Foot assessment in people with diabetes: A quantitative diagnostic approach

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Contents

Abstract

Background: Diabetic foot ulcers are a serious and costly complication of diabetes. The leading causes of diabetic foot ulceration are mechanical trauma and the breakdown of plantar soft tissues. Biomechanical factors linked to an increase in diabetic foot ulceration are changes in plantar soft tissue mechanical properties and increased plantar pressure. These represent important internal and external risk factors for ulceration that are not commonly assessed within clinical practice due to a lack of clinically applicable measurement techniques.

The measurement of Shore hardness has been identified as a potential method to assess these internal and external biomechanical factors due to its previous use in various soft tissue applications and its simplicity, ease of use, and low cost. However, key questions remain regarding the physical meaning of Shore hardness when used within biological soft tissues to assess the mechanical properties of the plantar soft tissues of the foot. In addition, the clinical relevance of Shore hardness when applied to the diabetic foot needs further exploration. Finally, the association between Shore hardness and plantar pressure in people with diabetes has not been fully investigated. Nevertheless, Shore hardness presents a potential method to assess the external risk factors associated with ulceration.

Aim: The primary aim of this research was to investigate if the measurement of Shore hardness can be used within a clinical setting as a method to assess the mechanical

properties of the plantar soft tissues. The secondary aim of this research was to investigate if the measurement of Shore hardness is associated with changes in plantar pressure during walking in people with diabetes and, if so, can Shore hardness in combination with other biomechanical measurements be used to predict these changes.

Methods: Finite element (FE) analysis was conducted to investigate the physical meaning of Shore hardness using an anatomically accurate model of the heel pad. Additionally, the ability of Shore hardness to individually assess the mechanical properties of skin and subcutaneous soft tissue was investigated.

The clinical relevance of Shore hardness was assessed within a cohort of 40 adults with diabetes and diabetic peripheral neuropathy classified as having a high risk of foot ulceration. The average age of participants was 63(±9) years, with an average duration of diabetes of 15(±9) years. To assess the clinical relevance of the measurement of Shore hardness, Spearman's rank correlation tests were performed between Shore hardness and the previously established parameters found to increase the risk of mechanical trauma to the foot, such as blood biochemistry, loading, and age.

The association between Shore hardness and plantar pressure as the external risk factor for ulceration was also investigated within this cohort of 40 adults using multiple regression analyses. Specifically, the ability of Shore hardness in combination with

measurements of 2D sagittal plane range of motion, to predict regional changes in plantar pressure and loading was assessed.

Results: The results of the FE analysis showed that the measurement of Shore hardness offers an assessment of stiffness that is a combination of both the mechanical behaviour of the skin and the underlying subcutaneous tissue. It was concluded that, on its own, the measurement of plantar soft tissue Shore hardness does not provide an assessment of the stress-strain behaviour of the heel pad's constituent layers but instead offers an assessment of the bulk tissue's overall capacity to deform. As a result, differentiating between the stiffness of skin and that of the subcutaneous tissue based on the conventional assessment of Shore hardness remains a challenge.

Additionally, through FE analysis, it was found that by altering the size of the Shore hardness indenter within the currently available limits, the measurement of Shore hardness cannot independently assess the mechanical properties of the skin or subcutaneous soft tissue. However, the results of the FE analysis also highlighted that an indenter that is less than 2mm in diameter and 1mm in length might potentially be able to infer differences between the mechanical properties of the skin and subcutaneous soft tissue.

The clinical relevance of Shore hardness was shown by confirming correlations with age, blood biochemistry, and loading, whereby an increase triglyceride levels was associated with increases in tissue hardness. In contrast, an increase in loading causes a decrease in plantar tissue hardness. These results were all found to align with current literature indicating that Shore hardness can indeed be a clinically viable approach for assessing the internal risk factors associated with ulceration.

Finally, Shore hardness, in combination with foot and ankle range of motion, was able to predict changes in peak plantar pressures and pressure time integral within the midfoot region. A reduction in midfoot dorsiflexion and an increase in Shore hardness at the midfoot are predictive variables for an increase in peak plantar pressure and pressure time integral. These results thus highlight the potential usefulness of the assessment of Shore hardness as a method to monitor changes in the external risk factors associated with ulceration.

Conclusion: These findings show that Shore hardness can be a simple, cost-effective and reliable method for assessing both the internal and external biomechanical risk factors associated with diabetic foot ulceration within a clinic setting. This is specifically relevant to low resource settings where access to sophisticated equipment such as ultrasound elastography or plantar pressure platforms can be limited.

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Glossary of Terms

ADA	American Diabetes Association
AGEs	Advanced Glycated end-products
ANSYS	Finite Element Analysis Software
BMI	Body Mass Index
Calcaneus	Heel bone of the foot
DFU	Diabetic foot ulcers
Diabetic Foot	Any necrosis, gangrene, or full-thickness skin defect occurring distal to the ankle in a diabetic patient
Dorsiflexion	Upward movement of the foot in the sagittal plane
DPN	Diabetic peripheral neuropathy
DSN	Diabetic Specialist Nurses
E	Youngs Modulus
FBS	Fasting Blood Sugar
FE	Finite Element
FEA	Finite Element Analysis
G	Shear Modulus
GDM	Gestational Diabetes
Goniometer	A device shaped like a protractor to measure joint angles
HbA1c	Glycated Haemoglobin
Hyperglycaemia	Clinical term for high blood sugar
IWGDF	International Working Group Diabetic Foot
PP	Plantar Pressure
PPP	Peak Plantar Pressure
Pronation	Triplanar movement comprising abduction, eversion, and dorsiflexion
PTI	Pressure Time Integral
PVD	Peripheral vascular disease
ROM	Range of Motion
RSS	Risk Stratification Systems
Shore-00 hardness durometer	Shore hardness device used for soft materials and biological tissues
SIGN	Scottish Intercollegiate Guideline Network
SSOTP	Staffordshire and Stoke-on-Trent Partnership NHS Trust

T1DM	Type 1 Diabetes
T2DM	Type 2 Diabetes
UTFS	University of Texas Foot Risk Stratification
VPT	Vibration Perception Threshold (measurement of peripheral neuropathy)
WHO	World Health Organisation

1. Chapter 1: Introduction

1.1. Diabetes

Diabetes comprises of many disorders characterised by hyperglycaemia, also more commonly referred to as high blood sugar. Traditionally when referring to diabetes, there are two major types: type 1 diabetes (T1DM) and type 2 diabetes (T2DM), in addition to gestational diabetes (GDM), a form of diabetes that can occur during pregnancy (WHO, 2019). The distinction between T1DM and T2DM has historically been based on age at onset, degree of loss of pancreatic β-cell function, degree of insulin resistance, presence of diabetes-associated autoantibodies, and requirement for insulin treatment for survival (Leslie *et al.*, 2016).

T1DM has typically been found in younger persons. It is a complex process whereby genetic and environmental factors produce an autoimmune response, leading to the destruction of pancreatic β-cells resulting in an absolute insulin deficiency (Forbes and Cooper, 2013; Tamayo *et al.*, 2013). In contrast, T2DM incidence is typically associated with older persons, those that are overweight, and those that present with poor dietary choices. However, there is also growing evidence that indicates that T2DM can be associated with post viral incidence specifically the SARS-CoV-2 (COVID19) virus (Lim *et al.*, 2021; Rathmann, Kuss and Kostev, 2022). Additionally, there is also evidence to that

suggest genetic factors that relate an intolerance and reduced synthesis of glucose leading to T2DM (Hansen, 2002).

T2DM has traditionally been characterised and separated into subtypes depending on if the hyperglycaemia is caused by a decline in pancreatic islet secretory function or tissue resistance to insulin. T2DM is the most common type of DM, accounting for approximately 90%-95% and has become a major global public health problem, particularly in low and middle-income countries (Bi *et al.*, 2012).

Within recent years the classification of T1DM and T2DM has come under review (Kazi and Blonde, 2019), with the differentiation between T1DM and T2DM becoming less distinctive with an increasing prevalence of obesity at a young age, recognition of the relatively high proportion of incident cases of T1DM in adulthood and the occurrence of T2DM in young people. Secondly, developments in molecular genetics have allowed clinicians to identify growing numbers of subtypes of diabetes, with important implications for treatment choice in some cases. In addition, increasing knowledge of pathophysiology has resulted in a trend towards developing personalised therapies and precision medicine (Leslie *et al.*, 2016).

A new set of diabetes classifications has been recommended by the World Health Organisation (WHO) (WHO, 2019). This new set of classifications still differentiates between T1DM and T2DM; however, the classifications no longer differentiate between the subtypes of T1DM and T2DM and instead includes new types of diabetes referred to as "hybrid types of diabetes" and "other diabetes" in addition to GDM. Attempts to distinguish T1DM from T2DM among adults have resulted in this new "Hybrid Diabetes" category and includes two specific forms of diabetes: slowly evolving immune-mediated diabetes and ketosis-prone T2DM (Atkinson, Eisenbarth and Michels, 2014). In addition, "Other Diabetes" includes other specific types of diabetes that occur because of several factors ranging from genetic defects, diseases of the exocrine pancreas, endocrinopathies, infections, and drugs.

Within clinical care, diabetes is generally considered to be a lifelong condition, and as such, diabetes, especially T1DM and T2DM, have been associated and linked with several severe comorbidities and complications, including heart disease, stroke, blindness, kidney disease, nerve damage, and foot complications (van Acker *et al.*, 2014)

1.2. Prevalence and cost of diabetes

The rate of new cases of diabetes has been increasing exponentially over the last few years. As a result, the predicted worldwide prevalence of diabetes is thought to range between 500 million by the year 2025 (Boulton, 2000) up to 560 million by 2030 (Saeedi

et al., 2019). In Europe alone, it is estimated that between 46.3 and 80.2 million people currently have diabetes (Saeedi *et al.*, 2019).

Type 2 diabetes accounts for approximately 90% of this total and can be attributed to several factors, including ageing, a rapid increase in urbanisation, and obesogenic environments (Cho *et al.*, 2018; Saeedi *et al.*, 2019; WHO, 2019). Worryingly there has been a sharp rise in the number of cases of type 2 diabetes in younger adults in recent years, primarily due to sedentary living, high-energy dietary intakes and other, as yet unknown factors (Zimmet *et al.*, 2014). In addition, incidence rates of Type 1 diabetes are also rising, contributing to the increase in diabetes prevalence (Karvonen, 2006; Patterson *et al.*, 2009). The cause of this rise in the number of cases of type 1 diabetes remains unclear. Finally, An additional contributor to the increased prevalence is better survival (in some populations) of people with diabetes through early detection, improved management of diabetes, and, consequently, a reduction in premature mortality (Chatterjee, Khunti and Davies, 2017).

Current data shows that Asian countries, such as China and India (116 and 77 million cases respectively) have high rates of diabetes prevalence when compared to Western populations, with more than 80% of the people with diabetes currently living in low and middle-income countries (Federation, 2012). This represents a significant health challenge due to a lack of access to treatment, primarily due to a lack of resources.

The increase in the number of cases of diabetes can be seen in the expenditures of health care systems around the world. In 2010, global health expenditure due to diabetes was estimated to be USD 376 billion (12% of all global health expenditures). Moreover, by 2030, global health expenditure is expected to reach between USD 490 billion and USD 893 billion, representing an increase of 30 – 34% from 2010 (Zhang *et al.*, 2010; Zimmet *et al.*, 2014). However, this expenditure varies hugely by region. For instance, more than 90% of global health expenditure on DM is in the world's richest countries, 57% in North America, 28% in Europe, and 10% in the Western Pacific (Zhang *et al.*, 2010; Zimmet *et al.*, 2014). The direct and indirect costs associated with diabetes in the UK currently stands at GBP 23.7 billion per annum (Kerr, Rayman and Jeffcoate, 2014). This shows the burden that diabetes currently places on health care systems throughout the world.

1.3. The diabetic foot

Of the complications associated with diabetes, the diabetic foot, is one of the most common and costly. In the UK alone, up to 176 people per week (Source: Diabetes UK) have a limb amputated as a result of the diabetic foot, while the management of diabetic foot costs more than the five most costly forms of cancer combined. Up to 80% of these amputations could have been prevented with correct clinical management, and the issues relating to the diabetic foot presents a significant burden for health systems.

The World Health Organization (WHO) defines the diabetic foot as:

"*The foot of diabetic patients that has the potential risk of pathologic consequences including infection, ulceration and or destruction of deep tissues associated with neurologic abnormalities, various degrees of peripheral vascular disease and/or metabolic complications of diabetes mellitus in the lower limb"* (Abdulghani *et al.*, 2018).

The two leading causes of the diabetic foot are diabetic peripheral neuropathy and peripheral vascular disease, which are the two most common comorbidities of diabetes. More than half of diabetic patients who have been suffering from the disease for 15 years or more present with diabetic neuropathy (Boulton *et al.*, 2010). Diabetic peripheral neuropathy causes a loss of sensation within the extremities. This typically manifests itself within the feet but can also be found in the hands. This causes a loss in protective sensation and increases the likelihood of ulcer formation, and it has been shown that peripheral neuropathy is linked to higher plantar pressures in people with diabetes. Increases in plantar pressure are highly associated with skin breakdown and ulceration in people with diabetes and peripheral neuropathy (Lott *et al.*, 2007).

Peripheral vascular disease affects 8 – 13% of people with diabetes (Abbott *et al.*, 2005). This is a condition whereby the veins and arteries within the foot stiffen, in addition to an increase in blood viscosity and decreased red cell deformability (Tooke, 1989). In terms of the diabetic foot, the stiffening of the arteries and the increased blood viscosity leads to a reduction in the overall perfusion rate of the foot. This is the mechanism by which blood and nutrients reach the soft tissues within the foot. This causes the skin to

become starved of oxygen, also known as hypoxia (Tooke, 1989). A person with diabetes and peripheral vascular disease will develop distal ulcers or gangrene in up to 40% of cases due to the overall reduction in oxygen supplied to the distal tissues (Kannel, 1994).

When peripheral neuropathy and peripheral vascular disease are present simultaneously, they lead to what is known as diabetic foot syndrome, whereby the person is at a significantly greater risk of developing a diabetic foot ulcer.

1.3.1. Diabetic foot ulcers

A diabetic foot ulcer is an inherent failure of the foot's skin and plantar soft tissues and is the leading cause of amputation in people with diabetes. As previously stated, it is estimated that by 2025 more than 0.5 Billion people worldwide will be living with diabetes, and 15% of those will, at some point, develop a diabetic foot ulcer (Boulton, 2000).

A diabetic foot ulcer is defined as "any necrosis, gangrene, or full-thickness skin defect occurring distal to the ankle in a diabetic patient" (Schaper *et al.*, 2012). People with diabetes often have impairments with their immune systems, which reduces their ability to heal from wounds and directly increases their risk of infection (Leung, 2007). As ulcers act as an entry point for infections if left untreated or inadequately treated, these ulcers lead to severe complications such as partial foot amputations or, in the most severe cases, limb loss (Barshes *et al.*, 2013).

Within clinical practice, DFUs are often described without using a classification system, but in reference to likely ulcer aetiology (neuropathic versus ischemic versus neuroischemic) or foot location(Yotsu *et al.*, 2014). Neuropathic foot ulcers occur where this is DPN, but no ischemia caused by Peripheral Vascular Disease (PVD). Ischemic foot ulcers occur where there is PVD but no involvement with DPN. Finally, neuroischemic foot ulcers occur where the person has both DPN and ischemia resulting from PVD (Yotsu *et al.*, 2014; Armstrong, Boulton and Bus, 2017; Pena *et al.*, 2020). Each of the three types of diabetic foot ulcer described above has its own and shared mechanisms that lead to ulceration, with each type of ulceration increasing in severity and potential long-term complications (Pena *et al.*, 2020).

Neuropathic foot ulcers are most commonly associated with trauma and the mechanical breakdown of the plantar soft tissues due to the loss of protective sensation and foot deformity resulting from motor neuropathy (Pena *et al.*, 2020). The loss of protective sensation increases the vulnerability of the foot to physical and thermal trauma (Singh, Armstrong and Lipsky, 2005) due to the inability to detect the pain signals that warn of impending tissue trauma.

As stated in section 1.3, people with DPN also tend to have an impaired ability to distribute forces applied to the plantar surface of the foot due to the loss of protective sensation and the effects of motor neuropathy. Motor neuropathy is linked to the

development of foot deformities such as hammer toes, claw toes, prominent metatarsal heads, and pes cavus due to a weakening of the intrinsic muscles of the foot. The combination of the loss of protective sensation and the presence of foot deformity leads to increased plantar pressures, especially near to the bony prominences of the foot, such as the metatarsal heads and the calcaneus, hastening tissue damage leading to ulceration (Dinh and Veves, 2005; Lott *et al.*, 2007; Dinh *et al.*, 2012).

It is important to note, however, that not all foot ulcers occur because of mechanical damage. Neuropathic foot ulcers can also form as a result of infection. Ulceration as a result of infection is associated with autonomic sympathetic neuropathy and sudomotor dysfunction (Bowering, 2001; Vinik *et al.*, 2003; Boulton, 2008; Alexiadou and Doupis, 2012; Amin and Doupis, 2016). Autonomic neuropathy is linked to vasodilation and a reduction in the function of sweat and sebaceous glands of the foot. This, in turn, causes the skin of the foot to become warm and overly dry. As a result of losing the natural moisturising ability of the foot, the mechanical properties of the overlying skin change causing the skin to become more brittle and therefore more vulnerable to breaks, cracking and wound development (Bowering, 2001; Vinik *et al.*, 2003; Boulton, 2008; Alexiadou and Doupis, 2012; Amin and Doupis, 2016). The loss of skin integrity, as a result, provides an ideal site for microbial invasion, potentially leading to infection and potentially subsequent ulceration.

Peripheral vascular disease is the leading cause of ischemic foot ulcers and is commonly found in patients with diabetes (Tapp *et al.*, 2007; Paneni *et al.*, 2013). Approximately 50% of patients with a diabetic foot ulcer have coexisting PVD (Prompers *et al.*, 2007, 2008; Hinchliffe *et al.*, 2016). Peripheral vascular disease is associated with atherosclerotic blockages of large and medium-sized arteries, such as femoropopliteal and aortoiliac vessels, which lead to acute or chronic ischemia whereby ulcers can develop and instantaneously progress to gangrene due to inadequate blood flow (Noor, Zubair and Ahmad, 2015; Pena *et al.*, 2020). Additionally, PVD can cause a reduction in the supply of blood to the peripheries, also known as perfusion. This is the primary mechanism whereby blood and nutrients are delivered to the soft tissues within the foot. A reduction in prefusion is associated with impaired wound healing, increased rates of infection and higher rates of lower extremity amputation (Ghanassia *et al.*, 2008)

When looking at the breakdown of the three different forms of ulceration (neuropathic, ischemic, neuroischemic), it is estimated that 90% of foot ulcers have neuropathy as a common factor (Alexiadou and Doupis, 2012), with approximately 45% to 60% of all ulcerations in patients with diabetes being mainly due to neuropathy (Boyko *et al.*, 1999; Reiber *et al.*, 1999; Abbott *et al.*, 2002; Boulton, Kirsner and Vileikyte, 2004), with the leading causes of ulceration being foot deformity, trauma, and the use of inappropriate footwear (Boulton, 2008). It is also estimated that approximately 45% of the ulcers are due to combined neuropathic and ischemic factors, especially in older patients (Boyko *et al.*, 1999; Reiber *et al.*, 1999; Abbott *et al.*, 2002; Boulton, Kirsner and Vileikyte, 2004;

Boulton, 2008) where the presence of PVD is 2-8 times higher compared to younger people with diabetes (Alexiadou and Doupis, 2012).

The high percentage that neuropathy plays in ulceration is reflected in this thesis study population. All 40 recruited participants had neuropathy; additionally, all participants were screened for PVD, with 7 out of the 40 (17.5%) presenting with PVD.

1.4. Clinical Assessment of the Diabetic Foot

As the diabetic foot entails a number of different serious complications, such as neuropathy, peripheral vascular disease, retinopathy or nephropathy, these complications put patients at different levels of risk of foot ulceration, lower limb amputation or, in the most severe cases, death. National guidelines currently recommend that patients classified as high-risk of developing a foot ulcer routinely see members of their diabetic care team in an attempt to prevent diabetic foot ulcers from forming. Various groups such as the American Diabetes Association (ADA) and International Working Group Diabetic Foot (IWGDF) have published guidelines that recommend foot screening for all diabetic patients at least every 12 months (Boulton *et al.*, 2008), with those patients that are at greatest risk for serious foot problems visiting podiatric care services an average of three to four times a year (Gabbay *et al.*, 2011). However, this is not an easy task, which could increase the risk of ulceration if not carried out appropriately.

1.4.1. Current Clinical Practice for assessing the diabetic foot

Clinical guidelines for diabetic foot care state that "all diabetic patients should be examined at least once a year for potential foot problems, and patients with demonstrated risk factor(s) should be examined more often (every 1-6 months). The absence of symptoms does not mean that the feet are healthy since the patient can have neuropathy, peripheral vascular disease or even an ulcer without any complaints.

Typically, diabetic foot ulcers occur when two or more risk factors for ulceration are present at the same time. The two most common risk factors are diabetic peripheral neuropathy and abnormally high plantar pressures (Lepäntalo *et al.*, 2011).

The presence of peripheral vascular disease and foot deformity such as claw/hammer toe are also risk factors for ulcer formation (Boulton et al., 2010; Malhotra, Bello and Kominsky, 2012; Fernando et al., 2013). The path to diabetic foot ulceration can be seen in Figure 1-1.

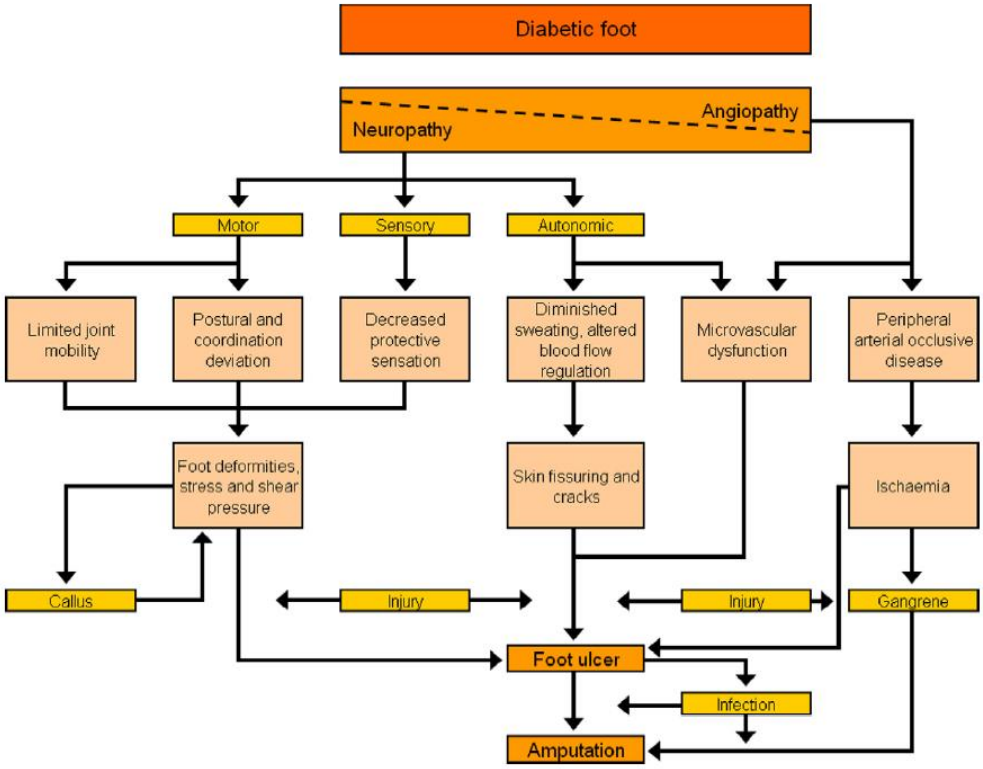


Figure 1-1: Pathway to ulceration adapted from (Lepäntalo *et al.*, 2011)

In addition to the previously mentioned risk factors, other complications that contribute to ulceration include poor vision, limited joint mobility and cardiovascular and cerebrovascular disease (Jeffcoate and Harding, 2003; Boulton *et al.*, 2010; Turns, 2013). Of these additional complications, limited joint mobility is of great interest as limited joint mobility directly affects the biomechanics of the foot (Mueller *et al.*, 1989; Zimny, Schatz and Pfohl, 2004). Limited joint mobility within the foot and ankle as a result of

peripheral neuropathy has a direct effect on the gait pattern of people with diabetes and diabetic peripheral neuropathy by limiting foot flexibility and restraining the forward progression of the body during the stance phase of gait (Fernando *et al.*, 1991, 2013).

Due to limited joint range of motion, when compared to healthy participants, people with diabetes and diabetic peripheral neuropathy walked slower and had a reduced stride length. (Fernando *et al.*, 1991). As a result, people with diabetic peripheral neuropathy spend a more extended period of time in the stance phase of gait compared to subjects with diabetes and no peripheral neuropathy. The lack of normal joint mobility and the altered gait pattern leads to increased plantar pressures due to changes in loading magnitude and loading pattern, which increase the risk of ulceration (Payne, Turner and Miller, 2002; Turner *et al.*, 2007).

Each of these individual complications that are associated with diabetic foot ulceration, such as peripheral neuropathy, peripheral vascular disease, foot deformity, limited range of motion, etc. can therefore be taken and used to stratify (group) people with diabetes into risk categories based on their likelihood of developing a foot ulcer. Thus, these systems are commonly referred to as Risk Stratification Systems.

There are currently five main risk stratifications systems used throughout the world to assess the risk of a person with diabetes developing a foot ulcer. These are the International Working Group on Diabetic Foot (IWGDF), University of Texas Foot Risk

Stratification (UTFS), Scottish Intercollegiate Guideline Network (SIGN), American Diabetes Association (ADA) and The Seattle Diabetic Foot Study (Boyko *et al.*, 2006). Each of these risk stratification systems has its own criteria for classifying a person as a low, medium, and high risk of ulceration; however, common complications between systems include the presence of peripheral neuropathy, peripheral vascular disease, and previous history of ulceration. Furthermore, whilst these systems consider the clinical aspects of ulceration, they do not account for the direct physical and biomechanical changes to the foot due to diabetes.

1.5. Biomechanical risk factors for diabetic foot ulceration.

As previously mentioned, a diabetic foot ulcer occurs as a result of the inherent failure of the plantar soft tissues of the foot. The primary cause of this failure is a result of repeated overloading of the soft tissues of the foot as a result of diabetic peripheral neuropathy. This is due to the loss of the protective sensation to the foot due to peripheral neuropathy. This repeated overloading of the plantar soft tissues of the foot causes microdamage and microtears within the tissues of the foot. It has been shown within the literature to be a contributing factor to skin breakdown in people with diabetes and diabetic peripheral neuropathy, which can ultimately lead to a diabetic foot ulcer (Abouaesha *et al.*, 2001; Patry *et al.*, 2013).

Biomechanical factors that are commonly directly associated with diabetic foot ulceration include an increase in plantar soft tissue stiffness, increases in skin hardness, increases in plantar pressure, and changes in the morphology of the foot manifesting as

foot deformities such as claw/hammer toes in addition to a reduction in the range of motion of the foot and ankle during gait.

In particular current literature has shown that the biomechanical measurements of plantar pressure and soft tissue biomechanics can contribute to assessing the likelihood that a person with diabetes will ulcerate (Boulton *et al.*, 2008; Armstrong, Boulton and Bus, 2017; Naemi *et al.*, 2017). However, these biomechanical measurements have not been incorporated into routine clinical assessment due to poor quality of evidence, cost, and lack of clinically viable techniques.

Previous studies have indicated that the mechanical properties of the plantar soft tissue change as a result of diabetes; however, the causes of these changes and their possible implications are not yet fully understood. Literature shows that in people with diabetes and diabetic peripheral neuropathy, the plantar soft tissues of the foot tend to be thinner (Chao *et al.*, 2010), stiffer (Klaesner *et al.*, 2002; Chao, Zheng and Cheing, 2011), harder (Piaggesi *et al.*, 1999) and also tend to have less energy return efficiency (Hsu *et al.*, 2000). The measurements of plantar soft tissue mechanical properties to enhance the clinical management of the diabetic foot is currently limited by the availability of clinically viable testing techniques.

The existing methods used within the literature to quantitatively assess the mechanical properties of the plantar soft tissue of the foot are based on the use of complex, bespoke

indentation testing devices (Zheng *et al.*, 2000; Hsu, Lee and Shau, 2002; Klaesner *et al.*, 2002; Erdemir *et al.*, 2006; Spears and Miller-Young, 2006; C C Hsu *et al.*, 2007; Chih Chin Hsu *et al.*, 2007; Behforootan, P. E. Chatzistergos, *et al.*, 2017a, 2017b) which are not yet clinically viable. On the other hand, the use of ultrasound elastography systems (Naemi *et al.*, 2016, 2017) can provide a clinically viable solution for the assessment of the mechanical properties of the foot; however, considerations must be made with regards to cost in the context of low resource settings (i.e. developing countries).

The measurement of Shore hardness, using a handheld durometer, has successfully been used to assess soft tissue biomechanics in vivo and appears to be a good candidate to fill this gap (Falanga and Bucalo, 1993; Aghassi, Monoson and Braverman, 1995; Romanelli and Falanga, 1995; Piaggesi *et al.*, 1999; Thomas *et al.*, 2003; Charanya *et al.*, 2004; Kissin *et al.*, 2006; Periyasamy, Anand and Ammini, 2012). Specifically, Shore hardness has been used to investigate the effect of various skin pathologies such as scleroderma (Falanga and Bucalo, 1993; Aghassi, Monoson and Braverman, 1995), systemic sclerosis (Kissin *et al.*, 2006) and lipodermatosclerosis (Romanelli and Falanga, 1995) on skin biomechanics. In addition, Shore hardness has been previously used within the diabetic foot (Piaggesi *et al.*, 1999; Thomas *et al.*, 2003; Charanya *et al.*, 2004; Periyasamy, Anand and Ammini, 2012) to measure foot sole hardness and to investigate its relationship with plantar pressure in people with and without diabetic peripheral neuropathy. These studies highlight the potential clinical value of Shore hardness in assessing the

mechanical properties of the plantar soft tissues for the prevention of diabetic foot ulcers.

While Shore hardness could be used to assess the internal changes to the mechanical properties of the plantar soft tissues that may lead to ulceration, literature has indicated that assessing plantar pressure can aid in the clinical management of the diabetic foot by examining and quantifying the external factors that may lead to ulceration. However, plantar pressure measurements are not currently considered part of routine clinical practice due to poor quality of evidence and high cost (Leese *et al.*, 2006; Crawford *et al.*, 2007, 2015; Schaper *et al. al.*, 2016).

Several factors are associated with an increase in plantar pressure in people with diabetes these include foot deformity, history of previous ulceration and/or amputations, changes in soft tissue stiffness, and limited joint movement (Payne, Turner and Miller, 2002; Waldecker, 2012; Barn *et al.*, 2015; Searle *et al.*, 2017). These factors occur in people with diabetes as a result of structural changes within both the tendons and plantar soft tissues of the foot. The effect of these structural changes appears to be greatest in those people with diabetes and diabetic peripheral neuropathy. These structural changes lead to a decrease in elasticity of both the plantar soft tissues and tendons, in addition to a reduction in the tensile strength of the tendon. These changes in the mechanical properties subsequently increase the instability at joints of the foot and ankle, causing subluxations or an overall increase in the stiffness of the foot.

As a result of these internal changes to the morphology of the foot, a number of studies have aimed to try and predict external plantar pressures in people with diabetes based on a varying number of internal factors (Morag and Cavanagh, 1999; Payne, Turner and Miller, 2002; Mueller *et al.*, 2003; Barn *et al.*, 2015). These internal factors included measurements such as foot and ankle range of motion (Morag and Cavanagh, 1999; Payne, Turner and Miller, 2002), soft tissue properties (Payne, Turner and Miller, 2002), neuropathy (Payne, Turner and Miller, 2002; Barn *et al.*, 2015), joint angles (Payne, Turner and Miller, 2002), foot deformities (Mueller *et al.*, 2003; Barn *et al.*, 2015), and electromyography (EMG) (Morag and Cavanagh, 1999). Based on these factors, these studies were able to predict plantar pressures at the heel and the 1st Metatarsal head, which are the most common locations for foot ulcer formation.

Overall, the results of the previous studies illustrate that plantar pressures can be predicted by a range of different internal biomechanical factors and indirect individual characteristics such as BMI, age, duration of diabetes, and history of ulceration. However, to measure the different biomechanical parameters used in these studies, such as joint angle and joint motion, techniques that are not readily available were used. This included CT scans and X-rays to assess joint angle and joint motion (Payne, Turner and Miller, 2002; Mueller *et al.*, 2003).

Therefore, to fully explore and understand the role that these external and internal biomechanical factors of plantar pressure and plantar soft tissue mechanical properties have on ulceration, there is a need for simple, cost-effective and reliable methods to assess these factors within the clinic setting. This is specifically relevant to low resource settings (i.e., developing countries) where access to sophisticated equipment such as ultrasound elastography or plantar pressure platforms is limited.

1.6. Aim and objectives of this thesis

Diabetic foot ulcers are a disabling complication for both the patient and for health care services across the world. Given the cost, reduction in the patient's quality of life, and the risk of limb amputations, there is an urgent need to be able to measure the biomechanical factors that relate to an increase in the risk of diabetic foot ulceration. Two main biomechanical factors linked to an increase in ulceration are changes in the plantar soft tissues mechanical properties and increases in plantar pressure, representing internal and external biomechanical risk factors. Unfortunately, these important biomechanical risk factors are not commonly assessed within clinical practice due to a lack of clinically applicable measurement techniques.

Therefore, the aim of this PhD is to investigate if the measurement of Shore hardness can be used to assess the mechanical properties of the plantar soft tissues and to predict plantar pressures during walking in people with diabetes.

The objectives of this PhD were, therefore, to:

1. Study the physical meaning of the measurement of Shore hardness and assess its feasibility in assessing the mechanical properties of the plantar soft tissues (Chapter 3).
2. To study the clinical relevance of the Shore hardness measurement by investigating its relationship with parameters that were previously found to be associated with the risk of ulceration (Chapter 3).
3. Assess the efficacy of the Shore hardness measurement in quantifying the stiffness of the skin or the underlying subcutaneous soft tissue (Chapter 4).
4. Investigate if changes in plantar pressure during walking can be predicted using Shore hardness and foot range of motion (Chapter 5).

1.7. Scope and Boundaries

1.7.1 Scope of the Investigation

The scope of the reported work is as follows:

1. To investigate, through the use of FE analysis, the physical meaning of the measurement of Shore hardness and whether it can be considered an indirect measurement of stiffness.
2. To assess the ability of Shore hardness to monitor changes in the mechanical properties of the skin or the underlying subcutaneous soft tissue of the heel pad.
3. To assess the clinical viability of Shore hardness by investigating the ability of Shore hardness to confirm established associations between changes in the

mechanical properties of the plantar soft tissue and loading, blood biochemistry, and age.

4. To assess the efficacy of the Shore hardness measurement in quantifying the stiffness of the skin or the underlying subcutaneous soft tissue using large and small diameter Shore hardness indenters.
5. To investigate if regional plantar pressures for the forefoot, midfoot, and heel can be predicted using a 2D motion analysis and the plantar soft tissue Shore hardness.

1.7.2 Boundaries of the Investigation

The boundaries of the reported work are as follows:

1. To assess the efficacy of quantifying the stiffness of the skin or the underlying subcutaneous soft tissue, only the effect of indenter width and indenter length is investigated. This is to allow the effect of indenter size to be isolated and to gain a further understanding of the parameters that may affect the measurement of indentation of a layered structure and to investigate if it would be possible to isolate the effect of changes in the mechanical properties of each constituent layer by using different sizes of indenter.
2. This work will not look at the development of a specific new device for the assessment of the mechanical properties of the skin and subcutaneous soft tissues of the foot. The aim however was to assess if the diameter of the Shore hardness indenter can be changed to more accurately assess and differentiate between the mechanical properties of the plantar soft tissue skin and

subcutaneous layer with a view of increasing the clinical applicability of the results in diabetic foot.

3. Finally, while acknowledging the effect that external factors such as foot deformities, blood biochemistry, and demographics have on the measurement of plantar pressure, these parameters are not included in the prediction models. is due to the fact that these changes should show their effect on plantar pressure through the changes in biomechanical measures such as Shore hardness and range of motion. Hence only the Shore hardness and range of motion were included in the model as parameters that directly affect plantar pressures

1.8. Structure of the Thesis

This thesis is set out in 6 chapters.

Chapter 1 introduces the subject matter, providing a background to the thesis. This includes an introduction to diabetes and the diabetic foot, an overview of current clinical practice and highlights the biomechanical risk factors associated with ulceration. This first chapter also highlights the rationale and need for this research in addition to the scope, boundaries, aims and objectives.

Chapter 2 is a review of the current literature. This chapter aimed to explore current clinical practice for preventing diabetic foot ulcers, specifically the use of risk stratification systems to assess ulceration risk and to highlight the gaps within these

systems. The chapter starts with an introduction to the diabetic foot and the five main risk stratification systems currently in use. The gaps identified in the current risk stratification systems included the lack of biomechanical risk factors, particularly the mechanical properties of the plantar soft tissue and the assessment of plantar pressure. This chapter then goes on to explore the methods used to assess both the mechanical properties of the plantar soft tissues and plantar pressures and highlights that there is a need for a simple, clinically applicable method to measure the mechanical properties of the plantar soft tissues and that the measurement of Shore hardness may be a suitable new method to assess these risk factors. By summarising the literature at the end of this chapter, the measurement of Shore hardness appears to be a good candidate to fill this need; however, some key questions remain regarding its actual physical meaning and its clinical relevance.

Chapter 3 addresses the first and second objectives to assess the physical meaning of the measurement of Shore hardness and assess its feasibility in assessing the mechanical properties of the plantar soft tissues. It does this through a combination of finite element analysis to assess the physical meaning and a clinical study to assess its feasibility of assessing the mechanical properties in a clinical setting.

The clinical relevance of Shore hardness was assessed by confirming the association between Shore hardness and previously established parameters, such as demographics,

blood biochemistry, and loading, that were found to increase the risk of mechanical trauma to the foot in a cohort of 40 people with diabetic neuropathy.

