Stiffness of Intrinsic Foot Structures in Diabetic Individuals

and the Effect of Stiffness on Plantar Pressures During Gait

by

Erica A. Bell

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Director of Dissertation: Zachary J. Domire

Department of Kinesiology

Abstract

Plantar foot ulcers are a severe and common complication associated with diabetes that overwhelmingly lead to non-traumatic major amputations among diabetic individuals. There are several known factors that contribute to the development of these ulcers, however it is possible that stiffening of foot structures (i.e. muscles, tendons, ligaments) is another important factor that has yet to be fully investigated. Increased soft tissue stiffness on the plantar surface of the foot has been found in diabetic individuals, but stiffness of individual foot structures has yet to be investigated. It has been proposed in literature that stiffening of muscles and tendons in diabetic feet cause increased plantar pressures, which often precede development of ulcers. However, to date, no study has comprehensively examined stiffness of individual foot structures in diabetic individuals and the effect of stiffness on plantar pressures during gait. Therefore, the ultimate purpose of the following work was to investigate the relationship between foot structure stiffness and plantar pressures during gait in diabetic individuals. Firstly, it was hypothesized that stiffness of foot structures would be directly and linearly related to plantar pressures during gait.

Secondly, it was hypothesized that diabetics would exhibit higher stiffness and higher plantar pressures than controls.

There is also evidence of structural changes in the diabetic foot compared to controls, including thickening of the plantar fascia (PF) and Achilles tendon. Plantar fasciitis is a common musculoskeletal disorder that, like diabetes, is associated with thickening of the PF. To date, few studies have investigated material properties of the PF, and there are currently no studies that have assessed material properties of other arch supporting structures (i.e. muscles, tendons) . It is possible that, in addition to thickening of the PF, plantar fasciitis populations exhibit material property changes of the PF and other arch supporting structures that contribute to the plantar fasciitis injury mechanism. Investigating material properties of the PF and arch supporting structures and how these properties relate to plantar pressures in individuals with plantar fasciitis may help provide relevant information to injury development in the foot in plantar fasciitis and diabetic populations. Therefore, material properties of foot structures and plantar pressures during gait were also assessed in individuals with plantar fasciitis. First, it was hypothesized that individuals with active plantar fasciitis symptoms would exhibit altered stiffness of foot structures compared to controls and individuals with a history of plantar fasciitis who are currently asymptomatic. Secondly, it was hypothesized that stiffness of PF stiffness would inversely and linearly relate to plantar pressures during gait in individuals with plantar fasciitis.

The studies herein provide evidence that: 1) relationships are present between individual foot structures and plantar pressures in diabetic individuals and; 2) individual foot structures exhibited higher stiffness in diabetic individuals for some, but not all examined foot structures

compared to controls. Contrary to the primary hypothesis, the observed relationships were mostly negative, suggesting that lower stiffness of individual foot structures relates to higher pressure. There is evidence that individuals with plantar fasciitis exhibit structural property changes similar to those observed in diabetic individuals, thus material properties of foot structures and their relationships with plantar pressures were also assessed in this population. Interestingly, individuals with plantar fasciitis exhibited mostly positive relationships, which was also contrary to the hypothesis for that population. Although some differential relationships existed within these groups, the diabetic and plantar fasciitis population displayed similar values for proximal plantar fascia stiffness that was negatively correlated with peak pressure under the heel. Structurally, diabetic individuals and individuals with plantar fasciitis similarly displayed decreased thickness of muscles and tendons which is suggestive of weakening and/or damage occurring to these structures. Taken together, these results support the idea of foot structure stiffness relating to plantar pressures and more specifically, are suggestive of damage occurring to the plantar fascia that is directly influencing plantar pressure distributions and foot function in diabetic individuals and individuals with plantar fasciitis. Thus, stiffness may still be an important factor to consider in understanding alterations of foot function and potentially in the ulcer injury mechanism in diabetic individuals.

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Erica A. Bell

APPROVED BY:

DISSERTATION ADVISOR: _____

Zachary J. Domire, PhD

COMMITTEE MEMBER: _____

P. Darrell Neufer, PhD

COMMITTEE MEMBER: _____

John D. Willson, PT, PhD

COMMITTEE MEMBER: _____

Matthew B. McCullough, PhD

COMMITTEE MEMBER: _____

Stacie I. Ringleb, PhD

CHAIR OF THE DEPARTMENT OF KINESIOLOGY:

_____

JoonKoo Yun, PhD

DEAN OF THE GRADUATE SCHOOL:

_____

Paul J. Gemperline, PhD

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Chapter 1

Introduction and Literature Review

Diabetes affects approximately 29 million US adults (aged 20-79 years) (CDCP 2014) and its related complications are the seventh leading cause of death in the United States (CDCP 2014). Plantar foot ulcers are one of the most severe and costly complications commonly associated with diabetes (Barshes et al. 2013, Rice et al. 2014). When left untreated or if these ulcers become infected, amputation becomes a necessary treatment option, leading to approximately 84% of non-traumatic major amputations among diabetics (Pecoraro et al. 1990). These ulcerations affect 15% of diabetics, occur twice as frequently as in non-diabetics, and may have an estimated lifetime incidence as high as 25% (Singh et al. 2005). Thus, there is still a need to better understand the injury mechanism of diabetic foot ulcers to both improve current and develop new prevention interventions and treatment options.

The causes of these plantar foot ulcerations are multifactorial. Known contributing factors to the development of plantar foot ulcers include glycation of soft tissues, increased plantar pressures, peripheral neuropathy, and poor vascular supply (Pai & Ledoux 2010, Gefen 2003). Glycation of soft tissues has been observed in diabetic individuals, which causes an increase in stiffness of these soft tissues, and subsequently impairs their ability to dissipate internal stresses in the diabetic foot, an essential part of healthy locomotion (Gefen 2003). This inability to dissipate internal stresses leads to external stress concentrations (i.e. plantar pressures), and several studies have shown significantly increased plantar pressures in diabetic individuals at various locations under the foot, with few including comparisons to controls (Boulton et al. 1983, Jan et al. 2013, Zou et al. 2007, Sartor et al. 2008, Payne et al. 2002, Veves et al. 1992, Mueller et al. 2008, Abouaesha et al. 2001) (Table 1.1). Abnormal stiffening of foot

soft tissue on the plantar surface of the foot and increased pressures under the foot lead to mechanical trauma/damage occurring to the diabetic foot (Gefen 2003, Pai & Ledoux 2010).

Many diabetic individuals also experience peripheral neuropathy, a common complication associated with diabetes that decreases sensation in the foot, which allows mechanical trauma to occur to the foot unnoticed (Mueller et al. 1990, Reiber et al. 1995, Sumpio 2000) due to the presence of neuropathy inhibiting the ability to sense gait changes that need to be made in order to reduce or stop subsequent mechanical trauma from occurring. Without these necessary gait changes, repetitive mechanical trauma will occur and continue to damage the foot. A normal functioning vascular supply should be able to deliver the nutrients necessary to repair the damage that is occurring to the feet in a timely manner to decrease an accumulation of damage. However, many diabetics exhibit a poor vascular supply, which decreases the body's natural ability to heal the foot (Sumpio 2000) between these occurrences of damage, leading to further injury at the initial injury site. Thus, mechanical trauma continues to occur to the foot in a repetitive fashion, leading to an accumulation of damage, and therefore, it is likely that the mechanical stresses responsible for the accumulation of damage are the most critical and direct cause of plantar ulcers, although the presence of all the aformentioned factors contribute to the development of diabetic foot ulcers.

Table 1.1 Sample comparison of plantar pressure values using pressure insoles from previous literature. All diabetic groups were neuropathic. PP = Peak pressure. PTI = Peak-time integral. Units: PP (kPa), PTI (kPa*s).

	Payne et al. 2002	**Sartor et al. 2008**	
	Diabetic	**Control Diabetic**	**Intervention Diabetic**
PP Heel	216.4 (56.7)	293.6 (68.4)	314.4 (88.0)
PP 1st Met Head/Lateral Forefoot	230.0 (81.9)	297.9 (83.9)	316.8 (79.5)
PP Hallux	178.7 (74.7)	214.8 (69.2)	206.9 (96.8)
PTI Heel	61.8 (26.3)	79.1 (22.3)	81.0 (26.8)
PTI 1st Met Head/Lateral Forefoot	71.1 (33.0)	90.9 (24.6)	92.4 (22.4)
PTI Hallux	43.3 (25.5)	48.6 (22.6)	47.2 (21.4)

Increased plantar pressures are anisotropic in nature (Thomas et al. 2004) and tend to occur in specific locations, as some plantar areas are more prone to ulceration than others (Pai & Ledoux, 2010, Cowley et al. 2008). Common locations that are susceptible to ulceration include the hallux, metatarsal heads, and calcaneus (Pai & Ledoux 2010). Previous studies using finite element modeling have shown increased normal stresses during standing under the first and second metatarsal heads (Gefen 2003) and increased normal and shear stresses at the foot-ground interface in the forefoot during the push-off phase of walking (Thomas et al. 2004) in diabetic individuals compared to controls. Increased peak stress has also been found in diabetic individuals compared to controls in five common ulceration sites (hallux, first, third, and fifth metatarsal heads, and calcaneus) and in the lateral midfoot (Pai & Ledoux 2010).

Increased plantar pressures often precede ulceration in diabetic individuals. 35% of diabetic individuals with abnormally high plantar pressures eventually developed plantar foot ulcers in a prospective study (Veves et al. 1992). Increased pressures have been shown to be related to previous foot ulcer sites in diabetic individuals with and without peripheral neuropathy (Jan et al. 2013, Pai & Ledoux 2010, Gefen et al. 2001, Klaesner et al. 2002, Zheng et al. 2000), and plantar areas with the highest peak plantar pressures have been found to be strongly

correlated with diabetic foot ulcer development sites during walking (Thomas et al. 2004, Robertson et al. 2002, Armstrong et al. 1998). These increased pressures have been observed in Type 1 and Type 2 individuals (D'Ambrogi et al. 2003, D'Ambrogi et al. 2005, Giacomozzi et al. 2005, Abouaesha et al. 2001, Craig et al. 2008). Although weight and BMI are typically elevated in diabetic individuals compared to non-diabetic individuals, increased pressures cannot be simply explained by increased weight as they have been shown to not be related to BMI (Abouaesha et al. 2001). Thus, it is important to better understand what causes these increased pressures in diabetic individuals and how altered properties of plantar soft tissue relate to increased pressures, as it has been suggested that peak plantar pressures alone are not enough to predict development of skin breakdown (potential ulcer development) (Lavery et al. 2003, Jan et al. 2013, Mueller et al. 2005). However, the direct cause of these increased pressures in diabetics is still largely unknown.

Instead, it has been proposed that these high pressures in diabetic individuals are related to altered properties of plantar soft tissue (Abouaesha et al. 2001). Structural properties of the soft tissue of the sole of the foot (Robertson et al. 2002) and intrinsic foot muscles (Robertson et al. 2002, Cheuy et al. 2013, Greenman et al. 2005) are altered in diabetic individuals compared to controls across the span of the foot. Specifically, compared to controls, diabetics exhibit decreased plantar muscle density (Robertson et al. 2002, Cheuy et al. 2013, Greenman et al. 2005), decreased lean muscle mass (Cheuy et al. 2013), and increased intramuscular fatty infiltration (Cheuy et al. 2013) in foot musculature. These changes have been shown in individuals with (Robertson et al. 2002, Cheuy et al. 2013, Greenman et al. 2005) and without peripheral neuropathy (Robertson et al. 2002, Greenman et al. 2005). These findings

demonstrate geometric and compositional changes in diabetic muscular tissue that could indicate changes in material properties and function of muscles in diabetic feet.

Stiffness describes how much a material or an object deforms in response to the amount of force applied and is derived from the linear relationship between stress and strain. Stress is defined as force normalized to the amount of material, given by the equation:

$$\sigma = F/A$$

where σ is stress, F is the internal force, and A is the cross-sectional area at the analysis plane. Measures of stress take out the effect of the size and shape of a material, allowing a pure measure of the quality of the material that effectively measures the matter that composes the material. Strain is defined as normalized deformation given by the equation:

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

where ε is strain, ΔL is change in length, and L is the original length. Strain is effectively the percent change in length from the original length of a material.

The stress-strain curve for all materials has an elastic region where stress and strain exhibit a linear relationship, and the slope of this line gives a measure of the stiffness of the material, known as the Young's Modulus. Stiffer materials have steeper slopes, and thus a high Young's modulus. Less stiff materials have flatter slopes, and thus a lower Young's modulus. Similarly, modulus of materials can be described by shear modulus, which relates shear stress to shear strain. It describes how much a material or object deforms in response to shear stress (force applied parallel to the surface). Shear modulus can also be used to describe the elastic modulus (stiffness) of biological tissues and directly relates to Young's modulus with the equation:

$$E \cong 3G$$

where E=Young's modulus, G= shear modulus (Prado-Costa et al. 2018). The stiffness of a material influences its function and level of deformation before reaching its points of irreversible damage and failure. Thus, increased stiffness of soft tissue is important because this altered stiffness of the soft tissue will ultimately influence its function and its ability to withstand load without incurring damage.

Subsequent to physiological and structural changes in the diabetic foot, altered material properties of the soft tissue at the plantar surface of the foot are related to plantar pressures and previous foot ulcer sites in diabetic individuals (Jan et al. 2013, Pai & Ledoux 2010, Gefen et al. 2001, Klaesner et al. 2002, Zheng et al. 2000). One study found altered in vivo biomechanical properties that were related to plantar pressure distributions of the plantar soft tissue in diabetics with peripheral neuropathy (Jan et al. 2013). Specifically, it was found that peak pressure gradient, defined as the rate of spatial changes at the peak plantar pressure site, was positively related to the soft tissue thickness, viscoelasticity, and stiffness (measured by the effective Young's modulus) under the first metatarsal head using the ultrasound indentation method, which measures force-deformation responses of soft tissues in vivo (Jan et al. 2013). Pai & Ledoux (2010) extracted plantar soft tissue from beneath the foot at commonly susceptible ulceration sites (hallux, first, third, and fifth metatarsal heads, and calcaneus) and performed material testing of the extracted tissue with compression loading at multiple loads and frequencies. Increased peak stress was found in the plantar soft tissue of the diabetic cadavers compared to controls in plantar soft tissue, but the increased stress was not accompanied by an increase in strain, indicated by the significantly increased modulus (stiffness) observed in

diabetics compared to controls. This observation of increased stiffness is consistent with studies using living subjects which have also shown increased stiffness of soft tissue at the plantar surface of the foot under the first metatarsal head (Gefen et al. 2001, Klaesner et al. 2002, Zheng et al. 2000).

