injection.

What are the alternatives for treatment?

Alternatives to the blood injection procedure could include surgery, or leaving patients alone with no further treatment, and these options will be discussed with you.

What are the possible disadvantages and risks of taking part?

Before any procedure is carried out this will be discussed with you in person by Dr Wheeler and you will have ample time to ask any questions that you wish.

The two procedures involve an injection to the sole of the foot, which can be painful. Whilst Dr Wheeler will use local anaesthetic to reduce the pain, this injection can be sharp for a few seconds. Rarely people could be allergic to local anaesthetics, and Dr Wheeler will ask about medical history including allergies before undertaking the procedure to check that these procedures would be suitable to you.

The procedures will also involve a blood test taken from the arm, which can be uncomfortable. 5mls (a teaspoon) of blood will be taken from a vein in your arm. This is a very routine and safe procedure.

The procedure in your foot can aggravate your foot pain for a week or so, although experience shows this is normally only for a couple of days. In this time you will be advised about taking painkillers and activity modification if needed.

As the dry needling and injection is to the area of damage to the plantar fascia, there is a theoretical risk of causing an injury to the plantar fascia. However experience shows this to be a very rare occurrence.

In addition, any time an injection is done there is a very small risk of introducing infection, which is very rare and is thought to be in the order of one in every fifty thousand injections.

If the dry needling procedure is not as effective as the Autologous Blood Injection, and you are allocated initially to receive the dry needling injection then there could be a delay in you receiving the other injection. However we would not be able to tell if there was benefit until 3-6 months after the injection, at which point if needed the other procedure could be offered to you.

What are the side-effects of any treatment received when taking part?
The side-effects of the two treatment options are the same, and are discussed in the previous section.

What are the possible benefits of taking part?
We hope that the information we get from this study will help improve the treatment of people with chronic plantar fasciitis symptoms, although we cannot give a guarantee of benefit of any particular treatment.

What happens when the research study stops?
When your involvement in the research study stops you will continue to remain an NHS patient under the care of Dr Wheeler as long as is thought to be clinically appropriate.
To gain longer-term follow-up of the procedure, and to avoid bringing you back to the clinic unnecessarily, you may be contacted again by post about a year after the procedure and asked to complete a brief questionnaire. You will be asked specifically whether you give permission for this to happen.

Will my taking part in the study be kept confidential?
Yes. We will follow ethical and legal practice and all information about you will be handled in confidence.
All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you that Dr Wheeler uses and which leaves the hospital will have your name and address removed so that you cannot be identified.
You will be asked for permission to inform your General Practitioner about your involvement in this study, and if permission is granted then this will be within the clinic letter that we normally send to your General Practitioner each time that you are seen in the hospital.

Involvement of the General Practitioner/Family doctor (GP)
As is normal practice Dr Wheeler, or a member of his team, will write to your GP after each and every consultation with you. You will receive a copy of this letter. This letter will detail the clinical care that you receive from Dr Wheeler's clinic, and will inform your General Practitioner that you are assisting in this research project.
Dr Wheeler will ask for specific permission from you that this is acceptable to you on the study consent form.

What will happen to any samples I give?
The only sample that is taken is the small blood sample that is taken as a part of the procedure.
All patients will have 5mls of blood taken from a vein in their arm, this way patients cannot easily tell which treatment group they are in. No sample will be kept; any excess blood sample will be destroyed at the end of the procedure, as is normal practice.

Will any genetic tests be done? - No, these are not carried out within this study.

Expenses and payments - There is no payment available for participation in this study.

What if relevant new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens, your research doctor (Dr Wheeler) will tell you and discuss whether you should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If you decide to continue in the study he may ask you to sign an agreement outlining the discussion.

If the study is stopped for any other reason, we will tell you and arrange your continuing care.

What will happen if I don't want to carry on with the study?

You can withdraw from the study at any time, although we would appreciate it if you keep in contact with us to let us know your progress. Information collected may still be used but this will be kept anonymous.

What will happen to the results of the research study?

The results of this study will be shared with Dr Wheeler's colleagues through means such as publication in scientific journals, and it is possible that a summary of the findings will be published via the hospitals communications team. All the information from this study will be kept anonymous and you will not be able to be personally identified from any results.