Chapter 4 addresses the third objective, the efficacy of Shore hardness measurement in quantifying the stiffness of the skin or the underlying subcutaneous soft tissue whereby the aim of this study is, through the use of finite element analysis, to examine the effect of the size of a Shore hardness indenter on the measurement of indentation in a layered structure and to understand what does this measurement represent. Additionally, this chapter represents the secondary aim of this study to investigate the feasibility of measuring the mechanical properties of each layer, such as skin or subcutaneous soft tissue, directly using different sizes of Shore hardness indenters.

Chapter 5 addresses the fourth and final objective to investigate if changes in plantar pressure during walking can be predicted using Shore hardness and foot range of motion. This was conducted through a clinical study using the same participant population as in Chapter 3.

Finally, Chapter six provides a summative discussion, conclusions and recommendations. Each study will have a discussion, where the various issues of each investigation will be critiqued and summarised, tying together the findings of the whole research. This will result in a summary of evidence regarding the use of the measurement of Shore

hardness to assess the mechanical properties of the plantar soft tissues and plantar pressures during walking in people with diabetes.

A thesis flow chart [Figure 1-2 and Figure 1-3] has been included to highlight the journey taken through this thesis and to give an overview of the key disciplines involved, such as podiatry, endocrinology, clinical practice, tissue engineering, and finite element analysis.

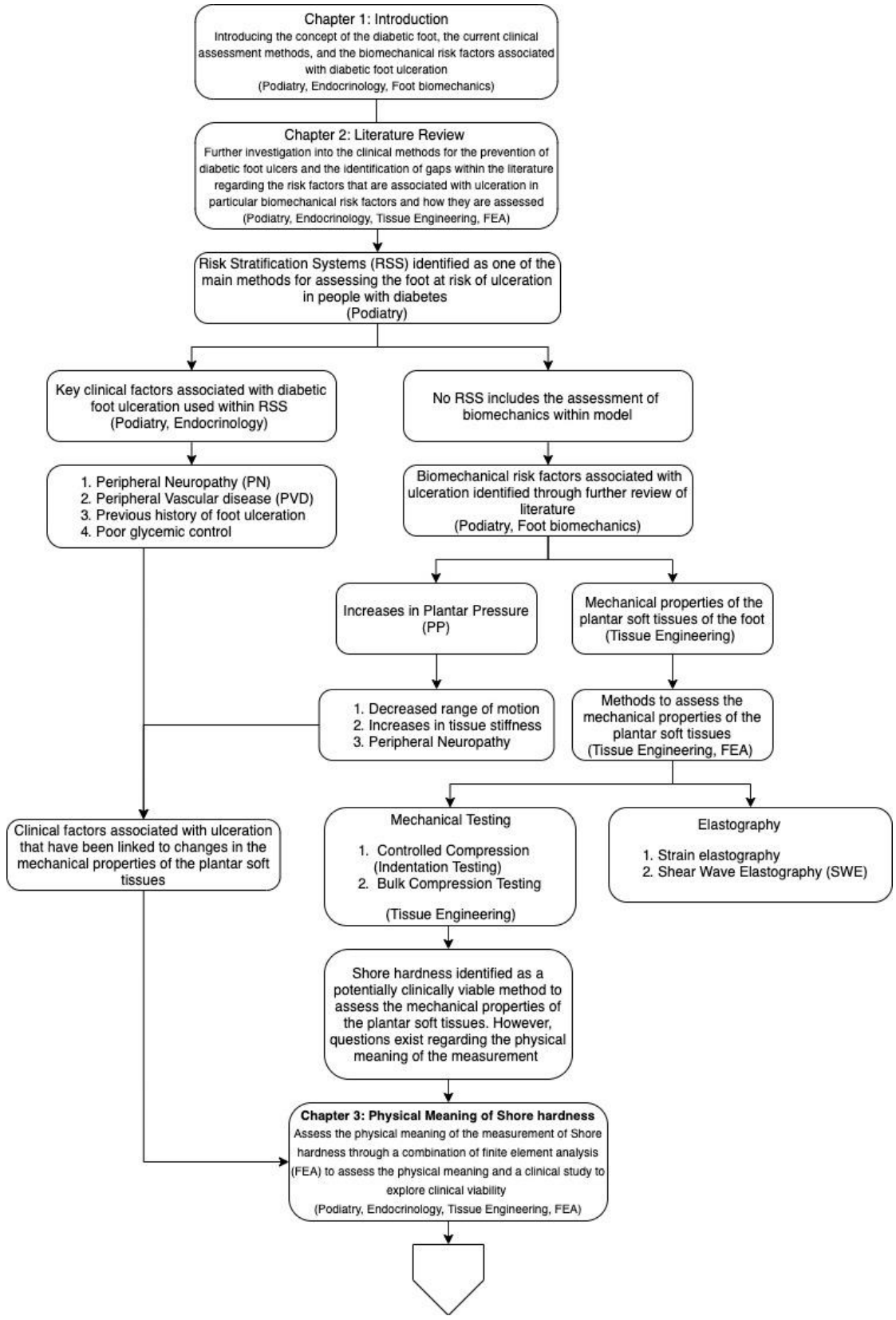


Figure 1-2: Thesis flowchart highlighting the journey taken the various different disciplines involved

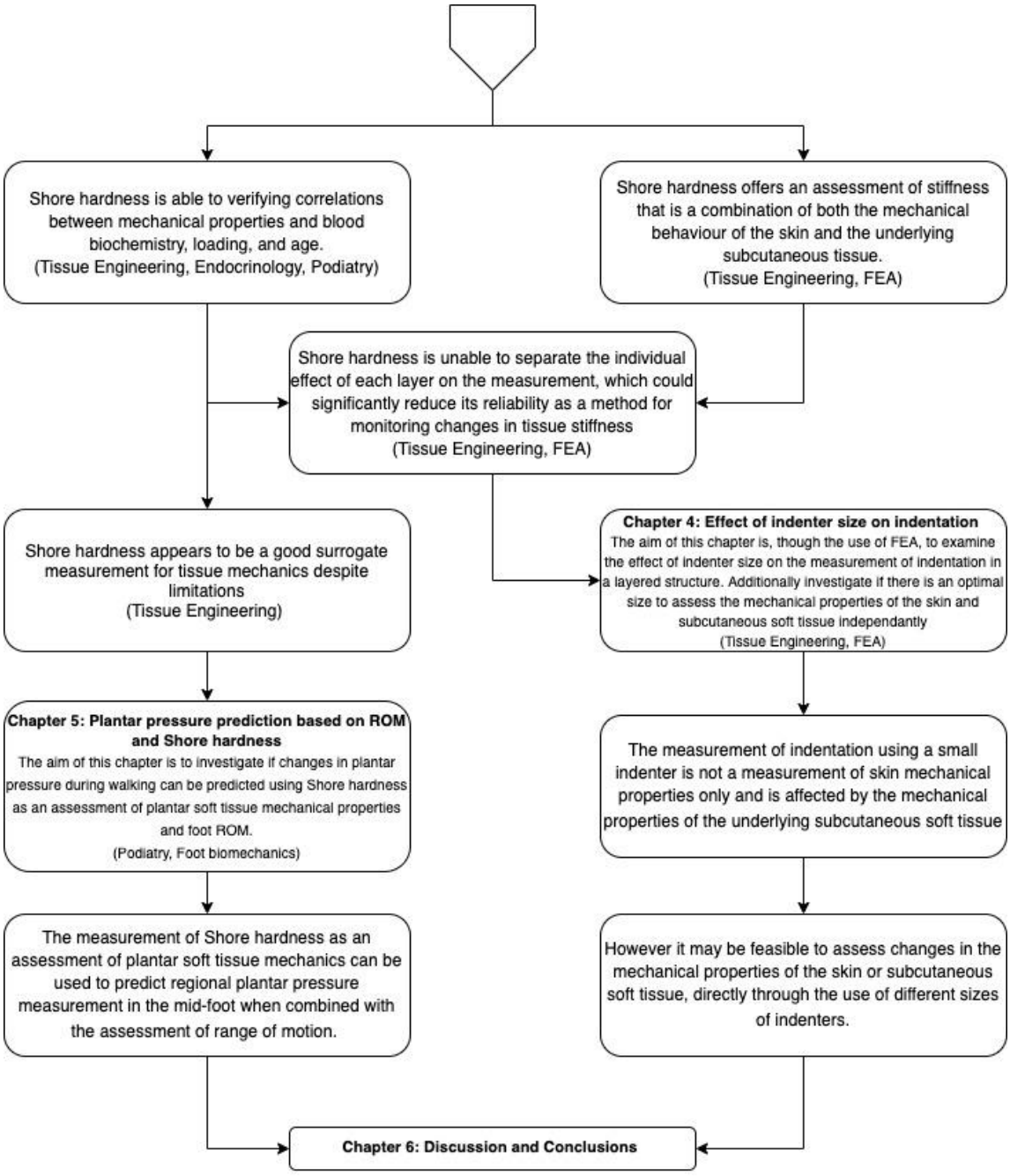


Figure 1-3: Thesis flowchart highlighting the journey taken the various different disciplines involved (cont.)

1.9. Ethical Approval

For data collection within the UK, appropriate ethical approval was sought, and granted by Staffordshire University Ethics Committee, Staffordshire and Stoke-on-Trent Partnership NHS Trust (SSOTP), and the National Research Ethics Service, Ethics Committee West Midlands – Black Country (Ref: 17/WM/0019). This ethical approval was specifically to recruit people with diabetes at high risk of ulceration from podiatry clinics within SSTOP. All participants provided written informed consent.

However, during the duration of this study, several issues occurred which severely limited recruitment for this research and subsequent data collection. Prior to the successful ethical approval for this data collection, routine foot care and foot examinations were performed by the podiatry teams within SSOTP. However, during the review process, the primary care pathway for people with diabetes was changed within NHS England. Routine foot examinations for people with diabetes changed to being performed within GP clinics by diabetic specialist nurses (DSN) and practice nurses[1]. Only patients with active diabetic foot ulcers and/or previous history of ulceration were referred to the podiatry teams[2].

To change the setting for patient recruitment from the podiatry clinics to GPs, a new, separate ethical approval would have been required. Therefore, the decision was made

[1] https://www.diabetes.org.uk/guide-to-diabetes/complications/feet/what-can-i-expect-at-my-annual-foot-check
[2] https://www.mpft.nhs.uk/services/podiatry

to stay at the podiatry clinics already approved and see how many participants could still be recruited. As a result of this, only a total of 9 participants were recruited. Due to the differences in demographics, these 9 participants have not been included within the data set used within this thesis.

Regarding the main data collected in the thesis (from 40 patients in India at Sri Ramachandra University and Dr A. R. Ramachadran's Diabetes hospital), ethical approval was granted based on the documents submitted and approved by Staffordshire University and the National Research Ethics Service. The participant information sheet and consent form were translated into the local language (Tamil). All participants provided written consent prior to commencing testing

All documents pertaining to obtaining ethical approval can be found in Appendices I-X

2. Chapter 2: Literature Review

2.1. The diabetic foot and current clinical practice

Diabetic foot ulcers are produced when two or more risk factors are present simultaneously (Lepäntalo *et al.*, 2011). The two most common risk factors identified are peripheral neuropathy and abnormally high plantar pressures (Lepäntalo *et al.*, 2011). The presence of peripheral vascular disease and deformity are also risk factors for ulcer formation (Boulton *et al.*, 2010; Malhotra, Bello and Kominsky, 2012; Fernando *et al.*, 2013)

A patient suffering from diabetic foot syndrome will not develop an ulcer spontaneously; a combination of factors will ultimately result in skin breakdown and ulceration. Therefore, it is of fundamental importance to identify the main risk factors leading to ulceration. Common risk factors closely associated with an increased risk of developing a foot ulcer are peripheral neuropathy, peripheral vascular disease, and a previous history of diabetic foot ulceration(Crawford *et al.*, 2015).

These risk factors associated with ulceration can be taken and used to stratify people with diabetes into risk categories based on their likelihood of developing a foot ulcer. Clinical guidelines for diabetic foot care state that “all diabetic patients should be examined at least once a year for potential foot problems, and patients with demonstrated risk factor(s) should be examined more often (every 1 -6 months)”. These

systems are commonly referred to as Risk Stratification Systems and are used to identify the patient's risk level.

2.2. Risk Stratification Systems

There are currently five main accepted risk stratification systems in use worldwide that categorize people with diabetes into risk groups based on the clinical signs present at the time of examination. These clinical signs include the presence of peripheral vascular disease, loss of peripheral sensation, foot deformity, and previous history of ulceration. A systematic review conducted by Monteiro-Soares and co-workers (Monteiro-Soares, Boyko, *et al.*, 2012) outlines these five main systems. These systems are the International Working Group on Diabetic Foot (IWGDF) (Monteiro-Soares, Vaz-Carneiro, *et al.*, 2012), the University of Texas Foot Risk Stratification (UTFS) (Lavery *et al.*, 1998), Scottish Intercollegiate Guideline Network (SIGN) (SIGN, 2001, 2010), American Diabetes Association (ADA) (Mayfield *et al.*, 1998), and The Seattle Diabetic Foot Study (Boyko *et al.*, 2006). The systematic review by Monteiro-Soares and co-workers (2012) outlines the differences between the clinical diagnostic measurements used in these systems in addition to the measurements that are common across systems (Monteiro-Soares *et al.*, 2011).

Table 2-1: Summary of the five main risk stratification systems indicating the risk factors associated with each system. Adapted from (Monteiro-Soares et al., 2011)

Stratification	Variables										
	DN	PVD	Foot deformity	Previous ulcer	Previous amputation	Visual impairment	Physical impairment	Callus	HbA_{1c}	Tinea pedis	Onychomycosis
UTFRS	O		O	O	O						
IWGDF	O/R	O/R	O/R	O/R	O/R						
SIGN	O/R	O/R	O/R	O/R	O/R	O/R	O/R	O/R			
ADA	O/R	O/R	O/R	O/R	O/R						
Boyko et al.	O/R			O/R	O/R	O/R			O/R	O/R	O/R

DN, diabetic neuropathy; O, present in the original stratification; R, present in the revised stratification

2.2.1. International Working Group on the Diabetic Foot (IWGDF)

The IWGDF was created by 45 expert clinicians and researchers and involves five different variables, including diabetic neuropathy (DN), peripheral vascular diseases (PVD), foot deformities, previous ulcers and previous amputations. Since its inception, it has had a few modifications, mainly to subdivide the groups to provide better grouping. (Monteiro-Soares, Vaz-Carneiro, *et al.*, 2012)

2.2.2. University of Texas Foot Score

UTFS was first described in 1998 by Lavery and colleagues (Lavery *et al.*, 1998) using a case-controlled study of 225 age-matched patients, 46.7% male, with a ratio of approximately 1:2 cases: controls (76 case-patients and 149 control subjects). Case patients were defined as subjects who met the enrolment criteria and had existing foot ulceration or a recent history of foot ulceration. Control subjects were defined as subjects with no history of foot ulceration. Stepwise regression modelling was used to develop the model. Their results indicated that an elevated plantar pressure (>65 N/cm2), history of amputation, lengthy duration of diabetes (>10 years), foot deformities (hallux rigidus or hammertoes), male sex, poor diabetes control (glycosylated haemoglobin>9%), one or more subjective symptoms of neuropathy, and an elevated vibration perception threshold (>25 V) were significantly associated with foot ulceration. In addition, 59 patients (78%) with ulceration had a rigid deformity directly associated with the site of ulceration.

When looking at the tests that can easily be incorporated into a routine clinical examination of a diabetic patient's foot, those patients that presented with only peripheral neuropathy and no other risk factors were at 1.7 times greater risk for ulceration when compared to the control subjects. Patients with neuropathy and foot deformity were 12.1 times more likely to have an ulcer. Patients with neuropathy, deformity and history of amputation were 36.4 times more likely to develop a wound. As such, these are described as parameters that increase the levels of risk used for this system

There has been no additional research investigating the effectiveness of this system. Based on the data provided by (Lavery *et al.*, 1998), this system's sensitivity, specificity, and accuracy cannot be calculated. As such, there have been no amendments made to the parameters that were originally selected. Due to the study being a case-control design and the lack of follow-up research being performed, the system's efficacy in assessing the risk of diabetic foot ulcer incidents is limited. As this system is now 23 years old and the treatment and care of diabetes have now changed, it is unlikely that there will be any future follow up being performed with regards to the sensitivity, specificity, and accuracy of the proposed model by (Lavery *et al.*, 1998).

2.2.3. Scottish Intercollegiate Guidelines Network (SIGN)

At the same time as the IWGDF, another system was developed called SIGN, initially published in 2001(SIGN, 2001). It has since been superseded by a revised version in 2010 (SIGN, 2010) and is based on a multidisciplinary, evidence-based systematic review. This

system is one of the most elaborate, using seven different parameters diabetic neuropathy, peripheral vascular disease, foot deformities, previous ulcers and amputations, visual and physical impairments and evidence of callus on the feet. It has clearly laid out groups whereby if a person presents with no risk factors, they are low risk; one risk factor classifies them as being at medium risk, and those with two or more factors make them at high risk of forming an ulcer.

This risk stratification system is one of the few that has been validated (Leese et al., 2006), but the system was not in its original format. As part of the study by Leese et al. (2006) intra-observer agreement of the stratification system was assessed using 50 participants and two healthcare professionals; this led to a kappa value of 0.95. The study also shows that from individuals that were classified as high risk, 29.4% of participants developed a foot ulcer. For the medium-risk group, only 2.3% developed an ulcer (Leese et al., 2006). This indicated that other factors and comorbidities might affect those at the highest risk that are not covered by both the original system and the modified version. Unfortunately, there has been no recent research looking into the current iteration's validity.

2.2.4. The American Diabetes Association (ADA)

The ADA risk stratification system is based on a literature review (Mayfield *et al.*, 1998). It stated that if a person presented with diabetic peripheral neuropathy, altered biomechanics, peripheral vascular disease, foot deformities, previous ulcers or amputation, they are classed as high risk and have the greatest risk of ulcer development (Mayfield *et al.*, 1998). The altered biomechanics includes evidence of increased pressure, bony abnormalities and limited joint mobility (Mayfield *et al.*, 1998). In 2008 a modification was proposed (Boulton *et al.*, 2008) through a task force asked to concisely summarize the literature to form a comprehensive foot exam. The system aims to reduce the occurrence of diabetic foot ulcers by grading the risk based on the estimated cumulative risk of ulceration. This task force was formed with members from primary care, orthapeadic and vascular surgery, physical therapy, podiatric medicine and surgery and members of the American Association of Clinical Endocrinologists.

Risk category	Definition	Treatment recommendations	Suggested follow-up
0	No LOPS, no PAD, no deformity	• Patient education including advice on appropriate footwear.	Annually (by generalist and/or specialist)
1	LOPS ± deformity	• Consider prescriptive or accommodative footwear. • Consider prophylactic surgery if deformity is not able to be safely accommodated in shoes. Continue patient education.	Every 3–6 months (by generalist or specialist)
2	PAD ± LOPS	• Consider prescriptive or accommodative footwear. • Consider vascular consultation for combined follow-up.	Every 2–3 months (by specialist)
3	History of ulcer or amputation	• Same as category 1. • Consider vascular consultation for combined follow-up if PAD present.	Every 1–2 months (by specialist)

Figure 2-1: ADA risk stratification system based on comprehensive foot examination. Adapted from (Boulton et al., 2008)

Figure 2-1 shows the system created by Boulton et al. (2008); this is a very basic system that only considers two symptoms of diabetes at a time to define patients into risk groups. Therefore, this system can potentially miss allocate the risk easily, leading to unnecessary additional care and wasting valuable resources. To date, no study has been conducted to look at the sensitivity and specificity of this system. As such, it is difficult to definitively say if this system can reduce the possible chance of a person developing a diabetic foot ulcer.

2.2.5. The Seattle Diabetic Foot Study

The Seattle Diabetic Foot Study was developed through a study that aimed to evaluate "individual and combined effects of commonly available clinical information in the prediction of diabetic foot ulcer occurrence" (Boyko *et al.*, 2006). Its parameters, which were identified through Cox proportional hazard regression models, were diabetic peripheral neuropathy, previous history of ulceration and amputations, visual impairments, HbA1c (glycated haemoglobin), tinea pedis (athlete's foot) and onychomycosis (fungal nail infection).

Cox proportional hazards regression is a method of conducting survival analysis whereby it examines the effect of several variables upon the time a specified event takes to happen (Fox, 2002). When looking at the diabetic foot, the outcome of interest is the development of a foot ulcer.

The results of the proportional hazard model gave a continuous score equation that allocates participants into risk groups based on weighted odds ratios. The score was obtained from the following equation: score = A1C × 0.0975 + 0.7101 (neuropathy present) + 0.3888 (poor vision) − 0.3206 (tinea pedis present) + 0.4579 (onychomycosis present) + 0.7784 (past history of foot ulcer) + 0.943 (past history of lower limb amputation). A score of ≥2.62 places a subject in the highest risk quartile. They showed that through commonly available clinical information, this model could predict the development of diabetic foot ulcers over one and five year periods of time with a high degree of accuracy.

2.3. Gaps in Risk Stratification Systems

Biomechanical risk factors such as elevated plantar pressure (>65N/cm^2) (Lavery *et al.*, 1998), foot deformities (hallux rigidus or hammertoes), and evidence of callus on the feet are rare among the parameters that were considered or which were identified as significant in the prediction of diabetic foot ulcers. Furthermore, of the five main risk stratification systems, only the University of Texas Foot Score Systems and the Scottish Intercollegiate Guidelines Network considered biomechanical measurements in assessing the foot at risk.

Two previous systematic reviews have been conducted to identify which parameter best predicted diabetic foot ulceration (Crawford *et al.*, 2007; Monteiro-Soares, Boyko, *et al.*, 2012). Monteiro-Soares et al. (2012), identified that: a) foot deformity, b) peripheral neuropathy (Vibration Perception Threshold -VPT or cutaneous insensitivity to monofilament), c) peripheral vascular disease (pulses and/or ABI), d) previous amputation, e) the presence of callus, f) HbA1c, g) Tinea pedis, and h) onychomycosis are all risk factors that are commonly used in the prediction of diabetic foot ulceration. The systematic review by Crawford et al. (2007), which included a meta-analysis, reported that insensitivity to a 10-g monofilament or one absent pedal pulse would identify patients with a moderate or intermediate risk of foot ulceration. Additionally, patients with a history of foot ulcers or lower-extremity amputation were found to be at the highest risk of ulceration.

While the above-mentioned parameters have been recognised as the common predictive risk factors for diabetic foot ulceration, it has been established that the majority of the injuries to the foot happen as a result of mechanical trauma or the mechanical failure of the plantar soft tissues of the foot. As previously mentioned, a diabetic foot ulcer is an inherent failure of the plantar soft tissues of the foot. This failure occurs as a result of repeated overloading of the soft tissues of the foot, primarily as a result of diabetic peripheral neuropathy. This overloading causes microtears within the tissues of the foot. In addition, it has been shown within the literature to be a contributing factor to skin breakdown, especially when repeated at a specific area in

patients with diabetes and peripheral neuropathy (Abouaesha *et al.*, 2001; Patry *et al.*, 2013).

As one of the leading causes of diabetic foot ulcers is mechanical trauma or the mechanical failure of the plantar soft tissues of the foot, there is a need for biomechanical predictors that are directly related to the foot. Therefore, biomechanical measurements such as plantar pressure, limited joint mobility, forefoot deformities like hammer/claw toes, and soft tissue mechanical properties need to be assessed.

As mentioned above, increased plantar pressures are critical in the onset of diabetic foot ulceration due to the overloading of the plantar soft tissues. Within the literature, a number of studies have investigated the use of plantar pressure and how it can be used to prevent ulceration (Lavery *et al.*, 1998; Mayfield *et al.*, 1998; Crawford *et al.*, 2007). For example, Lavery et al. (1998) suggested that when assessing and screening people with diabetes that are at high risk for ulceration to include plantar pressure distribution as a relevant risk factor and proposed a risk threshold of 65N/cm^2 whereby people with diabetes that exhibited pressures over this threshold value were at greater risk of ulceration (Lavery *et al.*, 1998).

Mayfield et al. (1998) outlined the relevance of conducting thorough biomechanical assessments, including plantar pressure, while analysing other risk factors, such as age, gender and disease duration, whilst offering clinical advice to prevent foot ulcers

(Mayfield *et al.*, 1998). Finally, Crawford et al. (2007) in a systematic review, found that diagnostic tests for either diabetic peripheral neuropathy or high plantar pressure distribution to be associated with diabetic foot ulcers. However, both peripheral neuropathy and plantar pressure distribution gathered limited evidence regarding their predictive power.

Owing to this lack of scientific evidence, as highlighted by Crawford et al. (2007), assessing the foot at risk has changed in the last thirteen years with risk stratification systems and ulcer prevention approaches, no longer considering plantar pressure distribution as a valid predictor of ulceration. The currently persisting lack of evidence for the use of plantar pressure measurements to assess the foot at risk might be due to poorly standardized methods, study costs and complexities in study implementation.

In addition to plantar pressure, another biomechanical parameter linked to an increased risk of ulceration is an increase in the stiffness of the plantar soft tissues of the foot. As the breakdown of the plantar soft tissues results from the mechanical failure of the soft tissues, it is important to assess the effect of soft tissue mechanical properties on diabetic foot ulceration.

Previous studies have indicated that the heel pads of people with diabetes tend to be thinner (Chao *et al.*, 2010), stiffer (Klaesner *et al.*, 2002; Chao, Zheng and Cheing, 2011), harder (Piaggesi *et al.*, 1999) and also tend to have less energy return efficiency (Hsu *et*

al., 2000) when comparing age-matched populations of people with no diabetes. A possible reason for this could be the histological changes inside the tissues due to glycation (Pai and Ledoux, 2010). In addition, Naemi et al. (2017) have previously shown that the addition of plantar soft tissue mechanics can aid in the prediction of plantar foot ulcers in people with diabetes (Naemi *et al.*, 2017). However, the methods used by Naemi et al. (2017) involved the use of expensive ultrasound equipment that is not readily accessible in a clinical setting. Therefore, there is a need for a clinically applicable method of assessing the mechanical properties of the plantar soft tissues of the foot to aid in foot ulcer prediction.

2.4. The importance of biomechanical risk factors

Diabetic foot ulcers predominantly occur on the plantar surface of the foot. As such, assessing the effect of changes in the mechanical properties of the plantar soft tissues is of great importance. The mechanical properties of the soft tissues of the foot have been shown to rapidly change over time due to the presence of increased blood glucose levels. These increased blood glucose levels lead to the production of advanced glycated end-products (Singh *et al.*, 2014), which damage the collagen fibrils that make up the skin and plantar soft tissue. In addition, advanced glycated end-products cause the collagen fibrils to become more crosslinked and thus change the mechanical properties of the collagen fibrils, which has been shown to result in a brittle and more rigid collagen fibre (Avery and Bailey, 2006). This increase in the rigidity of the collagen, through collagen

crosslinking, has been linked to an increase in the stiffness of both the skin and plantar soft tissues of the foot (Hsu, Lee and Shau, 2002).

There have been several studies looking into how diabetes affects the plantar soft tissues of the foot. The first study looks at what changes occur to the fat pad of people with diabetes (Bus *et al.*, 2004). Bus et al. (2004) found that the fat pads of the heel were significantly thinner in people with diabetes compared to those without diabetes. Bus and co-workers (Bus *et al.*, 2005) also found that people with diabetes who presented with a form of foot deformity had significantly less fat pad at the metatarsal head over the phalangeal level, suggesting thinning and distal displacement dislocation due to contracture of the digit.

As well as thinning of the heel pad, the stiffness of the fatty tissues also increases (Yvonne Y Cheung *et al.*, 2006). The stiffness of the heel pad was found to be correlated with high levels of triglycerides within the blood (Chatzistergos *et al.*, 2014). The increased stiffness and the reduced thickness of the fatty tissues within the foot could limit the tissues' ability to evenly distribute loads, making them more vulnerable to trauma and ulceration.

The increase in stiffness of the plantar soft tissues reduces the damping effect of the tissues and leads to an overloading of the soft tissue of the foot. This overloading causes microtears within the tissues, particularly at pressure points such as the 1st Metatarsal

head, 2nd Metatarsal head, and heel. If left untreated, the skin and soft tissue will fail, causing the formation of a foot ulcer (Abouaesha *et al.*, 2001; Patry *et al.*, 2013).

While previous research has investigated the effect that external factors, such as plantar pressure and loading, have on diabetic foot ulceration, little research has investigated how the assessment of internal factors such as the mechanical properties of the plantar soft tissues may affect ulceration.

One of the reasons for this limited research is the methods used to assess the mechanical properties of the plantar soft tissues of the foot. The existing methods for the quantitative assessment of plantar soft tissue mechanical properties are based either on the use of complex, bespoke indentation testing devices (Zheng *et al.*, 2000; Hsu, Lee and Shau, 2002; Klaesner *et al.*, 2002; Erdemir *et al.*, 2006; Spears and Miller-Young, 2006; C C Hsu *et al.*, 2007; Chih Chin Hsu *et al.*, 2007; Behforootan, P. E. Chatzistergos, *et al.*, 2017a, 2017b) or the use of expensive ultrasound elastography systems (Naemi *et al.*, 2016, 2017).

Exploring the potential value of measurements of plantar soft tissue mechanical properties to enhance the clinical management of the diabetic foot is therefore severely limited by the lack of clinically viable testing techniques that would enable the measurement of plantar soft tissue biomechanics as part of everyday clinical practice. The techniques, as mentioned earlier, of indentation testing and ultrasound

elastography, are expensive, time-consuming, and the results can be operator dependent. A potential solution to this limitation is the use of Shore hardness as an assessment of the mechanical properties of the plantar soft tissues. The measurement of Shore hardness, using a handheld durometer, has successfully been used to assess soft tissue biomechanics in vivo and appears to be a good candidate to fill this need for a simple, clinically applicable method to measure the mechanical properties of the plantar soft tissues of the heel (Falanga and Bucalo, 1993; Aghassi, Monoson and Braverman, 1995; Romanelli and Falanga, 1995; Piaggesi *et al.*, 1999; Thomas *et al.*, 2003; Charanya *et al.*, 2004; Kissin *et al.*, 2006; Periyasamy, Anand and Ammini, 2012)

The current research has shown that quantifying the stiffness of plantar soft tissues can enhance the prediction of diabetic foot ulceration and heel pain syndrome (Lin *et al.*, 2017; Naemi *et al.*, 2017), enhancing the clinical management of the diabetic foot. The results presented by Naemi et al. (2017) regarding the prediction of diabetic foot ulceration showed that by adding measurements of plantar soft tissue stiffness and thickness to an ulcer prediction model, its accuracy was improved by 25%. Furthermore, compared to previous foot ulcer prediction models (Boyko *et al.*, 2006; Monteiro-Soares and Dinis-Ribeiro, 2010), the prognostic strength of the model was higher in the study by Naemi et al. (2017). Therefore, indicating that adding parameters related to the plantar soft tissue biomechanics can increase the accuracy of the models in diabetic foot ulcer prediction.

In addition to assessing the mechanical properties of the plantar soft tissues of the foot, Shore hardness may potentially be used to predict plantar pressures in people with diabetes. It is well established in the literature that plantar soft tissue stiffness has an effect on plantar pressures in healthy participants, in addition to people with diabetes with and without peripheral neuropathy (Payne, Turner and Miller, 2002; Lepäntalo et al., 2011; Giacomozzi et al., 2018). Thus, using the measurement of Shore hardness as quantification of stiffness may allow for a clinically applicable method to predict areas of high plantar pressure when combined with other biomechanical parameters.

One previous study (Morag and Cavanagh, 1999) has attempted to predict plantar pressure using soft tissue mechanical properties in association with other parameters. Within these predictive models derived by Morag and Cavanagh, soft tissue stiffness was not found to be a significant predictor of plantar pressure; however, soft tissue thickness was found to be a significant predictor. This would indicate that soft tissue mechanical properties may indeed play a role in the prediction of plantar pressures

2.5. Functional anatomy and mechanical properties of the heel pad

The heel pad of the foot is the first point of contact with the ground during normal gait. Its main role is to act as a shock absorber to dampen the effect of ground reaction forces during weight-bearing activities such as walking and standing by promoting more even distribution of plantar loads. During the stance phase, the rear foot acts as semi-rigid support for body weight, provides stability for uneven terrain, and maintains balance.

Due to the functional role that the plantar soft tissues of the foot play during activities such as gait, the soft tissues of the foot, which form the heel pad, are highly specialized with nonlinear, viscoelastic mechanical properties and a complex internal structure.

The heel pad of the foot has a honeycomb structure which consists of individual spherical fat cells called adipocytes and fat globules and ranges in thickness between 14.4 and 24.5 mm with an average value of 18 mm (Uzel *et al.*, 2006) [Figure 2-2a] measured using ultrasound (Cavanagh, 1999), magnetic resonance imaging (MRI) (Petre, Erdemir and Cavanagh, 2008), and radiographs (De Clercq, Aerts and Kunnen, 1994; Prichasuk, Mulpruek and Siriwongpairat, 1994). The anatomical structure of the heel pad of the foot can be divided into three distinct layers. First, superficially the plantar surface of the foot has a thick skin layer that acts as an impermeable barrier to protect the underlying soft tissues from damage and mechanical trauma (Blechschmidt, 1982; Jahss *et al.*, 1992). Second, deep to the skin is the fat pad which can be anatomically divided into two separate layers. A superficial layer of small fat chambers (microchambers) and a deep layer of larger fat chambers (macrochambers) [Figure 2-2b]. Each of these layers has its own functional role within the heel pad (C C Hsu *et al.*, 2007).

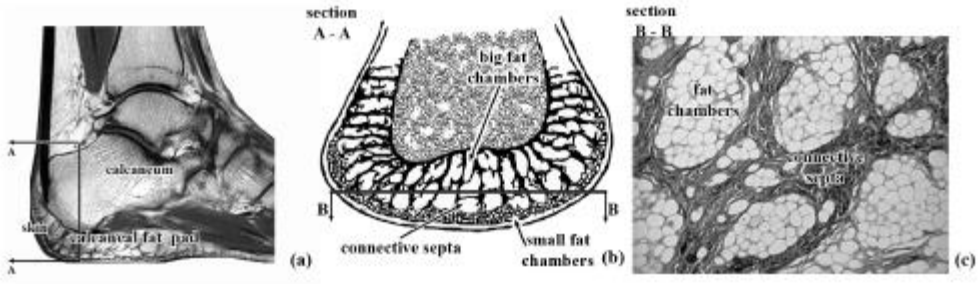


Figure 2-2:a) Morphometric and histological configuration of the heel pad: magnetic resonance image according to sagittal section. b) Longitudinal section by a schematic representation. c) Optical microscope picture of a transversal section. Adapted from Weissengruber et al. (2006)

The microchambers layer consists of a densely packed fibroadipose structure. This layer is primarily a collagen matrix with small, regularly spaced globules of adipose tissue (Blechschmidt, 1982; Jahss *et al.*, 1992). The role of the microchambers layer is to act as a heel cup that provides shape to the heel in addition to preventing excessive bulging during loading (C C Hsu *et al.*, 2007).

The macrochamber layer consists of a sparser, fibro-adipose structure. This layer consists of large fatty chambers bound by thick fibrous septae (Blechschmidt, 1982; Jahss *et al.*, 1992). The chambers are arranged in an overlapping spiral formation around the process of the calcaneus, and the septae align with the curvature and torsion of the calcaneus so that the heel pad bulges outwards during weight-bearing (Blechschmidt, 1982). Each chamber is further divided into globules by fibro-elastic bundles of collagen and elastin, forming a closed-cell honeycomb structure (Jahss *et al.*, 1992). The globules

are filled with adipose tissue, which is a combination of unsaturated and saturated fatty acids.

The macro-chamber layer is bound to the calcaneus through a thick fibrous tie called the plantar aponeurosis (Blechschmidt, 1982). The plantar aponeurosis originates at the medial and lateral processes of the calcaneus from within the fibres of the fibrous tie. The deepest structure of the heel pad is that of the calcaneus, which has medial and lateral processes; these provide attachment to the plantar aponeurosis and give a broad base to allow distribution of force to the soft tissue.

2.5.1. The Mechanical Properties of Viscoelastic Materials

To understand the effect of the complex internal structures of the heel pad and what effect this has on the complex nonlinear, viscoelastic behaviour of the heel pad, the main principles related to viscoelasticity must be understood.

2.5.2. Basic mechanical principles

2.5.2.1. *Stress*

Stress is defined as the force required to extend or compress material in an axial direction, normalised to the cross-sectional area of the material being extended or compressed. The units of stress are N/m^2

$$\sigma = F/A$$

(EQ 2.1)

Whereby σ is stress, F is the force (N), and A is the cross-sectional area (m^2)

In this body of research, the term stress refers to the force used to compress an area of plantar soft tissue.

2.5.2.2. *Strain*

Strain is the change in length of a material when subjected to an axial load. Strain is defined as the ratio of the change in length of the material to its original length. Strain has no units

$$\varepsilon = \Delta L/L$$

(EQ 2.2)

Whereby ε is strain, ΔL is the change in the material's length (or thickness), and L is the original length (or thickness) of the material.

In the context of this research, strain refers to the ratio between the unloaded tissue thickness and the tissue thickness when compressed.

2.5.2.3. *Shear*

Shear is the response of a material to stress or strain in the parallel direction to its surface, which causes the shape of the structure to deform. The shear stress can be defined as:

$$\tau = F/A_{(parallel\ surface)}$$

(EQ 2.3)

Where τ is shear stress, F is applied shearing force, and A is area parallel to the applied force.

The effects of shear are not directly studied in this thesis and have had little investigation in the previous literature; however, concepts related to shear are explored as part of this thesis.

2.5.2.4. *Stiffness and Young's Modulus*

In the context of material characterisation, stiffness describes the gradient of the load-displacement curve and is generally expressed in N/m. Young's Modulus is used to describe the gradient of the stress-strain curve and is expressed in kPa as strain is a unit-less variable.

$$Stiffness = \Delta K/\Delta L$$

$$Young's\ Modulus = \sigma/\varepsilon$$

Where ΔK is change in Load, ΔL is change in length, σ is stress, ε is strain.

Comparisons to previous studies will use a combination of stiffness and modulus due to the wide range of previous methodologies used to characterise the tissue's response.

2.5.3. Principles of viscoelasticity

A viscoelastic material is a material that consists of a solid phase in addition to a viscous fluid phase. The solid phase of a viscoelastic material consists of elastic components (Hookean or Non-Hookean), whilst the viscous fluid phase consists of viscous components (Newtonian or Non-Newtonian).