Gefen (2003) simulated the effects of a progression of increased severity of stiffening of the plantar pad, related to hyperglycemia experienced by diabetics. A "tissue stiffness ratio", κ, was defined by the following equation:

$$\kappa = \sigma_d(\varepsilon) / \sigma_n(\varepsilon)$$

where $\sigma_d(\varepsilon)$= diabetic plantar tissue stress-strain relation and $\sigma_n(\varepsilon)$= normal stress-strain relation (Gefen 2003). Within this progression, increased values of κ, indicate stiffening of the diabetic plantar pad by progressive glycation. As stiffness severity increased, it was estimated that peak forefoot contact may increase by 38 and 50% for tissue under the first and second metatarsal heads, respectively (Gefen 2003). Furthermore, the increase in averaged internal stresses may rise by 82 and 307% for tissue under the first and second met heads, respectively (Gefen 2003). Increased stiffness results in rigid structures with decreased ability to disperse forces evenly throughout deformation (Gefen 2003). This increased stiffness may lead to stress concentrations, or areas of increased plantar pressure, which may ultimately form an ulcer. Thus, it has been proposed that the abnormally high plantar pressures observed in diabetics are a result of altered material properties, which cause stiffening of foot tissue at the plantar surface of the foot, decreased plantar pressure distribution evenly across the sole of the foot, eventually leading to ulcer development (Gefen 2003, Jan et al. 2013, Klaesner et al. 2002, Zheng et al. 2000). However, stiffness of individual foot structures (i.e. muscles, tendons, ligaments) remains an

important factor in the development of diabetic foot ulcers that has not been thoroughly investigated.

It was hypothesized that limited joint mobility in diabetic feet is due to stiffened plantar muscles and tendons, and therefore, these stiffer muscles and tendons are related to increased pressures (Caravaggi et al. 2016, Fernando et al. 1991, Mueller et al. 2003, Zimny et al. 2004).The foot has 33 joints that, under normal conditions, are highly mobile, due to foot muscles and structures (Lundgren et al. 2008, Caravaggi et al. 2016). Intrinsic foot muscles are important for safe ambulation, standing balance, stabilizing the foot and arch (Mickle et al. 2013), and can have significant effects on stiffness and function of the longitudinal arch (Hashimoto & Sakuraba 2014, Wong 2007, Fiolkowski et al. 2003) and center of pressure under single and double leg stance loads (Kelly et al. 2012, Kelly et al. 2013). Abnormal stiffening of foot muscles and tendons therefore could alter the normal foot function of the diabetic foot. Because foot musculature can have significant impacts locally and on overall foot function, it is important to explore and better understand changes in both the material and structural properties of individual foot structures (i.e. muscles, tendons, ligaments) in diabetics and how they may potentially impact plantar pressures and ulcer development.

Structural changes do not only occur in intrinsic foot musculature, but also in connective tissue, like the plantar fascia and Achilles tendon in diabetic individuals compared to controls. Several studies have observed increased thickening of the plantar fascia (D'Ambrogi et al. 2003, D'Ambrogi et al. 2005, Ursini et al. 2017, Craig et al. 2008, Giacomozzi et al. 2005, Duffin et al. 2002, Abate et al. 2012) and the Achilles tendon (D'Ambrogi et al. 2005, Giacomozzi et al.

2005, Abate et al. 2012) in diabetic individuals compared to controls. Furthermore, many of these studies have suggested that plantar fascia and Achilles tendon thickness is related to altered force loading under the foot (D'Ambrogi et al. 2003, Giacomozzi et al. 2005,) and that plantar fascia thickness is related to increased plantar pressures in diabetic individuals (Craig et al. 2008).

A musculoskeletal clinical population may more readily exhibit changes in soft tissue similar to those observed in diabetic individuals. Plantar fasciitis is a common musculoskeletal disorder that, like diabetes, is associated with thickening of the plantar fascia in both the symptomatic and asymptomatic limbs (Granado et al. 2018, Tsai et al. 2000, Ermutlu et al. 2018, McMillan et al. 2009), which has been suggested to be related to regional loading (Wearing et al. 2007). However, literature rarely reports occurrence of plantar fasciitis in diabetic individuals, as only one study investigating risk factors for plantar fasciitis included diabetes as part of the medical history screening (Werner et al. 2010). It is very likely that these changes in thickness are accompanied by changes in material properties that have yet to be investigated in both plantar fasciitis and diabetic populations. Investigating differences between diabetic individuals and plantar fasciitis patients, in addition to healthy controls, would give further insight into the effect these structural changes have on foot function when compared to another clinical population that exhibits similarly altered structural properties to the diabetic population.

Some studies have attempted to address plantar pressure and PF stiffness independently in plantar fasciitis populations, but results have been conflicting. Some report increased plantar pressures (Kelly et al. 1995) and vertical ground reaction forces (Werner et al. 2010) in

individuals with plantar fasciitis, while others support decreases (Sullivan et al. 2015, Yoo et al. 2017) or no differences (Hsu et al. 2013, Kanatli et al. 2001) in the affected limb. Other studies report differential loading across the forefoot, midfoot, and hindfoot in individuals with plantar fasciitis (Bedi & Love 1998, Wearing et al. 2002, Wearing et al. 2003). Stiffness of the plantar fascia in individuals with plantar fasciitis remains a new area of exploration. Few studies have assessed material properties of the PF and have found decreased stiffness compared to controls using both compression (Sconfienza et al. 2013, Wu et al. 2011, Wu et al. 2015, Lee et al. 2014) and shear wave elastography (Gatz et al. 2019). Evidence of decreased PF stiffness in individuals with plantar fasciitis led us to the hypothesis that lower stiffness is indicative of damage occurring to the PF in plantar fasciitis populations.

To date, material property measures of foot structures aside from the PF have yet to be investigated in individuals with plantar fasciitis. It is possible that the plantar fasciitis population exhibits material and structural property changes in foot musculature in addition to the PF. The observed thickening of the PF in individuals with plantar fasciitis and diabetic individuals may be related to changes in material properties of the PF, which may in turn be related to plantar pressures, and thereby contribute to injury development. Investigating the alterations of structural and material properties, as well as the role stiffness plays in foot function in another clinical population may provide valuable insight into the ulcer injury mechanism that may not otherwise be possible with sole comparison to control, non-diabetic individuals.

Diabetic foot ulcers start with intrinsic damage that eventually works its way to the outer surface of the foot, yet many studies focus on more external measures of foot soft tissue at the

surface of the foot to predict ulcer development. Most studies that have assessed stiffness of plantar tissues in diabetics have used cadaveric values for material properties or indentation methods to infer stiffness (Gefen et al. 2001, Jan et al. 2013, Klaesner et al. 2002, Pai & Ledoux 2010, Zheng et al. 2000) and have small sample sizes (Gefen et al. 2001, Jan et al. 2013, Pai & Ledoux 2010, Zheng et al. 2000). Few studies have assessed multiple sites known to be susceptible to ulceration (Gefen 2003, Pai & Ledoux 2010, Zheng et al. 2000) and, to our knowledge, only one study included both experimental plantar pressure measures and stiffness measures in living participants (Jan et al. 2013). In addition, few studies have directly examined material properties of plantar soft tissue in diabetic feet (Pai & Ledoux 2012, Pai & Ledoux 2010), but these were done using cadavers.

Although internal stress cannot be measured in vivo, structural and material properties can. Ultrasound has recently been shown to reliably measure muscle tissue in the foot (Mickle et al. 2013, Crofts et al. 2014). Ultrasound elastography is an innovative imaging technology that can be used to non-invasively examine tissue material properties in vivo by exerting a focused ultrasound pulse that induces tissue deformation. This method uses standard B-mode imaging to visualize the motion of shear waves through a tissue and then calculates a quantitative measure of the tissue material properties based on the mechanics of the wave propagation. The shear modulus (μ) of the muscle is calculated as

$$\mu = f^2.\lambda^2.\rho$$

where f = frequency, λ = wavelength, and ρ = tissue density. Shear modulus is linearly related to Young's modulus and both measures have been used to describe elastic modulus of materials (Eby et al. 2013, Chino et al. 2012). Elastography was originally developed to detect non-

uniformity in tissue (Ophir et al. 1991). However, it has been shown to be sensitive enough to measure muscle material property changes resulting from a variety of pathological conditions (Ringleb et al. 2007), in aging (Domire et al 2009), and to measure differences in material properties of foot soft tissues between different groups of runners (Bell et al. 2013).

Ultrasound elastography has been shown to be a valid (Eby et al. 2013, Chino et al. 2012), reliable (Chino et al. 2012), and repeatable (Bell et al. 2014) method for assessing muscle stiffness (Table 1.2). Modulus, a measure of tissue material properties indicating stiffness, is the quantitative output of ultrasound elastography measures. It has been used to show increases in strength in response to loading, mostly in tendons (Heinemeier & Kjaer 2011, Reeves et al 2003, Seynnes et al 2009), and is an especially useful indicator of strength in the absence of hypertrophy (Reeves et al 2003, Seynnes et al 2009). The foot returns between 8% and 17% of the mechanical energy required for one stride via passive mechanisms alone (Ker et al 1987, Stearne et al 2016), and intrinsic foot muscles contribute to this mechanical energy, acting in parallel with the PF to stiffen the longitudinal arch in response to load (Kelly et al 2012, Kelly et al 2014, Kelly et al 2015). Thus, passive measures of material properties of individual foot structures (i.e. muscles, tendons, ligaments) will provide relevant and meaningful information pertaining to understanding the individual contributions of foot structures to the foot's overall mechanical response to loading. Proximity of the foot structures to the surface of the skin make ultrasound elastography a feasible and convenient option to measure stiffness for the purposes of the subsequent studies.

Table 1.2 Reliability values of a selected, representative intrinsic muscle of the foot, the flexor hallucis brevis, from previous work (Bell et al. 2013).

	ICC	SEM
Volume	0.97	1.55 cm^3
Thickness	0.99	1.00 cm
Stiffness	0.86	4.67 kPa

To our knowledge, there have been no studies that have made subject-specific measures of material properties of individual foot structures (i.e. muscles, tendons, ligaments) in the diabetic foot. The presented findings, along with gaps in current literature, suggest a need to isolate the link between foot structure stiffness and plantar pressures. Several studies suggest a relationship between these measures, but a study comprehensive enough to make a direct connection has yet to be done. Foot muscles, tendons, and ligaments are important for proper foot function and local changes in these structures can have great impacts on overall foot function in response to loading during stance and gait (Gefen et al. 2001, Kelly et al. 2013, Mickle et al. 2013). Therefore, it is important to understand the separate contributions individual foot muscles, tendons, and ligaments have to overall foot function and what effect stiffening of these structures can have on foot function. The results of this work will add important knowledge to current literature to better understand how foot ulcers develop to potentially lead to targeting prevention interventions and treatments options for diabetics suffering from ulcer risk.

Therefore, the ultimate purpose of the following studies is to investigate the relationship between foot structure (i.e. muscles, tendons, and ligaments) stiffness and plantar pressures during gait in diabetic individuals. Firstly, it was hypothesized that stiffness of foot structures

will be directly and linearly related to plantar pressures during gait. Secondly, it was hypothesized that diabetics will exhibit higher stiffness and higher plantar pressures compared to controls. Although individuals with diabetes and plantar fasciitis have both been shown to have increased thickness of the PF and Achilles tendon compared to controls, it is expected that these groups will have opposite changes in material properties. Diabetic individuals have been shown to have increased stiffness of soft tissues at the plantar surface of the foot compared to controls, while individuals with plantar fasciitis have been shown to have decreased stiffness of the PF compared to controls using compression and shear wave elastography. Thus, we believe stiffer structures in diabetic individuals will relate to higher pressure, while decreased stiffness of the PF in individuals with plantar fasciitis is indicative of damage that will relate to lower stiffness. Thus, structural and material properties will be compared between diabetic individuals and individuals with plantar fasciitis.

If stiffness alters plantar pressures in both the higher and lower directions in these two populations, it would be beneficial to examine how stiffness is related to pressure outside of the disease states. Comparison to another clinical population could provide valuable insight into the alterations of properties of foot structures, their effect on plantar pressures, and potentially the ulcer injury mechanism that is otherwise unattainable by sole comparison to non-diabetic controls. The following experiments will test this hypothesis with experimental measures of material and structural properties of foot musculature and connective tissue using ultrasound technology in addition to plantar pressure mapping.

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Chapter 2

Material Properties of Individual Foot Structures in Diabetic Individuals

Abstract

Plantar foot ulcers are a severe complication associated with diabetes that, subsequent to physiological changes, are often preceded by increased plantar pressures. However, it remains unknown why plantar pressures are elevated in diabetic individuals. Increased soft tissue stiffness has been found in living and cadaveric diabetic foot soft tissue and related to commonly susceptible ulcer locations as well as previous ulcer sites in diabetic individuals. Stiffening of muscle and tendons has also been suggested to be related to decreased mobility and function in the diabetic foot. Thus, stiffness of foot soft tissue has been suggested to be related to these increased pressures which may play an important role in ulcer development. To date, no studies have made subject-specific measures of material properties of multiple individual plantar structures (muscles, tendons, ligaments) in the diabetic foot of living individuals. Thus, the purpose of this study was to measure material properties (modulus) and structural properties of intrinsic foot structures in diabetic and non-diabetic individuals. It was hypothesized that diabetic individuals will exhibit higher modulus (stiffness) and greater thickness of plantar musculature and connective tissue than non-diabetic individuals and that HbA1c levels will positively correlate with stiffness across all participants, suggesting that glycemic control influences severity of stiffness.

Bilateral ultrasound scans were performed on 15 individuals with diabetes (Type 1 n=7 , Type 2 n= 8) and 10 healthy controls. Longitudinal material stiffness was assessed and quantified with shear modulus using ultrasound SWE. Thickness was assessed for each structure using standard B-mode ultrasound. No significant differences in stiffness were found between diabetics and controls, but diabetic individuals exhibited high variability in stiffness. Diabetic

individuals exhibited greater thickness of the heel pad, while thinner muscles and tendons, particularly the flexor hallucis brevis, were found compared to controls. HbA1c levels were not significantly related to stiffness in control or diabetic individuals, nor to thickness of intrinsic foot structures in diabetic individuals. While there was not a group effect, findings of high stiffness in select diabetic individuals suggests that stiffness could still be a variable to explain increased pressures. Evidence of increased stiffness and altered thickness of individual intrinsic foot structures in some diabetic individuals may indicate altered foot function that could potentially contribute to increased plantar pressures and subsequent ulcer development.

Introduction

Plantar foot ulcers are a severe and costly complication associated with diabetes (Barshes et al. 2013), and lead to approximately 84% of non-traumatic major amputations among diabetics (Pecoraro et al. 1990). The cause of these plantar foot ulcers is multifactorial, including peripheral neuropathy decreasing sensation in the foot, a poor vascular supply that decreases the ability to heal, increased pressures, and repetitive mechanical trauma that occur to the foot unnoticed (Pai & Ledoux 2010). However, it is currently unknown what causes plantar pressures to be elevated in diabetic individuals.

In addition to physiological changes, mechanical property changes were found in plantar soft tissue in diabetics that may be related to these increased pressures and ulcers. Glycation of proteins has been observed in diabetic individuals and is believed to increase soft tissue stiffness (Gefen 2003, Pai & Ledoux 2010). Increased soft tissue stiffness would produce a more rigid structure, impairing the ability to adequately dissipate internal stress evenly throughout normal tissue deformation (Gefen 2003), leading to external stress concentrations (i.e. increased plantar pressures). Increased stiffness of soft tissue has been found in diabetics compared to controls in living participants (Gefen et al. 2001, Jan et al. 2013, Klaesner et al. 2002, Zheng et al. 2000), in commonly susceptible ulcer locations in diabetic cadavers (Pai & Ledoux 2010), and in diabetics with peripheral neuropathy and a history of plantar ulcers (Klaesner et al. 2002). Therefore, these changes to foot soft tissue have been proposed to play an important role in the ulcer injury mechanism (Gefen 2003, Pai & Ledoux 2010) as increased stiffness of soft tissue may be another critical factor in the development of plantar ulcers in diabetics that has yet to be thoroughly investigated.