If you would like to be informed of the results of the study once they are completed, then please let us know and we can arrange for you to receive a copy of the summary at the end of the study. You will need to give specific consent for us to keep hold of your address for this purpose.

Who is organising and funding the research?

Dr Wheeler, Head of Service and Consultant in Sport & Exercise Medicine at the University Hospitals of Leicester is organising the research, which is being supported from both within the Sports Medicine Department, and within University Hospitals of Leicester. The research has been conducted in such a way to minimise any costs, and the costs of the research that are needed are being covered by the Sports Medicine Department. No-one is being paid directly by or for this study.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the local Research Ethics Committee in Leicester.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. If you have a concern about any aspect of this study, you should ask to speak to Dr Wheeler who will do his best to answer your questions. This can done during the time that you are with him, or this can be via the normal clinic telephone number (0116 2584365.) If you remain unhappy and wish to complain formally, you can do this and the hospital Patient Information Liaison Service (PILS) will be able to assist you with this. They can be reached by a Freephone number 0808 178 8337, or emailed at pils@uhl-tr.nhs.uk

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the University Hospitals of Leicester NHS Trust but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Further information and contact details

Please ask one of the staff in the clinic, or Dr Wheeler if you have any other questions about the study that have not been addressed by this information leaflet. The contact details are as at the top of this letter:

Dr Patrick Wheeler, **Consultant in Sport and Exercise Medicine**
Department of Sport & Exercise Medicine
University Hospitals of Leicester NHS Trust,
Leicester General Hospital, LE5 4PW

Direct clinic telephone number: 0116 2584365

In addition to this study information form you will be also given to read a copy of the "information for the public" documents written by the National Institute for Health and Clinical Excellence (NICE) concerning the use of Autologous Blood Injections for Plantar Fasciitis (dated January 2013).
This document will discuss the treatment option that is being studied here in some detail and Dr Wheeler considers it good practice for you to read this impartial information about the procedure being studied.

Department of Sport and Exercise Medicine
University Hospitals of Leicester NHS Trust

University Hospitals of Leicester NHS
NHS Trust

Dr Patrick Wheeler
Consultant in Sport and Exercise Medicine
Leicester General Hospital
University Hospitals of Leicester NHS Trust
Gwendolen Road, Leicester, LE5 4PW
Telephone: 0116 258 4365

UHL Study Number: 11334

Patient Identification Number for this trial:

CONSENT FORM

Title of Project: Investigating the effects of ultrasound guided autologous blood injection for chronic plantar fasciitis versus ultrasound guided dry-needling alone

Name of Researcher: Dr Patrick Wheeler *Please initial boxes below*

1. I confirm that I have read and understand the information sheet dated 14th August 2014 (version 3.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by Dr Wheeler, and if necessary from the appropriate regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to my GP being informed of my participation in the study. ☐

5. I agree to take part in the above study. ☐

This last section gives you two options to choose from.

6. If you would like to receive it, a simple copy of the final results of the study can be sent to you after the study concludes, however please be aware that this is likely to take a couple of years at the earliest. Please initial the first of the two boxes below if you would like a copy of the results, in which case the study team will keep a copy of your postal address for this summary to be sent to you, or initial the second box if you do not require a copy to be sent to you.

a) I give consent for the study team to keep a copy of my address so that they can send me a summary of the results at the end of the study ☐

b) I do not wish for a copy of the results to be sent to me ☐

Name of Participant	Date	Signature
Name of Person taking consent.	Date	Signature

Consent form date of issue: 14th August 2014
Consent form version number: 2.0

Page 1 of 1

Appendix 2: Home Exercise Programme (HEP)

Patients presenting with symptoms of plantar fasciitis to the Sports Medicine Department at the University Hospitals of Leicester NHS Trust are routinely given a structured Home Exercise Programme (HEP) as a part of their treatment package. This draws upon both research findings and clinical experience from senior team members in the department and seeks to address the biomechanical faults that are commonly seen in patients with these symptoms. It is recognised that various other clinics and settings may have their own specific patient information and rehabilitation programmes, and there may be some differences between these, depending on the specific focus taken of the rehabilitation strategy. No date there is little evidence that supports one particular strategy over another, and as always this could the focus of further work.