A Hookean solid has a highly ordered arrangement of atoms with rows and columns joined by stiff atomic bonds, such as can be found in metals, ceramics, and bone. When stressed, the response of a Hookean solid is determined by Hooke's law, which states that strain and stress are directly proportional and thus is the result of the summed responses at each atomic bond. A Non-Hookean solid has an initially random configuration of atoms with loose atomic bonds, such as in rubbers. Under stress, the atoms are brought into order due to the strain of the inter-atomic bonds/spacing resulting in a region of initial compliance where the tissue is strained with little application of force.

A Newtonian fluid permits flow with force proportional to the rate of shear strain; Newtonian fluids can be found as the components of many mechanical lubricants. A Non-Newtonian fluid does not show a proportional relationship between shear strain and force and is the predominant fluid found in biological systems. Non-Newtonian fluids can occur in two forms: shear thinning and shear thickening. With shear thinning,

increasing the applied force will result in a greater than proportional increase in shear rate, thus making it relatively easier to deform at high shear rates. Shear thickening shows the inverse, in which increasing the applied force will result in a lower than proportional increase in the shear rate, thus making it relatively easy to deform at low shear rates.

As viscoelastic materials can exist as any combination of solid and fluid phases, this leads to a spectrum of viscoelasticity that spans the space between purely elastic, solid like and purely viscous, fluid-like behaviour. As with a viscous fluid, the rate of strain affects the amount of work that must be done to deform a viscoelastic material. However, the material will return to its original shape when stress or strain is removed, unlike the fluid. Therefore, a discrepancy exists between the loading and unloading response path due to energy lost within a viscoelastic material because of the increased work required to deform the tissue against the viscous resistance to loading, also known as hysteresis.

Characterising the mechanical properties of viscoelastic materials involves the use of compression testing, whereby a sample of material is subjected to either a prescribed amount of stress or displacement. In tests where the applied load (stress) is controlled, the peak strain, i.e., the largest change in initial size, can be used to give an indication of the compressibility of material, with incompressible materials displaying a sharp increase in the stress required to impose deformation. In tests where the applied displacement is controlled, the peak stress can be used to give an indication of the

stiffness of a material, with stiff materials producing large stresses in response to compression.

The linear relationship between peak stress and peak strain permits the characterisation of the secant modulus; this value is highly dependent on the imposed compression conditions. However, when conditions are controlled, this permits the comparison of various materials to be conducted using a single value.

The nonlinear relationship between stress and strain can also be characterised throughout compression via curve fitting; the curve's shape is determined by the interaction of the elastic and viscous components in response to compression. To determine the properties of the elastic and viscous components, a method has been proposed by Naemi et al. (2016), using indentation testing whereby numerically integrating the area below the stress-strain curve during loading and unloading the energy input and energy returned densities can be calculated (Naemi *et al.*, 2016). Elastic energy and energy absorbed densities were calculated as the sum of and the difference between energy input and energy returned densities, respectively. By fitting the energy function, derived from a nonlinear viscoelastic model to the energy density–strain data, the elastic and viscous model parameters can be quantified.

The hysteresis of the curve can be quantified by calculating the area bound by the loading and unloading curves and provides an indication as to the degree to which the

viscous response has resulted in energy loss within the tissue. In addition, modelling techniques can be used to isolate the elastic and viscosity of the stress-strain response by assigning components of the response to simplified elements represented as springs or dampeners. However, due to the simplified assumptions upon which these models are dependent, the application to a complex biological tissue is often extremely difficult and can pose challenges when proving the efficacy.

2.6. Methods of measuring the mechanical properties of the heel pad

Within the current literature, several methods have been used and developed to measure and quantitively assess the complex viscoelastic mechanical properties of the heel pad of the foot both in-vitro and in-vivo. The methods used range from material testing studies, controlled compression testing, and ultrasound sonoelastography.

2.6.1. Material Testing Studies

In-vitro material testing studies are a powerful tool in investigating the mechanical properties of biological tissues, specifically with regards to their elastic, dampening, and time-dependent behaviour. In-vitro testing considers the specimen geometry, the boundary conditions, and the mechanical properties of the tissues under investigation. Within the literature, the mechanical properties of the plantar soft tissues vary considerably (DeFrate *et al.*, 2006), with many different factors affecting the measurement of the mechanical properties. These factors include age (Johnson *et al.*, 1994), alignment and geometry of the specimen (Atkinson, Ewers and Haut, 1999), the

temperature and hydration of the testing environment (Haut and Powlison, 1990) and time-dependent effects (Johnson *et al.*, 1994; Natali *et al.*, 2004).

In-vitro material testing studies are conducted using tissue samples and highly accurate material testing machines such as an Instron material testing machine (Ledoux and Blevins, 2007). In addition, the tissue samples used are geometrically symmetrical, which allows for the stress imposed within the tissue to be accurately and easily calculated (Miller-Young, Duncan and Baroud, 2002).

The tissues samples used to assess the mechanical properties of the heel pad in-vitro are typically taken from the calcaneal tuberosity of cadaveric feet and range in size and shape with square (20mmx20mm) (Ledoux and Blevins, 2007) and circular (19mm diameter) (Pai and Ledoux, 2010) being previously used. The calcaneal tuberosity is the area of the heel pad that experiences the highest level of stress under normal conditions; this is the most appropriate location of the heel pad to study its mechanical properties (Spears *et al.*, 2007).

For the material testing of soft tissues, the tissue samples are compressed between two plates (one fixed and one dynamic), whereby the movement of the dynamic plate is directly related to the compression of the tissue sample. By compressing the tissue sample using the dynamic plate, it allows for accurate displacements to be applied to the tissue of which the displacements can be adjusted for each tissue sample based on

the tissues' thickness or to allow loading, which produces target stress within the tissue sample (Ledoux and Blevins, 2007).

Previous in-vitro work by Miller-Young et al. (2002), investigated the mechanical properties of the calcaneal fat pad whereby cylindrical samples of plantar soft tissues were taken from 20 cadaveric feet (6 male, 4 female) (Miller-Young, Duncan and Baroud, 2002). These samples were subjected to unconfined compression testing using quasi-static, stress-relaxation, and dynamic compression methodologies. The quasi-static test allowed for the quantification of the hyperelastic mechanical properties of the soft tissue samples. The stress-relaxation test allowed for the calculation of the viscoelastic time constants. Finally, the dynamic compression test enabled the viscoelastic behaviour of the samples to be extracted. Based on the results of this study, the stress-strain relationship for the fat pad was found to be nonlinear and thus indicated that the fat pad of the heel possesses viscoelastic, time-dependent mechanical properties.

Additional studies have also investigated the use of in-vitro material testing to calculate the plantar fat pad's elastic and viscoelastic mechanical properties (Ledoux and Blevins, 2007). The calculation of both elastic and viscoelastic mechanical properties allowed Ledoux et al. (2007) to develop a mathematical model of the plantar fat pad of both healthy participants and diabetic participants (Ledoux and Blevins, 2007). Ledoux et al. (2007), indicated that the stiffness of the fat pad and the energy dissipation of the fat pad increases as the frequency of loading increases (Ledoux and Blevins, 2007).

Whilst material testing can be a powerful tool to investigate the mechanical properties of the plantar soft tissues by providing potentially more reliable data, there are limitations to this testing method. As the sample of tissue is removed from the foot, this restricts the sample to that point in time, and as such, the effect of time, conditioning, or treatment cannot be assessed. Additionally, removing the tissue from the foot will remove the natural boundary conditions such as the microchamber layer, which controls the deformation of the macrochamber layer (C C Hsu *et al.*, 2007). This will, therefore, alter the tissue's structural arrangement, preventing a realistic assessment of mechanical behaviour under realistic loading conditions.

2.6.2. Controlled Compression studies

Controlled compression studies use a dynamic platen to compress a region of the plantar soft tissue whilst the foot or foot region is fixed. In comparison to material testing studies, this method of assessing the mechanical properties of the plantar soft tissues retains the structural integrity of the plantar soft tissue. Therefore, the functional response of the plantar soft tissues, when subjected to realistic loading conditions, can be assessed. Controlled compression studies fall into two categories: indentation testing and bulk compression testing.

2.6.2.1. Indentation Testing

Indentation testing studies are used to investigate the mechanical properties of a certain region of the foot through the use of a small diameter probe (Lemmon *et al.*, 1997; Zheng

et al., 2000; Klaesner *et al.*, 2001; Rome *et al.*, 2001; Erdemir *et al.*, 2006; Gu *et al.*, 2010; Lin *et al.*, 2014) For indentation testing, a rigid indenter with dimensions that are significantly smaller than the area being tested is pressed against the plantar aspect of the foot. These indentation probes can vary in size from 1cm to 5cm in diameter (Zheng *et al.*, 2000; Klaesner *et al.*, 2001). The force applied by the indenter is measured using a load sensor which is placed in series with the indenter while the deformation of the tissue is assessed either based on indenter displacement (Thomas, Patil and Radhakrishnan, 2004; Gu *et al.*, 2010) or using real-time measurements such as ultrasonography to measure the displacement of the tissue sample (Lemmon *et al.*, 1997; Tong, Lim and Goh, 2003; Erdemir *et al.*, 2006; Lin *et al.*, 2014; Chatzistergos, Naemi and Chockalingam, 2015; Behforootan, P. E. Chatzistergos, *et al.*, 2017a). In this case, ultrasonography is used to measure the distance of the indenter to the apex of the calcaneus with the ultrasound probe used to load the tissue and therefore plays the role of the indenter (i.e., ultrasound indentation).

2.6.2.2. *Ultrasound indentation*

Ultrasound indentation is most commonly used when investigating the mechanical properties of the plantar soft tissues of the foot. Similar to that of non-ultrasound based indentation testing, a load cell and an ultrasound probe are placed in series to simultaneously measure the applied force and the deformations of biological soft tissue structures within the heel pad (Erdemir *et al.*, 2006; Chatzistergos *et al.*, 2014; Chatzistergos, Naemi and Chockalingam, 2015; Naemi *et al.*, 2016; Behforootan, P. E.

Chatzistergos, *et al.*, 2017a, 2017b). This information is then used to assess the stiffness of underlying soft tissue.

Ultrasound indentation testing is most commonly used to establish mathematical models to assess the force-deformation behaviour of the heel pad. Traditionally the heel pad has been typically modelled as a homogeneous, single-layer material rather than a three-layer biological structure (macro, micro, and skin layers) (Erdemir *et al.*, 2006; Behforootan, P. Chatzistergos, *et al.*, 2017; Behforootan, P. E. Chatzistergos, *et al.*, 2017b, 2017a). However, in a few cases, thanks to ultrasound indentation, the heel pad has been modelled as a dual-layer composite structure (fat and skin) (Spears *et al.*, 2007; Gu *et al.*, 2010).

This is one of the main advantages of ultrasound indentation compared to non-ultrasound indentation testing, whereby it allows for a closer examination of functional differences between structures of the foot, particularly the microchambers and macro-chamber layers (C C Hsu *et al.*, 2007). The results of the study by Hsu et al. (2007) indicated that the superficial microchamber layer of the heel was significantly stiffer (450kPa) when compared to that of the deep macrochamber layer (46.4kPa). Substantial deformations of the macrochamber layer during the loading-unloading examination were also witnessed. The macrochamber layer was immediately deformed during the compression of the heel pad and rebounded quickly to its original state after loading was removed, thus indicating the resilience of the heel-pad soft tissues, i.e., the ability of the

tissue to recover its shape after deformation. This resilience to prolonged tissue deformation may be due to the major role that the macrochamber layer plays during walking and its responsibility for providing a cushioning effect to the heel pad (C C Hsu *et al.*, 2007).

Under the same loading condition, the microchamber layer deformed faster, but the change in thickness is much less than the macrochamber layer. This may be due to the increase in microchamber stiffness compared to that of the macrochambers. Hsu et al. (2007), therefore, propose that the function of the microchamber layer of the heel is that of a "heel cup", which contains the macrochamber layer beneath the calcaneus and prevents excessive macrochamber layer deformation (C C Hsu *et al.*, 2007).

In addition to measuring the mechanical properties of the individual structures of the foot, more recently, ultrasound indentation devices have been developed to measure and quantify the mechanical properties of the foot when a participant is in a standing position (Cavanagh, 1999; Parker *et al.*, 2015; Ahanchian *et al.*, 2017). These devices are reported to be able to implement complex loading patterns similar to gait (Parker *et al.*, 2015), were used to calculate the material properties of the heel pad sub-layers using a Finite Element approach (Ahanchian *et al.*, 2017). Although these ultrasound indentation devices can produce compression rates to replicate the deformation of the heel pad during walking, the exact replication of this behaviour would be challenging. Ahanchian et al. (2017) is the first study to combine both approaches whereby estimating the

mechanical properties of the macro-chamber, microchambers, and skin layers during gait through the use of inverse finite element analysis and in-vivo experimental data.

2.6.3. Introduction to Finite Element Analysis

Finite element analysis (FEA) is a powerful numerical method that can used to study the mechanical behaviour and the mechanical properties of soft tissues of the human body and can be used to solve problems with complicated geometry, material properties and loading. For example, FEA has been used to assess the effect that diseases such as diabetes have on the mechanical properties and behaviour of the plantar soft tissues of the foot (REF). FEA allows these complex objects and structures to be divided into an equivalent system comprising a finite number of individual smaller bodies known as "elements". Elements are connected at "nodes", which holds the individual elements together, making a grid of connected elements called a "mesh."

Many engineering problems are solved based on linear approximations. Linear models use linear Hookean material and assume that the deformations are small, and loads are independent of displacements. Therefore, a set of linear equations are used to describe the behaviour of FE models as bellow:

$$[K]\{X\} = \{F\} \qquad \text{(EQ 2.4)}$$

In equation 2.4, [K] is the stiffness matrix, which defines the geometric and material properties of elements, F represents the loading/boundary condition, and X is the

unknown deformation of the engineering problem. For linear analysis in which the stiffness never changes, the unknowns can be found by solving the equations once with no need to update anything while the structure is deforming. In reality, however, the mechanical behaviour of most structures is nonlinear. For example, when large deformation occurs under loading or the material behaves nonlinearly, the engineering problem needs a nonlinear solution. These kinds of nonlinear problems lead to an equation which includes a stiffness response that is not constant and depends on deformation (x) [EQ 2.5].

$$[K(x)]\{X\} = \{F(x)\} \quad \text{(EQ 2.5)}$$

As a result, FEA has been used for many years to solve a number of engineering problems and has been applied to biomechanics to investigate and better understand the mechanical properties of various structures and tissues of the human body. For instance, FEA has been previously used in the modelling of the shoulder, cervical spine, eye and the plantar soft tissues of the foot. (Büchler *et al.*, 2002; Schutte *et al.*, 2006; Toosizadeh and Haghpanahi, 2011; Behforootan, P. E. Chatzistergos, *et al.*, 2017a, 2017b).

In order to be able to perform FEA on a single component or on an assembly of components there are three main steps required: Pre-Processing, Processing, and Post-Processing.

1. Pre-Processing

The pre-processing step is the first step to performing an FEA. In this step, the object that is analysed is set up and prepared. There are four main parts to pre-processing:

- Development of the physical geometry of a problem in 2D or 3D using CAD (Computer-Aided Design) software such as Solidworks, AutoDesk, Creo, etc.
- Dividing the CAD generated object into elements of selected size to create the mesh for analysis.
- Assign the relevant material properties to the object or objects being analysed.
- Apply loading/displacement conditions, boundary conditions, and define the interactions or contact pairs between components.

The pre-processing stage can be one of the more time-consuming aspects of FEA to ensure that the FE model acts and behaves as expected.

2. Processing

Processing is the second step in preforming FEA. This step involves:

- Running the analysis and computing the unknowns

During this stage, the model is analysed using commercial FEA software such as ANSYS, Abaqus and Ls-Dyna. Additionally, there are specialist FEA software available such as FEBio, for investigating areas such as biological tissues. This stage begins by the software setting up the governing equations for each element into a matrix and solving the elements numerically. The time taken to complete this process depends on the type of analysis undertaken (e.g., static or dynamic), type of elements, material properties, and boundary conditions.

3. Post-Processing

Post-processing is the final step in preforming FEA whereby post-processing involves:

- Display the results

Once the analysis has been completed, variables such as stress, displacement, and deformed shape of the model can be graphically viewed within the FEA software. Additional calculations can also be performed in the post-processing stage, such as relative movement of two objects, for example, the indentation of one object into another.

As FEA is a computational method to assess unknown variables, considerations are taken with regard to computational load and computational complexity. As a result, when

performing FEA, it is common to simplify the problem, such as simplifications to geometry, mesh density, the total number of elements, and loading and boundary conditions. Common examples of simplifications used in FEA include turning a 3D model into a 2D model, looking at axes of symmetry, and using a coarser mesh. However, to ensure the accuracy of the model using simplifications, it is vital to validate the FE model by comparing the predicted results to experimental results.

2.6.3.1. *Using Finite Element Analysis to assess the mechanical properties of the plantar soft tissues of the foot.*

In the study by Ahanchian et al. (2017) experimental data for the mechanical properties of the heel pad was collected through a custom-built tissue indentation system. The custom-built tissue indentation system (STRIDE) applied controlled vertical compression cycles of various speeds and load profiles to the heel pad in-vivo. A series of slow and rapid compression tests on the same heel was used to obtain the force-strain responses of the heel pad and its sub-layers.

The STRIDE system used by Ahanchian et al. (2017) uniformly compresses the heel pad of the foot using a 150-mm diameter flat rigid steel plate with a 20-mm diameter circular plastic window at the centre of the steel plate to allow for imaging of the tissue (Ahanchian *et al.*, 2017). An ultrasound system (MyLab 70, Esaote, Italy) is used to track changes in the heel pad thickness and changes in the boundaries between the skin, microchambers and macrochambers during both loading/unloading (Ahanchian *et al.*, 2017). All tests were performed using STRIDE, with the participant standing with their

calcaneal tuberosity above the window's centre. The foot is placed in a foot brace (Aircast boot) which allows for vertical compression of the heel without lifting the foot from the platform.

Ultrasound images of the deformation of the heel pad collected by Ahanchian et al. (2017), were used to measure the unloaded and loaded thickness of the heel pad, macro-chamber, and microchambers.

Using STRIDE, both slow compression tests at 5mm/s and rapid compression tests at 225mm/s (comparable to the velocity of vertical impact in slow walking) were performed in order to determine the material properties of the heel pad sub-layers (Ahanchian *et al.*, 2017).

The engineering strains of the skin, microchambers and macrochambers layers were then calculated similarly to those described previously (C C Hsu *et al.*, 2007). The load recorded under the heel pad by the miniature load cell was used as input into an FEA model of the heel. The hyperelastic and viscoelastic material properties were then optimised using the FEA model for each of the three layers of the heel pad (Ahanchian *et al.*, 2017).

This study by Ahanchian et al. (2017), has allowed for a quantification of the mechanical properties of the individual layers of the heel pad. However, one of the main limitations

of the STRIDE systems and ultrasound indentation as a whole is that the values obtained for the mechanical properties of the heel pad are only a representation of the average stiffness of the heel pad and do not allow for an assessment related to the individual aspects of the heel pad.

2.6.3.2. *Clinical applications of Finite Element Analysis*

As highlighted in Section 2.6.3.1, FEA has been used to assess and calculate the mechanical properties of the plantar soft tissues of the foot using mathematical models. This has given researchers the ability to assess the in-vivo stresses that develop within the human foot during clinically relevant scenarios such as gait and have enhanced our understanding of foot biomechanics and foot-related pathologies such as diabetic foot ulceration.

However, the actual contribution of FE analyses for the improvement of the therapeutic and clinical outcomes of the diabetic foot is limited (Behforootan, P. Chatzistergos, *et al.*, 2017) as FE modelling cannot be easily utilised outside the research domain setting (Behforootan, P. Chatzistergos, *et al.*, 2017). One of the main challenges for implementing FE modelling into everyday clinical practice is the development of reliable and affordable techniques for the subject-specific modelling of the foot.

The ability of a modelling technique to be used within a clinical setting is determined by five main factors:

1. Is the technique easy to use?
2. Is the technique non-invasive?
3. Is the technique low cost?
4. Can the technique be used to enhance clinical practice?
5. Are the results of the technique accurate and clinically relevant?

A recent systematic review looking into the use of FEA of the foot for clinical applications (Behforootan, P. Chatzistergos, *et al.*, 2017) highlighted a number of fundamental challenges still existing before patient-specific FEA can become a clinical tool for the management of diabetic foot or other foot pathologies. The fundamental challenges identified by the review include:

1. Model design
2. Material properties assignment
3. Loading
4. Validation of the FEA model.

2.6.3.2.1. Model Design

The first fundamental challenge for implementing FEA into clinical practice is related to the model's design. Of which, three key challenges were identified.

The first key challenge being faced is collecting reliable information regarding the geometry of the foot in a cost-effective and non-invasive manner. The two most commonly used imaging modalities are CT and MRI due to superior image quality enabling the accurate reconstruction of bone or soft tissue geometry. In situations where CT/MRI imagine is part of standard clinical care, using these images in FE modelling would be the best option. However, for conditions such as diabetic foot, particularly diabetic foot ulceration, CT/MRI is not part of standard clinical care. In these situations, it has been proposed that the use of ultrasound imaging may be used instead.

As highlighted in Section 2.6.2.2, ultrasound imaging has been reliably used to collect information about the geometry of the foot. The advantage of using ultrasound imaging is its relatively low cost, low risk for patients and high availability within clinical settings (Chatzistergos, Naemi and Chockalingam, 2015). There are, however, limitations with the use of ultrasound imaging whereby ultrasound imaging offers a relatively limited field of view with lower accuracy compared to gold standard MRI or CT. Additionally, the quality of the images can be strongly affected by the scanning technique and skill of the user. Another limitation of ultrasound is that it cannot penetrate bony structures and, therefore, image only their outer surfaces. Therefore, the use of ultrasound is restricted to focusing on soft tissues close to the surface of the foot, such as skin, fat pad, tendons etc.

Finally, X-ray and surface topography have also been used to reconstruct the geometry of the foot. However, there are concerns with the use of X-rays regarding ionising radiation and the difficulties in distinguishing overlapping anatomical structures. Surface topography offers a relatively quick, cost-effective and accurate reconstruction of the 3D geometry of the external surfaces of the foot. However, it cannot offer any information on the internal structure of the foot, which makes its stand-alone use for the design of FE models challenging to justify.

The second key challenge for model design is being able to accurately reconstruct tissue geometry in a non-labour-intensive way and without the need for specialist knowledge/training. The majority of reviewed studies identified by the systematic review employed specialised software for the manual segmentation/identification and 3D reconstruction of tissue geometry. For FEA to be clinically applicable, reliable automated techniques are required to reconstruct tissue geometry with minimum user input.

Two automated techniques for the design of 3D models of the foot have been identified. The first uses an automatic outlining tool to segment bones in a series/stack of CT images and produce 3D objects by combining the bone outlines of successive slices (Camacho *et al.*, 2002). The second solution used a generic model of the foot, which was modified and adapted to match the external geometry of the subject's foot (Lochner, Huissoon and Bedi, 2014). However, neither of these methods have yet been validated nor used

in big cohort studies indicating that further development is needed in order to determine if either of these approaches is clinically applicable.

Finally, the third key challenge related to model design is minimising the computational cost associated with FE analyses to enable immediate feedback on results without specialised high-performance computational units. As stated in Section 2.6.3, the computational cost of FE simulations increases with the size of the model and the complexity of the analysis. Additionally, the computational cost is significantly increased by using materials with nonlinear and/or time-dependent mechanical behaviour (e.g., hyperelastic materials, viscoelastic etc.) and by the use of contact elements.

Two generic approaches were identified within the literature as potential methods of reducing the computational cost. The first method uses anatomically focused models, whilst the second method uses simplified/ idealised models. The studies that followed the first approach designed highly specialised models of parts of the foot (e.g., heel) simulating very specific loading scenarios (e.g., heel strike). By significantly limiting the range of scenarios that the model can simulate, these studies were able to design anatomically detailed models of parts of the foot and reduce the models' degrees of freedom (Budhabhatti *et al.*, 2007; Gu *et al.*, 2010; Sopher *et al.*, 2011; Chokhandre *et al.*, 2012; Fontanella *et al.*, 2012, 2013, 2014, 2016; Petre *et al.*, 2013) and in some cases eliminate the need for simulating joint function (Gu *et al.*, 2010; Sopher *et al.*, 2011; Chokhandre *et al.*, 2012; Fontanella *et al.*, 2012, 2013, 2016). Based on the published

data, it is clear that a drastic reduction in computational cost can only be achieved through radical simplifications in tissue geometry and foot function (Dai *et al.*, 2006; Yarnitzky, Yizhar and Gefen, 2006; Spirka *et al.*, 2014; Chatzistergos, Naemi and Chockalingam, 2015).

At this point, it needs to be re-iterated that accuracy is the ultimate deciding factor for clinical applicability. Considering that accuracy and minimal computational costs are two objectives that are usually mutually exclusive means that the target for future developments in this field should be finding methods that can achieve satisfactory accuracy with the minimum possible computational cost.

2.6.3.2.2. Material Properties

All biological tissues exhibit complex non-linear and time-dependant mechanical behaviour which makes simulating their behaviour inherently difficult. The majority of studies assign material properties based on literature. Identifying the right material model and mechanical properties from the wide range of possible options is difficult; however, for FEA to be clinically relevant, material properties need to be estimated on a patient-specific basis. To achieve this, a combination of in vivo mechanical testing and advanced computational and/or mathematical analysis techniques is required.

Additionally, for these in-vivo techniques for estimating mechanical properties to be applicable in the clinic, in vivo mechanical testing will have to be non-invasive and easy

to perform in a clinical setting, and the techniques for the calculation of material properties should be robust and fast.

Two similar types of non-invasive mechanical tests are used in this context, namely indentation and compression testing, as discussed in section 2.6.2. The combination of these loading devices in conjunction with MRI or ultrasound imaging can significantly enhance the reliability of the measurements by enabling the direct measurement of internal tissue deformations (Erdemir *et al.*, 2006; Petre *et al.*, 2013; Chatzistergos, Naemi and Chockalingam, 2015). Moreover, the use of medical imaging enables the separate material characterisation of different tissues, namely skin, fat etc., instead of the common practice of characterising only as a bulk plantar soft tissue (Petre *et al.*, 2013).

In terms of the computational aspects of tissue mechanical characterisation, the reviewed studies (Erdemir *et al.*, 2006; Petre *et al.*, 2013; Chatzistergos, Naemi and Chockalingam, 2015) highlighted the use of inverse engineering from in vivo testing using optimisation driven procedures. These iterative methods are associated with high computational costs, which can significantly limit their clinical applicability. A possible solution to this problem is using surrogate models that can be trained to predict the output of FE analyses, thus reducing the computational cost of the inverse engineering process (Halloran and Erdemir, 2011). At this point, it needs to be stressed that the reliability of these surrogate models is still to be proven, especially in wide cohorts;

therefore, it is fair to say that a considerable amount of work is still needed to ensure validity and accuracy before deciding the applicability of such techniques in the clinic.

2.6.3.2.3. *Loading*

One of the main challenges in terms of defining boundary conditions and loading for FEA models of the foot is being able to assign clinically relevant loading without the need for specialised equipment and time-consuming measurements. Literature suggests that the simplest method to simulate loading is by scaling previous normative measurements from literature or in vivo testing using the patient's body weight. However, this approach would limit the patient specificity of the analysis.

In cases where accurate measurements of truly patient-specific loading are critical for the reliability of the analysis, such as predicting foot ulceration thresholds, measurements of ground reaction forces using force plates, pressure mats or in-shoe pressure sensors could be used to directly inform loading in the form of externally applied forces (Fontanella *et al.*, 2013) or as a combination of external and internal forces (Yarnitzky, Yizhar and Gefen, 2006).

2.6.3.2.4. *Validation*

The biggest challenge for FEA implementation into clinical practice is ensuring that the results produced are reliable for any person belonging to the population for which it was developed. This means that the accuracy of every part of the modelling process (modelling, material properties, and loading) and the entire process needs to be

validated for both populations and individual participants. Validation of FEA models can be done using two different approaches: direct validation and indirect validation. Direct validation compares numerical results obtained by the FEA against in vivo or in-vitro experimental data, whilst indirect validation compares the results of the FEA against data from the literature.

In the case of indirect validation, studies have compared numerically estimated plantar pressures or stress/strain behaviour of specific tissues (Yarnitzky, Yizhar and Gefen, 2006; Agić *et al.*, 2008; Jamshidi *et al.*, 2010; Shin, Yue and Untaroiu, 2012) compared to the respective data within literature (Yarnitzky, Yizhar and Gefen, 2006; Wu, 2007; Agić *et al.*, 2008; Jamshidi *et al.*, 2010; Shin, Yue and Untaroiu, 2012).

In the case of direct validation against in vivo data, studies have been found to compare the results of the FEA against barefoot or in-shoe plantar pressure distribution and/or peak plantar pressure. Additionally, numerically calculated ground reaction forces have been compared against in vivo measured ones (Gefen, 2002). Finally, one other study has compared numerical and experimental displacements of specific bones using direct motion capture and reflective markers (Tao *et al.*, 2009).

Besides validating the ability of the entire process to generate reliable models for specific patient populations, additional validation protocols are required for situations where subject-specific models are required (e.g., patients with foot deformities, amputated

toes, Charcot foot, etc.). In this case, simpler validation protocols will be needed that can be implemented within the clinic setting without significantly increasing the time and cost of the whole process. Therefore, it has been suggested in the literature that more basic pressure-based validation approaches could be used to validate these patient-specific models.

2.6.3.3. *Uses of Finite Element Analysis to reduce ulceration risk*

In addition to studies using FEA as a method of assessing and predicting the mechanical properties and the mechanical behaviour of the plantar soft tissues of the foot, several studies have used FEA to investigate methods of reducing ulceration risk in people with diabetes. In particular, these studies have primarily investigated the effect of footwear and insoles with a wide range of clinically used materials being tested, whereby the elasticity of the footwear material was found to be the most influential factor in reducing plantar pressures. (Lemmon *et al.*, 1997; Chen, Ju and Tang, 2003; Lewis, 2003; Barani, Haghpanahi and Katoozian, 2005; Cheung and Zhang, 2005, 2008; Erdemir *et al.*, 2005; Goske *et al.*, 2006; Budhabhatti *et al.*, 2007; Shariatmadari, 2009; Shariatmadari, English and Rothwell, 2010)

In addition to investigating the effect of insole/footwear materials, FE analysis has also been utilised to explore the effects of environmental influences on the performance of the insole material. For example, Shariatmadari et al. (2010) used a 2D coronal plane model of the heel to assess the pressure-relieving performance of commonly used insole

materials from 10–40°C (Shariatmadari, English and Rothwell, 2010). The study results indicated that the temperature of the insole had a considerable effect on the ability of these commonly prescribed insole materials to reduce peak plantar pressures, with the performance of the insoles being the worst at 10°C.

Building on these studies, using both 2D (Goske *et al.*, 2006; Luo *et al.*, 2011) and 3D (Chen, Ju and Tang, 2003; Cheung and Zhang, 2005)models, FEA has allowed for the development of custom insoles that provide for increased reductions in plantar surface pressures when compared to flat insoles made from pressure relieving materials. In addition, the inclusion of arch support to an insole design was also found to be beneficial in redistributing plantar pressures away from at-risk areas such as below the metatarsal heads (Cheung and Zhang, 2005).

Modifications to insoles have also been investigated; in particular, research has been conducted into the effect of pressure-relieving plug modifications for insoles or footwear. “Plug” modifications are whereby a section of the insole is removed to aid in pressure relief with the effect of these modifications being examined at the forefoot (Erdemir *et al.*, 2005; Actis *et al.*, 2008) and heel (Gu *et al.*, 2010). Erdemir et al. (2005) demonstrated significant reductions in peak pressures under the metatarsal head could be achieved using these plug modifications where the simulations showed that locating the plug under the area of peak of the pressure was more effective in terms of reducing peak pressures compared to locating it directly under the metatarsal heads.

Actis et al. (2008) has further expanded upon this work from Erdemir by using a 2D model of the full foot to test the effects of smaller (>4 mm) plugs inserted into an area of a total contact insole under the metatarsal head. They found that while the small plugs did reduce peak plantar pressures, the magnitude of the reduction was found to be both numerically and experimentally lower compared to results reported by Erdemir et al. (2005).

Gu et al. (2010) looked at plug modifications at the heel and found that a medium hardness plug >10 mm thick with a diameter 95% of that of the calcaneus was the most effective at reducing plantar pressures. It is important to note that all three studies looking at these plug modifications identified the risk of edge effects, where pressure concentrations are seen at the interface between the cut-out or plug and the stiffer material of the insole.

2.6.4. Bulk Compression Testing

The other main form of controlled compression is that of bulk compression testing. Bulk compression testing differs from that of indentation testing in that with bulk compression testing, the whole surface of the tissue is subjected to a uniform load rather than just a small area as in indentation testing. For bulk compression testing of the heel pad, a platen, of larger diameter than the heel, is used to compress the tissue either manually or mechanically (Aerts *et al.*, 1995; Ker, 1996; Tong, Lim and Goh, 2003; C C Hsu *et al.*, 2007). Additionally, ultrasound imaging can also be used in bulk compression

testing by using a large diameter disc containing a probe window to assess the underlying tissues' deformations.

Specifically, bulk compression causes the tissue to undergo uniaxial bulk compression whereby the strains within the tissue are governed predominantly by the least stiff material (i.e., fat in the case of the heel pad) (Aerts *et al.*, 1995; Tong, Lim and Goh, 2003).

During bulk compression testing, the applied load and displacement of the tissue, as a whole, is collected. The area of the platen, which is in contact with the tissue, can be derived through pressure measurement systems (Wearing *et al.*, 2009). With a known area, the effective stress within the whole tissue can be calculated for the foot region as the total measured load divided by the contact area. However, in calculating the effective stress within the tissue, assumptions must be made whereby the stress induced in the tissue is uniformly distributed throughout the tissue region being tested. Previous studies have shown that the internal distribution of stress is not uniform; thus, an effective stress measure for the whole foot region may not fully explain the response of the tissue under load (Chen, Tang and Ju, 2001; Spears *et al.*, 2007).

2.6.5. Sonoelastography

Sonoelastography (sometimes also referred to as Ultrasound Elastography) is an ultrasound imaging technique in which the stiffness of soft tissues can be quantified and visualised. The term elastography was first described by Ophir et al. (1999) to measure

and visualise the strain properties of biological tissues (Ophir *et al.*, 1999). Tissue strainability is the ability of a tissue to respond to a mechanical stimulus in the form of applied stress or pressure. It can be calculated for both the longitudinal and shear loads. A longitudinal strain occurs when tissue is compressed or stretched, whilst a shear strain is a response to angular forces, such as twisting (Bamber *et al.*, 2013).

In this method, the tissue needs to be deformed. Then, the deformation needs to be measured either to calculate and display strain (strain elastography) or to calculate and display shear-wave speed (shear-wave elastography). The tissue displacement can be in the form of either normal deformation usually produced by using an ultrasound transducer to deform the tissue surface; or in the form of shear deformation usually produced by acoustic radiation force (Bamber *et al.*, 2013).

In strain elastography, static, quasi-static, or dynamic force can be used, while shear wave elastography requires the creation of a shear-wave, which in turn requires the use of a dynamic force (Bamber *et al.*, 2013).

2.6.5.1. *Strain Elastography*

In strain elastography, the displacement of the soft tissues caused by the applied force produces a qualitative map of the elastic modulus distribution, called an elastogram. Elastograms are colour-coded, usually with blue colour indicating areas of low stiffness

and red indicating areas of high stiffness. In addition, the elastograms are often superimposed on a grey-scale B mode image to allow for a visualisation of the stiffness of the tissues with respect to the underlying anatomy.

The image's least and most deformable tissues in strain elastography are allocated the highest and lowest stiffnesses, respectively. Thus, any tissue in the image with the deformability between these upper and lower limits is associated with stiffness within this range. Hence, in its conventional form, a direct absolute quantitative measure cannot be taken from these elastograms, as the stiffness of each individual structure within the tissue depends on the range of stiffness detected in a frame. However, quantitative evaluations of stiffness are possible by determining the ratio of the displacement of the tissue of interest to that of an interface material (such as a standoff) with known stiffness (Naemi *et al.*, 2016).

Ultrasound strain elastography has been used in studying the mechanical properties of the heel pad and 1st sub-metatarsal fat pad in patients with diabetic foot ulceration (Naemi *et al.*, 2016). In this study, a low amplitude loading-unloading cyclic load was applied to the soft tissues under the heel pad and the 1st sub-metatarsal head. The soft tissue was compressed between the interface standoff material and the bony prominences of the calcaneus and the first metatarsal head. The stand-off material used

in this study was quoted as having similar mechanical properties to that of human soft tissue and therefore acted as a reference due to its known mechanical properties. A region of interest was defined as the area under compression between the ultrasound probe and the bony prominence, with the standoff and soft tissue defined separately using two ellipses. Thus, allowing for the strainability of the standoff and soft tissue to be compared. It was observed that a lower heel pad stiffness was observed in patients with active foot ulcers when compared to that of the non-ulcerated group (Naemi *et al.*, 2016). The use of this standoff material and post-processing approach enabled a quantitative assessment of stiffness using strain elastography.

2.6.5.2. *Shear wave Elastography*

Shear wave elastography is another non-invasive, ultrasound-based method for assessing the stiffness of the soft tissue. It involves the generation of shear waves inside the tissue and the measurement of their propagation speed as they expand laterally in the field of view. The speed of the shear wave is recorded by the ultrasound transducer and is used to estimate the tissues shear modulus (G) and Young's modulus (E) using the following equation:

$$\mathrm{E} = 3\mathrm{G} \approx 3\rho C^2 \qquad \text{(EQ 2.6)}$$

Where *C* is the recorded shear wave speed for the area of soft tissue and ρ is the density of the selected tissue ($\rho \approx 1000\mathrm{kg}/m^3$ for soft biological tissues). The stiffness of

different soft tissues can then be estimated based on the measured shear wave speed, based on which a stiffness map of different soft tissues can be generated.

The relationship between shear wave speed and Young's modulus [EQ. 2.6] assumes that the imaged material is incompressible, homogeneous, isotropic, and linearly elastic (Bercoff, Tanter and Fink, 2004; Widman *et al.*, 2015). Even though these assumptions might seem to be restrictive, shear wave elastography has already been successfully integrated into clinical practice for the diagnosis of conditions that are strongly associated with altered tissue stiffness, such as chronic liver disease or breast cancer, etc. (Sigrist *et al.*, 2017). However, the fact that no biological tissue fully complies with the aforementioned conditions means that careful validation of SW results in individual tissues is crucial for any clinical use.