Typically, the foot is highly mobile due to contributions from intrinsic foot muscles and structures (Lundgren et al. 2008, Caravaggi et al. 2016). These structures are important for safe ambulation, standing balance, and stabilizing the foot and arch (Mickle et al. 2013). They can have significant effects on stiffness and function of the longitudinal arch (Hashimoto & Sakuraba 2014, Wong 2007, Fiolkowski et al. 2003) and center of pressure under single and double leg stance loads (Kelly et al. 2012, Kelly et al. 2013). In addition to mechanical property changes, the plantar fascia and Achilles tendon is thicker in diabetics compared to controls (D'Ambrogi et al. 2003, D'Ambrogi et al. 2005, Ursini et al. 2017, Giacomozzi et al. 2005). Because these structures can have significant impacts on foot function, it is important to explore and better understand changes in tissue properties of individual intrinsic foot structures in diabetics.

Several studies have used cadaveric values for material properties or indentation methods to infer stiffness in diabetics (Gefen et al. 2001, Jan et al. 2013, Klaesner et al. 2002, Pai & Ledoux 2010, Zheng et al. 2000), but have small sample sizes (Gefen et al. 2001, Jan et al. 2013, Pai & Ledoux 2010, Zheng et al. 2000). The few studies that have directly examined material properties of soft tissue in diabetic feet used cadavers (Pai & Ledoux 2012, Pai & Ledoux 2010). To date, no studies have made subject-specific measures of material properties of multiple individual plantar structures (muscles, tendons, ligaments) in the diabetic foot of living individuals. Unlike indentation methods, ultrasound shear wave elastography (SWE) is an innovative imaging technology that allows the unique ability to non-invasively measure real-time subject-specific material properties (modulus) of individual soft tissue structures in-vivo.

Therefore, the purpose of the present study is to measure material properties (modulus) and structural properties of intrinsic foot structures in diabetic and non-diabetic individuals. First, it is hypothesized that diabetic individuals will exhibit higher modulus (stiffness) and greater thickness of plantar musculature and connective tissue than non-diabetic individuals. Second, it is hypothesized that HbA1c levels will positively correlate with stiffness across all participants, suggesting that glycemic control influences severity of stiffness.

Methods

Fifteen individuals with diabetes (Type 1 n=7 , Type 2 n= 8) and 10 healthy controls participated in this study (N=25). Individuals with previous foot surgery, diagnosed osteoarthritis, gross foot deformities that affect walking ability, edema, previous foot amputations/major surgeries, current plantar fasciitis, a current foot ulcer, or a wound history ≤ 3 months were excluded from study participation [similar to exclusion criteria from (Jan et al. 2013)]. Individuals were identified as diabetic upon previous diagnosis by a clinician and confirmed with an HbA1c level ≥6.5% according to the most recent guidelines of the American Diabetic Association (2015) using the A1CNow+ system (Bayer Healthcare, US) at the time of study participation. The A1CNow+ system has been validated as an accurate, precise, and easy to use HbA1C testing system (Bode et al. 2007, Knaebel et al. 2013). All participants provided written informed consent and all procedures were approved by the East Carolina University Institutional Review Board.

Controls were matched by physical activity levels with diabetic individuals using the International Physical Activity Questionnaire (IPAQ) short form. The IPAQ is a questionnaire

that allows self-reporting of physical activity over the previous seven days. It has been proven to be a valid tool to assess physical activity levels in adults in multiple countries, including the United States (Craig et al. 2003). Individuals report physical activity participation in terms of days, hours, and minutes involved in activities of vigorous intensity, moderate intensity, and walking, as well as hours and minutes sitting per day. Based on responses, the IPAQ scoring system rates the individual as having a high, moderate, or low physical activity level. Control participants were recruited to match the distribution of diabetic participants within these three categories (Table 2.1).

Bilateral ultrasound scans were performed on each participant while lying prone, in a relaxed position, on an examination table with their feet hanging just slightly off the end for the entirety of the scanning protocol. All images were taken in the longitudinal view. Structures measured included the plantar fascia (PF), flexor hallucis brevis muscle (FHB), abductor hallucis muscle (AHB) and tendon (AHT), Achilles tendon (AchT), and the heel pad (HP). The FHB has been shown to be a substantial contributor to foot posture (Angin et al. 2018) and increase medial longitudinal arch height along with other intrinsic flexor muscles following a strengthening intervention (Hashimoto & Sakuraba 2014). The ABH has previously been shown to act as a dynamic elevator (Wong 2007), support the medial longitudinal arch (Fiolkowski et al. 2003) and help maintain medio-lateral balance in quiet and single leg standing (Kelly et al. 2012). These structures were examined due to the contributions of these structures to the function of the longitudinal arch and ease of measurement. The HP was examined due to previous findings of altered mechanical properties in diabetics, particularly increased stiffness compared to controls (Pai & Ledoux 2010, Ledoux et al. 2016, Chatzistergos et al. 2014). The

AchT was also examined because it is typically evaluated and included in standard clinical foot examinations (Johnson et al. 2018, Boulton et al. 2008) and previous evidence of increased thickness in diabetic individuals (Duffin et al. 2002, Giacomozzi et al. 2005, Abate et al. 2012).

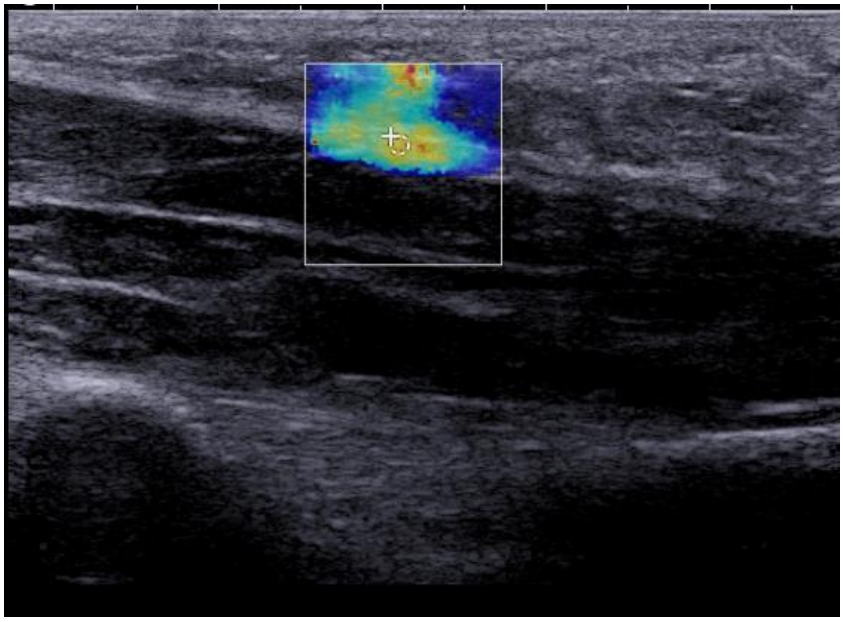
Table 2.1 Subject group demographics including IPAQ scores. Significance indicated by bold font and * ($p \leq 0.05$). Trends indicated by † ($0.05 < p \leq 0.10$).

Demographics	**Control**	**Diabetic**	**p**
N	10	15	-
Sex	2M/8F	2M/13F	-
Age (yrs)	36.0 (7.9)	35.9 (11.0)	0.99
Height (cm)	166.0 (8.9)	165.1 (13.2)	0.86
Weight (kg)	70.2 (12.3)	87.9 (19.8)	**0.019***
BMI (kg/m^2)	25.30 (3.1)	32.3 (6.1)	**0.003***
Fasted Blood Glucose (mg/dL)	91 (29.3)	146 (57.5)	**0.020***
HbA1c	4.7 (0.5)	6.9 (1.5)	**0.001***
Years with Diabetes	-	9.4 (9.5)	
IPAQ Scores			
High	5	5	-
Moderate	4	6	-
Low	1	4	-
Total MET Minutes	3148 (1782)	2524 (2918)	0.55

Longitudinal material stiffness was assessed and quantified with shear modulus using SWE taken on an Aixplorer ultrasound system (SuperSonic Imagine, Aix-en-Provence, France). The plantar fascia was assessed in two regions because of previous findings of significant site-dependent differences in stiffness along the length of the plantar fascia in healthy and plantar fasciitis populations using SWE (Gatz et al. 2019). The plantar fascia was measured at a proximal and distal site, located at ~50% and ~75% of foot length from the most posterior aspect of the heel, respectively. Shear modulus was determined in a 1 mm circular region of interest placed in the middle of the tissue at each measurement site (Figure 2.1). The mean shear

modulus of three measurements were averaged and reported as longitudinal stiffness for each site.

Figure 2.1 Example elastogram of the proximal plantar fascia site including the 1mm circular region of interest.



Thickness was assessed for each structure using the B-mode portion without the elastography overlay of the acquired elastography images using OsiriX (Pixmeo, Bernex, Switzerland) image processing software. The insertion site of the plantar fascia was measured vertically at the anterior edge of the inferior calcaneal border to the inferior border of the plantar fascia. All other measurements were taken centrally in the tissue, measured vertically, at approximately the same central placement of the elastography region of interest for each structure. The mean thickness of three measurements were averaged and reported for each structure.

Stiffness and thickness between the control and diabetic groups were compared using one-way ANOVAs for all examined structures. The alpha level for significance was set a priori to be 0.05. Trends were reported for values of $p>0.05$ and $p\leq0.10$ (Curran-Everett & Benos 2004). All regression analyses were conducted on averaged left and right foot values of stiffness and thickness for each measured site. To assess influence of diabetic status, stiffness and thickness values were correlated with HbA1c levels. To assess influence of physical activity, stiffness and thickness values were correlated with MET minutes calculated from the IPAQ questionnaire.

Results

Group subject demographics are shown in Table 2.1, including IPAQ scores. For the purposes of the present study, all analyses were between the control group and the diabetic group (as a whole) unless otherwise stated. No statistically significant differences in age nor height were observed between groups. Differences existed between groups in weight, BMI, fasted blood glucose, and HbA1c levels (all $p<0.05$). There was no significant difference between groups for weekly physical activity, reported as total MET minutes, but the diabetic group displayed more variability and less total MET minutes compared to controls (Table 1). Across all participants, no significant differences existed between sides for any of the examined structures, thus values for the left and right foot were both included for all subjects in the analysis.

Stiffness

There were no significant differences in stiffness between the control and diabetic group for any of the examined structures. However, there was a trend for a stiffer distal plantar fascia

(p=0.085) and a less stiff Achilles tendon (p=0.086) in the diabetic group compared to controls. Diabetics exhibited greater stiffness at multiple structures with large variability (Table 2.2). Notably, diabetics exhibited 29.9%, 21.3%, and 9.6% greater stiffness at the distal plantar fascia, proximal plantar fascia, and the heel pad, respectively, however these differences were not statistically significant due to large variability within the diabetic group. Conversely, the examined muscles and tendons were less stiff in diabetics than in controls. The Achilles and abductor hallucis tendons were 17.0% and 9.6% less stiff in the diabetic group compared to controls, respectively, while the flexor hallucis brevis and abductor hallucis muscles were 16.0% and 11.4% less stiff in the diabetic group compared to controls, respectively. Cohen's D effect sizes were calculated for stiffness, the main variable of interest in the present study (Table 2.2). All measured differences exhibited medium effect sizes, except for two structures.

Table 2.2 Comparison of shear modulus between groups. Significance indicated by bold font and * ($p \leq 0.05$). Trends indicated by † ($0.05 < p \leq 0.10$).

Shear modulus (kPa)	Control	Diabetic	p	Effect size
Proximal PF	130.0 (47.0)	161.0 (94.1)	0.18	0.41
Distal PF	72.0 (37.0)	97.2 (56.7)	0.085†	0.53
AHT	310.7 (73.4)	282.4 (74.3)	0.19	0.40
AchT	372.4 (109.2)	314.0 (119.7)	0.086†	0.53
FHB	30.0 (12.7)	25.5 (8.4)	0.145	0.46
AHB	31.1 (11.4)	27.7 (9.5)	0.27	0.34
Heel Pad	22.6 (15.3)	24.8 (25.8)	0.72	0.10

Thickness

Compared to controls, the diabetic group exhibited 12.8% greater thickness at the heel pad (p=0.001) and a thinner flexor hallucis brevis by 8.8% (p=0.014) (Table 3). No trends or other statistically significant differences in thickness were observed between groups for

structures examined in this study (Table 2.3). However, the diabetic group notably had a 9.6% thicker plantar fascia at the insertion site compared to controls.

Table 2.3 Comparison of thickness between groups. Significance indicated by bold font and * ($p \leq 0.05$). Trends indicated by † ($0.05 < p \leq 0.10$).

Thickness (cm)	Control	Diabetic	p
Proximal PF	0.187 (0.033)	0.190 (0.040)	0.78
Distal PF	0.140 (0.030)	0.144 (0.036)	0.69
PF Insertion	0.353 (0.080)	0.389 (0.092)	0.17
AHT	0.298 (0.063)	0.311 (0.075)	0.53
AchT	0.527 (0.078)	0.549 (0.082)	0.36
FHB	1.411 (0.176)	1.293 (0.150)	**0.014***
AHB	1.181 (0.390)	1.192 (0.207)	0.90
Heel Pad	1.317 (0.168)	1.498 (0.176)	**0.001***

Stiffness Correlations

No significant relationships existed between stiffness and HbA1c or stiffness and weekly MET minutes (physical activity) within the diabetic group for any of the examined structures (Table 2.4). However, in the diabetic group, there was a trend for a moderate relationship between Achilles tendon stiffness and MET minutes ($r=-0.45$, $p=0.089$).

Table 2.4 R and p-values of mean stiffness correlations with HbA1c and MET mins in the diabetic group. Significance indicated by bold font and * ($p \leq 0.05$). Trends indicated by † ($0.05 < p \leq 0.10$).

Diabetic	HbA1c		MET mins	
	r	p	r	p
Proximal PF	0.02	0.93	-0.16	0.56
Distal PF	-0.31	0.27	-0.16	0.58
AHT	-0.28	0.31	-0.04	0.88
AchT	0.34	0.21	-0.45	0.089†
FHB	0.17	0.55	-0.03	0.90
AHB	-0.01	0.96	0.13	0.64
Heel Pad	-0.09	0.75	0.40	0.14

Thickness Correlations

No significant relationships existed between thickness and HbA1c or thickness and weekly MET minutes in the diabetic group. (Table 2.5).

Table 2.5 R and p-values of mean thickness with HbA1c and MET mins in the diabetic group. Significance indicated by bold font and * ($p \leq 0.05$). Trends indicated by † ($0.05 < p \leq 0.10$).