This home exercise programme includes static stretches of the plantar fascia, the calf (selectively involving both gastrocnemius and soleus for different stretches), plus Flexor Hallucis Longus (FHL) and hamstrings, as well as calf and intrinsic foot muscle strengthening and balance training exercises.

Patients are shown these within the clinic setting by the healthcare professionals that they consult with. In addition, patient compliance with this programme is supported by the use of written material that is given to patients to remind them of their rehabilitation programme. The following document is a copy of v4 of the Plantar Fasciitis advice and rehabilitation leaflet (dated 15th January 2015) which is the version in use within the research studies included in this thesis.(42)

Department of Sport and Exercise Medicine
University Hospitals of Leicester NHS Trust

PLANTAR FASCIITIS - Advice & Rehabilitation Leaflet

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Patient information and rehabilitation leaflet

Plantar fasciitis is the most common cause of pain on the bottom of the heel. Plantar fasciitis occurs when the strong band of tissue that supports the arch of the foot becomes irritated, thickened and less flexible than it should be.

Plantar fasciitis is a condition that generally improves over time, although this can typically be 6-9 months and about 10% of patients can have symptoms for much longer. A range of treatments can be used to reduce symptoms, and hopefully speed up recovery. There is no single treatment that works for everyone, and often several simple treatments are used in combination for maximal effect. Prolonged immobility or rest can worsen the condition and therefore plantar fasciitis should be treated actively.

In most cases, Plantar Fasciitis develops without a specific, single, identifiable reason. However, the risk factors that make you prone to the condition include the following;

- *Diabetes – especially poor diabetic control*
- *High arched or low arched foot shape*
- *Impact activity*
- *Obesity*
- *Older age*
- *Poor footwear*
- *Prolonged time standing / walking*
- *Smoking*
- *Tight calf muscles*
- *Weak foot arch muscles*

Whilst we can't do anything about some of the risk factors such as age, it is important to reduce the ones that you can, and these include measures such as losing weight, reducing or stopping smoking, changing shoes, modifying activity and undertaking a specific rehabilitation programme as shown on the next few pages.

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The following is a reminder of the exercise that you should have been shown. It is difficult to learn these exercises from a piece of paper; instead this is to help you remember what you have been shown already.

Home Exercise Programme Guide

1. Stretches of the plantar fascia
2. Stretching of the rest of the whole muscle chain
3. Balance exercises
4. Intrinsic foot muscle strengthening
5. Calf muscle strengthening

Progressing the home exercise programme

Everyone will be starting this programme from different ability levels, and so it is difficult to create a standardised programme that will cater to everyone's needs. However the following timeline will give you a guide as to the changes that we would like to see you making to your programme.

Week	Summary Guide
1st & 2nd week	Perform the stretches (point 2) and balance work (point 3 above) Hold each of the stretches for about 15 seconds each – apart from the rolling stretch for the plantar fascia which should start for at least 30 seconds
3rd & 4th week	Increase the plantar fascia rolling stretch up to a minute or two Increase the duration of the other stretches to 20 seconds in week 3, and 30 seconds each for week 4 Add in the intrinsic foot muscle strengthening exercise (point 4)
5th & 6th week	Add in the calf-muscle strengthening (point 5)
Thereafter	Continue with the home exercise programme set Progress the calf-muscle strengthening exercises Steadily increase the amount of regular physical activity done, aim for a minimum of 30 minutes of moderate-intensity activity a day (a level of activity which makes you slightly sweaty, and raises the breathing a little), and aiming for at least 5 active days a week

The diagrams and discussions on the following pages will show you the specific exercises discussed in this regime.

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You will be given a couple of options for each of the following stretches, so that if one version is uncomfortable you are able to try the other one.

1. Specific plantar fascia stretches

i) rolling stretch	ii) self-massage
Stand holding onto a stable surface such as a kitchen work top Place a frozen drinks bottle (such as a half-litre soft drink bottle that was filled with water & kept in the freezer) under the standing foot's heel with a reasonable amount of weight through this. Roll the bottle slowly from the heel all the way to the toes and back again taking at least 5 seconds to progress from the heel to the toes each time. Do this for about 30 seconds to start with for each foot, increasing to a couple of minutes or more by week 3/4 *You can do this with a large wooden rolling pin, or a specific device of which several are available, however in practice an ice cylinder works well.*	Sit cross-legged on a stable chair and bring one foot over the other knee. Using your hand, pull back on the toes on the foot to stretch out the plantar fascia and the tendons on the sole of your foot. You can then directly massage the tight bands that you can feel with your other thumb. Do this for at least 30 seconds initially, gradually increasing over time.