The mechanical properties of the different soft tissues of the heel pad have been studied using shear wave elastography (Lin *et al.*, 2015, 2017; Schäfer *et al.*, 2015). In a study on healthy participants using shear-wave elastography, the mechanical properties of the heel pad were found to be highly heterogeneous, with the stiffness of the heel to be greatest beneath the plantar skin and continuously decreasing through the microchambers and then macro- chambers of the foot (Lin *et al.*, 2015, 2017).

In another study, the stiffness of lateral soft tissue of the heel was investigated, and it was found that prolonged loading (over 90 and 150 min) leads to the deep subcutaneous structures becoming less stiff (Schäfer *et al.*, 2015). While this was considered to play critical roles in pressure ulcer development, a "stiffness threshold" point was proposed to exist over which tissue damage may occur, which may aid in developing pressure redistributing devices (Schäfer *et al.*, 2015).

Despite ultrasound elastography being a versatile tool that allows the identification of tissue stiffness, there are limitations regarding the use of Strain and Shear Wave elastography within clinical and research practice. For Strain elastography, one of the main disadvantages is caused by the variability in the pressure applied to the tissue, adversely affecting the results. This may be because, in strain elastography, the relative deformability of imaged tissues in a single ultrasound image/trial is quantified, i.e., the stiffest and softest tissues in the image are allocated the highest and lowest stiffness in the image, and the tissues with moderate stiffness are associated with stiffness between the two. Hence, it does not allow comparison between different images or images from different trials and or patients in its conventional form. However, a stand-off material could be used between the ultrasound probe and the imaged tissue to overcome this limitation. Stand-offs are made from soft deformable materials that allow the passage of ultrasonic waves without producing any echoes from reflections. Thus, comparing the relative deformability of different tissues to that of the stand-off produces a quantitative

assessment of stiffness, which can be used in comparative biomechanical and clinical studies (Naemi *et al.*, 2016).

Shear wave elastography, in general, can provide a quantitative measure of the stiffness of various soft tissues by measuring the propagation speed of shear waves through tissues. However, in some cases, these shear wave speeds were displayed as a colour-coded image superimposed on the B-mode, with the colours adjusted to present a continuous spectrum ranging between the highest stiffness (in red) and the lowest stiffness (in blue) within the region of interest. This limitation does not allow a comparison of absolute soft tissues stiffnesses and has been highlighted by a number of studies.

2.6.6. Summary of Previous Methods

As the literature shows, a range of methodologies can be used to assess the mechanical properties of the plantar soft tissues of the heel pad, whether through material testing, controlled compression testing, or ultrasound elastography. However, one of the common aspects throughout these testing methodologies is that they require specialised equipment and specialized training to produce accurate and reliable results and are therefore not clinically viable. Therefore, there is a clear need for a simple, clinically applicable method to measure the mechanical properties of the plantar soft tissues of the heel. This is specifically relevant to the low resource settings like

developing countries, where access to ultrasound machines and sophisticated equipment is scarce.

2.7. Shore Hardness

The measurement of Shore hardness, using a handheld durometer, has successfully been used to assess soft tissue biomechanics in vivo and appears to be a good candidate to fill this need for a simple, clinically applicable method to measure the mechanical properties of the plantar soft tissues (Falanga and Bucalo, 1993; Aghassi, Monoson and Braverman, 1995; Romanelli and Falanga, 1995; Piaggesi *et al.*, 1999; Thomas *et al.*, 2003; Charanya *et al.*, 2004; Kissin *et al.*, 2006; Periyasamy, Anand and Ammini, 2012). The measurement of Shore hardness ranges from Shore A, which is used for the hardest materials, such as shoe soles, to Shore 00, which is predominantly used for softer materials such as low-density polymers and soft tissues (Piaggesi *et al.*, 1999; Oflaz and Baran, 2014; Zhao, Allanson and Ren, 2015). Shore hardness is a dimensionless value between 0 and 100. It is a measurement of a material's resistance to indentation whereby the value of Shore harness corresponds to the depth of indentation within the tissue. Thus, a high Shore hardness value indicates a low indentation within the material, signifying that the material is relatively hard. Conversely, a low Shore hardness value indicates a high amount of indentation into the material, signifying that the material is relatively soft.

For soft biological tissues such as the skin and fat pad of the heel, a Shore-0 or Shore-00 hardness durometer is used (Falanga and Bucalo, 1993; Aghassi, Monoson and Braverman, 1995; Romanelli and Falanga, 1995; Piaggesi *et al.*, 1999; Thomas *et al.*,

2003; Charanya *et al.*, 2004; Kissin *et al.*, 2006; Periyasamy, Anand and Ammini, 2012; International Organization for Standardisation, 2018).

Both Shore-0 and Shore-00 hardness scales have been previously used in clinic-based studies to investigate the effect of various skin pathologies such as scleroderma (Falanga and Bucalo, 1993; Aghassi, Monoson and Braverman, 1995), systemic sclerosis (Kissin *et al.*, 2006) and lipodermatosclerosis (Romanelli and Falanga, 1995) on skin biomechanics. In addition, Shore hardness has been used within the diabetic foot (Piaggesi *et al.*, 1999; Thomas *et al.*, 2003; Charanya *et al.*, 2004; Periyasamy, Anand and Ammini, 2012) to measure foot sole hardness in people with and without diabetic peripheral neuropathy, and its effect on the development of plantar foot ulcers. Even though these studies highlight the potential clinical value of Shore hardness, some key questions remain regarding its actual physical meaning and clinical relevance.

Within solid mechanics, the principles of stiffness and hardness are both well-defined independent mechanical properties with distinctive standardized methodologies for their assessment. However, in the case of soft tissue mechanics, performing standardized mechanical tests to assess stiffness is extremely challenging. As previously discussed, this has led many researchers to turn to indentation as an alternative method for the measurement of stiffness, in addition to the measurement of hardness (Zheng *et al.*, 2000; Hsu, Lee and Shau, 2002; Klaesner *et al.*, 2002; Erdemir *et al.*, 2006; Spears and Miller-Young, 2006; C C Hsu *et al.*, 2007; Chih Chin Hsu *et al.*, 2007; Behforootan, P. E.

Chatzistergos, *et al.*, 2017a, 2017b). The results of these indentation tests have been used directly as an assessment of stiffness (Zheng *et al.*, 2000; Chao, Zheng and Cheing, 2011; Chatzistergos *et al.*, 2014).

Even though resistance to indentation has been used before as a method to study soft tissue stiffness (Zheng *et al.*, 2000; Chao, Zheng and Cheing, 2011; Chatzistergos *et al.*, 2014), the exact relationship between Shore hardness and stiffness has not been explored in the literature. Thus, it is not clear which aspects, if any, of the complex non-linear mechanical behaviour of plantar soft tissue is assessed by Shore hardness and how Shore hardness is affected by the tissue's layered structure.

2.8. Plantar pressure

2.8.1. Relationship between plantar pressure and ulceration

As previously mentioned in Section 2.3, the occurrence of a diabetic foot ulcer is a multifactorial process that is primarily associated with diabetic peripheral neuropathy and high plantar pressures. In particular, the measurement of plantar pressure that is most commonly used is that of Peak Plantar Pressure (PPP). PPP is defined as the highest localised pressure under the foot within a region of interest. Elevated PPP has been shown within the literature to be a contributing factor to the mechanical breakdown of the soft tissues of the foot, especially when repeated loading is applied to the same area of the foot (Abouaesha *et al.*, 2001; Patry *et al.*, 2013).

As a result of this link between PPP and ulceration in people with diabetes, a number of studies have looked to establish a threshold value for PPP above which ulceration is more likely to happen. However, within the literature, there are many different plantar pressure thresholds for ulcer development, depending on whether the measurement of plantar pressure is performed barefoot or using an in-shoe measurement system (Armstrong *et al.*, 1998; Frykberg *et al.*, 1998; Owings *et al.*, 2009; Waaijman *et al.*, 2014; Chatwin *et al.*, 2020)

As a result, ulceration threshold values have been reported to range from 200 to 1100 KPa (Chatwin *et al.*, 2020). Armstrong *et al.* (1998b) was the first study to investigate ulceration threshold values whereby 219 patients with diabetes were recruited in a case-control study; patients with a recent history of ulceration were compared against controls that contained patients without a history of ulceration. Barefoot plantar pressure was collected with a novel Emed platform, where higher plantar pressures were found at the forefoot in patients with a history of ulceration. Although an initial threshold value for ulceration was set at 700 KPa, it was found that the sensitivity and specificity was not high enough, leading them to conclude that there is no threshold but that higher peak pressures lead to increased risk.

Frykberg *et al*. (1998) studied a cross-sectional group of 251 patients of different ethnicities to determine the risk of ulceration associated with high foot pressures and peripheral neuropathy. Pressure data were collected from 251 patients with diabetes and neuropathy using an F-scan mat system in addition to screening joint mobility. Using a logistic regression model between neuropathy, joint mobility variables, and pressure, it was concluded that both high foot pressures and neuropathy are independently associated with ulceration, leading to a suggested threshold of 588 KPa.

However, it must be noted that within these seminal studies, there are issues regarding the grouping of the participants, which ultimately weakens the applicability of the threshold value derived. Regarding Frykerbg et al. (1998), the control group of participants without DPN included patients with and without a history of DFU. Individuals with a history of DFU are reported to have significantly higher plantar pressures than those without DFU history; therefore, including participants without DFU history in such studies may have diluted the results (Bacarin, Sacco and Hennig, 2009). Grouping participants with active and previously healed DFUs together, as demonstrated in this study by Frykberg et al. (1998), weakens the conclusions drawn about the causal relationship between high plantar pressure and DFU due to patients with active DFUs potentially altering their gait (albeit without any sensory feedback) to avoid any further damage to the active wound (Fernando *et al.*, 2014). Similar to Frykberg et al. (1998), Armstrong et al. (1998) included active and healed DFUs within their “ulcerated”

cohorts, which may again have contributed to plantar pressure alone not being able to identify patients accurately at risk of ulceration

More recently, a threshold of 200 kPa for vertical plantar pressure has been suggested within in-shoe pressure research to highlight those at risk of DFU (Owings *et al.*, 2009). Owings *et al.* (2009) performed a cohort study whereby subjects with diabetes and neuropathy were potentially recruited from a database of 2625 eligible patients created over a period of 18 years whereby 190 surviving patients with prior plantar ulcers of the forefoot were identified, of which 49 patients agreed to participate. All participants had had a yearly follow up appointment for at least five years and had remained healed at least for over 90 days. Within this study, both barefoot and in-shoe plantar pressures were collected with Novel® devices. This study concluded that barefoot peak pressure is a poor predictor of peak in-shoe pressure, and that in-shoe pressure is more representative of ulceration risk in diabetic patients. A mean value of barefoot peak plantar pressure of 556 KPa was reported but had a large inter-subject variability (107 – 1,192 KPa) and a considerably lower mean in-shoe peak plantar pressure of 207 KPa. While the majority of the cohort's average pressure data remains in line with this 200KPa threshold, some individuals who remained ulcer-free did have pressure above the threshold and some who ulcerated had pressures below this threshold. Furthermore, one study reported 36% of ulcer-free patients and 51% of patients who ulcerated to have pressures above the threshold(Waaijman *et al.*, 2014)

However, as yet, a peak pressure threshold for ulceration risk has not been definitively established. The difficulty in establishing a PP threshold is mainly because DFU is a multifactorial process affected by direct vertical pressure but also by shear stress (Patry *et al.*, 2013). Moreover, DFU is also influenced by other factors such as peripheral vascular disease, glycaemic levels, activity, and lifestyle (Patry *et al.*, 2013). Thus, as detailed previously, several factors can influence plantar pressures. However, PP is only one factor in a multifaceted pathway to diabetic foot ulcer formation. Importantly, it has been shown that ulceration can occur in the presence of normal PP (Armstrong *et al.*, 1998a).

Due to the multifactorial nature of DFU ulceration, PP assessment was considered part of standard clinical practice up until 2007; whereby a systematic review by Crawford et al. (2007), found that while high plantar pressure distribution is associated with diabetic foot ulcers, there is little evidence regarding the predictive power of assessing plantar pressure distribution with regards to predicting ulceration in DPN patients (Crawford *et al.*, 2007).

Owing to this lack of scientific evidence regarding the predictive power of plantar pressure assessment, as highlighted by Crawford et al. (2007), the approach to assessing

the foot at risk has changed in the last thirteen years with risk stratification systems and ulcer prevention approaches, no longer considering plantar pressure distribution as a valid predictor of ulceration(Leese *et al.*, 2006; Schaper *et al.*, 2016). This systematic review by Crawford et al. (2007) concluded that the current persistent lack of evidence for plantar pressure might be due to poorly standardized methods, study costs and study implementation complexities.

Another suggested explanation for plantar pressure being a poor predictor of DFU is due to not considering shear plantar pressure (Yavuz *et al.*, 2007, 2015). The majority of plantar pressure studies focus on plantar pressure rather than shear; this is likely due to the greater magnitude of plantar pressure compared to shear plantar pressure. In addition, plantar pressures are easier to measure and assess with current commercial systems (Shaw *et al.*, 1998)

Investigating shear pressure may increase the understanding of plantar foot mechanics and their role in the development of DFU (Perry, Hall and Davis, 2002) However, the few studies that have measured both plantar pressure parameters found no general trend in the locations of the peak shear and pressures with participants having peak shear and peak pressure occurring at different sites.(Perry, Hall and Davis, 2002; Yavuz *et al.*, 2007, 2015)Furthermore, even fewer studies related peak shear pressure to DFU.

Two recent papers investigated the effect of shear pressure with regards to DFU (Yavuz *et al.*, 2015, 2017)whereby it was found sites of peak shear pressure match to sites of recently healed forefoot DFUs compared to peak pressure sites. However, the differences between shear and pressures were small. In addition, DFUs also occurred at sites where both peak shear and peak plantar pressures were at the same location, as well as at the sites where neither peak parameter were present, further highlighting the complex, multifactorial nature of DFU. Additionally, it has also been found that peak shear and plantar pressures are higher in the DFU groups. However, only peak shear plantar pressures were found to be higher in the DFU group compared to the non-ulcerated group. The authors of these studies believe this work to be the first of its kind and, whilst small in scale, believe the results to be clinically meaningful (Yavuz *et al.*, 2015, 2017).

The above studies measured shear pressure while barefoot, so results are unlikely to represent shear pressure applied in-shoe, which may also differ depending on footwear (Perry, Hall and Davis, 2002). Therefore, further investigation into in-shoe shear pressure with larger cohorts and of a longitudinal design are required before we can fully understand the role of shear pressure in the development of DFU.

In addition to recent research looking into the effect of shear plantar pressures, research has also investigated the daily-life activities of patients with diabetic peripheral neuropathy; although limited, the research indicates that more time is spent standing

and sitting compared to walking (Lemaster *et al.*, 2003; Najafi, Crews and Wrobel, 2010). Such findings suggest that perhaps a measure of cumulative pressure over time, such as pressure-time integral, maybe more indicative of DFU risk than peak pressure. (Owings *et al.*, 2009; Bus, 2012; Bus and Waaijman, 2013)

Pressure-time integral data is occasionally reported alongside the parameter of choice, peak pressure, with conflicting views on whether it adds any benefit (Bus and Waaijman, 2013). However, the majority of studies reporting both parameters found no differences between them; essentially, any significant result or pattern reported for peak pressure was also present for pressure-time integral.(Mueller *et al.*, 2006; Guldemond *et al.*, 2007; Arts and Bus, 2011)

A recent study by Giacomozzi et al. (2018) has indicated that the measurement of pressure-time integral might be a more reliable and generalizable measurement than peak plantar pressures when establishing risk thresholds and that changes in the plantar pressure distribution of patients considered at low risk of ulceration may be catastrophic (Giacomozzi *et al.*, 2018). Therefore it has been recommended by Giacomozzi et al. (2018) that when investigating the effect of plantar pressure on ulcer risk, regression models for the prediction of diabetic foot ulcers should contemplate the use of additional factors such as physical foot assessments, including segmental alignment, range of motion and function assessments, in addition to patients' disease duration, age

and BMI to account for the current limitations of plantar pressure assessment (Giacomozzi *et al.*, 2018).

The use of additional factors to account for the limitations in plantar pressure assessment has been previously investigated within the literature, whereby a series of papers have looked at using varying biomechanical parameters to predict plantar pressures in people with diabetes. The additional factors included in these studies are factors that are commonly associated with the complications associated with diabetes. These include diabetic peripheral neuropathy, foot deformity, foot and ankle range of motion, and changes to the mechanical properties of the plantar soft tissues.

Despite recent research into plantar pressure as a method to predict ulceration, the research tends to not look at the biomechanical factors associated with an increase in plantar pressure and instead focuses on clinical variables such as DPN, PVD, history of ulceration. However, as previously mentioned, causes of increased peak plantar pressures can also result from a range of biomechanical factors and complications, such as foot deformities, lack or loss of joint movement, changes in soft tissue stiffness (Payne, Turner and Miller, 2002; Waldecker, 2012; Barn *et al.*, 2015). As these factors and complications have a direct and significant influence on plantar pressure, they are key risk factors for diabetic foot ulcer formation, and their effect on ulceration needs to be examined.

2.8.2. The effect of foot shape and morphology

Foot shape and foot morphology have a direct influence on plantar pressure, especially under the metatarsal heads. Plantar pressures are highest at the metatarsal heads during the push-off phase of walking (80% of stance) as, at this point, weight-bearing and push-off forces are greatest, and the weight-bearing contact area is smallest (Kelly, Mueller and Sinacore, 2000)

Metatarsal head plantar pressures are typically higher in people with DM and peripheral neuropathy (Mueller *et al.*, 2003). This is due to a number of factors, namely changes in the morphology of the foot and the loss of protective sensation leading to an overloading of the soft tissues subsequently, leading to skin breakdown (Mueller *et al.*, 2006).

Changes in foot morphology are either caused because of deformities or limited joint movements. These deformities are thought to be caused by atrophy of the small muscles responsible for metatarsophalangeal plantar flexion, which leads to deformities such as hammertoes, claw toes, prominent metatarsal heads, and pes cavus (high arch) (van Schie *et al.*, 2004). These complications directly affect how plantar pressures and plantar loads are distributed across the plantar surface of the foot and, as a result, are one of the most significant underlying causes of diabetic foot ulcers (Singh, Armstrong and Lipsky, 2005). These changes in the morphology of the foot cause localised areas of high plantar pressure, which leads to high levels of internal stress, causing damage to the plantar soft tissues of the foot.

If the deformity directly causes an area of the foot to be adversely loaded during gait, such as the tips of the toes or the 1st and 2nd metatarsal heads (Gefen, 2003) where the plantar soft tissues meet the bony prominences, the likelihood of the formation of an ulcer rise. This is due to the tissue of that area not being designed to experience the loads typically caused by gait and everyday movement. Conversely, the deformities caused by neuropathy can lead to areas that normally experience loading to become unloaded.

Since foot structure can affect peak pressure (Ledoux *et al.*, 2005; Guiotto *et al.*, 2013) and peak pressure can predict ulceration, it is possible that ulceration may be predicted by foot structure. In line with this, foot deformities, such as hammer/claw toe deformity or hallux limitus, have been associated with an increased risk of ulceration (Ledoux *et al.*, 2005; Cowley *et al.*, 2008). Guiotto *et al.* (2013) found a close relationship between foot morphological alterations and plantar ulcerations. This agrees with Ledoux *et al.* (2005), who demonstrated that foot structure was one of the main factors that could explain differences in peak pressure. Moreover, there is a direct relationship between diabetes and changes in foot morphology, especially in the presence of neuropathy, due to its effect on muscles and tendons (Kim, 2013). A cavus foot was found to be frequent among patients with diabetes, and higher pressures were found when compared to non-diabetic feet (Ledoux *et al.*, 2005). Therefore, there is evidence that foot morphology can potentially impact peak plantar pressures, which can ultimately mean that it may influence ulcer development.

Additionally, literature has suggested an increase in the pronation of the foot that is linked to neuropathy and is more prevalent in people who have a longer duration of diabetes (Formosa, Gatt and Chockalingam, 2013). Pronation of the foot is defined as:

"a triplanar motion consisting of dorsiflexion in the sagittal plane, eversion in the frontal plane, and abduction in the transverse plane achieved through the multitude of free motion through the foot articulations" (Horwood and Chockalingam, 2017)

Whereby the pronation of the foot should be seen as the full kinematic chain of movements across the foot that allows the foot to move towards the midline of the body and to take up a more prone position.

Those patients who exhibit excessive foot pronation also have limited joint mobility of the first MPJ. The limited joint mobility of the foot has a prevalence of 8% to 58% in diabetes and may indicate a risk of developing pronation. This pronation may, in turn, lead to other foot deformities, such as hammertoes or hallux valgus and altered foot mechanics (Pecoraro, Reiber and Burgess, 1990; Robertson *et al.*, 2002; van Schie *et al.*, 2004; Crawford *et al.*, 2007; Barn *et al.*, 2015; Allan, Munro and Figgins, 2016) which produce increased pressures.

However, when looking at pronation as a clinical variable that may be associated with ulceration, there are several issues regarding the measurement of pronation and the overall meaning of increased, excessive, and hyper pronation (Horwood and Chockalingam, 2017; Nigg, Behling and Hamill, 2019). The quantification of pronation in real-life situations, such as gait, is difficult, if not impossible, since the talus bone cannot be accessed from the outside (Nigg, Behling and Hamill, 2019) and has led to a number of different variables being used within the literature and clinical practice to describe these pronation like movements.

The most common surrogate variable used within clinical practice is the rotation around the longitudinal foot axis. Rotations about this longitudinal axis are used as a surrogate variable for foot pronation, whereby foot pronation is referred to as foot eversion using the following definition:

"Eversion is an inward rotation of the foot with respect to the longitudinal foot axis."

(Nigg, Behling and Hamill, 2019)

However, the main weakness of these surrogate measurements of pronation is that they refer to movement around "clinical axes" and do not represent the movement around the actual physical anatomical axes *(Nigg, Behling and Hamill, 2019)*.

When looking at pronation and excessive pronation as a risk factor for ulceration, it is difficult to define a set value at which pronation is “excessive”. As pronation is a natural movement and a normal part of gait, each person will have an optimum amount of pronation; however, the literature does not give an insight into what this value might be as it will be specific to that individual.

Additionally, the terms related to increased pronation such as excessive-, over- and hyper-pronation are suggested to be avoided within the literature as there is no clinical definition for these terms (Horwood and Chockalingam, 2017). As the “normal” degree of pronation is unknown, it is impossible to determine what is in excess of “normal”.

As many aspects related to the pronation of the foot are either missed or only partially understood, there is a need within the literature to look at ulceration and its relationship with pronation from different and novel perspectives to understand better if there is indeed a relationship and if so, what overall effect does this have on ulceration risk.

2.8.3. The effect of limited foot and ankle range of motion

Limited joint mobility plays a crucial role in the abnormal biomechanics of the foot and ankle in people with diabetes (Mueller *et al.*, 1989; Zimny, Schatz and Pfohl, 2004). As a result, structural changes occur within the tendons of people with diabetes and peripheral neuropathy. These structural changes lead to a decrease in elasticity and tensile strength, which subsequently results in instability at joints causing subluxations or an overall increase in the stiffness of the foot. The primary hypothesis for these

structural changes is the crosslinking of collagen fibrils within the tendons due to the non-enzymatic glycosylation of soft tissues, thus making the tendon stiffer and less compliant.

These structural changes to the tendons within the foot; result in poor foot biomechanics (Kim, 2013). Primarily a reduction in the range of motion of the foot and ankle presenting itself as an increase in the ankle and forefoot rigidity (Guiotto *et al.*, 2013). Zimny *et al.* (2004) studied the relationship of joint mobility with plantar pressures in a cross-sectional study of 70 patients with diabetes and 30 healthy control subjects. It was concluded that the ankle joint and first metatarsophalangeal joint (MPJ) mobility showed a strong inverse correlation with the pressure-time integral of the forefoot.

The limited joint mobility within the foot and ankle as a result of peripheral neuropathy also has a direct effect on the gait pattern of people with diabetes and diabetic peripheral neuropathy by limiting foot flexibility and restraining the forward progression of body weight during the stance phase of gait (Fernando *et al.*, 1991, 2013). Increased unsteadiness has been observed in patients with diabetes, with it being linked to a thickening of the Achilles tendon and plantar fascia, thus making the foot more rigid and therefore less adaptable to walking on different surfaces (García-Álvarez *et al.*, 2013; Allan, Munro and Figgins, 2016). The lack of normal joint movement alters the persons

normal gait pattern, leading to increased plantar pressures due to changes in loading pattern and increases the risk of ulceration.

Additionally, when comparing healthy subjects and those with diabetes and peripheral neuropathy, Fernando *et al.* (2013) found that patients with neuropathy walked slower and had a reduced stride length when compared to people with diabetes and no peripheral neuropathy and healthy subjects. They also found that people with neuropathy spent a more extended period of time in the stance phase compared to subjects with diabetes and no peripheral neuropathy. In addition, patients with neuropathy demonstrated a reduced range of movement when compared to healthy subjects except for hip flexion. Therefore, it was concluded that elevated plantar pressure, coupled with a more extended period spent in the stance phase in neuropathic patients, increases the risk of ulceration through prolonged mechanical load on the plantar soft tissues of the foot.

Finally, ankle equinus has emerged as a possible contributor to increased plantar pressures (Lavery, Armstrong and Boulton, 2002; Amemiya *et al.*, 2014). Limited ankle joint dorsiflexion, or equinus, restricts the tibia's forward progression over the foot during the stance phase. To counter this change in the gait cycle, adaptations include early heel lift, excessive subtalar joint pronation and associated midtarsal joint pronation (Michaud, 2011). These changes likely lead to an increase in the time spent weight-

bearing at the forefoot and likely lead to the development of foot ulcers at the 1st and 2nd metatarsal heads (Mueller *et al.*, 1989; Aronow *et al.*, 2006).

One of the limitations of these studies assessing the effect of limited foot and ankle range of motion in people with diabetes is the method by which the foot and ankle range of motion is measured. As highlighted by a systematic review and meta-analysis by Searle et al. (2017), where the association between ankle range of motion and plantar pressure of 15 studies were reviewed, all studies measured the foot and ankle range of motion using a passive handheld goniometer. The ankle range of motion was measured with the participant lying in the prone position with the knee in the flexed or extended position. While this method of measuring the foot and ankle range of motion is the accepted method, it poses many questions as this passive measurement of ankle dorsi and plantarflexion is not the same as the corresponding values during gait. One of the methods used to address this limitation is the use of 3D motion capture systems and the assessment of the individual foot segments using a multisegmented foot model.

Multisegmented foot models allow for quantifying the mobility of different foot segments during clinical gait analysis (Baker and Robb, 2006; Deschamps *et al.*, 2011). The main requirement of these multisegmented foot models is to reliably and accurately identify foot segments and plantar regions of clinical relevance. These regions of clinical relevance include, but are not limited to, the rearfoot, midfoot, and forefoot segments. There are currently four main multisegmented foot models that are used within a clinical

context these are the Milwaukee Foot Model (Kidder *et al.*, 1996), Oxford Foot Model (Carson *et al.*, 2001), Rao et al. 2006 (Rao, Saltzman and Yack, 2007), and the Rizzoli Foot Model (Leardini *et al.*, 2007).

The major difference between these multisegmented foot models is the number and selection of foot segments. The tibia, rearfoot, and forefoot are the most tracked segments with the hallux – or the first metatarsophalangeal joint – seldom tracked, and the midfoot is tracked only by a few models (Macwilliams, Cowley and Nicholson, 2003; Leardini *et al.*, 2007; Rouhani *et al.*, 2011; Portinaro *et al.*, 2014).

Within the literature, the clinical usefulness of this multisegmented foot modelling in patients with diabetes has initially been explored by two different research groups (Rao, Saltzman and Yack, 2007; Sawacha *et al.*, 2009). Both Rao et al. (2007) and Sawacha et al. (2009), have observed a significant reduction in intersegmental foot mobility, especially in the rearfoot and the first metatarsal, in patients with diabetes and diabetic peripheral neuropathy (Rao, Saltzman and Yack, 2007; Sawacha *et al.*, 2009).

Multisegmented foot models can also be used to assess joint kinematics within the feet of people with diabetes. Multisegmented foot models are now starting to be implemented in assessing plantar pressures in people with diabetes. In addition, many of the plantar pressure systems that are currently available can be connected to 3D

motion capture systems to allow for the capture of joint motion and the capture of 2-dimensional video allowing for simple video analysis.

To assess the effect that changes in the intersegmental range of motion have on the plantar pressures of the foot, the foot is divided into regions of interest. These are typically the heel, midfoot, and forefoot. The simplest methods of defining these regions of interest rely only on the geometry of the footprint, without reference to measured pressure. The footprint is divided into predefined subareas based on medial and lateral tangents of the footprint, a bisecting longitudinal line, and lines drawn perpendicular to the bisecting line in correspondence with specific percentages of foot length. More complex methods also exploit pressure gradients and pressure distribution within the footprint map to refine the selection and identify anatomical structures such as metatarsal heads, the first metatarsophalangeal joint, and lesser toes (Menz and Morris, 2006; Scott, Menz and Newcombe, 2007; Gurney, Kersting and Rosenbaum, 2008; Ellis *et al.*, 2011).

More advanced methods to define regions of interest of the foot include the use of automated masking techniques. These automated masking techniques are more reliable, built-in and implemented by most plantar pressure measurement systems and are widely used in research and clinical settings (Cavanagh and Ulbrecht, 1994). These automated systems take the acquired footprint and automatically divide the foot up based on the shape of the foot and according to reliable and repeatable algorithms.

These algorithms differ according to the criteria applied to identify regions associated with anatomical structures or segments (Menz and Morris, 2006; Scott, Menz and Newcombe, 2007; Gurney, Kersting and Rosenbaum, 2008; Ellis *et al.*, 2011).

However, the limitations that affect the accuracy of this automated approach are the spatial resolution of the pressure measurement system, size and shape of the regions of interest, and of particular importance, incomplete or significantly altered footprint images. While the first two limitations can be mitigated with appropriate hardware and software, the latter, incomplete or significantly altered footprint images, represents a critical issue in clinical settings, where there is a high incidence of foot deformity, especially in people with diabetes and diabetic peripheral neuropathy.

To overcome this limitation, an automated procedure based on anatomical landmark positions has been proposed and validated by Giacomozzi et al. (Giacomozzi *et al.*, 2000). This method relies on integrating a 3D motion capture system, a pressure measurement system, a multi-segment foot model and an algorithm to identify regions of interest from the position of the anatomical landmarks. The advantage that this method presents, over traditional geometrical masking, is the use of objective anatomical landmarks to divide the plantar surface into regions of interest while also improving repeatability over conventional manual masking based on the subjective identification of these landmarks (Stebbins *et al.*, 2005; Stebbins, Giacomozzi and Theologis, 2008). An additional advantage of implementing this method to define the regions of interest is that it allows

the integration of simultaneous kinematic and pressure measurements due to the use of 3D motion capture. It may also improve the clinical relevance of plantar pressure measurements, especially in people with foot deformity, by offering a complete assessment of foot function.

Clinical implementation of this integrated pressure-kinematics method has already been used successfully to investigate a number of pathologies such as subtalar coalition (Giacomozzi *et al.*, 2006), foot deformities in children including cerebral palsy (Stebbins *et al.*, 2006), and diabetes (Guiotto *et al.*, 2013).

Regarding diabetes, there has only been one study to date that has used this method to assess foot loading with regards to patients with and without diabetic peripheral neuropathy (Sawacha *et al.*, 2012). Sawacha et al. (2012) used a three-segment foot model to integrate pressure and kinematic parameters associated with the rearfoot, midfoot, and forefoot (Sawacha *et al.*, 2012). In this study, Sawacha et al. (2012) used their own previously validated foot model. The forefoot was defined by the first metatarsal head, fifth metatarsal head, and the proximal epiphysis of the second toe phalanx (Sawacha *et al.*, 2009). The midfoot is defined by the cuboid, navicular tuberosity, and fifth metatarsal base phalanx (Sawacha *et al.*, 2009). Finally, the rearfoot was defined by the sustentaculum tali, trochlea peronealis, calcaneus phalanx (Sawacha *et al.*, 2009).

The results of this study by Sawacha et al. (2012) indicated that the group with diabetic peripheral neuropathy exhibited significantly excessive plantar pressures at the midfoot and forefoot, in addition to excessive ground reaction forces in all directions (medial-lateral, anterior-posterior, and vertical) (Sawacha *et al.*, 2012). A reduced loading surface on the midfoot subsegment was also noted. Furthermore, the midfoot subsegment displayed excessive dorsiflexion, external rotation, and eversion. Thus, it was concluded that the initial results of this study show that this methodology of integrating kinetics, kinematics, and plantar pressure may enable a more appropriate characterization of patients at risk of foot ulcerations and help planning prevention programs (Sawacha *et al.*, 2012).

While this method of integrating kinetics, kinematics, and plantar pressure may enable a more appropriate characterization of patients at risk of foot ulcerations, the clinical applicability of this method is open for discussion. While reducing in price, plantar pressure systems are still expensive, in addition to the cost of a 3D motion capture system, which puts this methodology out of the reach of the average clinician. They also require specialist training for their operation and interpretation of results. Therefore, a different approach is needed in order to adopt these multisegmented foot models into clinical practice. One potential option is in the use of 2D video capture. This approach may provide a more accurate approximation of foot and ankle range of motion compared to that of the traditional passive goniometer; it will also allow for an assessment of how intersegmental joint motion may affect plantar pressures.

2.8.4. The effect of soft tissue mechanics

There have been several studies looking into how diabetes affects the plantar soft tissues of the foot, in particular, the subcutaneous fat pad of the foot. Previous studies have indicated that the mechanical properties of the plantar soft tissue change as a result of diabetes; however, the causes of these changes and their possible implications are not yet fully understood. Literature shows that in people with diabetes and diabetic peripheral neuropathy, the plantar soft tissues of the foot tend to be thinner (Chao *et al.*, 2010), stiffer (Klaesner *et al.*, 2002; Chao, Zheng and Cheing, 2011), harder (Piaggesi *et al.*, 1999) and also tend to have less energy return efficiency (Hsu *et al.*, 2000).

Diabetes has been linked to morphological changes to fat pads of the foot, whereby diabetes has been linked to a thinning of the heel pad (Bus *et al.*, 2004, 2005). Additionally, Bus and co-workers (Bus *et al.*, 2005) have also indicated that those who presented with a form of foot deformity had significantly less fat pad at the metatarsal head level over the phalangeal level, suggesting thinning and distal displacement dislocation due to contracture of the digit. As a result, the capacity of the tissue in this region to reduce focal plantar pressure is severely compromised.

As well as a thinning of the fat pads of the foot, the stiffness of the fatty tissues also increases (Yvonne Y Cheung *et al.*, 2006). The stiffness of the heel pad was also found to be correlated with high levels of triglycerides within the blood (Chatzistergos *et al.*,

2014). The increased stiffness and the reduced thickness of the fatty tissues within the foot could limit the tissues' ability to evenly distribute loads, making them more vulnerable to trauma and ulceration. These changes, in particular the increase in the stiffness of the heel pad, reduce the shock absorption effect of the soft tissues and lead to higher levels of plantar pressures, which are commonly associated with the development of diabetic plantar foot ulcers (Payne, Turner and Miller, 2002; Lepäntalo *et al.*, 2011; Giacomozzi *et al.*, 2018).

In addition to the association between fat pad stiffness and plantar pressure, the association between Shore hardness, as a measurement of skin hardness, and plantar pressure has also been investigated within literature (Piaggesi *et al.*, 1999; Thomas *et al.*, 2003; Charanya *et al.*, 2004; Periyasamy, Anand and Ammini, 2012). The measurement of Shore hardness was used to measure foot sole hardness in people with and without diabetic peripheral neuropathy and to investigate its association with plantar pressure (Thomas *et al.*, 2003; Charanya *et al.*, 2004; Periyasamy, Anand and Ammini, 2012). In patients with diabetic peripheral neuropathy, the Shore hardness was found to be 20 % to 35 % higher compared to subjects without diabetic neuropathy (Thomas *et al.*, 2003; Charanya *et al.*, 2004). In addition, both Thomas et al. (2003) and Charanya et al. (2004) found that plantar pressure was highly correlated with Shore hardness with a correlation coefficient of 0.99 and 0.98, indicating that as skin hardness increases, so does plantar pressure. The reported strengths of the correlations are high, while very little explanation is provided by either author concerning the observations.

One potential reason may be the method in which plantar pressure was measured whereby an optical pedobarograph was used as opposed to the more standard walkway style systems.

2.9. Summary of Literature review

To summarise, when assessing the risk of a person with diabetes developing a diabetic foot ulcer, the literature has shown that there are several risk stratification systems that are currently in use worldwide (International Working Group on Diabetic Foot (IWGDF), the University of Texas Foot Risk Stratification (UTFS), Scottish Intercollegiate Guideline Network (SIGN), American Diabetes Association (ADA) and The Seattle Diabetic Foot Study (Boyko *et al.*, 2006)). While each system includes measurements associated with ulceration such as diabetic peripheral neuropathy, peripheral vascular disease, duration of diabetes, foot deformities and previous history of ulceration, these are indirect factors when it comes to the formation of a diabetic foot ulcer.

As a diabetic foot ulcer is primarily caused by an inherent failure of the planar soft tissues of the foot, the literature suggests that a direct assessment of the foot, in particular foot biomechanics, may further aid in the prediction and prevention of diabetic foot ulcers. More importantly, the literature indicates that the assessment of plantar pressure and plantar soft tissue biomechanics may be the most important direct factors with regard to ulceration.

Increased plantar pressures are critical in the onset of diabetic foot ulcers due to the repeated overloading of the plantar soft tissues of the foot. While the assessment of plantar pressure is not currently part of ulcer assessment protocols due to limited scientific evidence, current literature still indicates that elevated plantar pressure in people with diabetes is still a significant risk factor within ulceration prevention (Formosa, Gatt and Chockalingam, 2016; Giacomozzi *et al.*, 2018). Therefore, methods have been developed to try and account for the current limitations of plantar pressure assessment (Giacomozzi, Caravaggi and Stebbins, 2016; Giacomozzi *et al.*, 2018). Including the use of multisegmented foot models to provide accurate plantar pressure measurements within different regions of the foot. In addition, studies have been conducted looking into predicting plantar pressures in people with diabetes and identifying the associated changes within the foot that have the most significant effect on plantar pressure. These parameters include neuropathy, foot shape and morphology, foot and ankle range of motion, and soft tissue mechanical properties.