Diabetic	**HbA1c**		**MET mins**	
	r	p	r	p
Proximal PF	0.16	0.57	0.23	0.41
Distal PF	-0.20	0.47	0.09	0.76
PF Insertion	0.03	0.92	0.40	0.14
AbHT	-0.02	0.96	-0.40	0.14
AchT	-0.06	0.84	0.13	0.65
FHB	-0.26	0.35	0.04	0.88
ABH	0.10	0.71	-0.35	0.21
Heel Pad	0.00	0.99	-0.33	0.23

Discussion

The purpose of the present study was to measure material properties (modulus) and structural properties of intrinsic foot structures in diabetic and non-diabetic individuals. The results partially supported the original primary hypothesis as diabetic intrinsic foot stiffness was not significantly different from controls. However, diabetic individuals exhibited greater thickness of plantar musculature and connective tissue than controls, but not for all examined structures. The results did not support the original secondary hypothesis as no significant relationships were observed across all participants or within groups between HbA1c levels and stiffness for any of the examined structures.

The present study found increased stiffness of the plantar fascia and heel pad in diabetic feet compared to controls, however these findings were not significant. The proximal plantar fascia, distal plantar fascia, and heel pad exhibited a high variability of stiffness within the diabetic group, as evidenced by the much larger standard deviations and presence of outliers (Figure 2.2),

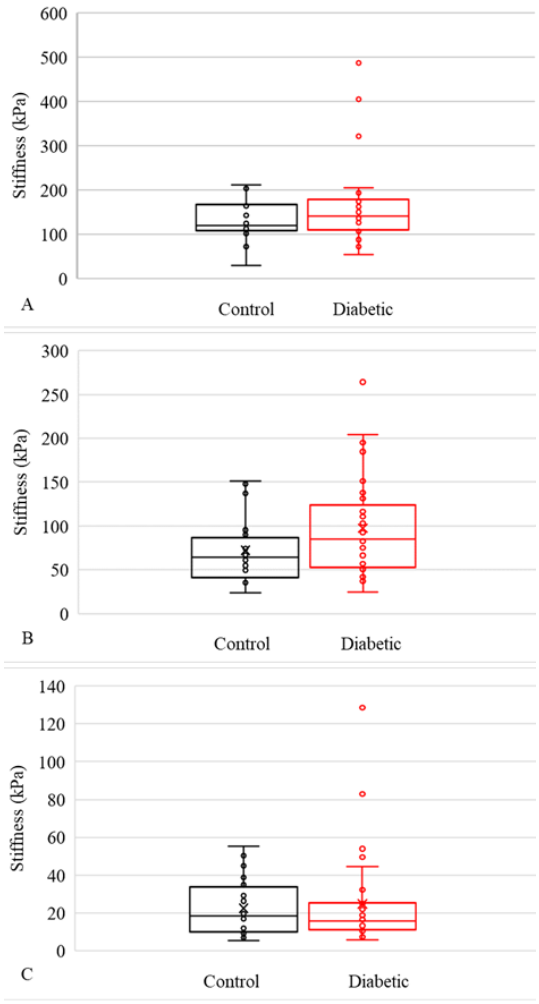
and thus, decreased the significance of these findings. This high variability was unexpected and future studies should consider this in sample size estimations. A post-hoc power analysis was calculated for stiffness, the main variable of interest in the present study (Table 2.6). The muscles and tendons measured in this study were less stiff in diabetics than controls, ranging from 9.5% to 17.0% less stiff. This could potentially indicate weakening, as measures of stiffness with ultrasound SWE has been previously suggested to be an indicator of passive muscle force (muscle tension caused by passive stretching of elastic elements of the muscle) (Sasaki et al. 2014, Koo et al. 2013). This is the first study to directly measure stiffness of multiple intrinsic foot structures with ultrasound SWE in diabetic individuals. However, based on the increased stiffness of the plantar fascia and heel pad which are located close to the plantar surface of the foot, the results of the present study seem to align with previous findings of increased plantar soft tissue stiffness in diabetics using indentation methods and cadavers (Pai & Ledoux 2010, Jan et al. 2013, Klaesner et al. 2002, Zheng et al. 2000, Gefen et al. 2001).

Table 2.6 Post-hoc power analysis for stiffness measures.

	β	N
Proximal PF	0.30	82
Distal PF	0.42	55
AbHT	0.24	107
AchT	0.38	61
FHB	0.28	87
ABH	0.19	148
HP	0.06	1367

Note: The β values were calculated from group means and standard deviations in the present study (N=25). The values in the N column were calculated to predict the sample size needed to reach significance with a large effect (β=0.8).

Figure 2.2 Boxplots of proximal plantar fascia (a), distal plantar fascia (b), and heel pad (c) stiffness.



Increased thickness of the plantar fascia and heel pad were observed in the diabetic group, while the flexor hallucis brevis was found to be thinner compared to controls. The heel pad was found to be significantly thicker in diabetics (by 12.8%), which supports previous findings (Pai & Ledoux 2010, Gooding et al. 1986). The plantar fascia was thicker at the insertion site in the diabetic group by 9.6%. Although this finding was not significant, it supports several previous findings of increased thickness of the plantar fascia in diabetic individuals (D'Ambrogi et al. 2003, D'Ambrogi et al. 2005, Giacomozzi et al. 2005, Abouaesha et al. 2001). In contrast, the flexor hallucis brevis was found to be significantly thinner in diabetic individuals

compared to controls by 8.8%, supporting previous findings of decreased plantar muscle density (Robertson et al. 2002) and intrinsic foot muscle deterioration (Cheuy et al. 2013) in diabetic individuals. More importantly, Cheuy and colleagues (2013) found decreased lean muscle mass and increased intramuscular fat within intrinsic foot muscles in diabetics with peripheral neuropathy. It is possible that our findings of decreased thickness of the flexor hallucis brevis coupled with its decreased stiffness (roughly 16.0% compared to controls) could indicate this compositional change in diabetic muscle tissue, which could have potential impacts on diabetic foot function.

No significant relationships were found between stiffness and HbA1c levels nor between stiffness and physical activity (MET minutes) for the control or diabetic group, for any of the examined structures. In the diabetic group, there was only a trend for a moderate negative relationship with Achilles tendon stiffness and MET minutes ($r=-0.45$, $p=0.089$). Interestingly, the distal plantar fascia and the Achilles tendon were the only two structures with trends for differences in stiffness between the groups and the only two structures to have trending relationships with HbA1c, but only in the control group. It is possible that differences exist among Type 1 and Type 2 diabetics that could explain the lack of relationship for these structures in the diabetic group.

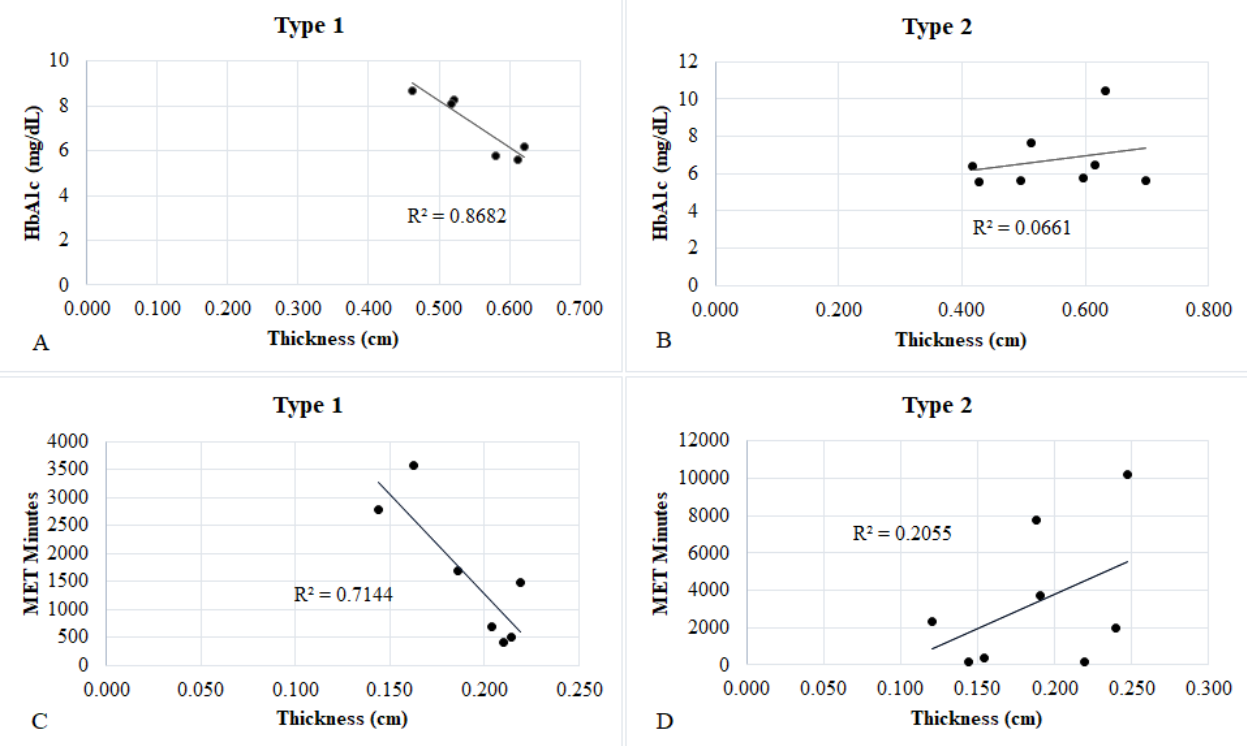
We briefly assessed relationships within the Type 1 and Type 2 diabetic individuals and although few relationships exist, there are drastic differences in the relationships of stiffness with HbA1c and MET minutes among Type 1 and Type 2 diabetics. For example, a strong relationship was observed between abductor hallucis tendon stiffness and MET minutes ($r=0.83$,

p=0.020) in Type 1 individuals that not only is not similarly present in Type 2 individuals (r=-0.211, p=0.62), but is also in the opposite direction. Demographic data for the diabetic group based on type (1 or 2) are displayed in Table 2.7. Similar differences between Type 1 and Type 2 diabetics were observed when assessing thickness relationships with HbA1c and MET minutes (Figure 2.3). Medication is likely to be a confounding variable as its primary job is to help regulate HbA1c levels, thus potentially masking the true severity of HbA1c levels in diabetic individuals and its potential relationships to stiffness and other variables. More work is warranted to better understand why relationships are present in controls, yet lacking in diabetic individuals, as well as the presence of differential relationships in Type 1 and Type 2 diabetics.

Table 2.7 Diabetic group demographics including IPAQ scores. Significance indicated by bold font and * ($p \leq 0.05$). Trends indicated by † ($0.05 < p \leq 0.10$).

Demographics	**Type 1**	**Type 2**	**p**
N	7	8	-
Sex	0M/7F	2M/6F	-
Age (yrs)	27.4 (4.3)	43.4 (9.5)	**0.001***
Height (cm)	158.4 (11.8)	171.0 (12.1)	0.06†
Weight (kg)	78.9 (12.7)	95.8 (22.2)	0.10
BMI (kg/m^2)	31.9 (7.2)	32.6 (5.4)	0.82
Fasted Blood Glucose (mg/dL)	177.0 (61.7)	119.4 (39.7)	**0.048***
HbA1c	7.1 (1.4)	6.7 (1.7)	0.66
Years with Diabetes	13.6 (10.6)	5.3 (6.6)	0.10
IPAQ Scores			
High	1	3	-
Moderate	4	2	-
Low	1	3	-
Total MET Minutes	1584 (1202)	3346 (3761)	0.26

Figure 2.3 Regression analysis comparison of Achilles tendon thickness and HbA1c levels (a, b) and proximal plantar fascia thickness and MET minutes (c, d) in Type 1 and Type 2 diabetic individuals.



In the diabetic group, thickness was not related to HbA1c or MET minutes for any of the examined structures. However, when accounting for diabetic type (1 or 2), strong relationships was observed between HbA1c and Achilles tendon thickness (r=-0.93, p=0.002) and between MET minutes and proximal plantar fascia thickness (r=-0.85, p=0.017) in Type 1 individuals (Figure 2.3). The negative relationships may indicate compositional changes in these structures due to decreased physical activity or presence of neuropathy (Cheuy et al. 2013). In addition, several strong relationships existed within the control group. There was a strong positive relationship between HbA1c and abductor hallucis muscle thickness (r= 0.71) in the control group. Because both stiffness and thickness of the abductor hallucis muscle was not different between groups, it is unclear why this relationship is present in controls but not in diabetic individuals. Although diabetics had lower average weekly MET minutes than controls, there was

no significant difference between groups for physical activity. However, strong positive relationships were observed in the control group for MET minutes with Achilles tendon thickness (r=0.75) and flexor hallucis brevis thickness (r=0.75), as well as a trend for a positive relationship between MET mins and proximal plantar fascia thickness (r=0.59). The positive relationships of MET minutes with these structures in the control group could indicate a training effect, especially the flexor hallucis brevis which was found to be significantly thicker in controls compared to diabetics. Given that muscles and tendons can respond to exercise training with hypertrophy, this relationship is intuitive. However, if atrophy of intrinsic foot muscles is prevalent in individuals with diabetes, especially if it is more pronounced with increased severity of diabetic status (HbA1c levels), weakened structures could be contributing to the increased plantar pressures observed that lead to ulcer development in diabetic individuals. The lack of relationships in the diabetic group for physical activity and muscle/tendon thickness may also indicate an altered response to physical activity in diabetic individuals suggesting an alteration of foot function that should be explored in longitudinal training studies.

One of the primary limitations of this study is that most of the diabetics were very well-regulated (several fell below the recommended cutoff value of 6.5), only three diabetics were neuropathic, and only four diabetics were considered “severe” based on our criteria. Some studies have found differences between diabetics with and without peripheral neuropathy (D’Ambrogi et al. 2003, D’Ambrogi et al. 2005). Inclusion of more diabetic individuals with a “severe” or less-regulated status and/or with peripheral neuropathy would provide a more robust comparison. Another primary limitation of this study is that majority of the participants are female. There are only two males in each group. This happened entirely by chance, as gender

was not a focus of the study nor was it an exclusive criterion. Inclusion of more males would make the results more generalizable and allow for gender comparisons. Lastly, because there were no significant differences between the left and right feet of all participants, and because feet can be affected differently, we treated each foot as independent for the group comparisons of stiffness and thickness. However, we acknowledge that because both feet are within subject, it would also be logical to consider the feet as dependent measures for each subject as bilateral observations from the same subject are likely to be more similar than observations from a different subject (Ranstam 2002, Ranstam 2012). Thus, we also ran the analyses considering the feet as dependent measures for each subject using a Z-factor ANOVA (side x group) for stiffness and thickness of all structures, and only found a trend for a difference in flexor hallucis brevis thickness, which found a thinner muscle in diabetic individuals compared to controls ($p=0.07$), agreeing with our above results from the preferred analysis. No other differences between stiffness or thickness were observed between groups using this method of analysis.

This is the first study to assess multiple intrinsic foot structures in diabetic individuals with ultrasound SWE. High variability of stiffness was measured among diabetic individuals that reduced some of the statistical significance of our findings, although large absolute differences were observed between diabetics and controls. It is possible that there are certain factors that make a diabetic individual more susceptible to increased stiffness than others that we did not address in the present study, as some diabetics have stiffness values similar to controls, while others are drastically increased (up to 200+ difference in kPa). Studies using ultrasound SWE to test for effects of diabetic status (i.e. HbA1c) on material properties of intrinsic foot structures are warranted. Future work should also assess the potential relationships between plantar

pressures and stiffness/thickness of intrinsic foot structures, as this study supports previous work suggesting a link between intrinsic muscle/tendon stiffness and plantar pressures (Caravaggi et al. 2016, Giacomozzi et al. 2008, Mueller et al. 1989, Francia et al. 2015).