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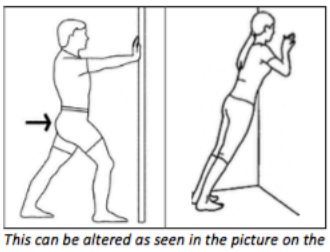
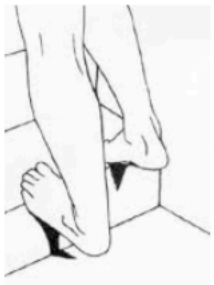
The previous stretches specifically target the plantar fascia. The following stretches focus on the muscle groups which if tight can have an adverse effect on the plantar fascia, and it is important to stretch these in addition to the plantar fascia to maximise benefit.

2. Stretches of the whole muscle chain

- With all of these stretches we normally recommend starting by holding the position for about 15 seconds, performing the stretch 3 times on each leg, and repeating these at least 3 times per day to start with.
- By the third week - hold each of the stretches for 20 seconds, and do 4 of each stretch 3 times per day
- By the fourth week – hold each stretch for 30 seconds, and do 5 of each stretch 3 times per day

- **A) Gastrocnemius stretches - (the "strength muscle" of the calf)**

i) stretching against the wall	**ii) stretching on bottom step**
Stand barefoot with feet facing forwards a little distance from a wall or chair Take a step forwards with the "good" leg Look at your back foot (which is the leg you are stretching) – make sure the foot is facing forwards & has not turned out, and has a straight knee and has the heel firmly on the floor Bend the front knee / push the back hip forwards into a lunge so that you feel the stretch on the back calf  *This can be altered as seen in the picture on the right into a press-up position on the wall, and you then cross one leg behind the other. This variation will require more arm strength to perform effectively.*	Stand barefoot on your bottom step with the weight evenly distributed between your feet and your heels and middle of the foot over the edge of the step. Slowly lower yourself down on one foot, feeling the stretching into your calf. 

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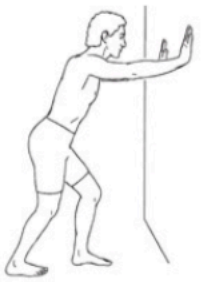
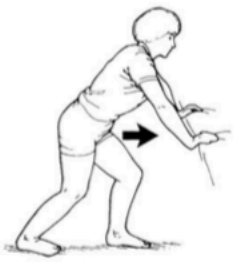
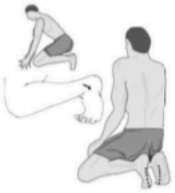
- **B) Soleus stretches - ("stamina muscle" of the calf)**

i) bent knee lunge	**ii) knee to wall stretch**
This is a similar way of stretching to the previous stretch, but instead will focus on stretching the deeper of the two calf muscles, the one that is more of a "stamina" than a "strength" muscle. Stand barefoot with feet facing forwards a little distance from a wall or chair Take a step forwards with the "good" leg Make sure your back leg is facing forwards and has not turned outwards Whilst keeping the heel on the floor, bend the knee on the back leg until you feel a stretch in the back of the calf. Make sure you bend the knee forwards over the middle of the foot, rather than letting it drift inwards.	Start with a similar position to the stretch shown on the left, but this time you are going to be stretching the front leg. Take a step forwards with the leg you are stretching pushing the knee over the 2nd toe (the one next to the big toe), Hold this position – you should feel that the stretch is "deeper" in the calf than the above stretch.
	