In particular, with regards to the assessment of soft tissue biomechanics, exploring the potential value of plantar soft tissue mechanical properties to enhance the clinical management of the diabetic foot is severely limited by the lack of clinically viable testing techniques. The measurement of Shore hardness, using a handheld durometer, has successfully been used to assess soft tissue biomechanics in vivo and appears to be a good candidate to fill this need for a simple, clinically applicable method to measure the

mechanical properties of the plantar soft tissues of the heel however some key questions remain regarding its actual physical meaning and its clinical relevance.

3. Chapter 3 – The physical meaning and clinical relevance of Shore hardness in diabetic foot research

3.1. Introduction

Plantar soft tissue is the first point of contact with the ground during normal gait. Its main role is to act as a shock absorber to dampen the effect of ground reaction forces during weight-bearing activities such as walking and standing by promoting more even distribution of plantar loads.

The heel pad of the foot is a highly specialised tissue with non-linear, viscoelastic mechanical properties (Naemi and Chockalingam, 2013) and a complex internal structure comprising of both skin and a fat pad. The fat pad comprises of fat globules enclosed within a matrix of fibrous connective tissue (septae) and is divided into two layers: microchambers and macrochambers (C C Hsu *et al.*, 2007).

The literature has shown that being able to quantify the stiffness of plantar soft tissues enhances the prediction of conditions such as diabetic foot ulceration and heel pain syndrome (Lin *et al.*, 2017; Naemi *et al.*, 2017) and could potentially improve the clinical management of those conditions. However, exploring the potential value of such measurements to improve patient outcomes is severely limited by the lack of clinically viable testing techniques that would enable the measurement of plantar soft tissue biomechanics as part of everyday clinical practice. Existing methods for the quantitative assessment of plantar soft tissue stiffness are based either on the use of complex,

bespoke testing devices (Zheng *et al.*, 2000; Hsu, Lee and Shau, 2002; Klaesner *et al.*, 2002; Erdemir *et al.*, 2006; Spears and Miller-Young, 2006; C C Hsu *et al.*, 2007; Chih Chin Hsu *et al.*, 2007; Behforootan, P. E. Chatzistergos, *et al.*, 2017a, 2017b) or the use of expensive ultrasound elastography systems (Lin *et al.*, 2017; Chatzistergos *et al.*, 2018).

In order to explore and fully understand the role of soft tissue biomechanics in ulceration, there is a need for simpler, cost-effective and reliable methods to assess and follow up on changes in the mechanical characteristics of the plantar soft tissue in the clinic.

The measurement of Shore hardness, using a handheld durometer, has successfully been used to assess soft tissue biomechanics in vivo and appears to be a good candidate to fill this gap (Falanga and Bucalo, 1993; Aghassi, Monoson and Braverman, 1995; Romanelli and Falanga, 1995; Piaggesi *et al.*, 1999; Thomas *et al.*, 2003; Charanya *et al.*, 2004; Kissin *et al.*, 2006; Periyasamy, Anand and Ammini, 2012). Shore hardness is a measurement of a material's resistance to indentation. It is commonly used in evaluating the hardness of various materials, predominantly rubbers as well as softer materials such as low-density polymers and soft tissues (Piaggesi *et al.*, 1999; Oflaz and Baran, 2014; Zhao, Allanson and Ren, 2015). For soft biological tissues such as the skin and fat pad of the heel, a Shore-0 or Shore-00 hardness durometer is used (Falanga and Bucalo, 1993; Aghassi, Monoson and Braverman, 1995; Romanelli and Falanga, 1995; Piaggesi *et al.*, 1999; Thomas *et al.*, 2003; Charanya *et al.*, 2004; Kissin *et al.*, 2006; Periyasamy, Anand

and Ammini, 2012; International Organization for Standardisation, 2018). The measurement of Shore hardness corresponds to the depth of indentation within the tissue and is given a dimensionless value between 0 and 100, with a high value of Shore hardness indicating a low amount of indentation within the material.

Both Shore-0 and Shore-00 hardness scales have been previously used in clinic-based studies to investigate the effect of various skin pathologies such as scleroderma (Falanga and Bucalo, 1993; Aghassi, Monoson and Braverman, 1995), systemic sclerosis (Kissin *et al.*, 2006) and lipodermatosclerosis (Romanelli and Falanga, 1995) on skin biomechanics. In addition, Shore hardness has been used within the diabetic foot (Piaggesi *et al.*, 1999; Thomas *et al.*, 2003; Charanya *et al.*, 2004; Periyasamy, Anand and Ammini, 2012) to measure foot sole hardness in people with and without diabetic peripheral neuropathy, and its effect on the development of plantar foot ulcers. Even though these studies highlight the potential clinical value of Shore hardness, some key questions remain regarding its actual physical meaning and clinical relevance.

Within solid mechanics, the principles of stiffness and hardness are both well-defined independent mechanical properties with distinctive standardised methodologies for their assessment. However, in the case of experimental soft tissue mechanics, performing standardised mechanical tests to assess stiffness is extremely challenging. This has led many researchers to turn to indentation as an alternative method for the measurement of stiffness, in addition to the measurement of hardness (Zheng *et al.*,

2000; Hsu, Lee and Shau, 2002; Klaesner *et al.*, 2002; Erdemir *et al.*, 2006; Spears and Miller-Young, 2006; C C Hsu *et al.*, 2007; Chih Chin Hsu *et al.*, 2007; Behforootan, P. E. Chatzistergos, *et al.*, 2017a, 2017b). In some studies, results from indentation tests were combined with finite element (FE) modelling to inverse engineer the tissue's stress-strain behaviour (Hsu, Lee and Shau, 2002; Spears and Miller-Young, 2006; Naemi, Chatzistergos and Chockalingam, 2016; Behforootan, P. E. Chatzistergos, *et al.*, 2017a; Chatzistergos *et al.*, 2018). However, there are also studies in which the indentation results are directly used as an assessment of stiffness (Zheng *et al.*, 2000; Chao, Zheng and Cheing, 2011; Chatzistergos *et al.*, 2014).

Even though resistance to indentation has been used before as a method to study soft tissue stiffness (Zheng *et al.*, 2000; Chao, Zheng and Cheing, 2011; Chatzistergos *et al.*, 2014), the exact relationship between Shore hardness and stiffness has not been explored in the literature. Furthermore, it is not clear which aspects, if any, of the complex non-linear mechanical behaviour of plantar soft tissues are assessed by Shore hardness and how Shore hardness is affected by the tissue's layered structure. Finally, it is also unclear whether Shore hardness is sensitive enough to changes in plantar soft tissue biomechanics to be used to assess differences between populations or to monitor the effect of various pathological conditions such as diabetes.

In this context, the primary aim of this study was to investigate, through the use of FE analysis, the physical meaning of the measurement of Shore hardness and whether it

can be considered an indirect measurement of stiffness. In addition, the ability of Shore hardness to monitor changes in the mechanical properties of the skin or the underlying subcutaneous soft tissue of the heel pad was investigated.

Previous research has indicated that the stiffness of plantar soft tissue is affected by age (Kwan, Zheng and Cheing, 2010) and loading (Challis *et al.*, 2008) and is correlated with the biochemical profile of people with diabetes (Hsu *et al.*, 2000; Wrobel and Najafi, 2010). Therefore, as the secondary aim, the clinical viability of Shore hardness was also tested by assessing the ability of Shore hardness to confirm the abovementioned established associations in a clinical investigation.

3.2. Methods

3.2.1. Finite Element Analysis.

The effect of changes in the mechanical properties, of the skin and subcutaneous tissue, on the measured value of Shore hardness was investigated using a 3D FE model of the in vivo test in the area of the heel. For this purpose, an anatomically accurate model of the heel was used (Behforootan et al., 2017).

The 3D FE model was designed based on MRI images collected from the left foot of a male participant (age: 39years) with a heel pad thickness of 16mm. The foot was scanned using a 1.5T MRI scanner whereby coronal T1 weighted 3D Fast Field Echo (FEE) images were recorded with an in-plane resolution of 0.23mm and an out-of-plane resolution of 1.00mm. From the recorded MRI DICOM images, the 3D geometry of the heel and

calcaneus was reconstructed and segmented using commercially available segmentation software ScanIP (Simpleware, UK).

The segmented model was exported into SolidWorks, whereby the 3D model was simplified to only include a cylindrical section of the heel pad structure perpendicular to the apex of the calcaneus to reduce computational complexity. Additionally, the model was modified to include a layer of skin (thickness=1mm) based on current literature (Strzalkowski *et al.*, 2015). The 3D model was then imported into ANSYS 18.1 for meshing. All numerical analyses were performed using ANSYS 18.1. (ANSYS, Canonsburg, PA, USA).

The model of the Shore-00 durometer comprises three main parts: a rigid cylindrical indenter with a semi-spherical tip (diameter of 2.4mm), a rigid disk (diameter 18mm) simulating the bottom surface of the durometer and a spring element that simulates the internal mechanism of the durometer [Figure 3-1b]. The model of the durometer is controlled with the help of a pilot node which is rigidly connected to the rigid disk and linked to the indenter's tip through the spring element [Figure 3-1b]. During the measurement of Shore hardness, the rigid disk is pressed against the skin's surface with a net force equal to the durometer's weight (1.96 N). At the same time, the force at the indenter's tip, defined by the durometer's internal mechanism, increases linearly with the tip's displacement relative to the rigid disk [Figure 3-1c]. The initial distance between the indenter's tip and the surface of the rigid disk (ds) is 2.4mm, and the magnitude of

the force on the tip increases linearly from zero (ds= 2.4mm) to a maximum value of 1.1 N when the tip is fully pushed inside the durometer (ds=0). Similarly, the value of Shore hardness also increases linearly with the relative displacement of the tip from zero (ds= 2.4mm) to a maximum value of a hundred (ds=0).

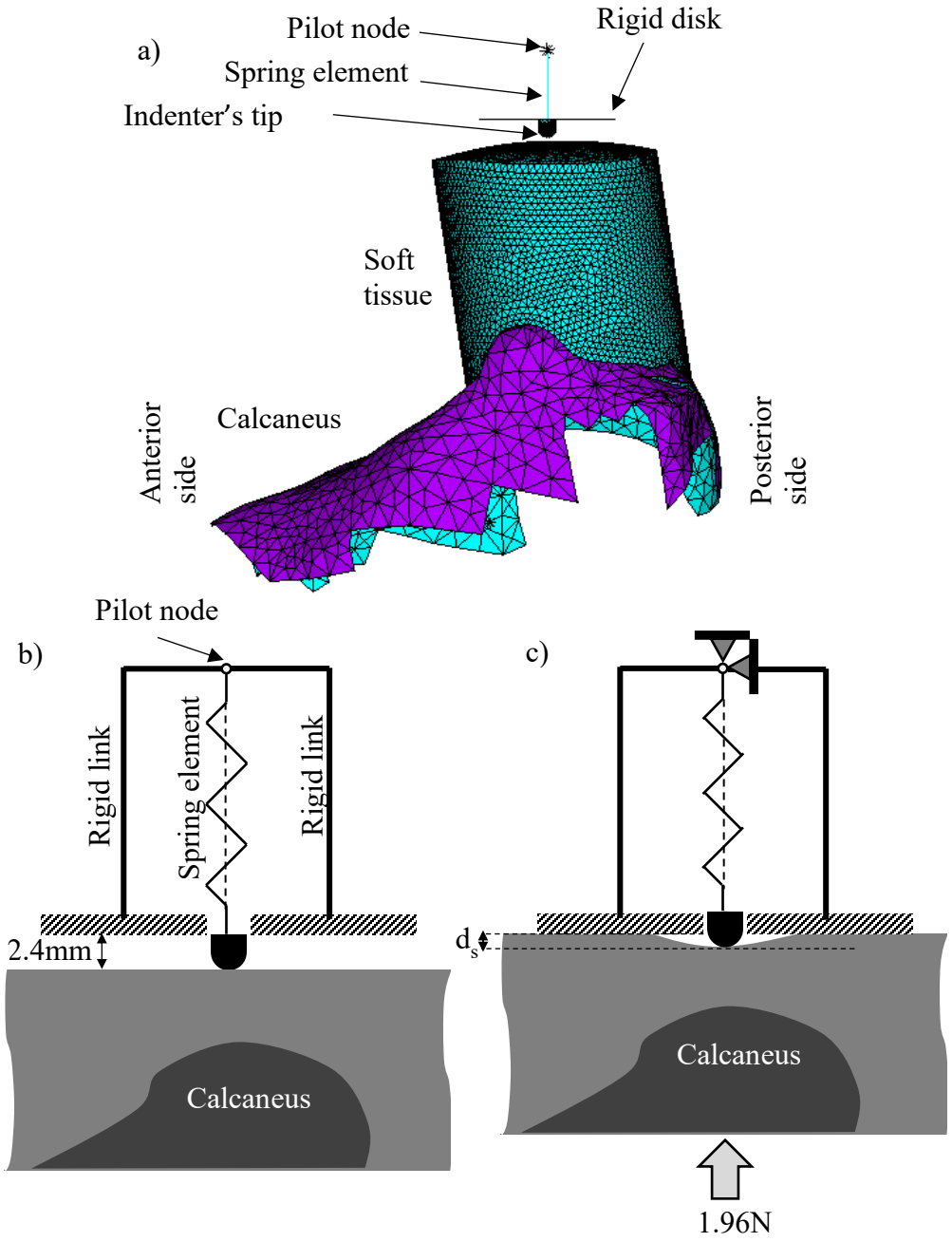


Figure 3-1:a) Pictorial representation of the meshed model of the heel model and the simulation of the Shore-00 durometer. b) A simplified view of the FE model showing the durometer in contact with the surface of the heel before indentation. c) Boundary conditions

For the simulation of the Shore hardness test, the pilot node was completely fixed, and a force of 1.96 N was imposed on the calcaneus in the direction of the durometer axis. Both the calcaneus and the tip of the indenter were constrained to allow movement only along the axis of the durometer. Shore hardness was calculated from the final relative distance between the indenter's tip and the rigid disk.

Due to the nature of the applied loading, only a cylindrical section of the heel model was meshed [Figure 3-1a]. This cylindrical section was directly over the apex of the calcaneus, and its diameter was significantly wider than the durometer (67% wider than the base of the durometer). A preliminary analysis indicated that the results of the simulation were not affected by this simplification; additionally, given that the calcaneus is considerably stiffer than the soft tissues (Popowics et al., 2002) with relatively small displacements and forces involved within the model, the relative deformation of the calcaneus is negligible. Therefore, these structures were assumed to be rigid with their effects on stress distribution simulated using boundary conditions whereby zero-displacement boundary conditions were assigned to all nodes that formed the surface features of the calcaneus [Figure 3-1a].

The final FE model comprised of 83,888 tetrahedral four-node elements. Element size was decided through sensitivity analysis to eliminate any mesh dependency phenomena.

The mechanical behaviour of the subcutaneous tissue and skin was simulated using the Ogden hyperelastic material model (1st order) [EQ 3.1] (Behforootan, P. Chatzistergos, *et al.*, 2017).

$$W = \frac{\mu}{\alpha}(\lambda_1^{-\alpha} + \lambda_2^{-\alpha} + \lambda_3^{-\alpha} - 3) + \frac{1}{d_k}(J-1)^2$$

EQ. 3.1

$$G_0 = \frac{1}{2}(\mu\alpha)$$

EQ. 3.2

Where λ_1, λ_2, λ_3 are the deviatoric principal stretches and μ (Pa), α (unitless), and d_k (Pa^{-1}) are material coefficients. Coefficient α is indirectly related to the tissue's strain hardening/softening behaviour, while both μ and α are directly linked to the material's initial shear modulus (G_0) [EQ 3.2]. Parameter d_k is a function of both the effective Poisson's ratio (ν) and the initial shear modulus (G_0) [EQ 3.3].

$$d_k = \frac{3(1-2\nu)}{G_0(\nu+1)}$$

EQ. 3.3

Reference values of μ and α were adopted from literature for skin (Petre *et al.*, 2013) and subcutaneous tissue (Erdemir *et al.*, 2006). The coefficient values used were μ_{skin}=3.57 kPa, α_{skin}=22.71 for skin and μ_{sub}=4.82 kPa, α_{sub}=6.82 for subcutaneous tissue.

The skin and subcutaneous tissue were both assumed to be nearly incompressible (v=0.475)(Behforootan, P. E. Chatzistergos, *et al.*, 2017a; Chatzistergos *et al.*, 2018).

A parametric investigation was performed to assess if changes in the measured Shore hardness are primarily caused by changes in skin stiffness or changes in the stiffness of the underlying subcutaneous tissue. For this purpose, the initial shear modulus of the skin or subcutaneous tissue was increased or decreased by independently adjusting the values of the coefficients μ or α [EQ 3.2]. More specifically, tissue softening or stiffening of 25% and 50% was simulated by keeping the value of α constant and increasing or decreasing μ by 25% and 50%, respectively. In order to understand the effect of the non-linear nature of the tissue's mechanical behaviour, the same change in initial shear modulus was also simulated by keeping μ constant and increasing or decreasing α by 25% and 50%, respectively [EQ 3.2]. The same procedure was performed separately for skin and for the underlying subcutaneous tissue to assess the sensitivity of Shore hardness to changes in the mechanical properties of different tissues. Seventeen scenarios were investigated in total.

3.2.2. In vivo testing

After ethical approval was obtained, forty participants with diabetes and DPN were recruited from two outpatient centres in Chennai, India (Dr A. Ramachandran Diabetes Hospital, Chennai, India and Sri Ramachandra University, Chennai, India). All participants provided full informed consent before testing. Inclusion criteria were history of diabetes (Type-1 or Type-2), the ability to walk unaided for more than 5m, a Vibration Perception

Threshold (VPT) value of over 25V at least two of eight sites (Hallux, 1st, 3rd, 5th Metatarsal head, Midfoot, Heel, Medial Malleolus and Dorsal aspect of Hallux) on both feet (measured using a biothesiometer – Kody Biothezi-VPT, Chennai, India). For this study, only adults were recruited.

Exclusion criteria were, history of foot or ankle surgery or bone fracture, the existence of active foot ulcer, any neurological disorder other than peripheral neuropathy including but not limited to Parkinson's disease, essential tremor, Huntington's disease etc., systemic diseases affecting mobility or leading to chronic inflammation, visual impairment leading to difficulties in walking or Charcot's foot. In addition, demographical data were recorded through a patient-led questionnaire, including questions related to their general health, diabetes management, duration of diabetes and history of foot-related pathologies.

Blood test results were collected as part of the participants' standard treatment during routine follow-up and were retrospectively retrieved from the hospitals' database. The parameters recorded included measurements of Fasting Blood Sugar (FBS), HbA1c, and triglycerides (TG). The parameters of FBS, HbA1c, and TG were selected as previous literature has indicated a relationship between these parameters and a change in the stiffness of the plantar soft tissues of the foot (Hsu, Lee and Shau, 2002; Chatzistergos *et al.*, 2014; Singh *et al.*, 2014). The results of these blood tests were taken within three days of the date of biomechanical testing.

Shore hardness was measured using a Shore-00 device (Shore 00, AD-100, Checkline Europe B.V, Dennenweg, The Netherlands). To measure Shore hardness, participants were asked to lie in a prone position face down on an examination couch with their shank in the air approximately 90 degrees to the thigh [Figure 3-2a]. With the foot relaxed, the durometer was lowered onto each of the plantar sites used for VPT testing [Figure 3-2b], allowing the tissue to be compressed by the full weight of the device before taking the reading of hardness. Due to the viscoelastic nature of the plantar soft tissues of the foot, prolonged exposure to load will cause a decrease in the measured value of Shore hardness; therefore, minimal time was taken between the application of the durometer to the foot and the recording of the measurement. Each site was tested three times, and the average value of Shore hardness for each site was calculated. The average of left and right for each region was also calculated (i.e., regional average).

Loading of the foot was assessed by measuring the distribution of plantar pressure (PP) during walking, at a self-selected pace, using a MatScan 0.5x0.5m pressure mat (Tekscan, Boston MA, USA). Three stance phases per foot were recorded at 100Hz using a two-step protocol (Bus and Lange, 2005). Values of the maximum total force, maximum PP (averaged over area), maximum peak PP and pressure time integral (Melai *et al.*, 2011) were assessed for six regions of the foot, namely: Hallux, 1st Metatarsal head, 3rd Metatarsal head, 5th Metatarsal head, Midfoot and Heel (Gurney, Kersting and Rosenbaum, 2008).

Shapiro-Wilk test was used to screen the data for normal distribution ($p<0.05$). Based on the non-normal distribution of the data, Spearman's rank correlation tests were run between Shore hardness and blood biochemical parameters, PP measurements, age, and duration of diabetes. Associations between the Shore hardness and PP were investigated only between measurements taken from the same site. In all cases, the left and right foot results were analysed separately (Menz, 2004). All statistical analyses were conducted using commercially available software (IBM® SPSS®v.24).

a

b

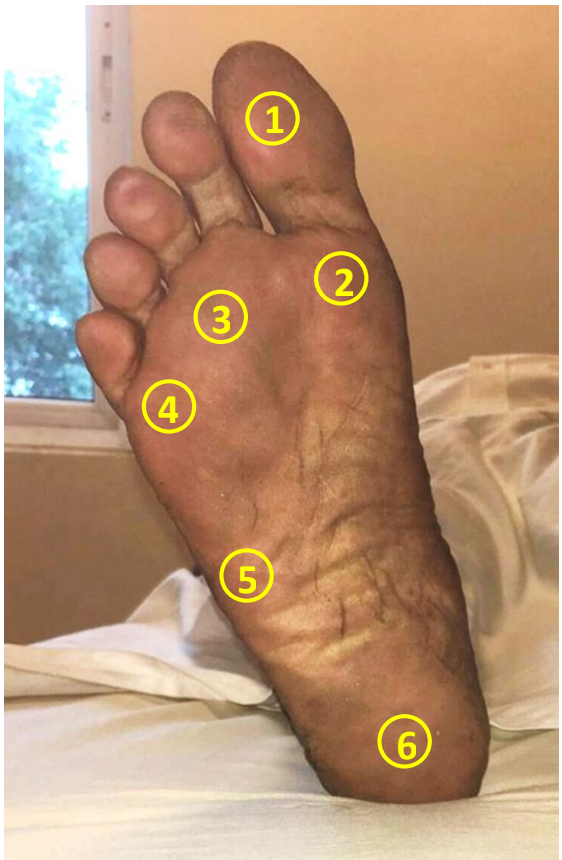


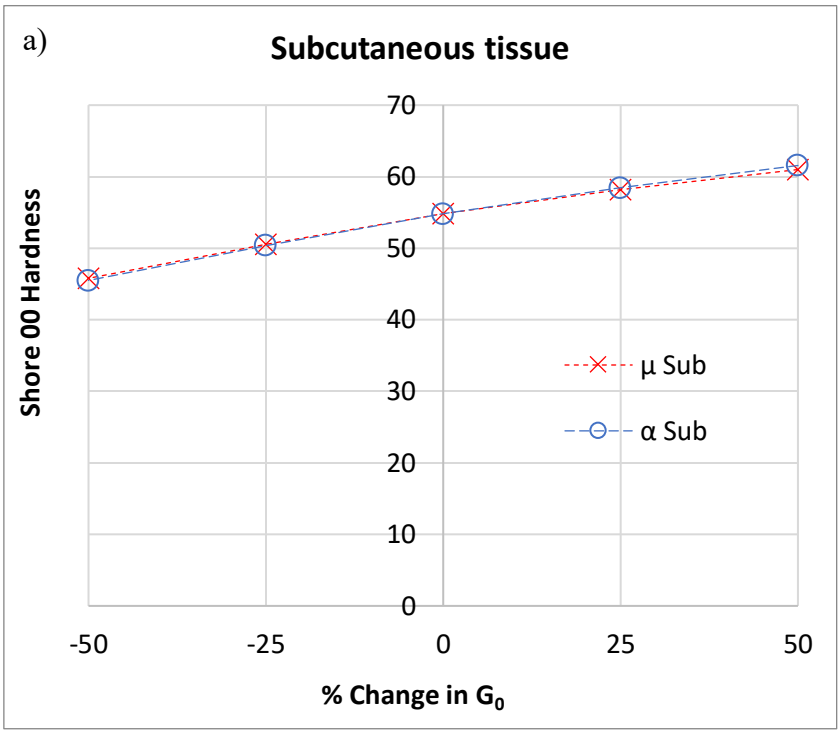
Figure 3-2:a) Position of the participant when performing the reading of Shore hardness. b) Eight anatomical positions used of the measurement of Shore hardness (1) hallux, (2) 1st metatarsal head, (3) 3rd metatarsal head, (4) 5th metatarsal head, (5) midfoot, (6)

3.3. Results

3.3.1. FE analysis

Shore hardness was calculated for the reference condition to be equal to 55, and it changed linearly with the value of the material coefficients [Figure 3-3]. Shore hardness was equally sensitive to changes in subcutaneous tissue or skin properties [Figure 3-3]. Indicatively, a 25% reduction or increase in the shear modulus of subcutaneous tissue led to an 8% decrease or 7% increase in Shore hardness, respectively.

Changing either of the two material coefficients of subcutaneous tissue (i.e., μ_{sub} or α_{sub}) had the same effect on Shore hardness [Figure 3-3a]. In this case, Shore hardness appears to be sensitive only to changes in the initial shear modulus regardless of how this change has been produced. On the contrary, when the properties of skin were changed, then Shore hardness was clearly more sensitive to changes in α_{skin} than to changes in μ_{skin} [Figure 3-3b]. A 25% reduction or increase in α_{skin} changed Shore hardness by 8% or 7%, respectively, while a 25% reduction or increase in μ_{skin} changed Shore hardness only by 3% or 2%. This difference in the effect of α_{skin} and μ_{skin} for the same initial shear modulus indicates that Shore hardness is not sensitive only to changes to skin initial shear modulus but also changes in its strain hardening/softening behaviour.



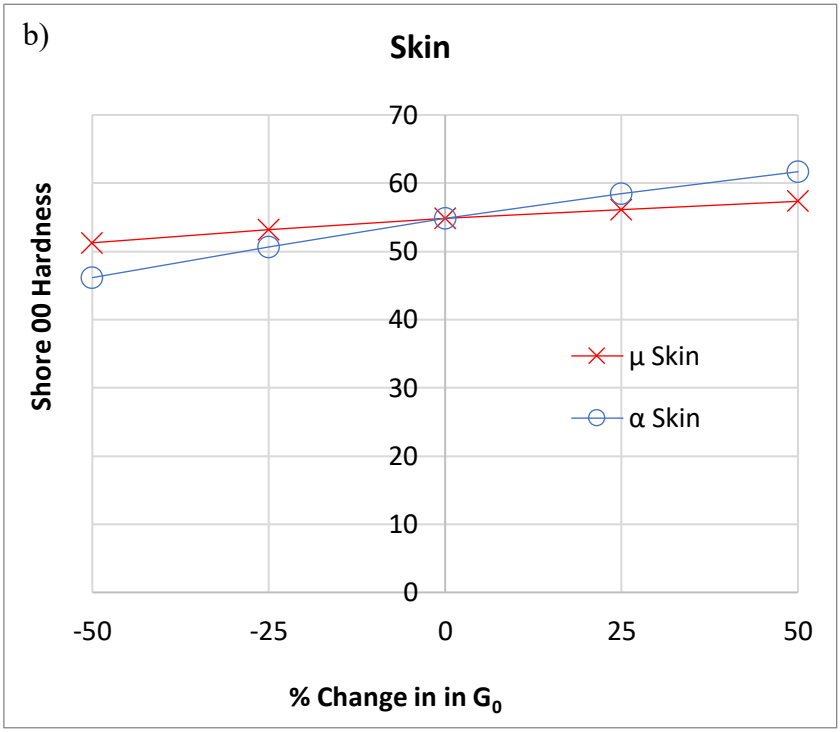


Figure 3-3: The relationship between the numerically calculated Shore hardness and changes in the stiffness of a) subcutaneous (Sub) tissue and b) skin. Percentage changes in tissues stiffness are presented relative to the reference condition.

3.3.2. In vivo testing

The participants that were recruited for this study had an average age of 63(±9) years and an average duration of diabetes 15(±9) years [Table 3-1]. Twenty-eight of the forty participants had blood biochemical data on record.

Table 3-1: The size of the participant group, the average values and standard deviations of their age, and duration of diabetes. The average values and standard deviations of the clinical parameters included in this study are also presented (if not otherwise indicated, the sample size (n) is equal to group size (i.e., 40)).

Group Size (M/F)	*40 (23/17)*
Age (y)	*63±9*
Duration of Diabetes (y)	*15±9*
FBS (mg/dl)	*177± 90(n = 28)*
HBA1c (%)	*9.0 ± 2.0(n = 26)*
Triglycerides (mg/dl)	*132 ± 56(n = 24)*

The areas with the lowest and highest Shore hardness were the 5th Metatarsal head and Hallux areas, respectively, for both feet [Table 3-2]. A detailed table with all biomechanical measurements can be found in Table 3-3.

Table 3-2: The average value and standard deviation of Shore-00 hardness for each of the plantar sites tested for left and right feet.

Shore-00 hardness	**Left Foot**	**Right Foot**
Hallux	42 ± 11	44 ±11
1st Metatarsal Head	38 ± 11	42 ± 9
3rd Metatarsal Head	38 ± 12	31 ± 8
5th Metatarsal Head	35 ± 12	35 ± 12
Midfoot	36 ± 10	41 ± 11
Heel	40 ± 10	40 ± 13

Spearman's rank-order correlation analysis showed that high Shore hardness in the left foot was associated with low-pressure time integral in the area of the heel (r=-0.445, n=39, p=0.005). This was the only significant correlation found between Shore hardness and any PP measurements.

A medium-strength positive correlation was found between the regional average Shore hardness at the heel of the left foot and the level of triglycerides (r=.410, n=24, p=0.047). There were no statistically significant associations found between Shore hardness and age or the duration of diabetes.

Table 3-3: This table highlights the mean and standard deviations for the results of Shore hardness and the parameters related to the plantar pressure distribution. (Force, peak and average pressure). The highest values of Shore hardness can be found at the Hallux on both the Left and Right feet, and the lowest values of Shore hardness can be found at the 5th Metatarsal Head on both Left and Right feet. The Heel experiences the highest values of force, whilst peak and average pressures are highest under the 3rd Metatarsal Head. Finally, Pressure Time Integral is highest under the 3rd Metatarsal head.

	Left Foot				Right Foot		
	N	Mean	Std. Deviation		N	Mean	Std. Deviation
Shore Hardness (Degrees Shore)							
1st Metatarsal Head	40	37.57	11.24		40	41.58	8.97
3rd Metatarsal Head	40	37.53	11.75		40	31.08	7.62
5th Metatarsal Head	40	35.12	11.91		40	34.80	11.71
Hallux	40	42.48	11.13		40	43.95	11.39
Heel	40	40.08	10.01		40	40.10	12.86
Mid-foot	40	36.16	10.20		40	41.33	11.03
Force (N)							
1st Metatarsal Head	39	159.86	51.08		40	156.00	47.49
3rd Metatarsal Head	39	190.80	61.74		40	177.20	53.75
5th Metatarsal Head	39	165.20	74.97		40	158.86	67.32
Hallux	39	107.75	44.37		40	108.08	53.56
Heel	39	436.61	127.06		40	440.20	120.04
Mid-foot	39	173.67	81.26		40	174.62	62.05
Peak Pressure (kPa)							
1st Metatarsal Head	39	216.92	70.14		40	204.78	67.63
3rd Metatarsal Head	39	265.86	80.50		40	260.38	74.94
5th Metatarsal Head	39	213.66	65.31		40	211.73	58.38
Hallux	39	222.39	71.57		40	217.70	92.88
Heel	39	242.90	66.62		40	236.06	67.63
Mid-foot	39	144.25	56.62		40	139.16	45.32
Average Pressure (kPa)							
1st Metatarsal Head	39	125.40	34.63		40	117.94	31.58
3rd Metatarsal Head	39	176.78	43.90		40	168.74	41.48
5th Metatarsal Head	39	133.28	41.53		40	135.57	34.83
Hallux	39	127.20	38.53		40	125.70	46.27
Heel	39	141.84	35.26		40	139.34	34.66
Mid-foot	39	80.46	28.27		40	76.73	21.85
Pressure Time Integral (kPa)							
1st Metatarsal Head	39	62.17	22.02		40	58.56	15.75
3rd Metatarsal Head	39	83.86	17.76		40	82.10	19.86
5th Metatarsal Head	39	68.63	19.13		40	69.73	18.02
Hallux	39	55.14	24.82		40	61.10	31.23
Heel	39	61.47	17.78		40	60.90	15.69
Mid-foot	39	39.62	13.58		40	39.18	10.88

3.4. Discussion

To understand the physical meaning of the measurement of Shore hardness of plantar soft tissue, FE analysis was used to simulate the measurement of Shore hardness using a handheld durometer.

Based on current literature regarding indentation of the plantar soft tissues of the foot, indentation using a small-sized indenter can be said to be relevant to the measurement of the stiffness of the skin, whilst indention using a large indenter is said to be a measurement of the bulk stiffness of entire plantar soft tissue (Spears and Miller-Young, 2006). In the literature, a small indenter is defined as an indentation probe that is less than 6mm in diameter (Spears and Miller-Young, 2006). As the tip of a Shore hardness durometer is approximately 2.4mm in diameter, it can be classed as a small indenter. Therefore, it can be hypothesised that the measurement of Shore hardness should be more representative of skin stiffness. However, the results of the FE analysis presented here have shown that the measurement of Shore hardness is also strongly affected by changes in the mechanical properties of the underlying subcutaneous tissue. Indeed, Shore hardness appears to be equally sensitive to changes in skin or subcutaneous tissue properties. This is a major limitation for using Shore hardness to follow up on possible changes in the mechanical properties of plantar soft tissues as changes in the properties of one tissue layer could be masked by changes in another layer; if these changes happen in opposite directions.

Regarding the actual physical meaning of Shore hardness, the results of this study indicate that this is different for skin and subcutaneous tissue. When the properties of skin were kept constant and those of the subcutaneous tissue were changed, Shore hardness was found to be affected only by changes in initial shear modulus regardless of how these changes were produced. Considering that in non-linear materials, such as plantar soft tissue, stiffness increases with deformation, the above observation indicates that Shore hardness offers an assessment of stiffness that is relevant to the initial slope of the stress-strain graph (i.e., stiffness for small deformations).

On the contrary, when the properties of skin were changed and those of the underlying subcutaneous tissue were kept constant, Shore hardness appeared to be affected not only by the initial shear modulus of the skin but also by the skin's strain hardening/softening behaviour. In this case, Shore hardness changed more rapidly with initial shear modulus when these changes were produced by controlling the value of coefficient α_{skin} rather than μ_{skin}.

As a result, it can be concluded that, on its own, the measurement of plantar soft tissue Shore hardness does not provide an assessment of the stress-strain behaviour of the tissue's constituent layers but an assessment of the bulk tissue's overall capacity to deform. In this context, a reduction in Shore hardness could be interpreted as increased macroscopic deformability of the bulk tissue. This increased deformability could be

caused either by tissue thickening or by tissue softening (in the skin or subcutaneous tissue level), or by a combination of these.

In addition to the proposed use of Shore hardness as a method to indirectly measure the stiffness of the plantar soft tissues, the clinical viability of the device has been assessed by attempting to confirm previously established correlations with demographics, biomechanical, and clinical parameters. Previous studies have shown that the mechanical properties of the heel pad are affected by loading, age and blood biochemistry in both healthy and diabetic populations (Hsu *et al.*, 2000; Challis *et al.*, 2008; Kwan, Zheng and Cheing, 2010; Wrobel and Najafi, 2010).

Examining the effect and association between loading, using plantar pressure, and plantar soft tissue mechanics, the only correlation found between plantar pressure parameters and Shore hardness was at the heel. This association was found between Shore hardness and pressure time integral. In this case, the correlation was negative, indicating that an increase in the cumulative load experienced by the foot causes a decrease in plantar tissue hardness. This finding is in agreement with previous observations by Challis et al. (2008), who indicated that habitual runners tend to have softer heel pads compared to habitual cyclists. (Challis *et al.*, 2008).

The level of triglycerides was the only blood biochemical parameter shown to be significantly correlated with Shore hardness in this study. Triglycerides were positively

correlated with Shore hardness, whereby an increase in Shore hardness is associated with an increase in the triglyceride levels in the blood. The association between triglycerides and soft tissue hardness are in line with the previous research (Chatzistergos *et al.*, 2014). Chatzistergos et al. (2014) established the connection between blood biochemical parameters and the stiffness of the heel pad, whereby higher values of triglycerides correlate with an increase in stiffness and the amount of energy absorbed by bulk plantar soft tissues in people with diabetes (Chatzistergos *et al.*, 2014).

This increase in plantar tissue hardness could be linked to the increased production of advanced glycated end-products (AGE). Previous research has shown that in people with diabetes, those with hypertriglycemia also tend to have poorer glycaemic control (hyperglycaemia) (Khan, Sobki and Khan, 2007; Khattab *et al.*, 2010; Meenu *et al.*, 2013). The International Diabetes Federation classifies hyperglycaemia as an HbA1c value of over 7% (53mmol/mol) (Aschner, 2017). As shown in Table 3-1, the average value of the study cohort HbA1c is 9% (75mmol/mol).

Hyperglycaemia has been shown to enhance the production of AGEs which damage the collagen fibrils that make up the skin (Avery and Bailey, 2006; Singh *et al.*, 2014). AGEs cause the collagen fibrils to become more cross-linked, thus changing the mechanical properties of the collagen fibrils, resulting in more brittle and rigid fibres (Avery and Bailey, 2006). Therefore, it can be speculated that hypertriglycemia or hyperglycaemia

can lead to an increase in collagen cross-linking, which could account for the increase in Shore hardness.

While the link between Shore hardness and the mechanical properties of the plantar soft tissues are not yet fully understood, the results of this study indicate that an increase in Shore hardness is associated with an increase in the initial shear modulus of the soft tissues of the foot. In particular, an increase in Shore hardness could represent an increase in stiffness of the plantar soft tissues whereby the foot becomes less compliant to loading.

When comparing the applicability of Shore hardness as a method to measure the mechanical properties of the plantar soft tissues to that of other approaches, such as ultrasound indentation or shear wave elastography, the main advantages of the Shore hardness measurement are: a) its ease of use and b) the speed in which a full examination can be conducted. The use of a handheld Shore hardness durometer requires little training and is safe to use in clinics. In addition, the time required to take a measurement is minimal. For example, a full examination of the plantar sites used in this study took no more than 5 minutes to perform. However, as discussed previously, there are some very serious limitations in the use of Shore hardness as a method to assess plantar soft tissue stiffness. As the FE analysis showed, Shore hardness is unable to separate the individual effect of each layer on the measurement, which could significantly reduce its reliability as a method for monitoring changes in tissue stiffness.