In conclusion, the present study did not find any significant differences in stiffness between diabetics and controls, but diabetic individuals exhibit high variability in stiffness. Diabetic individuals exhibited greater thickness of the heel pad, while thinner muscles and tendons, particularly the flexor hallucis brevis, were found compared to controls. HbA1c and physical activity levels do not seem to be significantly related to stiffness in control or diabetic individuals, nor to thickness of intrinsic foot structures in diabetic individuals. However, due to some strong relationships present in controls between thickness and Hba1c as well as thickness and physical activity, it is possible that relationships may exist differentially within the separate populations of control and diabetic individuals, as well as among Type 1 and Type 2 diabetics. Evidence of increased stiffness and altered thickness of individual intrinsic foot structures in diabetic individuals may indicate altered foot function that could potentially contribute to increased plantar pressures and subsequent ulcer development. While there was not a group effect, we did see individuals with high stiffness. Thus, stiffness could still be a variable to explain increased pressures in diabetic individuals and it is important to further investigate and discuss these differences. More work is warranted to establish the role of individual intrinsic foot structures on foot function and ulcer development in diabetic individuals.

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Chapter 3

Relationship between Foot Structure Stiffness and Plantar Pressures in Diabetic Individuals

Abstract

Diabetic foot ulcers remain a problem that affects 15% of diabetic individuals. In addition to many physiological factors, increased plantar pressures contribute to ulcer development, yet the direct cause of these pressure is still largely unknown. There is some evidence that suggests stiffening of foot structures (muscles and tendons) limit joint mobility in the foot and contribute to increased plantar pressures. However, there is no study to date that has directly or comprehensively examined stiffness of foot structures and how it relates to plantar pressure distributions in diabetic individuals. Therefore, the purpose of the present study is to investigate the relationship between stiffness of foot structures and plantar pressures in diabetic individuals. It is first hypothesized that plantar pressures will positively correlate with foot structure stiffness (i.e. higher plantar pressures will coincide with higher stiffness). It is secondly hypothesized that HbA1c levels will positively correlate with stiffness in diabetics, suggesting that glycemic control influences severity of stiffness.

Bilateral SWE measurements of various structures representing the soft tissue types present within the foot (muscle, tendon, ligament, and fat) were measured in 15 diabetic individuals. Bilateral walking plantar pressure data was collected using pressure insoles, which were then analyzed using a custom 10-region mask. Plantar pressure regions of interest included the medial heel, 1st met head, and hallux. Regression analysis was used to assess relationships between stiffness and plantar pressures, stiffness and HbA1c levels, and HbA1c levels and plantar pressures during walking at a self-selected and standard speed. Many relationships were found between foot structure stiffness and plantar pressures. Contrary to the hypothesis, majority of these relationships were negatively correlated, suggesting that higher pressures are related to

less stiff structures. HbA1c does not seem to be significantly related to stiffness or plantar pressures, suggesting that glycemic index alone is not predictive of altered stiffness or plantar pressures in diabetic individuals. The finding of relationships between stiffness and clinical foot measures, suggests that relationships exist between foot structure stiffness and foot function. Evidence of lower stiffness relating to higher pressures suggests weakened or damaged foot structures with a decreased ability to withstand load are present in diabetic individuals, which may contribute to altered foot function that could potentially lead to subsequent ulcer development.

Introduction

Diabetic foot ulcerations affect 3.9 million diabetics (15%) and have an estimated lifetime incidence as high as 6.5 million (25%) (Singh et al. 2005). Many physiological factors contribute to the development of diabetic foot ulcers, including peripheral neuropathy, glycation, and poor blood flow (Pai & Ledoux 2010). In addition, significantly increased plantar pressures has been observed in diabetics compared to non-diabetics (Armstrong et al. 1998, Gefen 2003, Robertson et al. 2002, Thomas et al. 2004), yet the direct cause of these pressures is still unknown.

The observed areas of increased plantar pressure may be caused by stiffening of foot structures. Specifically, a relationship between limited joint mobility and increased plantar pressures in diabetic feet was measured (Caravaggi et al. 2016, Fernando et al. 1991, Mueller et al. 2003, Zimny et al. 2004), suggesting that the limited joint mobility is due to stiffened plantar muscles and tendons and therefore, these stiffer muscles and tendons are related in increased pressures. Increased stiffness of soft tissue has been found in diabetics compared to controls in living participants (Gefen et al. 2001, Jan et al. 2013, Klaesner et al. 2002, Zheng et al. 2000), and in commonly susceptible ulcer locations in diabetic cadavers (Pai & Ledoux 2010). Stiffer plantar tissue has also been found in diabetics with peripheral neuropathy and a history of plantar ulcers (Klaesner et al. 2002). If this stiffness is occurring in soft tissue in the diabetic foot, this may impair foot function and dispersal of forces throughout the foot during stance and gait, possibly leading to areas of increased plantar pressure, which can ultimately form an ulcer. Thus, it is possible that mechanical stresses are likely the more direct cause of ulcer damage initiation.

Most studies that have assessed stiffness of plantar tissues in diabetics have used cadaveric values for material properties or indentation methods to infer stiffness (Gefen et al. 2001, Jan et al. 2013, Klaesner et al. 2002, Pai & Ledoux 2010, Zheng et al. 2000). A previous study, described in Chapter 2, did not find a statistical difference in stiffness of individual foot structures between diabetic individuals and controls due to large variability within the diabetic group. However, abnormally high stiffness was observed in some diabetic individuals (up to 200+ kPa difference). Few studies have assessed multiple sites known to be susceptible to ulceration (Gefen et al. 2003, Pai & Ledoux 2010, Zheng et al. 2000) and, to our knowledge, only one study included both experimental stiffness and plantar pressure measurements in living participants (Jan et al. 2013). In addition, few studies have directly examined material properties of soft tissue in diabetic feet (Pai & Ledoux 2012, Pai & Ledoux 2010), but these were done using cadavers. Several studies suggest a connection between intrinsic foot stiffness and plantar pressures in diabetic feet, but a study comprehensive enough to make a direct connection has yet to be done. Intrinsic structures contribute to proper foot function and local changes in these structures can have great impacts on overall foot function in response to loading during stance and gait (Gefen et al. 2001, Kelly et al. 2013, Mickle et al. 2013). Thus, it is important to understand the separate contributions individual foot structures have to overall foot function and what effect stiffening of these structures can have on 'normal' foot function.

Therefore, the purpose of the present study is to investigate the relationship between stiffness of foot structures and plantar pressures in diabetic individuals. First, it is hypothesized that plantar pressures will positively correlate with foot structure stiffness (i.e. higher plantar pressures will coincide with higher stiffness). Second, it is hypothesized that HbA1c levels will

positively correlate with stiffness in diabetics, suggesting that glycemic control influences severity of stiffness.

Methods

Fifteen individuals with diabetes participated in this study (Table 3.1). Type 1 and Type 2 diabetics were enrolled and will be assessed jointly in the analyses in this study. To ensure a homogeneous group, individuals with gross foot deformities that affected walking ability, edema, previous foot amputations/major surgeries, osteoarthritis, current plantar fasciitis, current foot ulcer, or a wound history ≤ 3 months were excluded from study participation. Group demographics are displayed in Table 1. All participants completed a Foot and Ankle Ability Measure (FAAM) questionnaire (Martin et al. 2005) to self-report foot and ankle function in addition to assessment of clinical foot measures including navicular drop (Menz & Munteanu 2006), arch stiffness (Menz & Munteanu 2006), longitudinal arch angle (Jonson & Gross 1997), arch index (Williams et al. 2000), and gastrocnemius and soleus flexibility (Rabin & Kozol 2010) by a licensed physical therapist (Table 3.1). All participants also completed the International Physical Activity Questionnaire (IPAQ) short form to self-report physical activity from the week prior to study participation (Table 3.1). The IPAQ is considered a reliable means for assessing physical activity levels among adults (18-65 years) in a variety of settings (Craig et al. 2003). All participants provided written informed consent and all procedures were approved by the East Carolina University Institutional Review Board.

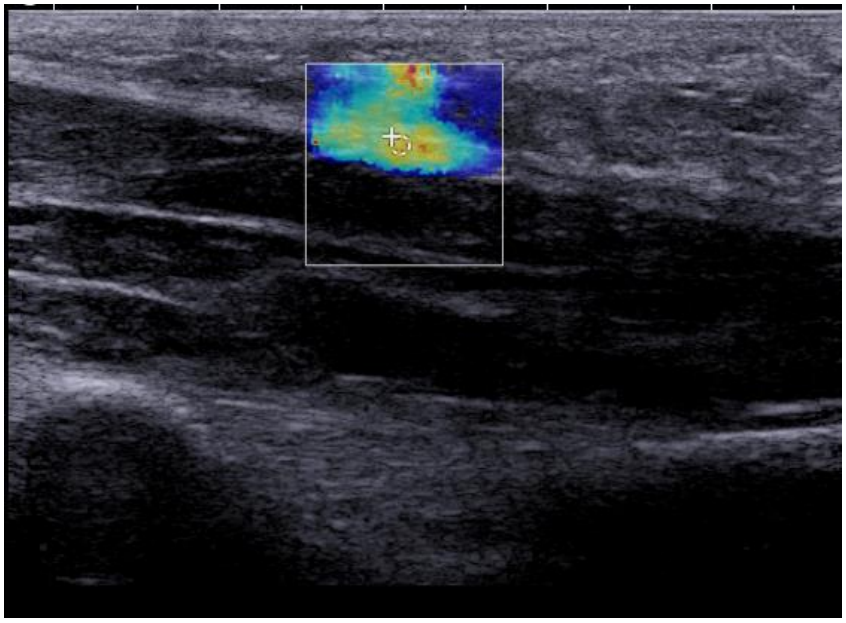
Table 3.1 Diabetic group demographics including IPAQ scores. Significance indicated by bold font and * ($p \leq 0.05$). Trending indicated by † ($0.05 < p \leq 0.10$).

Demographics	**Type 1**	**Type 2**	**p**
N	7	8	-
Sex	0M/7F	2M/6F	-
Age (yrs)	27.4 (4.3)	43.4 (9.5)	**0.001***
Height (cm)	158.4 (11.8)	171.0 (12.1)	0.06†
Weight (kg)	78.9 (12.7)	95.8 (22.2)	0.10
BMI (kg/m^2)	31.9 (7.2)	32.6 (5.4)	0.82
Fasted Blood Glucose (mg/dL)	177.0 (61.7)	119.4 (39.7)	**0.048***
HbA1c	7.1 (1.4)	6.7 (1.7)	0.66
Years with Diabetes	13.6 (10.6)	5.3 (6.6)	0.10
IPAQ Scores			
High	1	3	-
Moderate	4	2	-
Low	1	3	-
Total MET Minutes	1584 (1202)	3346 (3761)	0.26

Bilateral SWE measurements of the flexor hallucis brevis (FHB) muscle, abductor hallucis brevis (AHB) muscle and tendon (AHT), plantar fascia (PF), Achilles tendon (AchT) and macrochamber of the heel pad (HP) were performed. These structures will represent the soft tissue types present within the foot: muscle, tendon, ligament, and fat. The FHB has been shown to be a substantial contributor to foot posture (Angin et al. 2018) and increase medial longitudinal arch height along with other intrinsic flexor muscles following a strengthening intervention (Hashimoto & Sakuraba 2014). The AHB has previously been shown to act as a dynamic elevator of the arch (Wong 2007), support the medial longitudinal arch (Fiolkowski et al. 2003) and help maintain medio-lateral balance in quiet and single leg standing (Kelly et al. 2012). Due to the contributions of these structures to the function of the longitudinal arch and ease of measurement, these structures were examined. The AchT was also examined because it is typically evaluated and included in treatment of diabetic feet (ADA 2012, Boulton et al. 2008).

Participants lay prone, in a relaxed position, on an examination table with both feet hanging just slightly off the end for the entirety of the scanning protocol. Quantitative measurements of stiffness were assessed and quantified with shear modulus using SWE taken on an Aixplorer ultrasound system (SuperSonic Imagine, Aix-en-Provence, France). The PF was measured at a proximal and distal site, located at ~45% and ~75% of foot length from the most posterior aspect of the heel, respectively. All images were taken in the longitudinal view. Shear modulus was determined in a 1 mm circular region of interest placed in the middle of the tissue at each measurement site (Figure 3.1). Measurements are taken as a central, circular region due to higher variability in measurements taken along the periphery of the elastography data box. The mean shear modulus of three measurements were averaged and reported as stiffness for each site.

Figure 3.1 Example elastogram of the proximal plantar fascia site including the 1mm circular region of interest.



Bilateral walking plantar pressure data was collected using a Novel Pedar pressure measurement system (novel gmbh, Munich, Germany) which utilizes 2 mm thick sensor insoles that contain a matrix of 99 sensors to directly measure the pressure at the foot interface at a rate of 50 Hz or 100 Hz per foot. All participants wore standardized footwear to ensure against shoe design influence on plantar pressures and walking biomechanics. These data were then analyzed using a custom 10-region mask with Novel software. The 10 regions were: medial and lateral heel, medial and lateral arch, 1st metatarsal (met) head, 2nd met head, 3rd-5th met heads, hallux, 2nd toe, and lesser toes. Commonly susceptible ulcer sites include the heel pad, 1st met head, and hallux (Pai & Ledoux 2010), thus in the present study, plantar pressure distributions were analyzed only at these locations. Variables calculated included peak pressure and pressure-time integral (PTI) at both a self-selected (average of 1.11m/s) and standardized walking speed (1.30m/s).

Linear regression analysis was used to assess relationships between stiffness and plantar pressures, stiffness and HbA1c levels, and HbA1c levels and plantar pressures at a self-selected and standard speed. Plantar pressure regions of interest included the medial heel, 1st met head, and hallux.

Results

Subject demographics are shown in Table 1, including IPAQ scores. No statistically significant differences in height, weight, BMI, or HbA1c levels were observed between Type 1 and Type 2 individuals. As expected, there was a significant difference in age ($p=0.001$) and fasted blood glucose ($p=0.048$) among Type 1 and Type 2 individuals, as well as a trend for a

difference in height (p=0.063). There were no significant differences in physical activity levels, measured in weekly MET minutes between Type 1 and Type 2 diabetics. Several relationships were observed between stiffness and peak pressure at both the self-selected and standard speeds for various structures. However, contrary to the hypothesis, most of the relationships were negative. Select correlations between stiffness and plantar pressure variables are displayed in Figure 3.2. Mean plantar pressures for each region of interest are displayed in Table 3.2.

Table 3.2 Mean plantar pressures among the diabetic group.