	*Sometimes this stretch can feel uncomfortable on the front of the knee on the front foot, and if this is the case you may be better with the version on the left.*

PLANTAR FASCIITIS - Advice & Rehabilitation Leaflet

- **C) FHL stretches (Flexor Hallucis Longus) - big toe tendon**

i) crouching	**ii) against wall**
Kneel down with a pillow under your knees with your weight on your knees. Support yourself initially with your hands if you need to. Tuck your feet under you, up on your toes. Slowly lean back so that the weight is transferred from your knees to your heels. Hold this position before returning your weight to your knees.  This stretch works best if done for longer than some of the others, and a guide is to hold it for double the length of the other stretches in this group.	Stand in a lunge position with toe either on a large book, or against the wall Similar position to the stretches above, but this time the foot is much closer to the wall The heel of the front foot is firmly on the floor, with the foot angled diagonally up the wall Bend the front knee to the wall – you should feel a stretch either in the low calf, ankle or under the foot *Alternatively, this stretch can be done placing an object like a large book under your toe & stretching as above.*

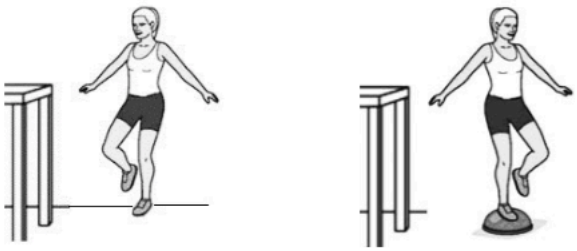
- **D) Hamstring stretches**

i) hurdle stretch	**ii) lying down**
Place a chair against a wall with the seat facing outwards. Place the heel of your foot for the leg you are stretching as far back into the chair as you can reach, which should keep the ankle flexed to about 90° Keeping your back straight and the knee straight of the leg you are stretching, slowly lean forwards sliding your hands down this leg until you feel a stretch at the back of your thigh and calf. Hold this stretched position 	Lie flat on your back with both legs straight. Bring one leg towards you, bending your knee and your hip, so that your hip is at about 90 degrees. Reach down with your hands and hold the back of your thigh. Using the muscles of the leg slowly straighten the knee as far as the hamstrings will allow it to. Hold this stretched position.

PLANTAR FASCIITIS - Advice & Rehabilitation Leaflet

These last two sets of exercises seek to improve balance and coordination, and improve intrinsic strength within the foot itself.

3. Balance exercise (proprioception) – *be careful not to fall & injure yourself with this exercise*
Start to practice by standing on one leg on a firm, flat surface with your eyes open.
It is ok to hold onto something stable like a worktop if you need to when starting out. Then gradually progress from holding onto something, to touching a worktop lightly, to intermittently touching & then not touching at all.
Look to stand on either leg for about 30 seconds in total x 3 each leg – at least 3 times per day
When you are getting good at these exercises, then to progress this further place a pillow under your standing foot (or wobble board) and gradually build up the time you are balancing for.
When you are getting very good, try standing on one leg on a firm surface, but this time with your eyes closed – this makes the exercise harder as you no longer have your eyes giving you clues about your wobbling.



4. Intrinsic foot muscle strengthening
These are the tiny muscles in the feet that help with all sorts of activities, and often pain can inhibit these from working, causing them to weaken.
To start this exercise, stand on a towel on the floor barefoot. Then practice by scrunching up the towel under your feet with both feet either together or singly. A tissue or piece of kitchen towel will also work just as well
Look to start with about 30 seconds, and progress this to several minutes each time, three times per day.

An alternative is to use pebbles or marbles on the floor, and practice trying to pick these up by scrunching your toes.

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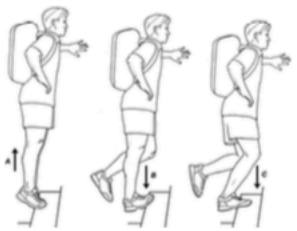
5. Calf strengthening

The last stage of this home exercise programme is to increase strength within the calf muscles to off-load the pain from the plantar fascia.

These exercises load the calf muscle/tendon using body weight, as it is being stretched – the medical phrase for this is "eccentric strengthening"; one of the most important things to do with this exercise is to do these very slowly to get benefit from them. There is some evidence that even if you have symptoms only on one side that these exercises should be done for both sides.

- Stand on your first step with weight evenly between both feet
- Slowly, raise yourself onto your tiptoes with your knees straight (Fig A)
- Hold this position for about 2 seconds
- Very slowly lower your heels as far as they can go, so that your heels go below the level of your toes – this needs to be done very slowly over about 7 seconds (Fig B)
- Hold this stretched position for 2 seconds
- Slowly push yourself back up to a tiptoe position, over about 7 seconds

(repeat)



We would normally ask you to do 3 sets of this exercise, once a day only – starting at a number of repetitions where you are starting to feel the load.