Regardless of its limitations, however, Shore hardness was able to confirm previously observed correlations between plantar soft tissue mechanics and loading in addition to correlations between plantar soft tissue mechanics and blood biochemical parameters. These correlations, therefore, indicate that the use of Shore hardness can have potential clinically viable applications.

One of the main limitations of this study is that the subcutaneous tissue of the heel is simulated as a single layer of homogeneous, bulk soft tissue. In reality, the fat pad of the heel consists of two distinct layers of visco-hyperelastic tissues (Hsu *et al.*, 2009; Matteoli *et al.*, 2012; Fontanella *et al.*, 2013; Behforootan, P. E. Chatzistergos, *et al.*, 2017b): the first being the microchamber layer, which is a thin layer of small septa comprised of elastin fibres, and the second, the macrochamber layer which is a thick layer of larger septa comprised of roughly equal amounts of elastin fibres and collagen. These two layers have been shown to exhibit different mechanical behaviour (Ahanchian *et al.*, 2017) and have different functional roles (C C Hsu *et al.*, 2007). Thus, simulating the visco-hyperelastic behaviour of the microchamber and macrochamber layers could expand on the association between the measurement of Shore hardness and the mechanical properties of the skin and different subcutaneous layers. However, the key conclusion that Shore hardness cannot be considered as a direct measurement of skin properties, but as an assessment of macroscopic deformability is highly unlikely to be altered by the inclusion of more layers with more complex mechanical behaviour.

It must be stressed that the purpose and application of this model and FE analysis presented here was solely to estimate the relative sensitivity of Shore hardness to altered stiffness (skin or subcutaneous tissue) at the heel. While this model appears to be a valid method of estimating the sensitivity of Shore hardness, validated subject-specific FE models of the in vivo hardness test will be needed to predict the absolute Shore hardness values directly. In particular, these subject-specific models must consider the thickness of the skin and subcutaneous soft tissue, which this model does not currently take into account. Based on the results of the FE analysis, the lack of information on thickness does not allow any conclusions to be drawn with regards to potential changes in the stiffness of plantar soft tissue. The reported Shore hardness results are therefore relevant only to the macroscopic deformability of bulk plantar soft tissue.

With regards to the further application of the results of this model and the FE analysis undertaken., the physical meaning of Shore hardness can also be applied and is relevant to other plantar areas of the foot, such as the midfoot and the metatarsal head regions. This is due to the similar anatomical structures of the foot within these regions, whereby a thick layer of subcutaneous tissue relative to the thickness of the skin covers the bony aspects of the foot. The results of this study could also therefore be applied to other areas of the body that present with similar anatomies, such as the buttocks and the biceps.

However, further research is required to look at the physical meaning of Shore hardness when used in areas such as the dorsal aspect of the foot and the rear of the heel where there is minimal thickness of subcutaneous tissue relative to the skin. In these cases, the physical meaning of Shore hardness may change whereby it can become a measurement of skin properties only instead of an assessment of macroscopic deformability.

In conclusion, the results of this study indicate that Shore hardness offers an assessment of stiffness that is a combination of both the mechanical behaviour of the skin and the underlying subcutaneous tissue. As a result, differentiating between the stiffness of skin and the subcutaneous tissue based on the conventional assessment of Shore hardness remains a challenge. Addressing this consideration about sensitivity and reliability, which is highlighted in this study, is a necessary prerequisite for exploring potential clinical uses of Shore hardness in the clinical management of foot-related conditions such as diabetic foot ulcer prevention. At the same time, this study also showed that Shore hardness could verify correlations between tissue biomechanics, loading and blood biochemistry that were previously identified using more complex testing techniques. This finding indicates that despite its limitations, Shore hardness can still be a useful research tool in the study of plantar soft tissue biomechanics.

4. Chapter 4: Examining the effect of indenter size on the indentation of a layered structure

4.1. Introduction

As discussed in Section 3.1, the heel pad of the foot is a highly specialised tissue with nonlinear, viscoelastic mechanical properties (Naemi and Chockalingam, 2013). Previous research has shown that the properties of the heel pad of the foot change over time as a result of diabetes, with the heel pads becoming thinner and stiffer as a result (Bus *et al.*, 2004, 2005; Yvonne Y Cheung *et al.*, 2006; Chatzistergos *et al.*, 2014). These changes, in particular the increase in the stiffness of the heel pad, reduce the shock absorption effect of the soft tissues and lead to higher levels of plantar pressures, which are commonly associated with the development of diabetic plantar foot ulcers(Payne, Turner and Miller, 2002; Lepäntalo *et al.*, 2011; Giacomozzi *et al.*, 2018).

Being able to quantify these changes in the mechanical properties of the plantar soft tissues of the foot, in particular, the stiffness of plantar soft tissues, has been shown in the literature to enhance the prediction of conditions such as diabetic foot ulceration and heel pain syndrome (Lin *et al.*, 2017; Naemi *et al.*, 2017) and could potentially improve the clinical management of those conditions. However, exploring the potential value of such measurements to improve patient outcomes is severely limited by the lack of clinically viable testing techniques that would enable the measurement of plantar soft tissue biomechanics to be part of everyday clinical practice.

Previous research has indicated that the measurement of Shore hardness may be a good candidate to fill this gap due to its previous use in assessing soft tissue biomechanics in vivo (Falanga and Bucalo, 1993; Aghassi, Monoson and Braverman, 1995; Romanelli and Falanga, 1995; Piaggesi *et al.*, 1999; Thomas *et al.*, 2003; Charanya *et al.*, 2004; Kissin *et al.*, 2006; Periyasamy, Anand and Ammini, 2012). However, it has been highlighted in section 3.4 that the measurement of Shore hardness offers an assessment of stiffness that is a combination of both the mechanical behaviour of the skin and the underlying subcutaneous tissue, and as such, Shore hardness is unable to separate the individual effect of each layer on the measurement.

Being unable to separate the individual effect of each layer on the measurement of Shore hardness significantly reduces Shore hardness's reliability as a method for monitoring changes in skin and subcutaneous soft tissue stiffness.

Based on the current literature regarding indentation testing of the plantar soft tissues of the foot, it is proposed that the measurement of indentation is more representative of the skin or soft tissue mechanical properties based on the size of the indenter being used (Spears and Miller-Young, 2006). Therefore, indentation using a small-sized indenter is proposed to be more relevant to the measurement of the stiffness of the skin. In the literature, a small indenter is defined as an indentation probe that is less than 6mm in diameter (Spears and Miller-Young, 2006). This has been hypothesised to be due to localised deformations being located in the superficial region of the heel (i.e., skin)

(Spears and Miller-Young, 2006). Whereby the induced strains are governed predominantly by the stiffness and thickness of the outer layer (i.e., skin).

In addition, it was found that skin thickness has a direct effect on the assessment of mechanical properties when using small probes. For example, in heel pads with a greater thickness of skin, it was found that the heel pads were less compliant to indentation using a small probe than heels with a thinner skin layer. This reduction in the compliance of the heel pad to indentation indicates that a thicker layer of skin has a greater influence on the assessment of the mechanical properties of the heel pad when using a small probe.

Indentation testing at the heel using a large indenter, i.e., any indenter with a diameter greater than 6mm, on the other hand, may be likened to uniaxial bulk compression. Uniaxial bulk compression testing differs from indentation testing. With bulk compression testing, the whole surface of the tissue is subjected to a uniform load rather than just a small area as in indentation testing. Specifically, bulk compression testing causes the tissue to undergo uniaxial bulk compression whereby the strains within the tissue are governed predominantly by the least stiff material (i.e., fat in the case of the heel pad) (Aerts *et al.*, 1995; Tong, Lim and Goh, 2003). It can, therefore, be said that indentation testing using an indenter greater than 6mm diameter is a measurement of the bulk stiffness of the entire plantar soft tissue (Spears and Miller-Young, 2006).

As previously stated in the literature, a small indenter is defined as an indentation probe that is less than 6mm in diameter (Spears and Miller-Young, 2006). As per ISO standards, the tip of a Shore hardness 00 durometer is hemispherical with a diameter of 2.4mm with a length of 2.54mm (International Organization for Standardisation, 2018). Therefore, as the tip of the Shore hardness 00 durometer is under 6mm in diameter, it can be classified as a small indenter. However, as the results of Chapter 3 show, the measurement of Shore hardness is not a measurement of skin stiffness only. Instead, it is an assessment of the bulk tissue's overall capacity to deform. Within the literature, the effect of large and smaller indenter sizes has not been fully explored or quantified, especially regarding indentation testing of layered structures such as the plantar soft tissues of the foot. Therefore, this study aims to investigate the feasibility of measuring the mechanical properties of each layer, such as skin or subcutaneous soft tissue, directly through the use of different sizes of indenters.

4.2. Methods

4.2.1 Finite Element Model

To examine the feasibility of measuring the mechanical properties of the skin and subcutaneous soft tissue using different sized Shore hardness indenters, a 2D axisymmetric Finite Element (FE) model of skin and soft tissue was created [Figure 4-1]. As the effect of indenter size was the primary variable under investigation, a simple model of the heel pad is used. The decision to model the heel-pad as axisymmetric was made on the basis that the foot remains stationary throughout heel-pad Shore hardness testing and the loads applied are uniaxial. Additionally, axisymmetric models are

commonly used to simulate indentation testing (Verdejo and Mills, 2004; Erdemir *et al.*, 2006; Khani *et al.*, 2012; Chen, Lee and Lee, 2014).

Reference values for skin and subcutaneous soft tissue were taken from the available literature regarding the mechanical and anatomical properties of the heel pad (Miller-Young, Duncan and Baroud, 2002; Spears *et al.*, 2007). More specifically, the model has a 3mm thick layer of skin and a heel pad layer with a thickness of 11.5mm (Spears and Miller-Young, 2006) [Figure 4-1]. A contact target pair was used to simulate the attachment of the skin to the subcutaneous soft tissue.

The model of the indenter is based on that of the Shore-00 durometer and comprises of three main parts: a rigid tip that will cause the indentation, a rigidly fixed surface simulating the bottom surface of the durometer and a spring element that simulates the internal mechanism of the durometer [Figure 4-1]. The model of the durometer is controlled with the help of a pilot node which is rigidly connected to the rigid surface and linked to the indenter's tip through the spring element [Figure 4-1]. During the measurement of indentation, a fixed displacement is applied to the soft tissues that is equal to the length of the indenter tip. This ensures full contact between the top surface of the skin and the rigid outer surface of the Shore hardness indenter. The length of the indenter tip is defined as the distance from the rigid outer surface to the tip of the indenter. At the same time, the force at the indenter's tip, defined by the durometer's internal mechanism, increases linearly with the tip's displacement relative to the rigid

disk [Figure 4-1]. The initial distance between the indenter's tip and the rigid surface is 3mm, and the magnitude of the force on the tip increases linearly from zero (ds= 3mm) to a maximum value of 1.1 N when the tip is fully pushed inside the durometer (ds=0). Both the heel pad (soft tissue and skin) and the tip of the indenter were constrained in a way that allowed movement only along the axis of the durometer. The indenter was assumed to be rigid, with the main contact between the indenter and skin being flat. The contact between the indenter and the skin was assumed to be frictionless to account for the smooth surface of the Shore hardness indenter.

To simulate the effect of the calcaneus the bottom surface of the model was considered to be rigid with the effect of the calcaneus on stress distribution simulated using boundary conditions whereby zero-displacement boundary conditions were assigned to all nodes along the bottom surface of the model [Figure 4-1].

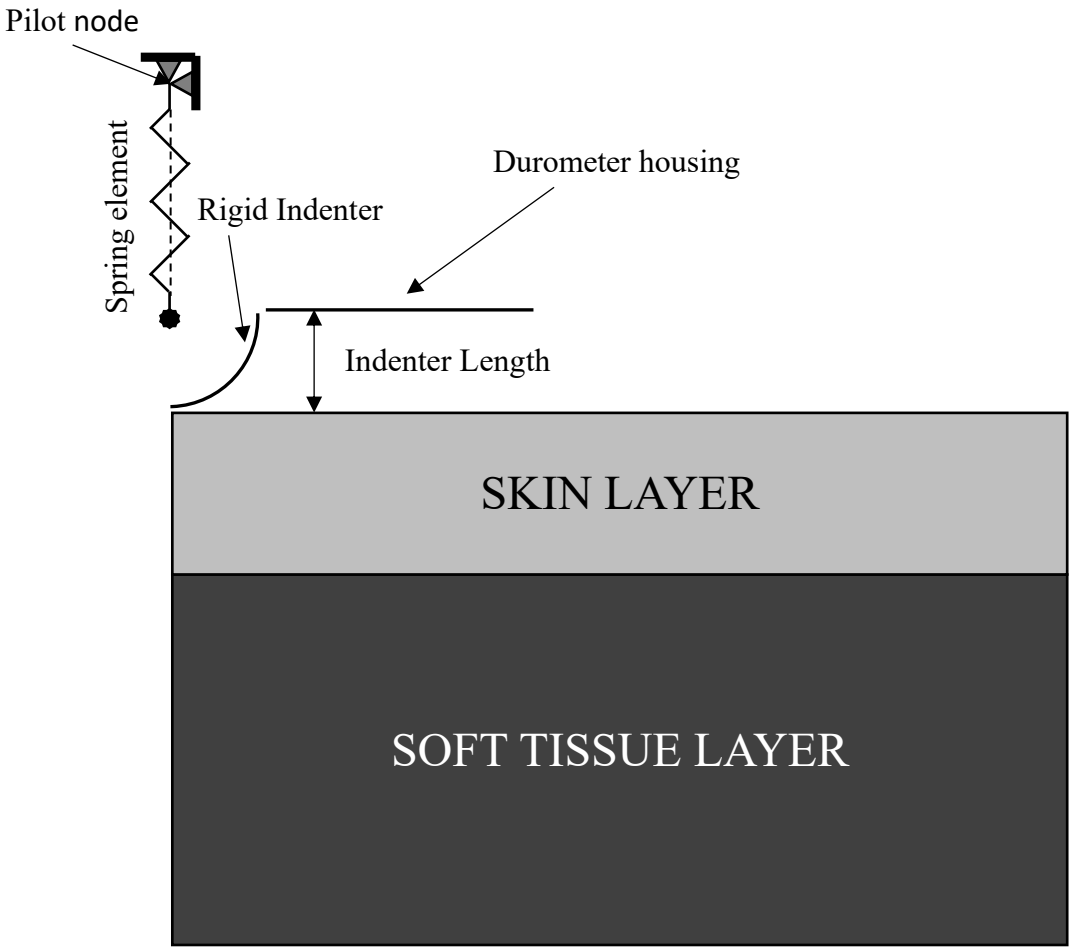


Figure 4-1: A simplified view of the FE model with boundary conditions showing the rigid indenter in contact with the surface of the skin and soft tissue model

The mechanical behaviour of the subcutaneous tissue and skin was simulated using the Ogden hyperelastic material model (1st order) [EQ 4.1] (Behforootan, P. Chatzistergos, *et al.*, 2017).

$$W = \frac{\mu}{\alpha}(\lambda_1^{-\alpha} + \lambda_2^{-\alpha} + \lambda_3^{-\alpha} - 3) + \frac{1}{d_k}(J-1)^2$$

EQ. 4.1

$$G_0 = \frac{1}{2}(\mu\alpha)$$

EQ. 4.2

Where λ_1, λ_2, λ_3 are the deviatoric principal stretches and μ (Pa), α (unitless), and d_k (Pa) are material coefficients. Coefficient α is indirectly related to the tissue's strain hardening/ softening behaviour, while both μ and α are directly linked to the material's initial shear modulus (G_0) [EQ 4.2]. Parameter d_k is a function of both the effective Poisson's ratio (ν) and the initial shear modulus (G_0) [EQ 4.3].

$$d_k = \frac{3(1-2\nu)}{G_0(\nu+1)}$$

EQ. 4.3

Reference values of μ and α were adopted from literature for skin (Petre *et al.*, 2013) and subcutaneous tissue (Erdemir *et al.*, 2006). The coefficient values used were μ_{skin}=640 kPa, α_{skin}=6.8 for skin and μ_{sub}=0.29 kPa, α_{sub}=8.8 for subcutaneous tissue. The skin and subcutaneous tissue were both assumed to be nearly incompressible (ν=0.495)(Behforootan, P. E. Chatzistergos, *et al.*, 2017a; Chatzistergos *et al.*, 2018).

The final FE model was meshed using 7224 eight-node planar elements. Element size was decided through sensitivity analysis to eliminate any mesh dependency phenomena. All numerical analyses were performed using ANSYS 18.1. (ANSYS, Canonsburg, PA, USA).

4.2.2. Parametric Analysis

To examine the feasibility of measuring the mechanical properties of the skin and subcutaneous soft tissue using different sized Shore hardness indenters, a parametric analysis was undertaken. Within this parametric analysis, the physical dimensions of the indenter, indenter length and indenter width were independently changed.

To examine the effect of Shore hardness indenter width, the width of the Shore hardness indenter was increased from 1mm to 10mm in 1mm increments. In addition, an extreme scenario of an indenter width ¼ of the overall width of the simulated tissue sample (15mm) was also included in this analysis.

To examine the effect of Shore hardness indenter length, three lengths of the indenter were used: 1mm, 3mm, 5mm. An indenter of three millimetres length was chosen as the baseline reference length to compare the results of the 1mm and 5mm lengths against. Three millimetres was chosen as this is the transition between the skin and subcutaneous soft tissue. One millimetre and five millimetres were chosen based on preliminary testing whereby the stress concentration fields generated by the indentation

testing were contained within the skin layer in the case of the 1mm length [Figure 4-2] and the subcutaneous soft tissue layer in the case of the 5mm length [Figure 4-3].

For each combination of indenter width and length, a baseline measurement of indentation was taken. The amount of indentation into the simulated skin and subcutaneous soft tissue was taken as the upward movement of the node linked to the indenter tip. The mechanical properties of the skin and subcutaneous soft tissue were then altered by adjusting the values of the coefficients μ or α changing the initial shear modulus of the skin or subcutaneous soft tissue [EQ 4.2]. Specifically, the initial shear modulus of the skin or subcutaneous soft tissue was increased or decreased by 50%. A value of indentation was taken for each change in the mechanical properties of the skin or subcutaneous soft tissue. A total of 297 scenarios are tested for this parametric analysis.

The primary outcome measure of this parametric analysis was the sensitivity of the measurement of Shore hardness indentation to changes in indenter width and length. The sensitivity of the measurement of indentation to changes in indenter width and length was assessed as the percentage change in the amount of indentation when the initial shear modulus of the skin or subcutaneous soft tissue were changed. Thus, a greater percentage change in the amount of indentation indicated a more sensitive measure to changes in the mechanical properties of the skin or subcutaneous soft tissue.

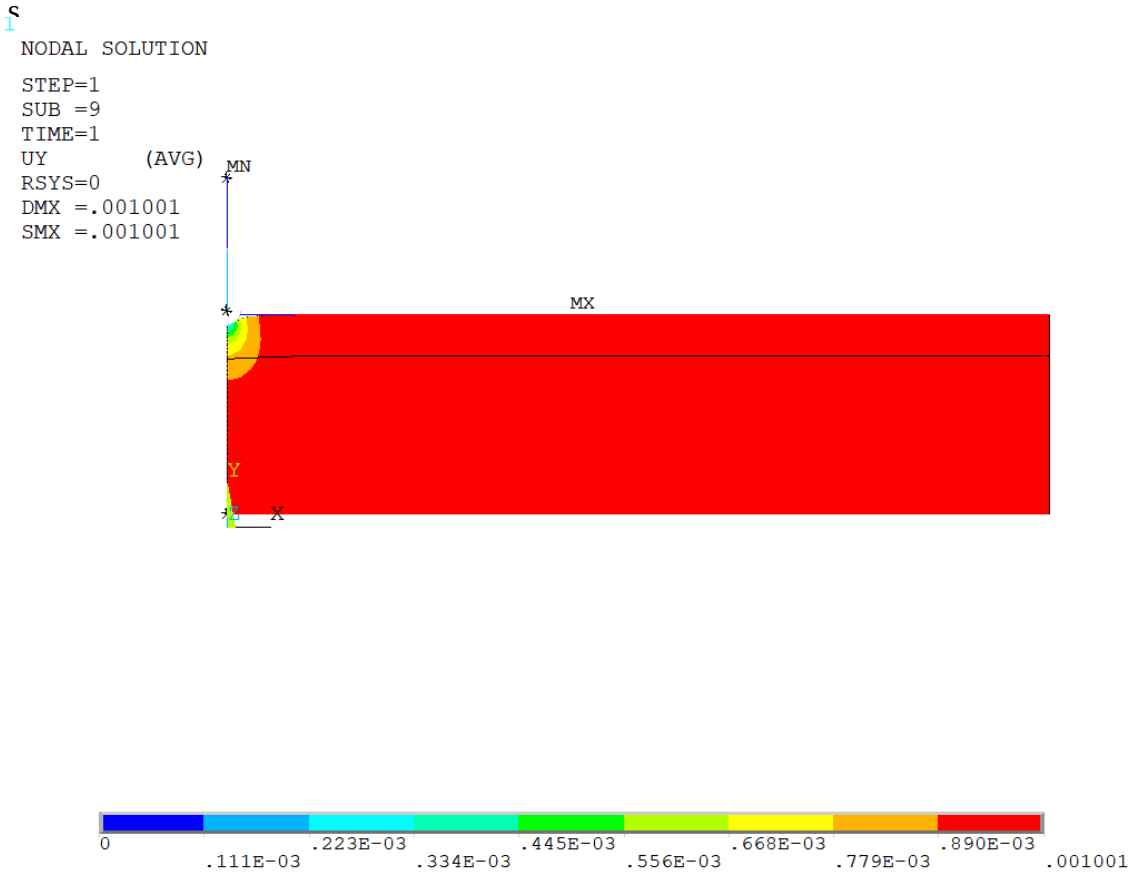


Figure 4-2: Displacement plot of the skin and subcutaneous soft tissue using a 1mm radius tip with an indenter length of 1mm

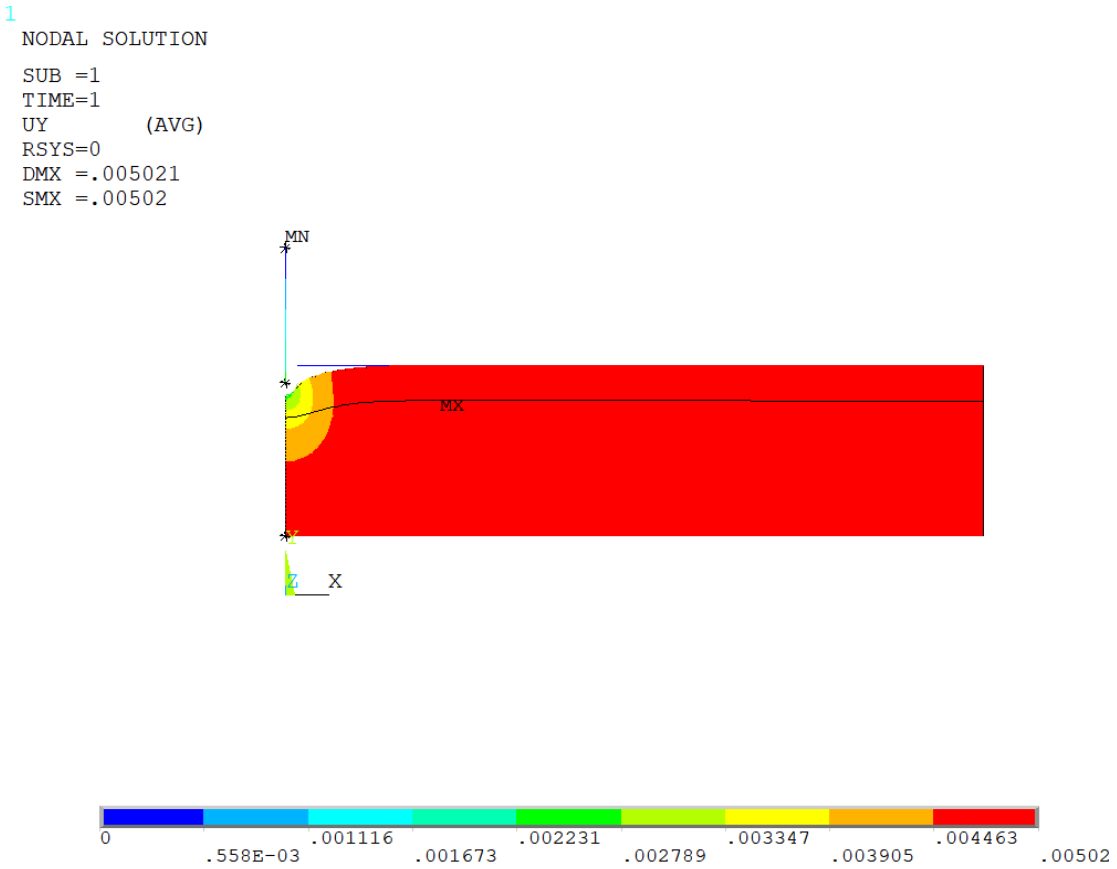


Figure 4-3: Displacement plot of the skin and subcutaneous soft tissue using a 1mm radius tip with an indenter length of 5mm

4.3. Results

As expected, when the width of the indenter increased, the indentation into the skin and the subcutaneous soft tissue layer decreased. The measurement of indentation with small indenters (1-5mm) was found to be more sensitive to changes in the α coefficient (the tissue's strain hardening/ softening behaviour) and was found to have a greater effect on indentation depth compared to changes in the μ coefficient (initial slope of the stress/strain curve). For example, for a 1mm wide indenter, a 50% increase in the mechanical properties of μ lead to a 17% increase in indentation depth, whilst a 50% increase in the mechanical property α lead to a 30% increase in indentation depth [Table

4-1]. A 50% decrease in the mechanical properties of μ lead to a 7% reduction in indentation depth, whilst a 50% decrease in the mechanical property α lead to an 11% decrease in indentation depth. [Figure 4-4]. For indenter sizes greater than 6mm, indentation was equally sensitive to changes in μ and α for skin, indicating the measurement to be sensitive only to changes in the initial shear modulus [EQ. 4.2] regardless of how this change has been produced. For changes in the subcutaneous soft tissue's mechanical properties, indentation with indenters less than 5mm was more sensitive to changes in the α coefficient than the μ coefficient [Figure 4-4]. For indenter sizes greater than 6mm μ and α for subcutaneous soft tissue had the same effect on the results of indentation testing again indicating that for indenters greater than 6mm, the measurement to be sensitive only to changes in the initial shear modulus [EQ. 4.2] regardless of how this change has been produced. [Figure 4-4]

Table 4-1: Percentage change in indentation for a 3mm long indenter for various widths. Both changes in skin and subcutaneous soft tissue presented

		Skin					Subcutaneous Soft tissue			
		% Change in indentation					% Change in indentation			
		Alpha +50%	Mew +50%	Alpha - 50%	Mew - 50%		Alpha +50%	Mew +50%	Alpha - 50%	Mew - 50%
Indenter Radius (mm)	1	17.39	6.96	-30.26	-11.30		11.30	9.57	-18.52	-16.52
	2	11.72	5.52	-20.00	-8.28		10.34	8.97	-17.24	-15.17
	3	7.65	4.12	-14.71	-7.65		8.82	7.65	-16.47	-14.71
	4	5.26	3.68	-10.53	-6.32		7.89	7.37	-14.74	-13.16
	5	3.85	2.88	-8.17	-5.77		6.25	6.25	-12.98	-12.50
	6	3.15	2.70	-5.86	-4.50		5.86	5.86	-11.26	-11.26
	7	2.13	2.13	-5.11	-4.26		4.68	4.68	-10.21	-10.64
	8	2.04	1.63	-4.08	-3.67		4.08	4.49	-8.98	-9.39
	9	1.58	1.58	-3.16	-2.77		3.95	3.95	-7.91	-8.30
	10	1.54	1.54	-2.69	-2.31		3.46	3.46	-6.92	-7.31
	15	0.71	0.71	-1.07	-1.07		1.78	1.78	-3.91	-3.91

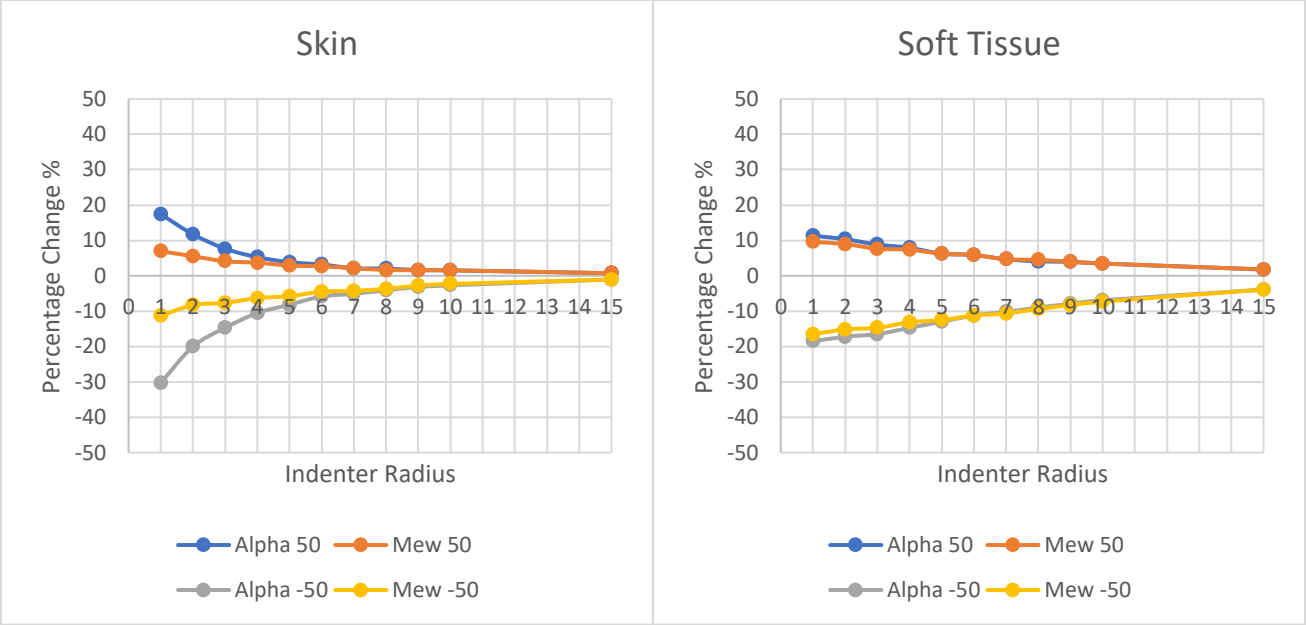


Figure 4-4: Results of baseline testing (3mm indenter length). Results are presented as a percent of the reference indentation

To examine the effect of indenter length on the measurement of indentation in a layered structure for the 1mm indenter length when the mechanical properties of the skin were changed, the measurement of indentation with small indenters (1-4mm) was more sensitive to changes in the α coefficient than the μ coefficient (33%/-40% vs 18%/-28% for 1mm indenter width) [Figure4-5]. For indenter sizes greater than 6mm μ and α for skin had the same effect on the results of indentation testing. However, for changes in the mechanical properties of the subcutaneous soft tissue, the measurement of indentation was affected equally by changes in μ and α regardless of indenter width [Figure 4-5].

Table 4-2: Percentage change in indentation for a 1mm long indenter for various widths. Both changes in skin and subcutaneous soft tissue presented

		Skin					**Subcutaneous Soft tissue**			
		% Change in indentation					% Change in indentation			
		Alpha +50%	Mew +50%	Alpha -50%	Mew -50%		Alpha +50%	Mew +50%	Alpha -50%	Mew -50%
Indenter Radius (mm)	1	33.01	18.93	-43.69	-27.67		8.25	8.74	-14.56	-15.53
	2	16.90	12.74	-28.25	-20.22		8.86	9.42	-16.34	-17.17
	3	10.06	8.83	-18.28	-15.61		8.62	9.03	-16.43	-17.25
	4	6.61	6.27	-12.88	-12.20		7.80	8.14	-15.59	-16.44
	5	4.48	4.48	-9.10	-9.10		6.87	7.16	-14.03	-14.93
	6	3.28	3.42	-6.83	-7.10		6.01	6.28	-12.43	-13.25
	7	2.69	2.69	-5.64	-5.38		5.13	5.38	-10.90	-11.41
	8	1.95	2.07	-4.39	-4.51		4.27	4.39	-9.63	-10.00
	9	1.65	1.65	-3.41	-3.53		3.65	3.65	-8.24	-8.59
	10	1.37	1.37	-2.86	-2.86		3.09	3.20	-7.21	-7.55
	15	0.53	0.53	-1.17	-1.17		1.49	1.59	-3.72	-3.83

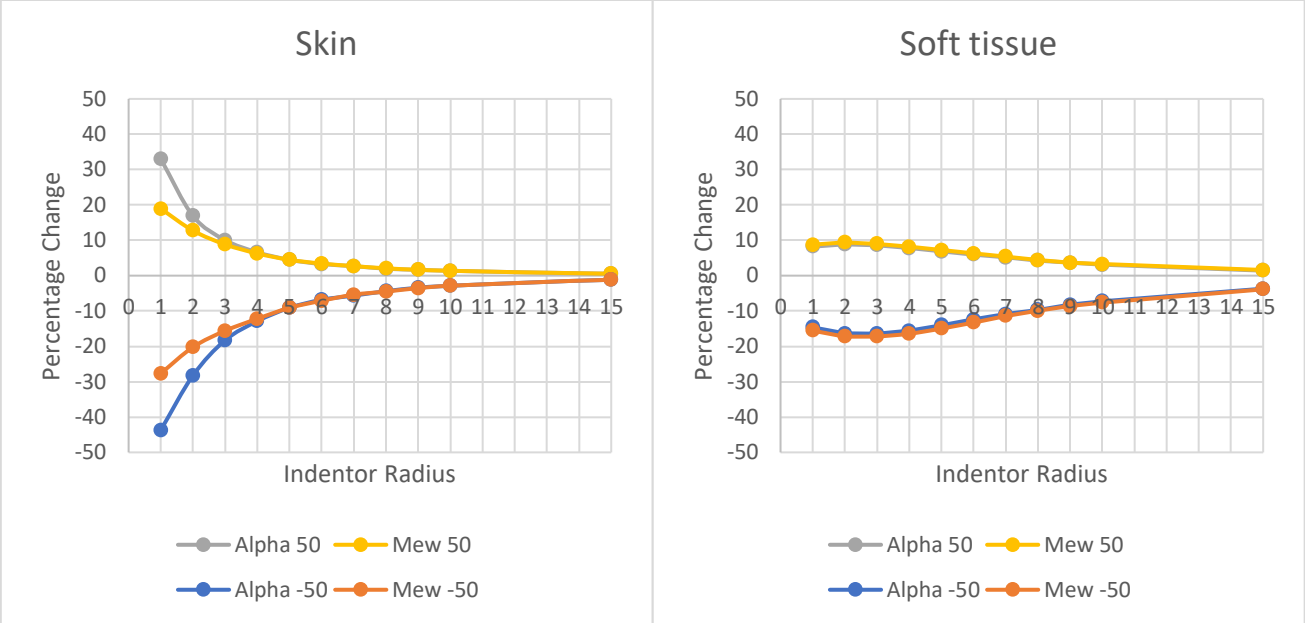


Figure 4-5: Results of testing for 1mm length indenter. Results are presented as a percent of the reference indentation

Finally, for the 5mm indenter length when the mechanical properties of the skin were changed, the measurement of indentation with small indenters (1-5mm) was again more sensitive to changes in the α coefficient than the μ coefficient (8%/-15% vs 3%/-5%) [Table 4-3]. For indenter sizes greater than 6mm μ and α for skin had the same effect on the results of indentation testing. For changes in the mechanical properties of the subcutaneous soft tissue, the measurement of indentation for indenters less than 9mm was found to be more sensitive to by changes in the α coefficient than the μ coefficient [Figure 4-6]

Table 4-3:Percentage change in indentation for a 5mm long indenter for various widths. Both changes in skin and subcutaneous soft tissue presented

		Skin					Subcutaneous Soft Tissue			
		% Change in indentation					% Change in indentation			
		Alpha +50%	Mew +50%	Alpha -50%	Mew -50%		Alpha +50%	Mew +50%	Alpha -50%	Mew -50%
Indenter Radius (mm)	1	7.79	2.87	-15.16	-4.92		8.20	13.52	-14.75	-22.95
	2	5.32	2.13	-10.28	-3.90		7.80	12.06	-13.83	-21.28
	3	3.85	1.92	-7.37	-3.21		7.37	10.58	-12.82	-18.91
	4	2.96	1.48	-5.33	-2.66		6.80	8.88	-12.13	-16.57
	5	2.22	1.39	-4.17	-2.22		6.11	7.50	-11.11	-14.44
	6	1.85	1.32	-3.17	-2.11		5.54	6.60	-10.55	-12.66
	7	1.52	1.01	-2.78	-1.77		5.05	5.56	-9.85	-11.11
	8	1.22	0.98	-2.20	-1.46		4.63	4.88	-9.02	-9.76
	9	0.95	0.95	-1.89	-1.65		4.02	4.02	-8.27	-8.75
	10	0.92	0.92	-1.62	-1.15		3.70	3.46	-7.62	-7.39
	15	0.43	0.43	-0.86	-0.86		1.71	1.71	-4.71	-4.50

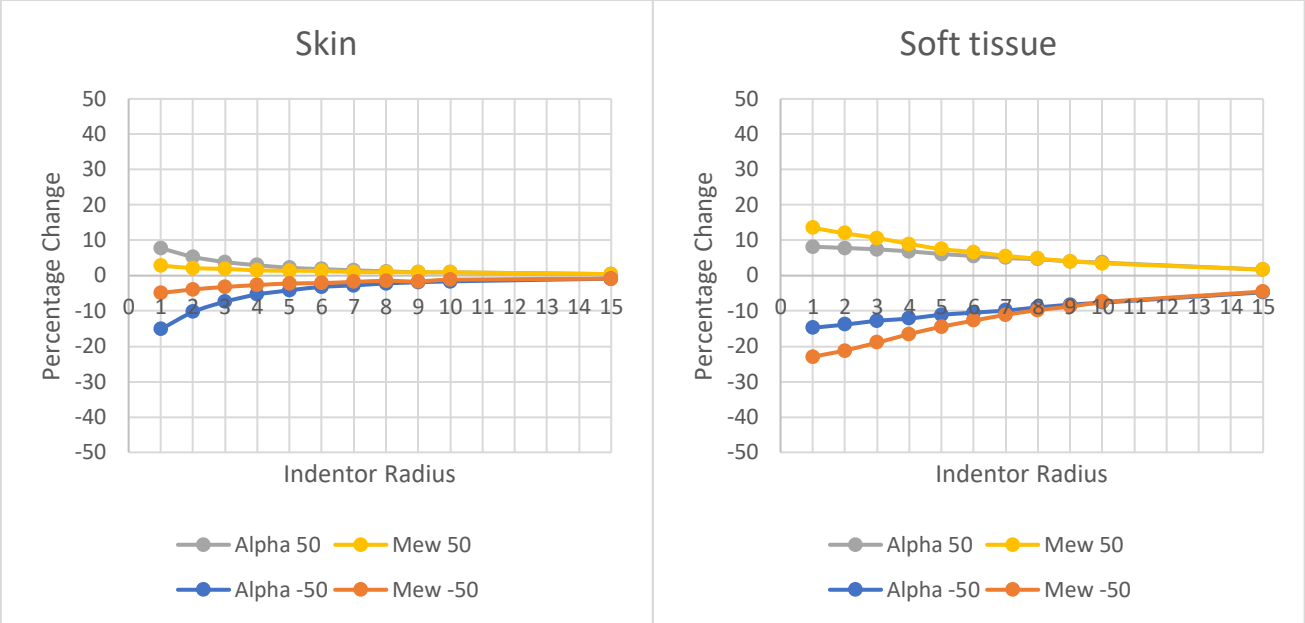


Figure 4-6: Results of testing for 5mm length indenter. Results are presented as a percent of the reference indentation

4.4. Discussion

To understand the effect of the size and length of an indenter has on the measurement of indentation in a layered structure, FE analysis was used to simulate the indentation of a layered structure consisting of both a skin layer and a subcutaneous soft tissue layer.