	Self-Selected Speed		**Standard Speed (1.3m/s)**	
	Peak Pr. (kPa)	**PTI (kPa*s)**	**Peak Pr. (kPa)**	**PTI (kPa*s)**
Medial Heel	106.1 (30.2)	22.2 (8.6)	123.2 (30.3)	22.3 (8.6)
1st Met Head	90.4 (31.9)	25.0 (9.7)	96.3 (34.6)	23.7 (8.5)
Hallux	69.9 (76.1)	14.8 (19.1)	77.6 (72.0)	14.5 (16.3)

Medial Heel

Many relationships were observed between plantar pressure variables and stiffness at the medial heel at both walking speeds (Table 3.3). Moderate relationships were observed between peak pressure and proximal PF stiffness at both the self-selected (r=-0.36, p=0.049) and standard speeds (r=-0.43, p=0.019). Similarly, the distal PF had moderate relationships with medial heel peak pressure at both the self-selected (r=-0.39, p=0.034), and the standard speeds (r=-.043, p=0.018). There were trends for a relationship for AchT stiffness and medial heel peak pressure only at the self-selected speed (r=-0.32, p=0.090), and for the AHT solely at the standard speed (r=-0.34, p=0.065).

Moderate relationships were observed between PTI and the proximal PF at both the self-selected (r=-0.43, p=0.018) and standard speeds (r=-0.40, p=0.030). Moderate relationships were

also observed with the AHT at both the self-selected (r=-0.37, p=0.041) and standard speeds (r=-0.39, p=0.033). There was a trend for a relationship with PTI and the AchT only at the self-selected speed (r=-0.34, p=0.068) and with the HP solely at the standard speed (r=0.31, p=0.091).

Table 3.3 R and p values for correlations between stiffness and plantar pressure variables at the medial heel. Significance indicated by bold font and * (p<.05). Trending correlations indicated by † (.10 ≤p≥ .05).

Medial Heel	**Self-selected Speed**				**Standard Speed (1.3m/s)**			
	Peak Pressure		PTI		Peak Pressure		PTI	
	r	p	r	p	r	p	r	p
Proximal PF	**-0.36**	**0.049***	**-0.43**	**0.018***	**-0.43**	**0.019***	**-0.40**	**0.030***
Distal PF	**-0.39**	**0.034***	-0.28	0.13	**-0.43**	**0.018***	-0.28	0.14
AHT	-0.23	0.21	**-0.37**	**0.041***	-0.34	0.065†	**-0.39**	**0.033***
AchT	-0.32	0.090†	-0.34	0.068†	-0.19	0.31	-0.30	0.10
FHB	0.09	0.64	0.21	0.26	0.15	0.42	0.17	0.37
AHB	-0.26	0.16	0.05	0.78	-0.17	0.36	0.12	0.52
HP	-0.01	0.96	0.17	0.37	0.21	0.28	0.31	0.091†

1st Met Head

At the 1st met head, a strong relationship was observed between peak pressure and the HP at both the self-selected (r=0.58, p=0.001) and the standard speeds (r=0.56, p=0.001) (Table 3.4). Moderate relationships were also observed with the proximal PF at both the self-selected (r=-0.39, p=0.034) and standard speeds (r=-0.38, p=0.037).

Strong relationships were observed between PTI and the HP at both the self-selected (r=0.60, p<0.0001) and the standard speeds (r=0.53, p=0.003) (Table 3.4). Moderate relationships were also observed with the proximal PF at both the self-selected (r=-0.37, p=0.047) and standard speeds (r=-0.37, p=0.046).

Table 3.4 R and p values for correlations between stiffness and plantar pressure variables at the 1st met head. Significance indicated by bold font and * (p<.05). Trending correlations indicated by † (.10 ≤p≥ .05).

1st Met Head	Self-selected Speed				Standard Speed (1.3m/s)			
	Peak Pressure		PTI		Peak Pressure		PTI	
	r	p	r	p	r	p	r	p
Proximal PF	**-0.39**	**0.034***	**-0.37**	**0.047***	**-0.38**	**0.037***	**-0.37**	**0.046***
Distal PF	-0.11	0.58	-0.09	0.65	0.01	0.97	-0.05	0.78
AHT	-0.19	0.30	-0.12	0.51	-0.15	0.43	-0.05	0.80
AchT	-0.30	0.11	-0.20	0.29	-0.22	0.24	-0.21	0.26
FHB	0.12	0.53	0.07	0.73	0.13	0.50	0.01	0.94
AHB	0.26	0.16	0.21	0.28	0.31	0.091†	0.19	0.31
HP	**0.58**	**0.001***	**0.60**	**<0.0001***	**0.56**	**0.001***	**0.53**	**0.003***

Hallux

At the hallux, moderate relationships were observed between peak pressure and the AchT at both the self-selected (r=-0.41, p=0.024) and standard speeds (r=-0.42, p=0.020) (Table 3.5). Trends for a relationship with the proximal PF were also observed at both the self-selected (r=-0.33, p=0.073) and standard speeds (r=-0.33, p=0.071). No other relationships existed between stiffness and peak plantar pressure at the first metatarsal head or hallux for any of the other examined structures.

Moderate relationships were observed between PTI and the AchT at both the self-selected (r=-0.39, p=0.031) and standard speeds (r=-0.42, p=0.021). No other relationships existed between stiffness and PTI at the 1st met head or hallux for any of the other examined structures (Table 3.5).

Table 3.5 R and p values for correlations between stiffness and pressure-time integral at self-selected speed. Significance indicated by bold font and * (p<.05). Trending correlations indicated by † (.10 ≤p≥ .05).

Hallux	**Self-selected Speed**				**Standard Speed (1.3m/s)**			
	Peak Pressure		PTI		Peak Pressure		PTI	
	r	p	r	p	r	p	r	p
Proximal PF	-0.33	0.073†	-0.30	0.11	-0.33	0.071†	r	p
Distal PF	-0.18	0.34	-0.18	0.34	-0.19	0.31	-0.30	0.11
AHT	-0.26	0.16	-0.24	0.21	-0.28	0.14	-0.19	0.31
AchT	**-0.41**	**0.024***	**-0.39**	**0.031***	**-0.42**	**0.020***	-0.25	0.18
FHB	0.01	0.97	0.00	0.98	-0.01	0.97	**-0.42**	**0.021***
AHB	0.16	0.39	0.17	0.37	0.19	0.32	-0.01	0.95
HP	0.07	0.72	0.11	0.58	0.14	0.45	0.19	0.32

Stiffness vs HbA1c

When treating feet independently, only a trend existed between AchT stiffness and HbA1c levels (r= 0.32, p=.096). However, when feet are averaged to compare a single value to HbA1c per participant, no relationships are present for any of the examined structures.

HbA1c vs Plantar Pressure Variables

No significant relationships were observed between HbA1c and peak pressure or HbA1c and PTI for any of the examined structures. There was only a trend for a relationship between HbA1c and peak pressure at the medial heel (r=-0.32, p=0.089) for the self-selected speed.

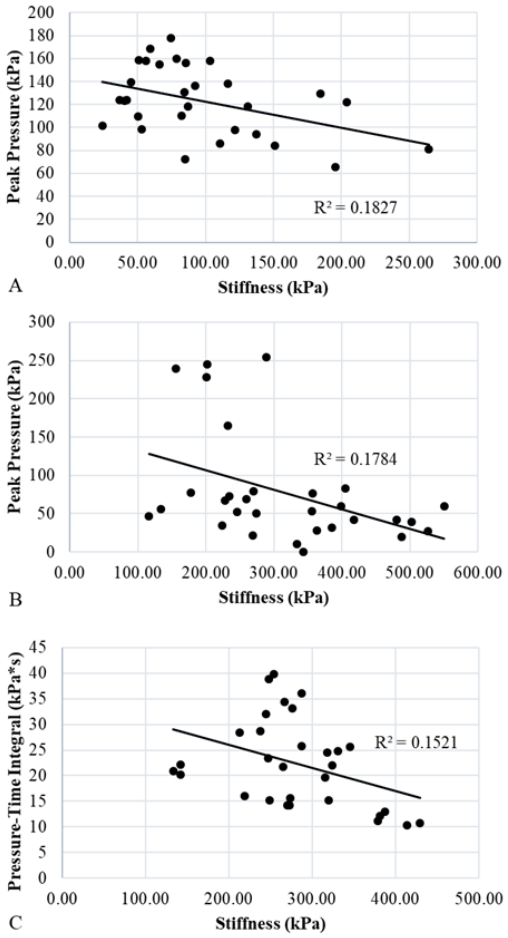
Discussion

The purpose of the present study was to investigate the relationship between foot structure stiffness and plantar pressures in diabetic individuals. The results partially supported the original primary hypothesis as diabetic foot structure stiffness positively correlated with plantar pressures for some but not all structures, and negative correlations were more commonly present. However, several correlations were observed among the examined structures and plantar

pressure sites. The results did not support the original secondary hypothesis as no significant relationships were observed between HbA1c levels and stiffness nor between HbA1c levels and plantar pressures variables.

The majority of these relationships between stiffness and plantar pressure variables were negative, which was contrary to the primary hypothesis. Among the examined structures, only the HP had positive correlations with peak plantar pressure and pressure-time integral, but only at the 1st met head. All other relationships were negative, suggesting that decreased stiffness of the PF and foot musculature is related to increased plantar pressures (Figure 3.2). This is contradictory to previous suggestions that increased stiffness of foot muscles and tendons contributes to decreased range of motion and increased plantar pressures in diabetic individuals (Caravaggi et al. 2016, Fernando et al. 1991, Francia et al. 2015, Giacomozzi et al. 2008, Mueller et al. 1989, Veves et al. 1992, Zimny et al. 2004). However, measures of stiffness with ultrasound SWE was suggested to be an indicator of passive muscle force (Sasaki et al. 2014, Koo et al. 2013), thus it is possible that decreased stiffness of foot structures is indicative of damage or weakened structures that have a decreased ability to withstand load, thus leading to potential foot collapse and increased pressures under the foot (Cheuy et al. 2013).

Figure 3.2 Regression analysis of select structures at the standard walking speed (1.3m/s): distal plantar fascia stiffness with medial heel peak pressure (a), Achilles tendon stiffness with hallux peak pressure (b), and abductor hallucis tendon with medial heel pressure-time integral (c).



In addition to the direction of the observed relationships between stiffness and plantar pressure variables, the functional implications of where these relationships are occurring is important. The PF (proximal and distal sites) negatively correlate with peak plantar pressure at the medial heel, while only the proximal PF negatively correlates with peak plantar pressure at the 1st met head. This suggests that decreased stiffness of the PF coincides with increased peak pressure and PTI at the medial heel and 1st met head. Considering that the PF spans the length of the foot, before branching among the metatarsals, it is intuitive that it would have functional

implications on pressure at both the heel and 1st met head. It is not entirely clear why the HP positively correlates with pressure at the 1st met head. It is possible that a stiffer HP is less compliant, deforms less, and thereby dissipates less pressure, thus as one progresses through the stance phase, pressure not dissipated by the HP is transferred to the plantar tissue under the 1st met head, leading to increased pressure at the 1st mead. Sullivan and colleagues (2015) found decreased pressure under the heel in patients with high heel pain compared to low heel pain and controls, as well as longer midfoot and forefoot contact times. In addition, higher stiffness and less energy absorption at the heel pad has been found in Type 2 diabetics compared to controls with no difference in heel pad thickness (Chatzistergos et al. 2014. Pai & Ledoux 2010). Assessing contact time as a percent of stance would further elucidate the functionality of this relationship, however, that was not an aim of the present study.

Negative relationships also existed for the AchT with peak pressures and PTI at the hallux, as well as the AHT with PTI at the medial heel. The AchT plays an important role in gait, with a mechanism similar to that of a catapult, slowly storing elastic energy during stance and quickly releasing this elastic energy in a recoil fashion to aid in propulsion during gait (Sawicki et al. 2009, Fukunaga et al. 2001). In addition, ultrasound evidence has shown that the Achilles tendon is responsible for generating majority of the power at the ankle during push-off (Ishikawa et al. 2005). It is likely that power generation at the ankle during push-off affects metatarsal heads force, which in turn may affect the amount of pressure at the metatarsals during gait. In diabetic individuals with neuropathic ulcers, Achilles tendon lengthening has been shown to decrease plantar pressures under the forefoot, and it has been suggested that peak pressures under the forefoot are related to plantar flexors generating push off force (Mueller et al. 2003). Thus,

the observed relationship of AchT stiffness with pressure at the hallux would indicate that a stiffer AchT effectively stores and releases energy that thereby decreases pressure at the hallux during propulsion in gait. However, gait and energy profiles would need to be assessed before making such a conclusion about the nature of this relationship.

The AHB is the most medial intrinsic foot muscle and has a proximal attachment (origin) at the medial process of the calcaneal tuberosity and a distal attachment (insertion) at the medial sesamoid on the first metatarsal head (Cameron et al. 2008). Previous work has shown the AHB to be active in late stance and push-off phases in gait (Reeser et al. 1983) and may contribute to raising the arch before toe-off (Wong 2007). Stimulation of the AHB has also been shown to have effects on calcaneal and metatarsal segment angles as well as center of pressure in response to load (Kelly et al. 2013). Although the function of the AHT has not been exclusively studied, it is possible that the relationship between AHT stiffness and pressure at the heel in the present study is indicative of the functional relationship that exists between the AHB muscle-tendon unit and the calcaneus.

If these negative relationships are in fact indicative of weaker foot structures in diabetic individuals, a similar association between foot structure and function should exist. Several relationships were observed between stiffness and clinical foot measures (Table 3.6). Navicular drop positively correlated with proximal PF ($r=0.44$, $p=0.015$) and AHT stiffness ($r=0.49$, $p=0.006$). Arch stiffness negatively correlated with AHT stiffness ($r=-0.40$, $p=0.029$) and positively correlated with FHB stiffness ($r=0.40$, $p=0.030$) (Figure 3.3). Trends also existed for a moderate positive relationship between navicular drop and distal PF stiffness ($r=0.33$, $p=0.073$)

and a moderate negative relationship with FHB stiffness (r=-0.32, p=0.088).These findings suggest that stiffness measured by SWE may be related to clinical measures of foot mobility and could provide further insight into tissue structure/function in conjunction with standard clinical measurements to better understand the effect of stiffness on foot function and its role in ulcer development.

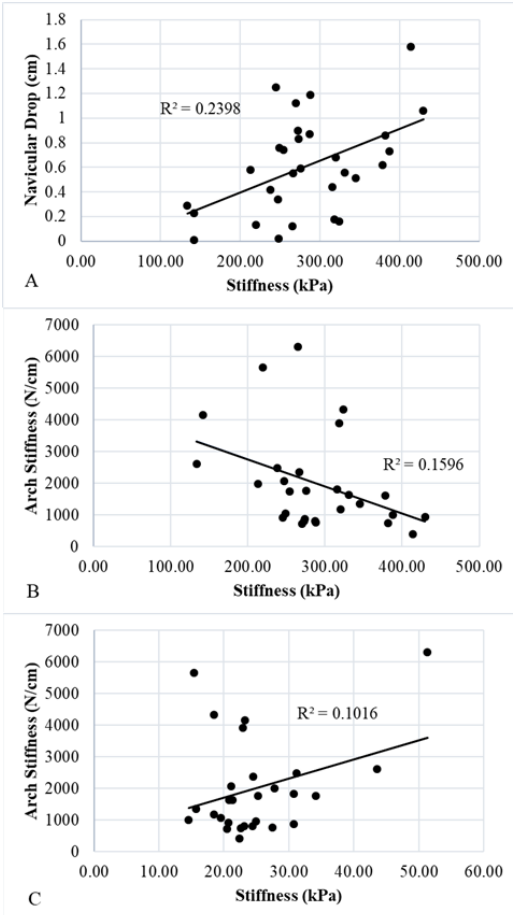
Table 3.6 R and p values for correlations between stiffness and clinical foot measures. Significance indicated by bold font and * ($p<.05$). Trending correlations indicated by † ($.10 \leq p \geq .05$).