Once you have completed this exercise with your knees straight, then repeat this exercise with your knees bent (figure C)

Normally we would look for you to increase slowly at weekly intervals, starting these normally from about the fifth week of rehabilitation. To progress this exercise, gradually increase the number of repetitions that you do.

- When you are able to do 3 x 15, progress on to raising onto tiptoes using both feet, but coming down on one foot (and then repeating to do the other side), before raising and lowering only with 1 foot at a time.
- To progress beyond this, the using a rucksack start cautiously adding weight to this. (as per the diagram above)

In conclusion

These exercises are designed to help your foot symptoms, they will take some time and effort to do well and you will be best advised to set aside some time at various points each day to ensure that you are able to do these effectively.
If you find a family member or friend to help you this can improve your perseverance with the programme.
Remember you will need to do these exercises regularly in order to benefit from them.

Appendix 3: Participant demographics

Almost 300 NHS patients with chronic plantar fasciitis have been enrolled within the different interventional studies included in this thesis. The following is a very brief description of some of the baseline characteristics recorded for these participants in each of the separate studies.

	Study A TNS case series	**Study B TNS RCT**		**Study C ESWT Case series**	**Study D ESWT RCT**		**Study E ABI case series**	**Study F ABI RCT**	
		"Intervention Group"	**"Control Group"**		**"Intervention Group"**	**"Control Group"**		**"Intervention Group"**	**"Control Group"**
intervention	Bespoke TNS	TNS + rehab	Rehab only	ESWT	ESWT	ESWT – minimal dose	ABI	dry needling + ABI	Dry needling only
n=	17	20	20	31	38	34	70	36	33
Age (years)	51.6 ± 12.2	53.4 ± 8.9	50.9 ± 11.7	49.9 ± 9.1	50.1 ± 9.1	52.5 ± 10.7	52.6 ± 11.9	48.0 ± 9.2	50.3 ± 9.6
Gender (male/female)	53% female (8M / 9F)	75% female (5M / 15F)	65% female (7M / 13F)	68% female (10M / 21F)	58% female (16M / 22F)	71% female (10M / 24F)	53% female (33M / 37F)	56% female (16M / 20F)	70% female (10M / 23F)
Symptom duration (months)	30.0 ± 34.7	30.3 ± 33.2	20.1 ± 9.2	30.8 ± 42.0	32.1 ± 42.0	28.1 ± 22.8	49.4 ± 50.9	43.3 ± 27.3	35.2 ± 23.7
BMI (m/kg^2)	.	32.6 ± 5.0	29.0 ± 4.9	.	.	.	.	30.2 ± 5.6	31.7 ± 6.1
Baseline PROMs									
• VAS ("average pain")	6.9 ± 2.7 (range 1-10)	6.8 ± 2.2 (range 3-10)	7.1 ± 1.7 (range 4-9)	6.8 ± 1.8 (range 3-10)	6.9 ± 1.6 (range 3-10)	6.6 ± 1.7 (range 2.5-9.0)	8.0 ± 1.5 (range 4-10)	7.2 ± 1.5 (rage 3-10)	7.2 ± 1.9 (range 1.5-10)
• FFI-r (total)	x	88.3 ± 24.5	95.5 ± 22.9	87.7 ± 25.4	82.3 ± 22.2	83.6 ± 23.3	86.7 ± 22.1	92.9 ± 19.8	89.3 ± 20.2
• MOXFQ	x	56.2 ± 14.5	64.5 ± 12.0	58.4 ± 10.7	55.7 ± 11.8	56.6 ± 14.0	x	60.8 ± 12.5	59.2 ± 10.7

Data are mean ± SD

Appendix 4: Study outcome measures

The following common outcome measures were used in the different interventional chapters in this thesis. This is a summary only, for full details, please see the specific experimental write-up sections.