Based on current literature regarding indentation of the plantar soft tissues of the foot, indentation using a small-sized indenter can be said to be relevant to the measurement of the stiffness of the skin, whilst indention using a large indenter is said to be a measurement of the bulk stiffness of entire plantar soft tissue (Spears and Miller-Young, 2006). In the literature, a small indenter is defined as an indentation probe that is less than 6mm in diameter (Spears and Miller-Young, 2006). Therefore, it can be hypothesised that the measurement of indentation using an indenter less than 6mm diameter should be sensitive only to changes in the mechanical properties of skin and

insensitive to changes in soft tissue. On the other hand, for indenters greater than 6mm, the measurement of indentation should be insensitive to changes in the mechanical properties of the skin and sensitive to changes in the mechanical properties of the subcutaneous tissue.

However, the results of the FE analysis presented here have shown that regardless of indenter width, the measurement of indentation for a layered structure is affected by changes in both the superficial layer (skin) and the deep layer (subcutaneous soft tissue). Therefore, it cannot be said that the measurement of indentation taken using a small indenter is a measurement of skin mechanical properties only.

It is interesting to note the change in the sensitivity to changes in the skin and soft tissue mechanical properties regarding the length of the indenter. As the length of the indenter increases, the sensitivity to changes in the mechanical properties of the skin decreases, and the sensitivity to changes in the subcutaneous soft tissue increases; as the length of the indenter decreases, the sensitivity to changes in the mechanical properties of the skin increases and the sensitivity to changes in the subcutaneous soft tissue decrease. Thus, the effect that changes in the mechanical properties of the skin and soft tissue has on the measurement of indentation using the different length of indenters could be due to how the layers of skin and soft tissue are strained differently.

For a shorter indenter, in this case, 1mm, the deformation and subsequent displacement of the layered structure occur more in the superficial skin layer [Figure 4-2]. In this case, the strains within the layered structure are governed predominantly by the stiffness and thickness of the outer layer (i.e., skin); therefore, small changes in the mechanical properties of the skin would have a greater effect on the measurement of indentation.

For indenters longer than the superficial skin layer 5mm, more deformation occurred deeper within the layer structure, in this case, the subcutaneous soft tissue [Figure 4-3]. Thus, though the skin layer would still have an effect on the measurement, the changes in the mechanical properties of the deep layer (soft tissue) will account for more of the change in the amount of indentation into the layered structure.

These results are in line with previous literature (Rome *et al.*, 2001; Spears and Miller-Young, 2006). Spears et al. (2006), concluded that the thicker the skin layer, the greater the effect the mechanical properties of skin have on the measurement of indentation. Whereby heels pads which presented with a greater thickness of skin are less compliant to indentation compared to that of heels with thinner skin. Whilst the thickness of the skin was not directly altered in this study, with skin thickness being held constant at 3mm, the length of the indenter was changed, thus changing the ratio of skin thickness to indenter length. Based on these results, the measurement of indentation using an indenter that is less than the total thickness of the skin is affected more by the mechanical properties of the skin than that of the underlying soft tissue. Therefore, the

measurement of indentation using a short indenter can be said to be more representative of the skin mechanical properties.

With regards to the feasibility of measuring the mechanical properties of each layer, such as skin or subcutaneous soft tissue, directly through the use of different sizes of indenters, the results of this study would indicate that to measure the mechanical properties of the skin a very short indenter would be needed. This is only to induce a deformation within the skin layer reducing the involvement of the underlying subcutaneous soft tissue. However, the indenter would also have to be wide enough so as the measurement is a measurement of shear modulus whereby indentation is equally affected by changes in μ and α. A long, wide indenter would be needed for the subcutaneous soft tissue to ensure a deformation that is predominantly within the subcutaneous soft tissue layer.

Axisymmetric models such as the one used within this study have previously been used within literature to look at the effect of mechanical properties, tissue thicknesses, and the estimation of mechanical properties (Rome *et al.*, 2001; Erdemir *et al.*, 2006; Spears and Miller-Young, 2006). Specifically, the model used within this study was developed to investigate the feasibility of measuring the individual mechanical properties of a layered structure, such as skin and subcutaneous soft tissue of the heel pad, directly through the use of different sizes of indenters. As the model was only looking at the effect of indenter

size, the geometry of the model is defined by a diameter and a thickness of skin and subcutaneous soft tissue only.

With regards to modelling of the skin layer and the subcutaneous soft tissue, previous literature has used this approach to assess and quantify the mechanical properties of the skin and subcutaneous soft tissues (Spears *et al.*, 2007; Gu *et al.*, 2010; Sopher *et al.*, 2011; Petre *et al.*, 2013; Ahanchian *et al.*, 2017). When the results of these studies were compared to in vivo testing, the results indicated that this simplified structure offers a good approximation of the mechanical behaviour and properties of the skin and subcutaneous soft tissues (Gu *et al.*, 2010; Ahanchian *et al.*, 2017).

The heel-pad surface and the underlying geometry of the bone structure of the model was also assumed to be flat [Figure 4-1] as only the effect of indenter size was being investigated. Furthermore, the indentation of the model was only occurring at a specific point with minimal potential bone deformation due to the low magnitude of loading.

However, it must be noted that the geometry of the underlying bone structure can have a significant effect on the measurement of indentation. For example, work by Erdemir et al. (2006) has shown that when calculating the mechanical properties of the heel pad using FEA changes in the curvature of the heel pad and subsequently the underlying bone structure directly influences the mechanical properties of the skin and soft tissues,

in particular the values of μ. Whereby, an increase in the convexity of the heel pad was found to elevate the value of μ.

Considering the geometry of the underlying bone geometry, however, it is felt to be more relevant to the reliability of the test, specifically when it comes to in vivo testing whereby the ability of the user to accurately target the durometer in the same position, such as the apex of the calcaneus, is more important. Being able to target the same location will minimise the effect the underlying geometry has on the measurement due to the low deformations and indentation area.

While it is acknowledged that the inclusion of more detailed geometry may improve the accuracy and clinical applicability of the results; the addition of more complex geometry does not aid in answering the initial research question of this study. The modelling of the heel pad as an axisymmetric problem, is a well-defined approach for the simulation of indentation testing and was identified as the best approach to investigating the effect of indenter size. (Verdejo and Mills, 2004; Erdemir et al., 2006; Khani et al., 2012; Chen, Lee and Lee, 2014). This approach allowed the simplification of the problem whereby the model of the heel pad could be fully described based on a diameter and thickness of the skin and subcutaneous soft tissue. In addition to the modelling of the internal workings of the Shore hardness device and indenter size.

By limiting the number of variables involved in describing the geometry of the heel pad model to just a thickness and diameter, the additional cofactors that have been shown to affect indentation testing, such as the curvature of the heel pad, were prevented from being introduced into the analysis. This approach therefore allowed for the effect of indenter size on indentation testing within a layered structure to be isolated and the effect of indenter size and indenter length to be more clearly understood.

In addition to the simplifications to geometry, the fat pad of the heel was modelled as one homogenous structure as in Chapter 3; in reality, the fat pad of the heel can be anatomically divided into two separate layers: A superficial layer of small fat chambers (microchambers) and a deep layer of larger fat chambers (macrochambers). Each layer has its own functional role within the heel pad (C C Hsu *et al.*, 2007). These two layers have been shown to exhibit different mechanical behaviour (Ahanchian *et al.*, 2017) and have different functional roles (C C Hsu *et al.*, 2007). Simulating the visco-hyperelastic behaviour of the microchamber and macrochamber layers could expand on the effect of indenter size with regards to indentation testing.

Finally, the design of this study was based on previous in vivo testing (Chapter 3) investigating the measurement of Shore hardness as a simple, cost-effective method for assessing the mechanical properties of the plantar soft tissues. It was found that the measurement of Shore hardness offers an assessment of the bulk deformity of the heel pad but is, however, unable to separate the individual effect of each layer on the

measurement. This prompted the study into indenter size to investigate if it is possible to assess changes in the mechanical properties of the skin and subcutaneous soft tissues separately. The results of the study presented to show that it may be possible to obtain a separate measurement of Shore hardness for both the skin and subcutaneous soft tissue with the next steps of this research looking into developing a more thorough subject-specific models to allow for a comparison with in vivo testing to identify if this method can be reliable and clinically applicable.

In conclusion, the results of this study indicate that the measurement of indentation using a small indenter is not a measurement of skin mechanical properties only as the measurement of indentation will be affected by the mechanical properties of the underlying subcutaneous soft tissue. Additionally, the measurement of indentation using a large indenter is not a measurement of subcutaneous soft tissue only. This study shows however, that it may be feasible to assess changes in the mechanical properties of the skin or subcutaneous soft tissue directly through the use of different sizes of indenters. An indenter that is less than 2mm in diameter and 1mm in length may potentially be able to infer differences between the mechanical properties of the skin and subcutaneous soft tissues by being sensitive to changes in the mechanical properties of the skin and insensitive to changes in the mechanical properties of the subcutaneous soft tissues. For the assessment of soft tissue, a wide indenter over 9mm that is also longer than the thickness of the skin is recommended so as to concentrate the deformation within the deeper layered structures of the heel pad.

5. Chapter 5 – Plantar pressure prediction based on Shore hardness and Range of Motion

5.1. Background

As highlighted in sections 2.3 and 2.7, the formation of a diabetic foot ulcer is a multi-factorial process whereby diabetic peripheral neuropathy and an increase in plantar loads play a significant role in ulcer formation. However, plantar pressure assessment is not currently considered standard clinical practice for the care of the diabetic foot. One of the potential reasons might be due to the poorly standardised methods, logistic requirements such as suitable clinical space, and equipment costs. Therefore, there is a need for a method to assess plantar pressure that is easily repeatable, does not require expensive equipment or a large amount of space. Therefore, it is hypothesised that variables commonly associated with an increase in plantar pressure in people with diabetes may be used as surrogate measurements.

Increases in plantar pressure in people with diabetes are commonly associated with changes in mobility of the joints within the foot and ankle (Searle *et al.*, 2017) in addition to changes in the plantar soft tissues of the foot(Bus *et al.*, 2004, 2005; Yvonne Y. Cheung *et al.*, 2006; Chatzistergos *et al.*, 2014).

The effect of changes in foot and ankle range of motion can be seen within current literature, whereby several studies have linked a reduction in the foot and ankle range

of motion to an increase in plantar pressure (Searle *et al.*, 2017). A systematic review with the meta-analysis by Searle et al. 2017 found that ankle equinus, a reduction in ankle dorsiflexion, was associated with a significant but small effect on plantar pressure. The reduction in ankle dorsiflexion and its effect on plantar pressure can be attributed to the effect that reduced ankle dorsiflexion has on the gait pattern of people with diabetes and diabetic peripheral neuropathy by limiting the foot movement and changing the moment arm. Additionally, people with diabetes and peripheral neuropathy walk slower. They have a reduced stride length compared to people with diabetes and no peripheral neuropathy and healthy subjects, thus causing the plantar soft tissues of the foot to be loaded for an extended amount of time (Fernando *et al.*, 2013).

In addition to the effects on the range of motion of the foot and ankle, diabetes has also been shown to affect the mechanical properties and structure of the plantar soft tissues of the foot, whereby diabetes has been shown to decrease the thickness of the plantar soft tissues in addition to causing a stiffening effect both of which limit the plantar soft tissues ability to distribute and manage loads. The increased stiffness and the reduced thickness of the fatty tissues within the foot limit the tissues' ability to evenly distribute loads, making them more vulnerable to trauma and ulceration. (Bus *et al.*, 2004, 2005; Yvonne Y Cheung *et al.*, 2006; Chatzistergos *et al.*, 2014)

The results presented in Chapter 3 show that despite its limitations in differentiating between the stiffness of skin and the subcutaneous tissue based on the conventional assessment of Shore hardness, the fact that Shore hardness was capable of verifying correlations between tissue biomechanics, loading and blood biochemistry shows that Shore hardness can still be a useful research tool in the study of plantar soft tissue biomechanics.

The association between different factors, such as foot and ankle range of motion and soft tissue mechanical properties, and their effect on plantar pressure has led to several studies that aim to predict plantar pressures based on a varying number of factors associated with an increase in plantar pressure.

Payne and co-workers (2002) recruited 50 subjects with diabetes. They collected socio-demographical variables, different radiographic angles, soft tissue properties and joint mobility at the ankle and 1st metatarsophalangeal joint, and data on neuropathy (Payne, Turner and Miller, 2002). Using stepwise regression modelling, it was found that positive neuropathy scores explained differences in peak pressures under the hallux, 1st metatarsal head and heel.

Mueller *et al*. (2003) investigated the effect of forefoot structure on regional plantar pressure measurements due to forefoot deformity being a strong predictor of peak pressures (Mueller *et al.*, 2003). Data was collected from 20 participants with diabetes

and neuropathy, including measurements of the foot from spiral x-ray computed tomography and dynamic peak pressures. Using hierarchical multiple regression analysis to predict regional peak pressures under the hallux and each one of the metatarsal heads, it was found that the metatarsophalangeal joint angle is the most important predictive plantar pressure variable. In addition, the results of this study found that the presence of hammertoe on the hallux predicts peak pressures under the metatarsal heads and hallux.

Barn *et al.* (2015) suggested that "local variables" such as foot deformity were stronger predictors than "global features" such as Body Mass Index (BMI) or age (Barn *et al.*, 2015). For this study, demographic data, foot structure, and function were collected from participants with diabetes, peripheral neuropathy, and ulceration history. Data weas analysed using multivariate linear regression. It was concluded that variables with local effects (e.g., foot deformity) were stronger predictors of plantar pressure than global features (e.g., body mass, age, gender, or diabetes duration). However, the model did not explain a significant amount of variance in the collected plantar pressure data, suggesting that plantar pressure measurements are still required in clinical settings to assess an individual patient's risk properly.

Finally, Morag and Cavanagh aimed to predict plantar pressures based on biomechanical and spatiotemporal data (Morag and Cavanagh, 1999). Data was collected from 55 healthy subjects based on foot characteristics, 3D foot motion and electromyography

(EMG) while walking in addition to peak plantar pressures. It was found that foot structure and function predicted only approximately 50% of the variance in peak pressure, although the relative contributions in different anatomical regions varied dramatically. The structure of the foot was dominant in predicting peak pressure under the midfoot and 1st metatarsal head, while both structure and function were important at the heel and hallux.

Taken together, the results of the studies described above illustrate that plantar pressures can be predicted by a range of different factors, including individual characteristics and biomechanical measurements. However, these studies all use techniques that are not clinically viable, for example, the use of CT scans and X-rays to assess joint angle and joint motion. Thus, to enable the predictions of plantar pressure to be used clinically, there is a need for a set of clinically viable methodologies to measure common variables such as joint range of motion and soft tissue mechanical properties. Therefore, the current study aims to investigate if regional plantar pressures for the forefoot, midfoot, and heel can be predicted using a 2D motion analysis and Shore hardness.

5.2. Methods

After obtaining ethical approval, forty participants with diabetes and diabetic peripheral neuropathy were recruited from two outpatient centres in Chennai, India (Dr A. Ramachandran Diabetes Hospital, Chennai, India and Sri Ramachandra University, Chennai, India). All participants provided full informed consent before testing. Inclusion

criteria were a history of diabetes (Type-1 or Type-2), the ability to walk unaided for more than 5m, a Vibration Perception Threshold (VPT) value of over 25V at least two of eight sites (Hallux, 1st, 3rd, 5th Metatarsal head, Midfoot, Heel, Medial Malleolus and Dorsal aspect of Hallux) on both feet (measured using a biothesiometer - Kody Biothezi-VPT, Chennai, India). For this study, only adults were recruited.

Shore hardness was measured using a Shore-00 device (Shore 00, AD-100, Checkline Europe B.V, Dennenweg, The Netherlands). To measure Shore hardness, participants were asked to lie in a prone position face down on an examination couch with their shank in the air approximately 90 degrees to the thigh [Figure 5-1a]. Then, with the foot relaxed, the durometer was lowered onto each of the plantar sites (Hallux, 1st, 3rd, 5th Metatarsal head, Midfoot, Heel) [Figure 5-1b] that were used for VPT testing allowing the tissue to be compressed by the full weight of the device before taking the reading of hardness.

a

b

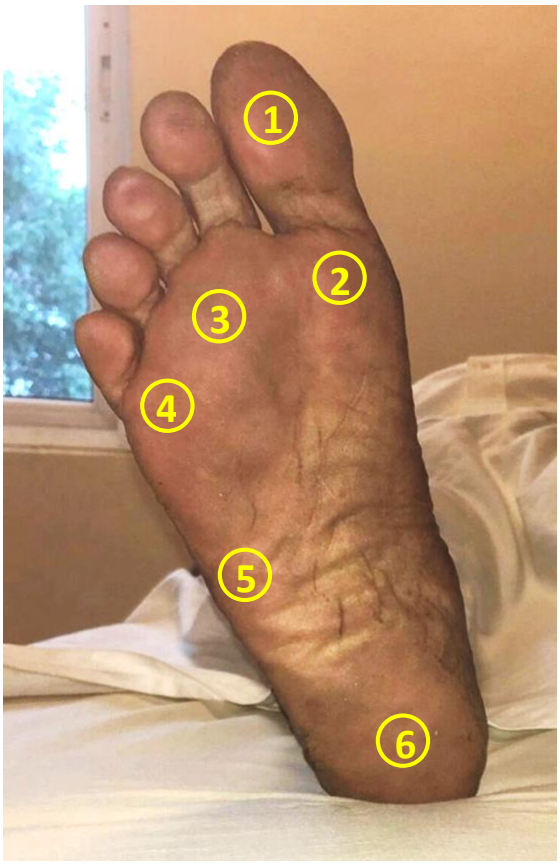


Figure 5-1:a) Position of the participant when performing the reading of Shore hardness. b) Eight anatomical positions used of the measurement of Shore hardness (1) hallux, (2) 1st metatarsal head, (3) 3rd metatarsal head, (4) 5th metatarsal head, (5) midfoot, (6)

Due to the viscoelastic nature of the plantar soft tissues of the foot, prolonged exposure to load will cause a decrease in the measured value of Shore hardness; therefore, minimal time was taken between the application of the durometer to the foot and the recording of the measurement. Each site was tested three times, and the average value of Shore hardness for each site was calculated. An average value of Shore hardness for the forefoot was also taken as the average value of the Hallux, 1st, 3rd, and 5th metatarsal head. An average value of Shore hardness was calculated to coincide with the measurement of range of motion which separated the foot into three segments—the heel, midfoot and forefoot.

Loading of the foot was assessed by measuring plantar pressure distribution during walking at a self-selected pace using a MatScan 0.5x0.5m pressure mat (Tekscan, Boston MA, USA) [Figure 5-2a]. Three stance phases per foot were recorded at 100Hz using a two-step protocol (Bus and Lange, 2005). Values of the maximum peak contact pressure and pressure time integral (Melai *et al.*, 2011) were assessed for six regions of the foot, namely: hallux, 1st metatarsal head, 3rd metatarsal head, 5th metatarsal head, midfoot and heel (Gurney, Kersting and Rosenbaum, 2008) [Figure 5-2b].

The plantar pressure data was analysed using a mask that divided the foot into the heel, midfoot, 1st metatarsal head, 3rd metatarsal head, 5th metatarsal head, hallux, and minor toes [Figure 5-2b]. The boundary between the heel and midfoot is located 73% of foot length. Foot length was measured as the length from the top of the hallux to the middle

of the rear aspect of the heel. The boundary between the midfoot and forefoot is located 45% along this length. The first, third and fifth metatarsals are separated by horizontal lines, with the regions are defined as being 30% (first), 25% (third) and 45% (fifth) of the medio-lateral axis located at the transition of the midfoot into the forefoot.

To obtain a maximum peak contact pressure and pressure time integral value for the forefoot, the sum of the contact area and sum of the forces for the hallux, 1st metatarsal head, 3rd metatarsal head, and 5th metatarsal head were used.

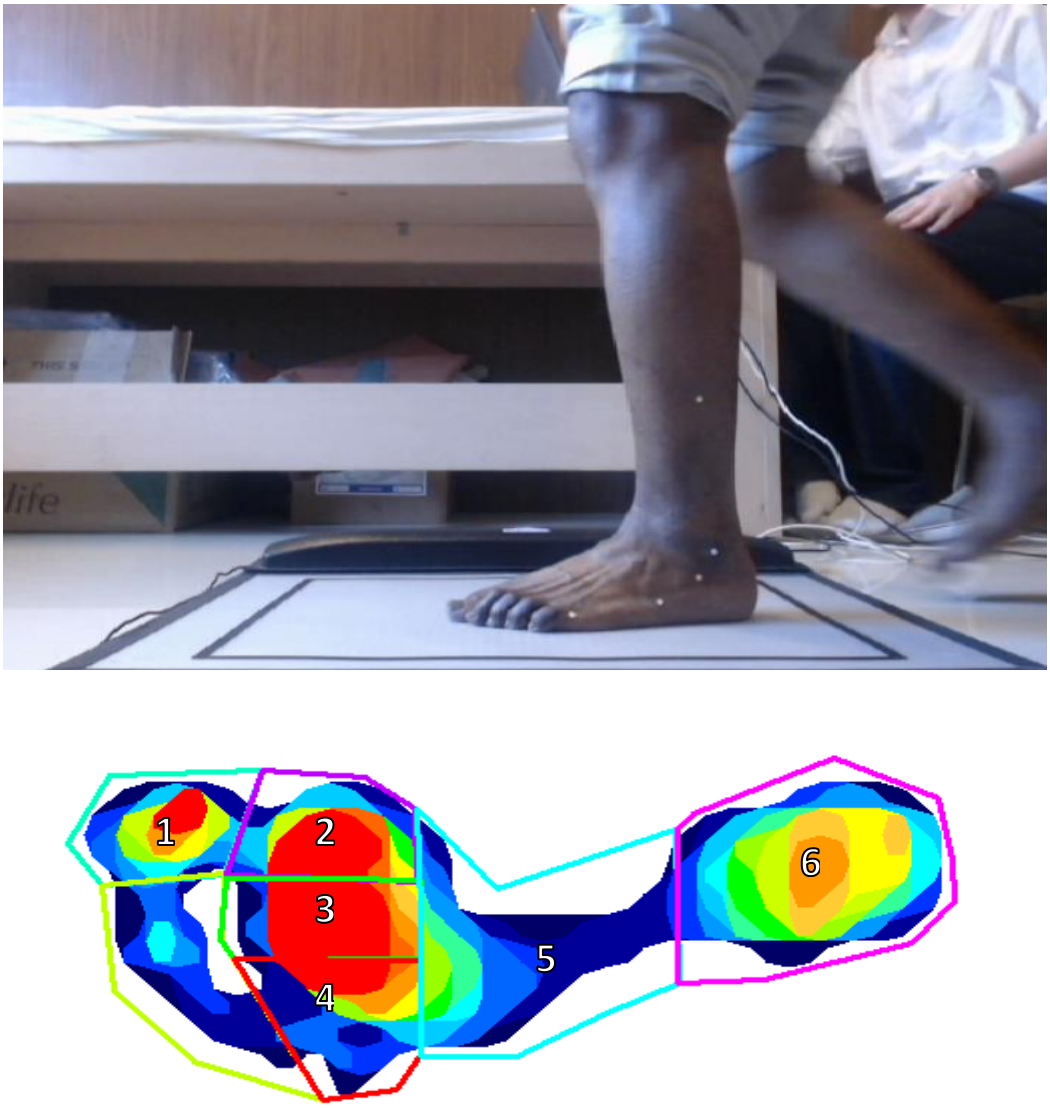


Figure 5-2: a) Participant during midstance using the TekScan Matscan 0.5mx0.5m pressure mat. b) Example of the output from the TekScan Matscan software with region of interest masks applied. 1. Hallux, 2. 1st metatarsal head, 3. 3rd metatarsal head, 4. 5th metatarsal head, 5. Midfoot, 6. Heel

To assess the range of motion of the foot and ankle, sagittal plane anatomical landmarks were taken from the Rizzoli foot model. The Rizzoli foot model was selected as it is one of the few multisegmented foot models that allow for a midfoot segment to be defined. The foot was therefore separated into three regions: the forefoot, midfoot and heel. 5mm circular paper markers were applied to five anatomical locations on the foot, ankle, and shank using a non-toxic adhesive. Markers were applied to the dorsolateral aspect of the head of the 5th metatarsal, base (proximal head) of the 5th metatarsal, dorsolateral aspect of the 5th metatarso-cuboid joint, lateral apex of the peroneal tubercle, lateral aspect of the malleolus, and approximately halfway up the lateral aspect of the shank [Figure 5-3]. A webcam (Logitech C920, Logitech, Lausanne, Switzerland) was connected to a computer with video recorded at 30Hz using the Tekscan software to synchronise the video recording with the plantar pressure measurements.

The measurement of ROM was only assessed using the lateral border of the foot due to considerations regarding the equipment being used in addition to the clinical relevance of the measurement (Morag and Cavanagh, 1999; Payne, Turner and Miller, 2002; Mueller *et al.*, 2003; Barn *et al.*, 2015; Searle *et al.*, 2017). Within current clinical practice, the measurement of plantar/dorsiflexion range of motion is performed using a handheld goniometer assessed on the foot's lateral aspect (Searle *et al.*, 2017). By assessing ROM at the lateral aspect following a similar protocol for the multisegmented foot model, it allows for potential direct comparison with previously published data regarding foot and ankle range of motion.

There are also experimental limitations with the hardware and software that was used as part of this study. As shown in Figure 5-2, there is a black bar attached to the pressure mat. It was found during initial testing that this bar blocked the view of the webcam to the medial border of the foot, blocking out the view of any medial markers.

Finally, technical limitations prevented ROM from being assessed in multiple planes and points of view. Specifically, the MatScan software used to power and control the pressure plate only allowed for a singular webcam to be connected at any one time. Therefore, it was decided that as the lateral view provided the most clinically relevant view of the foot with regards to the ROM of the foot and ankle only the lateral aspect of the foot would be assessed.

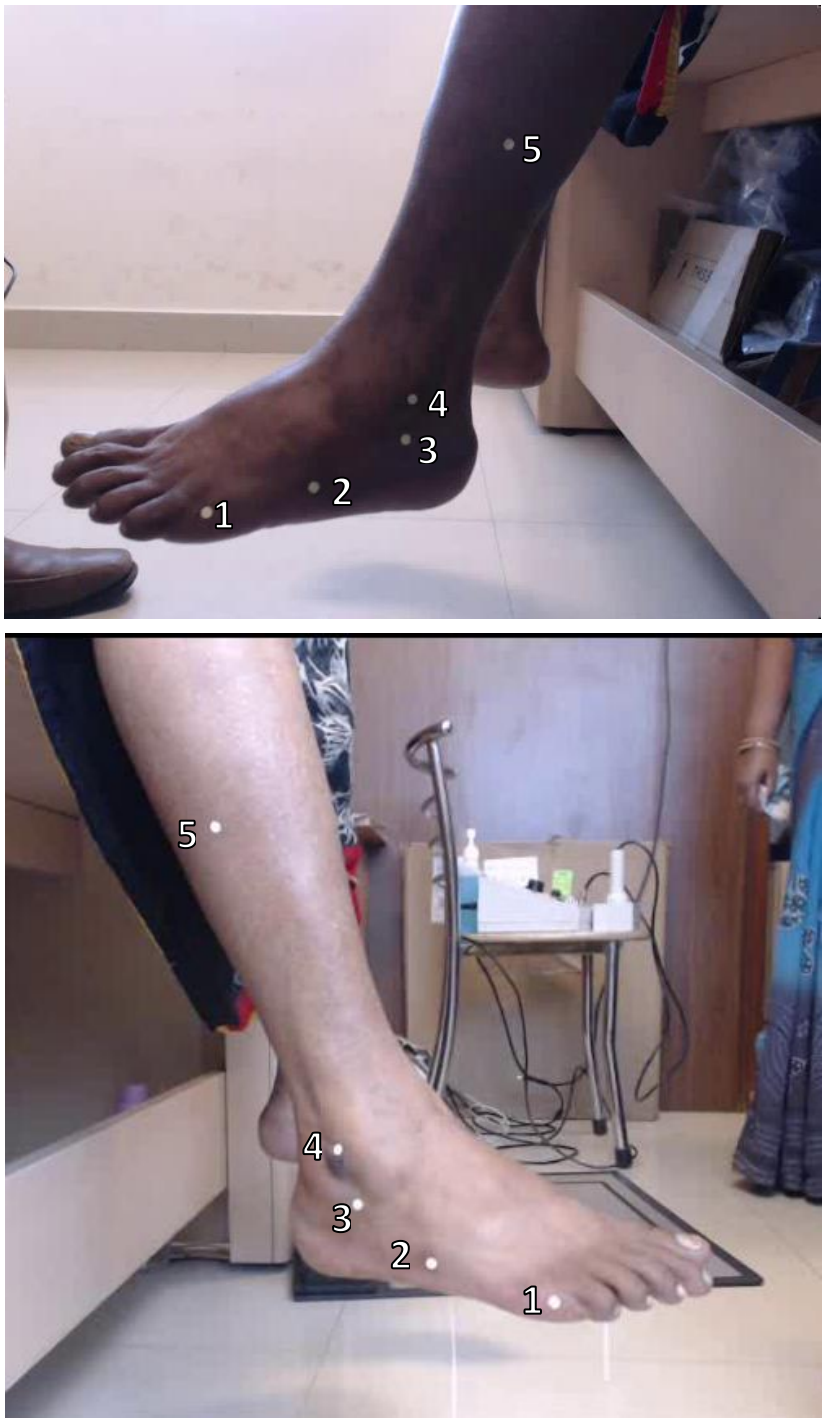


Figure 5-3: Marker placement for the left and right leg for the measurement of range of motion. Markers were applied to: 1) The dorsolateral aspect of the head of the 5th metatarsal, 2) base (proximal head) of the 5th metatarsal, dorsolateral aspect of the 5th metatarso-cuboid joint,3) lateral apex of the peroneal tubercle,4) lateral aspect of the malleolus, 5) approximately halfway up the lateral aspect of the shank

Video data was analysed using Kinovea v0.8.25, whereby forefoot, midfoot, and ankle ranges of motion were extracted for both heel strike and toe-off [Figure 5-4]. The forefoot was defined as the external angle between the dorsolateral aspect of the head of the 5th metatarsal, the base of the 5th metatarsal, dorsolateral aspect of the 5th matatarso-cuboid joint, and the lateral apex of the peroneal tubercle [Figure 5-4] (1). The midfoot was defined as the internal angles between the base of the 5th metatarsal, dorsolateral aspect of the 5th matatarso-cuboid joint, lateral apex of the peroneal tubercle, and the lateral aspect of the malleolus [Figure 5-4] (2). Finally, the ankle was defined as the external angle between the lateral apex of the peroneal tubercle, lateral aspect of the malleolus, and the marker approximately halfway up the lateral aspect of the shank [Figure 5-4] (3)

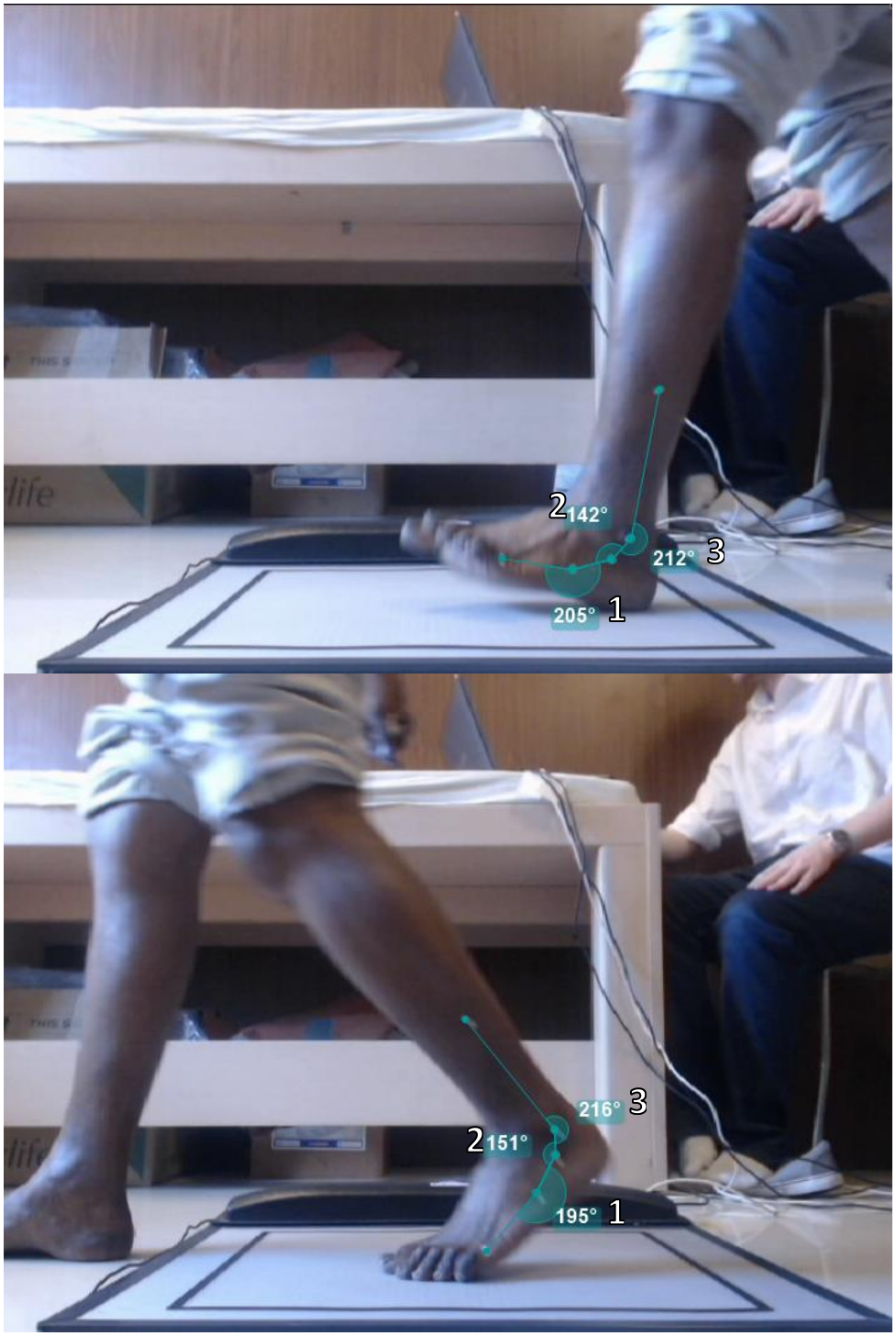


Figure 5-4: Joint angles measured during gait at heel strike and toe off for the left foot.

All statistical analyses were conducted using commercially available software (IBM® SPSS®v.27). Shapiro-Wilk test was used to screen the data for normal distribution ($p<0.05$). Based on the non-normal distribution of the data, Spearman's rank correlation tests were run between Shore hardness and regional plantar pressure measurements (pressure-time integral and peak contact pressure), in addition to correlations between the intersegmental range of motion and regional plantar pressure measurements (pressure-time integral and peak contact pressure). Associations between the Shore hardness and plantar pressure were investigated only at each site. In all cases, the left and right foot results were analysed separately (Menz, 2004).

Standard multiple regression modelling was used to assess the ability of Shore hardness and foot and ankle range of motion to predict localised plantar pressures. Preliminary analyses were conducted to ensure no violation of normality, linearity, multicollinearity, and homoscedasticity assumptions. The literature surrounding the use of standard multiple regression recommends that for each variable input into the regression model, a total of 15 samples is required. Due to the limited sample size of this study (38) and based on the literature that meant only a maximum number of 2 variables were entered into the regression model. To try and mitigate this, the most important of the two variables going into the model was entered first. In this case, for each regression model, the range of motion variable was entered first, followed by the Shore hardness variable.