	Navicular Drop (cm)		**Navicular Drop (cm) w/o outliers**		**Arch stiffness (N/cm)**		**Arch stiffness (N/cm) w/o outliers**	
	r	p	r	p	r	p	r	p
Proximal PF	**0.44**	**0.015***	**0.40**	**0.028***	-0.17	0.36	-0.29	0.12
Distal PF	0.33	0.073†	0.32	0.087†	-0.10	0.59	-0.27	0.15
AHT	**0.49**	**0.006***	**0.42**	**0.020***	**-0.40**	**0.029***	**-0.40**	**0.029***
AchT	-0.08	0.67	-0.12	0.51	-0.08	0.67	-0.01	0.96
FHB	-0.32	0.088†	-0.23	0.22	**0.40**	**0.030***	0.32	0.086†
AHB	0.10	0.61	0.30	0.10	0.26	0.17	-0.17	0.38
HP	0.13	0.51	0.16	0.39	0.11	0.57	-0.06	0.74

Given that we expected diabetic individuals to have abnormally increased stiffness of foot structures as well as abnormally increased plantar pressures, outliers were not removed from the analysis in the present study. However, it is important to note that only a few of the relationships observed would drastically change with their removal. Notably, the relationships between pressure and the proximal PF as well as pressure and the HP would be abolished with the removal of the outliers. With more subjects, a wider range of stiffness values could be measured to better interpolate between data points and confirm these relationships. Interestingly, 2 of the 3 participants with the outlier values were categorized as “severe” (HbA1c>8.0%) or neuropathic. Future work should assess potential differences in stiffness/plantar pressure

relationships between diabetic individuals with and without neuropathy. Two outliers also existed for navicular drop and arch stiffness. Extremely low navicular drop values (specifically, 0.01 and 0.02 cm) yielded extremely high arch stiffness values (95,647.5 N/cm and 34,972.7 N/cm, respectively). These outliers were removed for display purposes in Figure 3.3, but clinical measures correlations with and without the outliers present are reported in Table 3.6. However, the presence of these outliers only slightly decreases the strength of the relationships observed, thus the overall takeaway for these relationships with stiffness remains the same regardless of the presence of outliers.

Figure 3.3 Regression analysis of select structures with clinical foot measures: abductor hallucis tendon with navicular drop (a) and arch stiffness (b), flexor hallucis brevis with arch stiffness (c). Outliers were removed from arch stiffness for displayed correlations.



One of the primary limitations of this study is that most of the diabetics were well-regulated, with only three participants in our sample having peripheral neuropathy and only three participants considered "severe" based on our criteria. Some studies have found differences between diabetics with and without peripheral neuropathy (D'Ambrogi et al. 2003, D'Ambrogi et al. 2005). Inclusion of more "severe" or less-regulated diabetic individuals or with peripheral neuropathy would provide a more robust comparison. Another primary limitation of this study is that majority of the participants are female, which happened by chance. Gender was not a focus of the study nor was it an exclusive criterion. Inclusion of more males would make the results more generalizable and allow for gender comparisons. It may also be important to consider potential differences between control and diabetic individuals, as well as between Type 1 and Type 2 diabetics. Lastly, the plantar pressure values measured in this study are lower than those seen in the literature (previously described in Chapter 1), however this is possibly due to the measurements being with the insoles inserted into shoes with standard cushioning instead of barefoot (Sartor et al. 2008) or minimally cushioned shoes (like canvas shoes as used in Payne et al. 2002). Standard shoes were worn by all participants, thus the measurements are comparable between subjects. Future work comparing stiffness of foot musculature and plantar pressures should include plantar pressure measurements in the barefoot or in minimally shod state.

This is the first study to compare stiffness of multiple foot structures to plantar pressures in diabetic individuals. We found the majority of the significant relationships to be negative, suggesting that structures with lower stiffness correlate with increased pressure, and vice versa. Large variability in stiffness, indicated by the presence of outliers were also observed, thus it is

possible that there are certain factors that make a diabetic individual more susceptible to increased stiffness than others that we did not address in the present study. More studies using ultrasound SWE to test for effects of material properties of foot structures on plantar pressures are warranted. Recently, studies in individuals with plantar fasciitis have found lower stiffness of the PF in currently symptomatic patients than in individuals with and without a history of plantar fasciitis using compression (Wu et al. 2015, Lee et al. 2014, Sconfienza et al. 2013) and shear wave elastography (Gatz et al. 2019). Further investigation into material property changes of foot structures associated with the condition of plantar fasciitis and how stiffness relates to plantar pressures may provide useful information to better understand the observations of decreased stiffness relating to higher plantar pressures in diabetic individuals in the present study. Future work should also include gait analysis to assess potential gait variables or deviations that could help explain the nature of the observed relationships between stiffness and plantar pressures. Inclusion of EMG to assess activation of intrinsic foot muscles during walking is also warranted to better understand the functional relationships and active contributions of intrinsic foot musculature to plantar pressures. Lastly, more work investigating the composition of intrinsic foot musculature (i.e. lean muscle mass and intramuscular fat) in relation to stiffness would also help to explain the functional relationships these structures have with plantar pressure distributions in diabetic individuals.

In conclusion, the present study found many relationships between foot structure stiffness and plantar pressures, but most were negatively correlated, suggesting that higher pressures are related to less stiff structures. HbA1c does not seem to be significantly related to stiffness or plantar pressures, suggesting that glycemic index alone is not predictive of altered stiffness or

plantar pressures in diabetic individuals. However, stiffness does seem to be related to clinical foot measures, suggesting that a relationship exists between foot structure stiffness and foot function. Evidence of decreased stiffness relating to increased pressures could indicate weakening or damage of foot structures in diabetic individuals that may contribute to altered foot function that could potentially lead to subsequent ulcer development. More work is warranted to further investigate the role of foot structure stiffness on plantar pressures, foot function, and ulcer development in diabetic individuals.

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Chapter 4

Material Properties of Foot Structures in Individuals with Plantar Fasciitis

Abstract

Plantar fasciitis is a common musculoskeletal disorder affecting many populations. Diagnosis remains heavily reliant on patient history as little is currently known about the etiology of plantar fasciitis. Ultrasound technology has more recently been used to aid in diagnosis with an emphasis on structural properties via measurement of plantar fascia thickness. Few studies have attempted to examine material properties of the plantar fascia with compression elastography to better understand how these properties are altered in individuals with plantar fasciitis. However, it is likely that shear wave elastography may be a more functionally relevant and direct measure of plantar fascia material properties due to shear waves propagating in the same direction that the plantar fascia is primarily loaded. To date, no studies have assessed material properties of other arch supporting structures in addition to the plantar fascia in individuals with plantar fasciitis. Thus, this study was two-fold: 1) to assess material properties of the plantar fascia and foot structures supporting the longitudinal arch in individuals with and without plantar fasciitis; and 2) to assess thickness of the PF and foot structures supporting the longitudinal arch in individuals with and without plantar fasciitis. It was first hypothesized that individuals with current plantar fasciitis symptoms will have altered stiffness of the PF compared to those with and without a history of plantar fasciitis. It was secondly hypothesized that individuals with current plantar fasciitis symptoms will have increased thickness of the PF compared to those with and without a history of plantar fasciitis.

Bilateral shear wave elastography (SWE) measurements of the PF, flexor hallucis brevis, abductor hallucis muscle and tendon, and Achilles tendon were performed. Thickness of each structure was assessed using B-mode imaging. Clinical foot measures including navicular drop

(cm), arch stiffness (N/cm), longitudinal arch angle, arch index, and gastrocnemius and soleus flexibility were also measured. PF stiffness was significantly lower in currently symptomatic individuals compared to controls and to those with a history of plantar fasciitis who were currently asymptomatic. Symptomatic and asymptomatic individuals displayed greater thickness at multiple sites along the PF compared to controls. Measures of PF stiffness appear to normalize prior to restoration of structural properties (thickness). Taken together, the results suggest that SWE has the potential to be a useful tool to monitor recovery and treatment effectiveness. More work is warranted to assess clinical applications of SWE.

Introduction

Plantar fasciitis is a common musculoskeletal disorder that affects various populations including the active, sedentary, young, and elderly (Huffer et al 2017). Most frequently, plantar fasciitis presents as heel pain and results in substantial disability (Neufeld and Cerrato 2008). It is estimated that 1 in 10 people will develop plantar fasciitis in their lifetime (Neufeld and Cerrato 2008). However, the etiology of plantar fasciitis is unclear and diagnosis relies heavily on patient history (Goff and Crawford 2011). Little is known about how plantar fasciitis affects tissue properties prior to or after the resolution of symptoms. Knowledge of plantar fascia and surrounding tissue properties in individuals with and without plantar fasciitis is needed to better understand the etiology of plantar fasciitis and improve diagnostic methods.

Recent studies have used compression elastography to measure the plantar fascia (PF) and have found lower stiffness in currently symptomatic patients than in individuals with and without a history of plantar fasciitis (Wu et al. 2015, Lee et al. 2014, Sconfienza et al. 2013). However, compression elastography assesses the PF in a direction transverse to both the longitudinal collagen fiber orientation and the principal direction of physiological loading (Stecco et al. 2013, Prado-Costa et al. 2018). In addition, calculations of modulus (stiffness) using compression elastography is dependent on the applied force of the operator, which is not standardized and can be highly variable (Prado-Costa et al. 2018). Thus, it is difficult to directly quantify plantar tissue properties with compression elastography.

Unlike compression elastography, shear wave elastography (SWE) induces shear waves that propagate perpendicular to the probe surface (i.e. along the direction that the PF is primarily

loaded) and inverts shear wave speed to calculate shear modulus (Prado-Costa et al. 2018). Using SWE to measure plantar tissue stiffness in the longitudinal direction may be more likely to be functionally relevant. Two studies using SWE to assess properties of the PF in patients with plantar fasciitis found regional variation in PF stiffness (Putz et al. 2017, Gatz et al. 2019). However, only Gatz et al. (2019) included control participants with no history of plantar fasciitis, thus there is still limited understanding and significance of variation in PF longitudinal stiffness. Additionally, stiffness characteristics of intrinsic foot structures that help support the longitudinal arch have not been assessed and may give further insight to local tissue property changes induced by plantar fasciitis (Crofts et al. 2014).

The primary purpose of the present study was to assess longitudinal material stiffness of the PF and foot structures supporting the longitudinal arch in individuals with and without plantar fasciitis. It is hypothesized that individuals with current plantar fasciitis symptoms will have altered longitudinal stiffness of the PF compared to those with and without a history of plantar fasciitis. The secondary purpose of the present study was to assess thickness of the PF and foot structures supporting the longitudinal arch in individuals with and without plantar fasciitis. Thickening of the PF has been suggested to relate to severity of heel pain, arch shape, and regional loading (Wearing et al. 2007), and has been observed in patients with plantar fasciitis in both the symptomatic and asymptomatic limbs (Granado et al. 2018, Tsai et al. 2000, Ermutlu et al. 2018, McMillan et al. 2009). Thus, it is hypothesized that individuals with current plantar fasciitis symptoms will have increased thickness of the PF compared to those with and without a history of plantar fasciitis. In addition, clinical foot measures will be reported to give further characterization of foot/arch structure and function.

Methods

Eleven individuals with no history of plantar fasciitis (controls), 11 individuals with active plantar fasciitis symptoms (AG) and 6 individuals with history of plantar fasciitis symptoms, but currently asymptomatic (HxG) participated in this study (N=28). Individuals with previous foot surgery and diagnosed osteoarthritis were excluded from study participation. Individuals were assigned to the symptomatic group (AG) based on self-reported pain within the past week prior to study participation including: plantar medial heel pain most noticeable with initial steps after a period of inactivity but also worse following prolonged weight bearing, heel pain precipitated by a recent increase in weight-bearing activity, and pain with palpation of the proximal insertion of the PF. Individuals were assigned to the asymptomatic group (HxG) based on self-reported history of the above criteria, but currently exhibiting an absence of such symptoms for more than one week prior to study participation.

Participants completed a Foot and Ankle Ability Measure (FAAM) questionnaire (Martin et al. 2005) to self-report foot and ankle function in addition to assessment of clinical foot measures including navicular drop (Menz & Munteanu 2006), arch stiffness (Menz & Munteanu 2006), longitudinal arch angle (Jonson & Gross 1997), arch index (Williams et al. 2000), and gastrocnemius and soleus flexibility (Rabin & Kozol 2010) by a licensed physical therapist (Table 4.1). All participants provided written informed consent and all procedures were approved by the East Carolina University Institutional Review Board.

Table 4.1 Subject demographics including clinical foot measures and Foot and Ankle Ability Measures (FAAM) scores. Statistical significance indicated by * for difference from controls, a for difference from HxG (p<.05).

Demographics	**Controls**	**AG**	**HxG**
N	11	11	6
Sex	6M/5F	3M/8F	1M/5F
Age	30.5 (8.2)	50.9 (6.9)*[a]	42.5 (8.5)*
Height (cm)	171.7 (13.1)	171.7 (12.6)	166.6 (9.8)
Weight (kg)	78.0 (25.7)	92.2 (24.8)	78.7 (17.7)
Years with plantar fasciitis	---	2.9 (2.8)	4.3 (4.1)
Clinical Foot Measures			
Navicular drop (cm)	0.49 (0.24)	0.68 (0.23)	0.61 (0.37)
Arch stiffness (N/cm)	1668.8 (673.5)	1439.9 (519.8)	1839.5 (1131.8)
Gastrocnemius (°)	36.9 (6.2)	37.0 (5.0)	34.7 (12.1)
Soleus (°)	46.8 (6.1)	45.6 (5.6)	43.9 (7.1)
FAAM Self-Function Scores			
Normal	11	2	3
Nearly Normal	0	5	2
Abnormal	0	4	1

Since tissue property changes are reported in both the symptomatic and asymptomatic limbs in patients with plantar fasciitis (Granado et al. 2018, Tsai et al. 2000, Ermutlu et al. 2018, McMillan et al. 2009), we measured both feet in all groups. However, only the symptomatic foot or foot with history of plantar fasciitis symptoms was included in the analyses performed in the study (AG n=17 feet, HxG n=10 feet). Participants lay prone, in a relaxed position, on an examination table with their feet hanging just slightly off the end for the entirety of the scanning protocol. All images were taken in the longitudinal view. Structures measured included the PF, flexor hallucis brevis muscle, abductor hallucis muscle and tendon, and the Achilles tendon. The flexor hallucis brevis has been shown to be a substantial contributor to foot posture (Angin et al. 2018) and increase medial longitudinal arch height along with other intrinsic flexor muscles following a strengthening intervention (Hashimoto & Sakuraba 2014). The abductor hallucis has

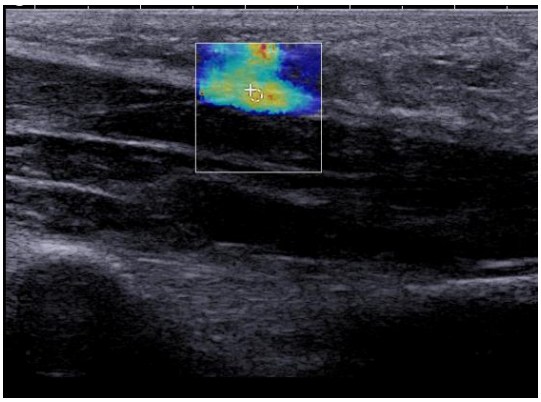
previously been shown to act as a dynamic elevator (Wong 2007), support the medial longitudinal arch (Fiolkowski et al. 2003) and help maintain medio-lateral balance in quiet and single leg standing (Kelly et al. 2012). Due to the contributions of these structures to the function of the longitudinal arch and ease of measurement, these structures were examined as the tissue properties of these structures may be altered in addition to the PF due to changes induced by plantar fasciitis. The Achilles tendon was also examined because it is typically evaluated and included in treatment of plantar fasciitis (DiGiovanni et al. 2003), and its anatomical relationship with the PF (Stecco et al. 2013).