	Study A **TNS case series** Rehab+ Bespoke TNS	**Study B** **TNS RCT** Rehab ± TNS	**Study C** **ESWT Case series** Rehab + ESWT	**Study D** **ESWT RCT** Rehab ± ESWT	**Study E** **ABI case series** Rehab + ABI	**Study F** **ABI RCT** Rehab + dry needling ± ABI
Patient reported:						
"VAS"						
Self-rated "pain" (0-10)	Yes	Yes	Yes	Yes	Yes	Yes
Self-rated "stiffness" (0-10)	.	Yes	Yes	Yes	.	Yes
Foot function PROMs:						
FFI-r	.	Yes	Yes	Yes	Yes	Yes
MOXFQ	.	Yes	Yes	Yes	.	Yes
FAAM	.		Yes	Yes	.	Yes
Wider functional aspect PROMs						
Global function (e.g. EQ-5D, ODI)	.	Yes	Yes	Yes	.	Yes
Mental health (e.g. HADS, PHQ9)	.	Yes	Yes	Yes	.	Yes
Sleep (e.g. PSQI)	.	Yes	Yes	Yes	.	Yes
Activity (e.g. IPAQ, vital signs)	.	Yes	Yes	Yes	.	Yes
Other						
"Satisfaction" scale	Yes	Yes	.	Yes	.	Yes
"Recommendation" scale	Yes	Yes	.	Yes	.	Yes
Observer rated:						
Flexibility measures	.	Yes	.	.	.	.
Ultrasound measurements	.	Yes	.	.	.	.
Follow-up period	(range 6-18months)	3-months	3 months	6-months	Mean >500days	6-months

Appendix 5: Summary of author's published papers from the material included in this thesis

Publications are listed in section order in which they appear in the thesis

Section		
5.2	Wheeler, P.C., The effectiveness and tolerability of Tension Night Splints for patients with chronic plantar fasciitis - a case-series study. *International Musculoskeletal Medicine*, 2014. **36**(4): p. 130-136.	(258)
5.3	Wheeler PC. The addition of a Tension Night Splint to a structured home rehabilitation programme in patients with chronic plantar fasciitis does not lead to significant additional benefits in either pain, function, or flexibility – a single-blinded randomised controlled trial. BMJ Open Sport & Exercise Medicine. 2017;3:e000234	(257)
6.2	Wheeler PC, Tattersall C. Extracorporeal Shockwave Therapy Plus Rehabilitation for Patients With Chronic Plantar Fasciitis Might Reduce Pain and Improve Function but Still Not Lead to Increased Activity: A Case-Series Study With Multiple Outcome Measures. The Journal of Foot and Ankle Surgery. 2018;57(2):339-45.	(276)
7.2	Wheeler, P., Autologous blood injections for chronic plantar fasciitis – a pilot case-series study shows promising results. *International Musculoskeletal Medicine*, 2013. **35**(1): p. 3-7.	(358)
7.2	Wheeler PC. The role of Autologous Blood Injections in the treatment for patients with chronic plantar fasciitis – a case series and longer-term follow-up. *International Musculoskeletal Medicine* 2015;**37**(2):47-53.	(346)

(These publications have been subject to modifications in layout, content, and presentation in the thesis experimental chapters.)

In addition, the following papers from the author are not explicitly included in the experimental chapters but are discussed in chapter 2, background and literature review. (These are displayed in chronological order of publication.)

Wheeler, P., K. Boyd, and M. Shipton, Surgery for Patients With Recalcitrant Plantar Fasciitis: Good Results at Short-, Medium-, and Long-term Follow-up. *Orthopaedic Journal of Sports Medicine*, 2014. **2**(3). (229)

Wheeler PC. Neuropathic pain may be common in chronic lower limb tendinopathy; a prospective cohort study. *British Journal of Pain*. 2017; 11: 16-22 (147)

Wheeler P. Up to a quarter of patients with certain chronic tendinopathies may have Central Sensitisation - a prevalence study. *British Journal of Pain* 2018; Online First - published 21st Sept 2018 (148)

There are a number of further publications that are planned from the material that has been presented here, including the following:

1. Extra-corporeal Shockwave Therapy randomised controlled trial for patients with chronic plantar fasciitis (Study D)
2. Autologous Blood Injections versus dry-needling randomised controlled trial for patients with chronic plantar fasciitis (Study F)
3. Prospective cohort study comparing outcomes following Extra-Corporeal Shockwave Therapy versus Autologous Blood Injection for patients with chronic plantar fasciitis (Chapter 8)

Full-text from the published works appear on the following pages in the closed-access version only. In this version, which will be marked as "open access" in the University Repository will have the full-text removed to avoid journal copyright issues. The references are as stipulated above.

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