5.3. Results

The participants recruited for this study had an average age of 63(±9) years and an average duration of diabetes 15(±9) years. Regarding the Spearman's rank correlation test, only Shore hardness at the 1st Metatarsal head on the right foot was found to be significantly associated with pressure-time integral at the right forefoot. This was a negative correlation of medium strength (r=-0.342, p=0.033, n=39). No other correlations between Shore hardness and peak contact pressure were found. Additionally, there were no significant correlations between the range of motion and peak plantar pressure. Results for the correlation testing can be seen in Table 5-1

*Table 0-1: Results of the Spearman's rank correlation test between plantar pressure parameters and Shore hardness. Only correlations between corresponding anatomical regions were considered. PCP (Peak Contact Pressure) PTI (Pressure Time Integral) * denotes significant correlation P<0.05*

Shore Hardness	Forefoot PCP	Midfoot PCP	Heel PCP	Forefoot PTI	Midfoot PTI	Heel PTI
Left 1st Met Head	0.021	-0.055	-0.01	-0.126	0.042	-0.066
Left 3rd Met Head	-0.034	0.046	0.054	-0.169	-0.035	-0.247
Left 5th Met Head	0.148	0.205	0.103	-0.147	0.061	-0.139
Left Hallux	0.123	0.1	0.102	0.27	0.093	-0.251
Left Heel	-0.118	0.005	0.141	-0.191	0	-0.149
Left Midfoot	0.035	0.044	0.055	0.015	0.08	-0.238
Right 1st Met Head	-0.232	0.138	-0.307	**-.342***	-0.062	-0.253
Right 3rd Met Head	0.132	0.113	0.068	-0.189	-0.144	-0.078
Right 5th Met Head	0.158	0.18	0.087	-0.128	-0.006	0.076
Right Hallux	0.106	0.207	0.026	-0.196	0.096	-0.104
Right Heel	0.233	.363*	0.255	-0.178	0.227	0
Right Midfoot	-0.011	0.132	-0.054	-.351*	-0.037	-0.061

*Table 0-2: Results of the Spearman's rank correlation test between plantar pressure parameters and range of motion during gait. Only correlations between corresponding anatomical regions were considered. PCP (Peak Contact Pressure) PTI (Pressure Time Integral) * significant correlation P<0.05*

Dorsiflexion	Forefoot PCP	Midfoot PCP	Heel PCP	Forefoot PTI	Midfoot PTI	Heel PTI
Left Forefoot	0.176	0.198	-0.081	-0.17	0.283	0.102
Left Midfoot	0.095	-0.047	-0.163	0.06	-0.019	0.158
Left Ankle	-0.197	-0.137	-0.263	-0.121	-0.039	0.029
Right Forefoot	0.231	0.231	0.051	-0.161	0.234	0.073
Right Midfoot	-0.048	-0.195	-0.11	-0.314	-0.163	0.001
Right Ankle	-0.165	-0.186	-0.282	-.383*	-0.187	-0.282

Multiple regression was conducted to see if the measurement of Shore hardness and segmental range of motion could predict localised plantar pressures in people with diabetes and diabetic peripheral neuropathy. Using the enter method, it was found that Shore hardness and segmental range of motion of the left midfoot could explain a significant amount of the variance in the value of pressure-time integral at the midfoot of the left foot ($F(2,31) = 11.541$, $p<0.05$, $R^2 = 0.43$, $R^2_{Adjusted} = 0.39$). The analysis showed that Shore hardness at the left midfoot did not significantly predict the value of pressure-time integral at the left midfoot (Beta = 0.65, $t(31) = 4.72$, ns), however midfoot dorsiflexion range of motion did significantly predict the value of midfoot pressure-time integral (Beta = 0.21, $t(31) = 1.54$, $p<0.05$)

Additionally, it was found that Shore hardness and segmental range of motion of the left midfoot explain a significant amount of the variance in the value of peak contact pressure at the midfoot of the left foot ($F(2,31) = 4.73$, $p<0.05$, $R^2 = 0.23$, $R^2_{Adjusted} = 0.18$). The analysis shows that Shore hardness at the left midfoot did not significantly

predict the value of peak contact pressure at the left midfoot (Beta = 0.19, t(31) = 1.18, ns); however midfoot dorsiflexion did significantly predict the value of midfoot peak contact pressure (Beta = 0.47, t(31) = 2.98, $p<0.05$). No significant predictive models were found for the left heel and forefoot nor any significant predictive models for either region of the right foot.

5.4. Discussion

This study aimed to investigate if changes in regional plantar pressures can be predicted using a simplified 2D multisegmented foot model and the measurement of Shore hardness as an assessment of plantar soft tissue mechanics. The results of this study have shown that it is possible to predict changes in the measurement of plantar pressure, namely pressure-time integral and peak contact pressure at the midfoot, using these methodologies. The predictor variables could explain between 18% to 39% of the variance in pressure-time integral and peak contact pressure at the midfoot, respectively, with range of motion in the midfoot being the significant predictor.

Based on the predictive models obtained, the range of motion in the midfoot was the only significant predictor for an increase in the peak contact pressure and pressure time integral. In both cases, the predictive model shows that a higher value of midfoot dorsiflexion is associated with the increase in peak contact pressure (Beta =0.47) and pressure time integral (Beta =0.21). The beta coefficient is the degree of change in the outcome variable for every 1-unit change in the predictor variable. As the beta

coefficient is positive, the interpretation is that for every 1-unit increase in the predictor variable (midfoot dorsiflexion), the outcome variable will increase by the beta coefficient value (peak contact pressure and pressure time integral). In this case, a 1-degree increase in midfoot range of motion will cause a 0.47kg/cm^2 increase in the peak contact pressure and a 0.21kg/cm^{2}s increase in pressure time integral.

The multisegmented foot model used in this study uses the sagittal plane anatomical landmarks from the Rizzoli foot model. (Leardini *et al.*, 2007). The anatomical landmarks from the Rizzoli foot model allow the foot to be separated into three regions: the forefoot, the midfoot, and the rear foot [Figure 5-4]. Within this model, the forefoot and rearfoot dorsiflexion are measured using the external angle [Figure 5-4], whereby a reduction in the measured angle is associated with a reduction in dorsiflexion. However, in the case of the midfoot, midfoot dorsiflexion is measured as an internal angle [Figure 5-4] and is coupled to the movement of the rearfoot/ankle. As a result, as the measured midfoot angle increases, the amount of dorsiflexion within the midfoot decreases.

This decrease in midfoot dorsiflexion is due to the earlier engagement of the calcaneocuboid joint within the foot, whereby the role of the calcaneocuboid joint is to lock the midfoot to the rearfoot allowing for the transition from midstance into and through propulsion. As people with diabetes tend to have a limited range of motion within the rearfoot and ankle, this causes the calcaneocuboid joint to be engaged earlier in the gait cycle as people with diabetes tend to spend less time in the initial stages of

gait. As the role of the calcaneocuboid joint is to lock the relative position of the midfoot to that of the rearfoot, the earlier engagement of the joint limits the maximum amount of dorsiflexion within the joint.

There could be several reasons for the relationship between the increase in plantar pressures and the reduction in the range of motion of the midfoot. Based on the regression analysis results, the model for the midfoot peak contact pressure shows that as midfoot dorsiflexion decreases, midfoot peak contact pressure increases. Additionally, the model for pressure-time integral indicates that as midfoot dorsiflexion decreases, midfoot pressure-time integral also increases. The primary hypothesis for this relationship between range of motion and plantar pressure parameters is due to changes in the normal gait due to changes in the morphology of the foot.

When looking at the midfoot peak contact pressure prediction model and the effect that midfoot range of motion has on gait patterns, there is little direct research regarding the range of motion of the midfoot. One of the reasons for this is the methods currently used to assess the range of motion. When assessing the effect of diabetes on the range of motion of the foot and ankle, studies have focused on the ankle and the 1st metatarsal head using a handheld goniometer. Whilst this is the clinically accepted method for assessing the range of motion of the ankle, this method only allows for a static assessment of the range of motion as opposed to a dynamic assessment during gait.

However, a couple of studies have assessed midfoot plantar pressure measurements and how these midfoot measurements are affected by a reduction in ankle range of motion.

In people with diabetes, a common change in the gait pattern is an earlier heel lift off caused by a reduction in ankle dorsiflexion. A stiffening of the Achilles tendon causes this reduction in ankle dorsiflexion due to non-enzymatic glycosylation. Limited dorsiflexion of the ankle acts to restrict the forward progression of the tibia over the foot during the stance phase. To counter this change in the gait cycle, people with diabetes tend to lift their heel early, have excessive subtalar joint pronation and associated midtarsal joint pronation (Michaud, 2011). In extreme cases of limited ankle dorsiflexion, people with diabetes will walk flat-footed, i.e., no heel strike as they lost the ability to dorsiflex the ankle. In addition, due to the early heel lift, people with diabetes and peripheral neuropathy will tend to initiate the push-off phase of gait before the metatarsal heads completely touch the ground and is accompanied by a reduction in the longitudinal excursion from the centre of support.

Extrapolating the effect of a reduction in ankle dorsiflexion range of motion to the midfoot, the research would indicate that a reduction in midfoot dorsiflexion range of motion would have a similar effect as a reduction in ankle dorsiflexion range of motion. Therefore, a reduction in midfoot dorsiflexion, as indicated by an increase in the measured midfoot angle, could be caused by an increase in the muscle/tendon stiffness caused by non-enzymatic glycosylation. This increase in the measured midfoot angle and

therefore the subsequent decrease in midfoot dorsiflexion would likely increase the plantar loads placed on the plantar soft tissues of the midfoot as the push-off phase of gait would have to be started earlier to allow the forward progression of the tibia over the foot during stance phase.

Pressure time integral is an assessment of the cumulative load experienced by the plantar soft tissues of the foot and is directly affected by the amount of load applied to the tissue and the duration of loading. Literature has shown that changes in the range of motion of the foot and ankle due to diabetes have a direct effect on the gait pattern. In people with diabetes and diabetic peripheral neuropathy, such as the group of participants recruited as part of this study, literature shows that people with diabetes and diabetic peripheral neuropathy exhibit a slower gait pattern, reduced stride length, and an increase in the duration of support time.

The combination of a slower gait pattern, reduced stride length and the increase in the duration of the support time all act to increase the value of pressure-time integral, i.e. an increase in the cumulative loading experienced by the soft tissues of the foot (Fernando *et al.*, 2013). In addition, the slower gait speed and the increased duration of support increase the amount of time spent during the midstance phase of the gait cycle, whereby the whole foot is in contact with the ground. This will increase the chance of ulceration for a person with diabetes and diabetic peripheral neuropathy as the shorter stride length will cause an increase in the number of steps being taken, and prolonged

midstance will increase in the total load experience by the soft tissues, potentially leading to a faster breakdown in the soft tissues of the foot (Van Dieren *et al.*, 2010; Fernando *et al.*, 2013).

As with peak contact pressure, previous literature has not investigated the effect that a reduction in midfoot dorsiflexion has on the measurement of pressure-time integral. As the midfoot and ankle function are interrelated during gait, assumptions can be formed that a reduction in midfoot dorsiflexion will have a similar effect of pressure-time integral as a reduction in ankle dorsiflexion. A reduction in midfoot dorsiflexion is likely to increase the contact between the foot and the ground due to early heel lift when transitioning from heel strike to midstance or, in extreme cases, a flat-footed gait pattern is adopted due to the lack of dorsiflexion within the foot. Additionally, due to a reduction in midfoot dorsiflexion, the soft tissues will experience greater initial loading due to the earlier transition from heel strike to midstance.

Comparing the results of this study to previous literature, this study was only able to predict peak contact pressure and pressure time integral at the midfoot of the left foot using midfoot dorsiflexion. Two studies have looked at predicting midfoot plantar pressures Barn et al. (2015), attempted to predict midfoot plantar pressures in people with diabetes based on 329 feet. In their model, 41% of peak plantar pressure variance was accounted for by the following variables: Body mass, duration of diabetes, ankle joint range of motion, Charcot midfoot deformity, pes planus, amputation, and previous

midfoot ulceration. In the second study by Morag et al. (1999), 55 healthy participants were recruited, ranging from 20 to 70, with 11 participants recruited per decade. In the model from Morag et al. (1999), 51.7% of the variance in midfoot plantar pressure was accounted for by age, weight, eversion, and inclination of the calcaneus.

The current models in this study were able to account for 18% of the variance of midfoot pressure-time integral and 38% of the variance in midfoot peak contact pressure using only two parameters as opposed to Barn et al. (2015) and Morag et al. (1999), who used a number of parameters. For this study, due to the limited sample size (n=38), only a select number of parameters are recommended for analysis; in this case, the parameters of most interest were dorsiflexion in addition to Shore hardness. Therefore, these parameters were placed into the model in the order of most importance.

The limited number of parameters involved in this model would improve the clinical applicability of this model as it reduces the number of tests and examinations required. However, a large amount of variance in the peak contact pressure and pressure time integral remains unexplained in this cohort of people with diabetes at high risk of ulceration. This suggests that plantar pressure measurement is still required to assess the foot at risk fully and should be an integral part of foot screening of high-risk patients.

The lack of a predictive model to predict plantar pressures at the forefoot and heel based on forefoot and ankle range of motion is an interesting result that warrants further being

explored in future. There is strong evidence within the body of literature that a reduction in ankle dorsiflexion and forefoot dorsiflexion cause an increase in the plantar pressures experienced at the heel and under the metatarsal head and can be used as a predictive measurement for plantar pressure. One of the primary reasons for this lack of a predictive model and lack of association is most likely due to the method used to obtain ankle and forefoot range of motion. Traditionally within the literature, range of motion is measured passively using a handheld goniometer whereby the foot is unloaded. In this study, however, the range of motion is measured during gait; as a result, the functional anatomy of the foot will cause a reduction in the range of motion of the foot and ankle due to the locking of the subtalar and midtarsal joints.

One of the main limitations of this study is the sample size. For this study, a total of 40 participants were recruited, with 38 participants eligible for analysis. Due to the strict inclusion/exclusion criteria set out initially, only participants at the highest risk of ulceration were recruited to this study. This dramatically reduced the number of potentially eligible participants for this study. As a result, the total number of variables that were able to be put into the predictive model was reduced. Based on the literature, to achieve a reliable predictive model, about 15 participants per predictor is required. Due to the small sample size this limited the analysis to two predictors, three predictors max. Additionally, left and right feet were treated separately, as is standard practice within diabetic foot research (Menz, 2004).

Additionally, while foot deformities have been linked to increases in regional plantar pressure (Barn *et al.*, 2015), foot deformities were not included in this data set. Images of the participant's feet were taken for documentation purposes; however, there was no one present with the expertise required to assess the foot accurately during the data collection. The images collected of the participant's feet were able to confirm the presence of claw/hammer toe and areas of callus. This may be a minor limitation of this study, as no significant associations were found regarding plantar pressure parameters, range of motion, and Shore hardness.

Finally, there are limitations with measuring ROM using only the lateral border of the foot. In particular, information is lost regarding the midtarsal joint and the relative dorsiflexion movement of the talonavicular joint. Due to its placement within the foot, most of the movement of the talonavicular joint would only be seen with a view of the medial border of the foot. However, due to the limitations of the experimental setup, whereby the medial view of the foot was blocked and the ability to only run one webcam with the pressure plate software, only the lateral aspect of the foot can be captured.

Being able to assess the talonavicular joint may explain more for the variance in the models as talonavicular motion directly affects the midtarsal joint, which facilitates midfoot dorsiflexion. A reduction in the ROM of the talonavicular joint may cause the midfoot to lock up earlier in the gait phase, preventing and/or limiting the dorsiflexion of the foot. In addition, this reduction in dorsiflexion ROM increases the likelihood of a

midfoot break which has been linked to an increase in plantar pressure at the midfoot. However, in order to assess talonavicular motion, either 3D motion analysis will be required or a new approach to 2D motion analysis whereby medial border of the foot is not obscured.

In conclusion, this study shows that a simplified 2D multisegmented foot model and the measurement of Shore hardness as an assessment of plantar soft tissue mechanics can be used to predict regional plantar pressure measurements at the midfoot. Due to the low number of parameters, these predictive models can be performed quickly within clinical settings. However, range of motion and Shore hardness only account for a small proportion of the variance in predicting changes in peak contact pressure and pressure time integral. A future large study would allow more variables to be included within the multiple regression models explaining more of the variance.

6. Chapter 6: Summary and Conclusions

In the preceding chapters, each study has been discussed independently of each other. The purpose of this section is to present the findings of the research in relation to each other and to offer clinically relevant conclusions regarding the use of Shore hardness as a method of assessing the mechanical properties of the plantar soft tissues of the foot in addition to the use of Shore hardness as a method of predicting plantar pressure.

This research aimed to investigate simple, cost-effective, and reliable methods to assess the biomechanical factors associated with ulceration within the clinic setting. Firstly, it was essential to examine the current literature regarding diabetic foot ulceration to assess what biomechanical parameters are used in clinical practice to prevent diabetic foot ulcers.

Examining the current literature, in particular, the risk stratification systems that are used within clinical practice as a method of preventing diabetic foot ulcers, biomechanical risk factors such as elevated barefoot plantar pressure (>65N/cm^2) (Lavery *et al.*, 1998), foot deformities (hallux rigidus or hammertoes) (Boulton *et al.*, 2010; Malhotra, Bello and Kominsky, 2012; Fernando *et al.*, 2013), and evidence of callus on the feet were found to be rare among the parameters that were considered or which were identified as significant in the prediction of diabetic foot ulcers. In addition, of the five main risk stratification systems, only the University of Texas Foot Score Systems

(Lavery *et al.*, 1998)and the Scottish Intercollegiate Guidelines Network (SIGN, 2001) considered biomechanical measurements in their assessment of the foot at risk.

As diabetic foot ulcers are primarily caused by an inherent failure of the planar soft tissues of the foot, the literature suggests that a direct assessment of the foot, in particular foot biomechanics, may further aid in the prediction and prevention of diabetic foot ulcers in particular assessments of plantar soft tissue biomechanics and plantar pressure.

One of the reasons identified for the lack of biomechanical measurements in the assessment of diabetic foot ulceration, particularly the assessment of the mechanical properties of the plantar soft tissues and plantar pressure, is due to the lack of clinically viable methodologies. The current methods used to measure the mechanical properties of the plantar soft tissues involve specialised equipment such as ultrasound elastography or bespoke indentation devices, which require specialised training to produce accurate and reliable results. Additionally, plantar pressure systems require a significant amount of space to be used effectively, greatly reducing their chances of being implemented within clinical settings where space is limited. Therefore, it was identified that there is a clear need for a simple, clinically applicable method to assess the mechanical properties of the plantar soft tissues of the foot in addition to assessing plantar pressures. This is specifically relevant to low resource settings such as developing countries, where access to ultrasound machines and sophisticated equipment is scarce.

The measurement of Shore hardness, using a handheld durometer, was identified as a potential new method of assessing the mechanical properties of the plantar soft tissue due to it having been successfully used to assess soft tissue biomechanics in vivo for various skin conditions; however, some key questions remain regarding its actual physical meaning and its clinical relevance.

6.1. Study 1: The physical meaning and clinical relevance of Shore hardness in diabetic foot research

Study 1 was designed to investigate: 1) the physical meaning of the measurement of Shore hardness, and whether it can be considered as an indirect measurement of stiffness; 2) the ability of Shore hardness to monitor changes in the mechanical properties of the skin or the underlying subcutaneous soft tissue; 3) the ability of Shore hardness to confirm associations between plantar soft tissue stiffness, age, loading, and blood biochemistry.

To answer the first two aims, a finite element analysis approach was taken whereby the heel pad of the foot, in addition to the inner mechanism of the Shore hardness durometer, was modelled [Figure 3-1]. The skin and the subcutaneous soft tissues were modelled as Ogden viscoelastic with skin and subcutaneous soft tissue mechanical properties taken from the literature. A parametric approach was taken to alter the mechanical properties of the skin or soft tissue from -50% of the starting values up to +50% in 10% increments.

The results of this finite element analysis indicated that Shore hardness offers an assessment of stiffness that is a combination of both the mechanical behaviour of the skin and the underlying subcutaneous tissue. As a result, differentiating between the stiffness of skin and the subcutaneous tissue based on the conventional assessment of Shore hardness remains a challenge.

This is the first study that has looked at investigating the physical meaning of Shore hardness when used to assess soft tissue biomechanics. Regarding the physical meaning of Shore hardness, the results of this study indicate that this is different for skin and subcutaneous tissue. For subcutaneous soft tissue, the measurement of Shore hardness offers an assessment of stiffness that is relevant to the initial slope of the stress-strain graph (i.e., stiffness for small deformations). For skin, Shore hardness appeared to be affected not only by the initial shear modulus but also by the skin's strain hardening/softening behaviour.

It was hypothesised that the measurement of Shore hardness should be more representative of skin stiffness due to the size of the tip of the Shore hardness device (Spears and Miller-Young, 2006). Literature has suggested that the measurement of indentation into the plantar soft tissues of the foot using an indenter is less than 6mm in diameter can be said to be relevant to the measurement of the stiffness of the skin. It is suggested that this is due to the localised deformation being governed predominantly

by the stiffness and thickness of the skin layer. However, the results of the FE analysis presented here have shown that the measurement of Shore hardness is also strongly affected by changes in the mechanical properties of the underlying subcutaneous tissue. The measurement of Shore hardness appears to be equally sensitive to changes in skin or subcutaneous tissue properties. This is a major limitation for using Shore hardness to follow up on possible changes in the mechanical properties of plantar soft tissues as changes in the properties of one tissue layer could be masked by changes in another layer

In addition to the proposed use of Shore hardness as a method to indirectly measure the stiffness of the plantar soft tissues, the clinical viability of the device has been assessed. The ability of Shore hardness to confirm associations between plantar soft tissue stiffness, age, loading, and blood biochemistry was tested using a clinical study whereby 40 participants with diabetes and diabetic peripheral neuropathy were recruited from two outpatient centers in Chennai, India.

The results of this part of the study investigating the clinical viability of the Shore hardness measurement showed that Shore hardness was capable of verifying correlations between tissue biomechanics, loading and blood biochemistry that were previously identified using more complex testing techniques such as indentation testing.

Overall, the results of this study show for the first time an insight into the physical meaning of the measurement of Shore hardness when used as a method to assess the mechanical properties of the plantar soft tissues of the foot. It also highlights that the measurement of Shore hardness is not an assessment of skin stiffness only as previously outlined within the literature.

6.2. Study 2: The efficacy of the Shore hardness measurement in quantifying the stiffness of a layered structure

Study 2 builds on the results of Study 1 whereby it was found that the measurement of Shore hardness offers an assessment of stiffness that is a combination of both the mechanical behaviour of the skin and the underlying subcutaneous tissue and as such, Shore hardness is unable to separate the individual effect of changes in the mechanical properties of each layer on the measurement of Shore hardness. Current literature regarding indentation testing of the plantar soft tissues of the foot proposes that the measurement of indentation is more representative of the skin or soft tissue mechanical properties based on the size of the indenter being used (Spears and Miller-Young, 2006). However, this effect of this indenter size has not been fully explored or quantified, especially regarding indentation testing of a layered structure such as the plantar soft tissues of the foot.

Based on this, Study 2 aimed to investigate the feasibility of measuring the mechanical properties of each layer, such as skin or subcutaneous soft tissue, directly using different sizes of Shore hardness indenters.

A finite element analysis approach was again taken to investigate these aims whereby a simplified 2D axisymmetric model of the Shore hardness test was used, and the length and width of Shore hardness indenter were parametrically altered. Mechanical properties of the skin and subcutaneous soft tissue were taken from literature and modelled as Ogden viscoelastic materials.

This study, for the first time, explores the relationship between indentation and indenter size. This study indicates that contrary to current literature, the measurement of indentation using a small indenter is not a measurement of skin mechanical properties only. The results show that the measurement of indentation using a small indenter probe (>6mm diameter) will be affected by the mechanical properties of the underlying subcutaneous soft tissue. Additionally, the measurement of indentation using a large indenter is not a measurement of subcutaneous soft tissue only, as changes in the mechanical properties of the skin were also found to affect this measurement of indentation.

The results also show that it may be feasible to assess changes in the mechanical properties of the skin or subcutaneous soft tissue directly through different sizes of indenters. For example, an indenter that is less than 2mm in diameter and 1mm in length may potentially be able to infer differences between the mechanical properties of the skin and subcutaneous soft tissues by being sensitive to changes in the mechanical properties of the skin and insensitive to changes in the mechanical properties of the subcutaneous soft tissues. For the assessment of soft tissue, a wide indenter over 9mm in radius that is also longer than the thickness of the skin is recommended so as to concentrate the deformation within the deeper layered structures of the heel pad.

6.3. Study 3: Plantar pressure prediction based on Shore hardness and Range of Motion

As diabetic foot ulceration results from the mechanical breakdown of the plantar soft tissues, both the internal and external factors associated with ulceration need to be explored. With the mechanical properties being the internal factor that leads to ulceration, plantar pressure can be said to be the external factor.

Measurement techniques for assessing plantar pressure include the use of either a walkway pressure platform system for the assessment of barefoot plantar pressures or an in-shoe pressure-based measurement system. Unfortunately, these systems also require a significant amount of space to be used effectively, greatly reducing their chances of being implemented within clinical settings where space is limited.

This has led to several studies that aim to predict plantar pressures based on biomechanical factors associated with an increase in plantar pressure (Morag and Cavanagh, 1999; Payne, Turner and Miller, 2002; Mueller *et al.*, 2003; Barn *et al.*, 2015). These factors being foot and ankle range of motion and soft tissue mechanical properties. These studies, however, have used techniques that are not readily available such as CT and X-Ray, to measure joint range of motion, joint angle, and joint motion. In addition to indentation testing for the plantar soft tissues.

To enable the predictions of plantar pressure to be used clinically, there is a, therefore, a need for a set of clinically viable methodologies to measure common variables such as joint range of motion and soft tissue mechanical properties.

Study 1 has shown that Shore hardness can verify correlations between tissue biomechanics and loading and, as a result, could be used to predict plantar pressures. Therefore, this study aimed to investigate if regional plantar pressures for the forefoot, midfoot, and heel can be predicted using 2D range of motion analysis and the measurement of Shore hardness.

The result of this study shows that a 2D multisegmented foot model and the measurement of Shore hardness as an assessment of plantar soft tissue mechanics can be used to predict changes in regional plantar pressure measurement in the midfoot. Shore hardness and segmental range of motion of the left midfoot explain a significant

amount of the variance in the value of pressure-time integral at the midfoot of the left foot ($F(2,31) = 11.541$, $p<0.05$, $R2 = 0.43$, $R2Adjusted = 0.39$). Additionally, it was found that Shore hardness and segmental range of motion of the left midfoot explain a significant amount of the variance in the value of peak contact pressure at the midfoot of the left foot ($F(2,31) = 4.73$, $p<0.05$, $R2 = 0.23$, $R2Adjusted = 0.18$).

6.4. Implications for future clinical practice.

The results of these studies show that the assessment of Shore hardness can be clinically viable when compared to current methods. When comparing the applicability of Shore hardness as a method to assess the mechanical properties of the plantar soft tissues to that of other approaches, such as ultrasound indentation or shear wave elastography, the main advantages of the Shore hardness measurement are a) its ease of use and b) the speed in which a full examination can be conducted. The use of a handheld Shore hardness durometer requires little training and is safe to use in clinics. In addition, the time required to take a measurement is minimal.

When looking at the prediction of plantar pressure based on Shore hardness and range of motion, the limited number of parameters involved in the prediction model would improve the clinical applicability of this model as it reduces the number of tests and examinations required.

It is, however, important to note that from a clinical perspective, the methods and predictive model presented here do not present a direct replacement for walkway or in-

shoe pressure measurements. Instead, the predictive model presented here provides an estimated prediction of how plantar pressure within a relatively large, selected area may have changed based on changes in Shore hardness and segmental ROM within the region.

The purpose of the model is to provide a potential alternative method to assess relative changes as opposed to absolute changes in plantar pressure over time, in situations where the use of walkway or in-shoe plantar pressure is either limited or unavailable. When used by itself, the predictive model cannot provide an absolute value of plantar pressure within the region, nor is it able to give a clinician the same level of detail and accuracy as conventional plantar pressure analysis. However, when this model is used in conjunction with previous collected plantar pressure data, the model may be able to predict the absolute change in plantar pressure within the broader area of the region of interest.

When looking at the use of the measurement of Shore hardness within a clinical setting, considerations need to be made regarding Shore hardness's impact on healthcare budgets and if the method will provide savings in terms of cost and time. In particular, consideration must also be made regarding how these new methods may fit into the existing infrastructure and clinical care of people with diabetes.

When looking at the time taken for the measurement of Shore hardness as a method to assess the mechanical changes to the plantar soft tissues, the time required to perform a complete evaluation of the foot is minimal. From experience, within the clinical setting, a complete examination of the 12 plantar sites used in these studies took no more than 5 minutes to perform. However, it is important to note that to acquire reliable readings, the foot must first be unloaded for a minimum of 15 minutes prior to assessment. This was not a factor in these studies as it took approximately 15 minutes to acquire informed consent, answer any questions that the participant may have had, and to complete the participant questionnaire. It is imagined that a similar setting and system could be set up within clinics within the limits of the different trusts' appointment times.

Regarding the prediction of plantar pressures to fully assess a participant using the two measurements of Shore hardness and ROM required no more than 20 minutes once familiar with the protocol and marker placement. This can be a significant time-saver compared to traditional walkway/in-shoe plantar pressure assessment, which can easily take upwards of an hour due to requirements such as calibration, recording, post-processing, and interpretation of the results.

Shore hardness and range of motion to assess changes in the plantar soft tissues and plantar pressure also provides significant monetary savings to the healthcare provider. A Shore 00 hardness durometer costs somewhere in the region of €400 as opposed to some of the other methods previously mentioned, like ultrasound elastography, where

these systems can cost upwards of £50,000. The initial low cost allows for potential easy uptake within trusts and clinics and places minimal financial strain on local healthcare budgets.

Additionally, the assessment of range of motion can be completed with something as simple as a webcam, mobile phone, or tablet whereby the video of the patient walking can be either exported to an external device for analysis or right there on the device where free software readily available such as Kinovea. This is in comparison to plantar pressure, where a single plantar pressure plate can cost in the region of £4000, not including the additional hardware such as computers etc. which again, if rolled out across a trust, provides significant cost saving.

With regards to how the measurements of Shore hardness and range of motion are proposed to fit into current clinical practice, Figure 6-1 below shows the current foot care pathway for people with diabetes within NHS England. These guidelines are currently based on the NICE guidelines (NG19) and the current SIGN risk stratification system (SIGN, 2001).

Figure 6-1: Flowchart showing the current clinical care pathway for the diabetic foot within the UK in addition to the actions taken at each stage of ulceration risk (SIGN, 2001)

It is proposed that the measurement of Shore hardness and range of motion will be used within a secondary care setting such as community podiatry for medium to high-risk patients [Figure 6-2]. More specifically, it is suggested that those at medium/increased risk of ulceration only have Shore hardness and range of motion assessed. This enables clinicians to monitor potential relative changes in plantar pressure without performing a full plantar pressure assessment.

For those patients at the highest risk of ulceration, the proposed changes outlined in Figure 6-2, in addition to undergoing Shore hardness and range of motion testing, recommends a full plantar pressure assessment provided the patient is willing and physically able. Including an initial plantar pressure assessment for those patients at highest risk of ulceration provides the clinicians with a baseline absolute value of pressure for the three main regions of the foot (forefoot, midfoot, heel). Having an initial value of plantar pressure and pressure time integral enables the absolute change in plantar pressures to be calculated using the predictive statistical equations generated within this research. Using the measurements of Shore hardness and range of motion within subsequent visits to calculate the change in plantar pressure saves time for both the clinician and the patient. This would potentially also allow clinicians a better idea of when to start interventions such as offloading in areas experiencing higher than desirable plantar pressures without having to perform a full plantar pressure assessment.

Figure 6-2: Flowchart showing the amended clinical care pathway for the diabetic foot with the inclusion of the measurements of Shore hardness and range of motion (ROM) Specifically it is recommended that a full plantar pressure assessment is performed for those at highest risk of ulceration to allow for an estimation of absolute plantar pressure and to allow for offloading interventions.

6.5. Limitations of the research undertaken

The studies outlined in this thesis have some limitations which should be acknowledged.

Regarding the finite element models in Studies 1 and 2 (Chapters 3 and 4), one of the main limitations of these studies is that the subcutaneous tissue of the heel is simulated as a single layer of homogeneous, bulk soft tissue. In reality, the fat pad of the heel consists of two distinct layers: the first being the microchamber layer, which is a thin layer of small septa comprised of elastin fibres, and the second, the macrochamber layer, which is a thick layer of larger septa comprised of roughly equal amounts of elastin fibres and collagen. These two layers have been shown to exhibit different mechanical behaviour (Ahanchian *et al.*, 2017) and have different functional roles (C C Hsu *et al.*, 2007). Therefore, simulating the mechanical behaviour of the microchamber and macrochamber layers could further expand on the association between the measurement of Shore hardness and the mechanical properties of the skin and different subcutaneous layers.

Additionally, the model's geometry used in Study 2 (Chapter 4) poses some limitations. The heel pad was represented by a simple axisymmetric model, defined by a radius and a thickness for the finite-element analysis. The overall thickness was of the heel pad was derived from literature; however, the radius was not. The radius of the heel pad was selected based on initial testing to an optimal size, whereby the radius of the heel pad

had minimal effect on the measurement of indentation. The heel-pad surface was also assumed to be flat [Figure. 4-1] as opposed to curved. Previous literature has shown that using finite element analysis, changing the curvature of the heel pad has a direct influence on the mechanical properties of the model.

There are a number of limitations and assumptions made regarding the clinical aspects of this research. The biggest limitation is the sample size used within Study 1 and Study 3 (Chapter 3 and Chapter 5). As a result of having strict inclusion-exclusion criteria, only 40 participants were recruited to these studies. This limited the research in terms of the statistical analyses that were able to be conducted, in particular regarding the prediction of plantar pressure. In addition, the limited sample size greatly limited the number of predictive variables that could be included in the regression model in Study 3 (Chapter 5).

There are also limitations with regards to the experimental set-up regarding the assessment of range of motion. In this case, only the range of motion at the lateral aspect of the foot could be assessed. This was due to a limitation in experimental set-up whereby the webcam could only be placed facing the lateral aspect of the foot due to the presence of a black bar on the plantar pressure mat that obscured a clear view of the medial aspect of the foot. This prevented the assessment of the talonavicular joint dorsiflexion, which could have been a contributor to the reduction in midfoot ROM seen within this study. Being able to assess the talonavicular joint may explain the variance in

the models. Furthermore talonavicular motion directly affects the midtarsal joint, which facilitates midfoot dorsiflexion. In addition, a reduction in talonavicular ROM may cause the midfoot to lock up earlier in the gait phase and increase the likelihood of midfoot break, which has been linked to an increase in plantar pressure at the midfoot. However, to fully assess talonavicular motion, 3D motion analysis will be required

Finally, with regards to the effect that a reduction in midfoot in range of motion has on the measurement of plantar pressure, a number of assumptions had to be made. This is primarily due to a lack of research looking into the role of the midfoot and its effect on plantar pressure. When assessing the effect of diabetes on the range of motion of the foot and ankle, most studies have focused on the ankle and the 1st MTP joint using a handheld goniometer. However, a couple of studies have assessed midfoot plantar pressure measurements and how these are affected by a reduction in ankle range of motion (Michaud, 2011).

More specifically, the effect that a reduction in midfoot range of motion had on plantar pressure and pressure time integral had to be extrapolated based on the effect that a reduction in ankle range of motion has on these plantar pressure variables. Limited dorsiflexion of the ankle acts to restrict the forward progression of the tibia over the foot during the stance phase (Michaud, 2011). This decrease in ankle range of motion causes an earlier engagement of the calcaneocuboid and talonavicular (midfoot) joints within the foot, whereby the role of the midfoot joint is to lock the midfoot to the rearfoot

allowing for the transition from midstance into and through propulsion. Therefore, it could be assumed that any reduction in midfoot dorsiflexion is also accompanied by a reduction in ankle dorsiflexion and, therefore, the literature regarding the effect of a reduction in ankle dorsiflexion on plantar pressures could be used to better understand the results seen at the midfoot.

6.5.1. Areas of further study.

There are a number of the areas highlighted throughout this thesis that require future study. As highlighted in sections 3.4 and 4.4, one consistent area of future research is in modelling the plantar soft tissues of the foot, particularly the subcutaneous soft tissues. Throughout this thesis, the subcutaneous soft tissues have been modelled as one bulk tissue. In actuality, the subcutaneous soft tissue comprises two distinct layers: the macrochamber layer and the microchamber layer. Each of these layers has its own distinct mechanical properties and perform different functional roles within the foot. Future research simulating the mechanical behaviour of the microchamber and macrochamber layers has the potential to further explain and expand on the physical meaning of the measurement of Shore hardness when being used as a method to assess changes in the mechanical properties of the plantar soft tissues of the foot.

Throughout this thesis, the use of FEA has been used to investigate a number of different scenarios. FEA has been a powerful tool to allow for the effect of indenter size on indentation to be investigated and has provided initial insight into this relationship.

Further research is required however, to understand how these results relate in vivo to the plantar soft tissues of the heel pad. Specifically, the effect of the geometry of the underlying heel pad structure on indentation needs exploring. Combining in vivo imaging techniques, such as ultrasound, to capture the shape of the calcaneus and the thickness of the heel pad, and the thickness of the skin with FEA may advance the understanding of indentation within a layered structure. Through iterative FEA and in vivo testing, there may even be the opportunity to develop a model of the heel pad that can directly calculate the mechanical properties of the constituent layers based on indentation testing using a simple system of different sized indenters. This would greatly increase the potential clinical use of mechanical properties of plantar soft tissue as a method to prevent diabetic foot ulceration.

Finally, regarding the prediction of changes in plantar pressure, whilst the tests and methodologies appear to be viable within a clinical setting, the applicability of the model and the accuracy of the model to predict these changes need to be assessed. Therefore, this would require a large-scale clinical trial.

Additionally, a larger-scale clinical trial may also provide more information for a model to predict the changes in plantar pressures at the forefoot and heel based on forefoot and ankle range of motion. This may enable additional variables such as foot deformities to be included within the models and more specific experimental methodologies to look at the involvement of the talonavicular joint in dorsiflexion. The addition of these

variables may aid to explain more of the variance, providing potentially more accurate predictions of changes in plantar pressure.

6.6. Conclusion

The primary objective of this research was to investigate if the measurement of Shore hardness can be used to assess the mechanical properties of the plantar soft tissues of the foot and the plantar pressures experienced during gait.

To the investigator's knowledge, the investigation into the use of Shore hardness as a method to assess the mechanical properties of the plantar soft tissues of the foot has not been carried out before

Following the various studies carried out as part of this PhD thesis, it can be concluded that.

- The measurement of Shore hardness offers an assessment of stiffness that is a combination of both the mechanical behaviour of the skin and the underlying subcutaneous tissue
- The measurement of Shore hardness is unable to differentiate between the stiffness of skin and the subcutaneous tissue
- The clinical relevance of Shore hardness was shown through confirming its correlations with loading and blood biochemistry which were found to be associated with tissue stiffness in previous literature

- The measurement of indentation using a small indenter (<6mm diameter) is not a measurement of skin mechanical properties only
- The measurement of indentation using a large indenter (>6mm diameter) is not a measurement of subcutaneous soft tissue only.
- It may be possible to assess and infer changes in the mechanical properties of the skin or subcutaneous soft tissue directly through the use of different sizes of indenters
- Changes in regional plantar pressures can be predicted using the measurement of Shore hardness and 2D multisegmented range of motion analysis

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