Longitudinal material stiffness was assessed and quantified with shear modulus using SWE taken on an Aixplorer ultrasound system (SuperSonic Imagine, Aix-en-Provence, France). The PF was assessed in two regions because of previous findings of inhomogeneous stiffness in healthy and plantar fasciitis participants by Putz et al. (2017) and Gatz et al. (2019). The PF was measured at a proximal and distal site, located at ~40% and ~75% of foot length from the most posterior aspect of the heel, respectively. Shear modulus was determined in a 1 mm circular region of interest placed in the middle of the tissue at each measurement site (Figure 4.1). The mean shear modulus of three measurements were averaged and reported as longitudinal stiffness for each site.

Thickness was assessed for each structure using the B-mode portion without the elastography overlay of the acquired elastography images using Osirix (Pixmeo, Bernex, Switzerland) image processing software. The insertion site of the PF was measured vertically at the anterior edge of the inferior calcaneal border to the inferior border of the PF. All other

measurements were taken centrally in the tissue, measured vertically, and corresponding with the same central placement of the elastography region of interest for each structure. The mean thickness of three measurements were averaged and reported for each structure.

Figure 4.1 Example elastogram with circular region of interest used to quantify stiffness for the proximal plantar fascia.



Longitudinal stiffness and thickness between groups were compared using one-way ANOVAs with follow up t-tests for all structures. The alpha level for significance was set a priori to be 0.05. Trends were reported for values of $p>0.05$ and $p<0.10$ (Curran-Everett & Benos 2004). Data were screened for sex-based differences; no differences existed for any of the measured variables in this study.

Results

Group subject demographics are shown in Table 4.1, including clinical foot measures and FAAM scores. Age differences existed between the groups ($p<0.05$), but no statistically significant differences in height and weight were observed. Years with plantar fasciitis ranged from 6 months to 10 years in both plantar fasciitis groups, with the majority (8 out of 11) of AG participants reporting plantar fasciitis symptoms for 3 years or less. No statistically significant

differences were observed between groups for any of the clinical foot measures (Table 4.1). Self-reported foot and ankle function on the FAAM was less than normal in 82% of AG participants and in 50% of HxG participants.

Stiffness

Longitudinal stiffness at the proximal PF was 39.0% and 47.6% lower in the AG than controls (p=0.036) and HxG (p=0.017), respectively (Table 4.2). Similarly, the AG had lower longitudinal stiffness compared to controls at the abductor hallucis tendon (17.9%) and at the abductor hallucis muscle (27.5%), but these differences were not statistically significant. No other statistically significant differences in longitudinal stiffness was observed between groups for structures examined in this study (Table 2). However, other substantial differences existed between groups. Longitudinal stiffness of the distal PF was 21.3% and 33.2% higher in the HxG than the AG and controls, respectively. In the muscles, longitudinal stiffness of the flexor hallucis brevis was 18.4% less stiff in the AG, and 18.2 % less stiff in the abductor hallucis compared to the HxG.

Table 4.2 Shear modulus of foot structures across all groups. Statistical significance indicated by * for difference from controls, a for difference from HxG (p<.05).

	Shear Modulus (kPa)		
	Controls	**AG**	**HxG**
PF Prox	169.41 (82.00)	114.08 (74.15)*[a]	185.40 (62.54)
PF Dist	81.54 (49.43)	92.03 (31.05)	113.97 (46.38)
AbHT	367.27 (41.84)	306.95 (102.05)	348.03 (72.24)
AchT	377.64 (131.05)	417.70 (134.24)	392.67 (81.25)
FHBM	24.93 (9.04)	22.46 (8.00)	27.01 (7.51)
AbHM	34.33 (17.27)	26.04 (6.53)	28.60 (11.41)

Thickness

The AG exhibited 19.8% and 42.2% greater thickness compared to controls at the proximal and insertion sites of the PF, respectively ($p<0.0001$ for each) (Table 4.3). Compared to the HxG, the AG exhibited 19.3% thinner PF at the distal PF site ($p=0.011$). The flexor hallucis brevis muscle exhibited 15.0% greater thickness in the AG ($p=0.004$) compared to the HxG. The HxG exhibited greater thickness at all PF measurement sites compared to controls: proximal PF (14.3%; $p=0.015$), distal PF (16.4%; $p=0.020$), and PF insertion (55.6%; $p<0.0001$). Conversely, the HxG exhibited a 12.2% thinner flexor hallucis brevis muscle compared to controls ($p=0.0496$).

Table 4.3 Thickness of foot structures across all groups. Statistical significance indicated by * for difference from controls, a for difference from HxG ($p<.05$).

	Thickness (cm)		
	Controls	**AG**	**HxG**
PF Prox	0.186 (0.028)	0.227 (0.026)*	0.215 (0.032)*
PF Dist	0.153 (0.031)	0.149 (0.031)[a]	0.181 (0.024)*
PF Insert	0.307 (0.046)	0.472 (0.107)*	0.544 (0.151)*
AbHT	0.346 (0.119)	0.339 (0.099)	0.377 (0.073)
AchT	0.562 (0.058)	0.535 (0.056)	0.582 (0.065)
FHBM	1.506 (0.249)	1.549 (0.189)[a]	1.332 (0.139)*
AbHM	1.156 (0.264)	1.205 (0.193)	1.205 (0.193)

Discussion

The primary purpose of the present study was to assess longitudinal material stiffness of the PF and foot structures supporting the longitudinal arch in individuals with and without plantar fasciitis. The results support the original hypothesis that individuals with current plantar fasciitis symptoms have decreased longitudinal stiffness of the PF compared to those with and without a history of plantar fasciitis. The secondary purpose of the present study was to assess

thickness of the PF and foot structures supporting the longitudinal arch in individuals with and without plantar fasciitis. The results partially supported the original hypothesis as individuals with current plantar fasciitis had increased thickness of the PF compared to those without a history of plantar fasciitis but not compared to those with a history of plantar fasciitis.

The present study found lower longitudinal stiffness of the PF in the AG using SWE. While there are differences in methodology and measurement locations, these results are consistent with findings from previous compression elastography studies (Wu et al. 2015, Lee et al. 2014, Sconfienza et al. 2013). Unlike the previous studies, the current study measured longitudinal stiffness of the PF at a proximal and distal site, more similar to a recent SWE study by Gatz et al. (2019). Anecdotally, the proximal measurement site corresponded with the site of most pain for most plantar fasciitis participants. The AG also exhibited lower longitudinal stiffness in arch supporting structures, specifically the abductor hallucis muscle and tendon. Because muscle stiffness measured by SWE has been suggested to be an indicator of muscle strength (Hug et al. 2015), lower stiffness could indicate a weakening of arch supporting muscles, which may contribute to or further exacerbate symptoms of plantar fasciitis. In addition, Kim et al. (2016) found PF stiffness measured by compression elastography to increase following collagen injection, with minimal change in PF thickness. Taken together, elastography has the potential to monitor recovery and effectiveness of treatment, especially in monitoring progress in the absence of visible changes in PF thickness.

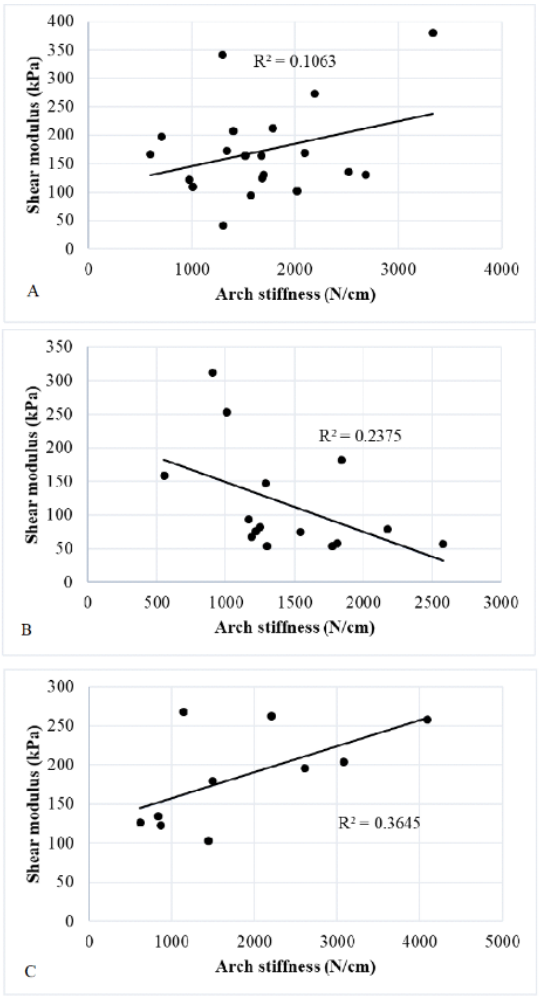
Longitudinal stiffness in the PF varied across both sites for all groups, consistent with previous plantar fasciitis studies using SWE (Putz et al. 2017, Gatz et al. 2019). Within group

comparisons suggested greater longitudinal stiffness of the PF at the proximal site compared to the distal site by 87.9kpa (70.0 % difference) in controls, 71.4kpa (47.7% difference) in HxG, and 22.0kpa (21.4% difference) in AG. These results support previous work by Gatz et al. (2019) that found inhomogeneous stiffness in proximal and distal sites of the PF in healthy and plantar fasciitis patients. Our analysis adds to the current state of literature by providing SWE data at a more distal PF site and supports the existence of inhomogeneity in the PF in both healthy and plantar fasciitis groups. Taken together with prior literature, our findings of inhomogeneous stiffness throughout the PF suggests that probe placement is an important consideration when assessing specific regions of the PF, especially if elastography, shear wave or compression, is to be used as a diagnostic or rehabilitation monitoring tool. It also suggests that there may be tissue changes contributing to or induced by plantar fasciitis happening along the PF, not just at the sight of pain.

An association between foot/arch tissue characteristics with foot structure and function likely exists. No differences were found between groups for any of the clinical foot measures (Table 4.1). These results support previous work that found no difference in arch index/medial longitudinal arch angle in patients with plantar fasciitis (Wearing et. al. 2004, Wearing et. al. 2007, Hsu et. al. 2013). However, post-hoc bivariate correlations revealed that longitudinal stiffness at the proximal PF site was moderately correlated with arch stiffness in controls ($r=0.33$, $p=0.14$) and the AG ($r=-0.49$, $p=0.065$), while the HxG displayed a strong correlation ($r=0.60$, $p=0.065$) (Figure 4.2), but none of these relationships reached statistical significance. The HxG also had a strong correlation between navicular drop and proximal PF stiffness ($r=-0.65$, $p=0.041$). These findings suggest that longitudinal stiffness measured by SWE may be related to

clinical measures of foot mobility and could provide further insight into tissue structure/function in conjunction with standard clinical measurements to monitor recovery and effectiveness of treatment.

Figure 4.2 Correlations of arch stiffness (N/cm) with proximal plantar fascia shear modulus (kPa) for all groups: healthy (r=0.33), symptomatic (r=-0.49), asymptomatic (r=0.60).



The AG exhibited greater thickness at the insertion and proximal PF sites compared to controls. Similarly, the HxG exhibited greater thickness of the PF at all three measured PF sites compared to controls, as well as at the distal PF site compared to the AG. These results support

several previous findings of increased thickness of the PF at the insertion in plantar fasciitis patients (Granado et. al. 2018, Tsai et. al. 2000, Ermutlu et. al. 2018, McMillan et. al. 2009). To the authors' knowledge, the present study is the first to measure thickness at sites other than the insertion of the PF in patients with plantar fasciitis. Findings of increased thickness across the length of the PF suggests that there are structural changes happening throughout the PF associated with plantar fasciitis, not just at the site of pain. In a long-term (5- to 15-year) follow-up study of 174 patients with plantar fasciitis, Hansen et al. (2018) found PF thickness to decrease over time regardless of symptoms, but only 24% of asymptomatic patients returned to "normal" values (below 4mm). Thus, it is possible that PF thickening is an adaptation that occurs in individuals with a history of plantar fasciitis that should be monitored with ultrasound technology in addition to current treatment interventions to better assess treatment outcomes and to better understand the time course and recurrence risk of plantar fasciitis.

A primary limitation of this study is the cross-sectional design. It is unknown whether stiffness and thickness were once similar between groups before injury occurred or how long the individuals in the HxG had been asymptomatic since their last episode of plantar fasciitis. Longitudinal studies assessing changes in stiffness and thickness in response to current treatment interventions (i.e. stretching, collagen injection, orthotics, corticosteroid injection) as well the ability of SWE to monitor recovery and effectiveness of treatment are warranted. Another primary limitation of this study is that majority of the plantar fasciitis participants are female, which happened by chance. Gender was not a focus of the study nor was it an exclusive criterion. Inclusion of more males would make the results more generalizable and allow for gender comparisons.

Because feet can be affected differently, as is the case in unilateral plantar fasciitis, we chose to treat each foot independently for all analyses. However, we acknowledge that because both feet are within subject, it would also be logical to consider the feet as dependent measures for each subject as bilateral observations from the same subject are likely to be more similar than observations from a different subject (Ranstam 2002, Ranstam 2012). Thus, we also ran the analyses considering the feet as dependent measures for each subject using a Z-factor ANOVA (side x group) for stiffness and thickness of all structures. Only stiffness at the proximal plantar fascia was different between groups ($p=0.033$). Post-hoc LSD tests showed that the AG group is significantly less stiff than controls ($p=0.029$) and HxG ($p=0.023$) at the proximal plantar fascia site. Regarding thickness, group differences existed at all plantar fascia sites: proximal ($p<0.001$), distal ($p=0.027$), and insertion ($p<0.001$); as well as in the flexor hallucis brevis ($p=0.038$). Post-hoc LSD tests showed that controls have thinner plantar fascia at the proximal ($p<0.001$) and insertion ($p<0.001$) compared to the AG, and at all measured sites compared to HxG (proximal: $p=<0.001$; distal: $p=0.20$; insertion: $p<0.001$). The HxG also had greater distal PF thickness than the AG ($p=0.011$) and thinner flexor hallucis brevis thickness compared to the AG ($p=0.013$) and controls ($p=0.037$). These results indicate that regardless of considering the feet as independent or dependent observations, similar differences in stiffness and thickness measures are observed between these groups.

PF longitudinal stiffness was significantly lower in individuals with active plantar fasciitis compared to those with a history of plantar fasciitis and controls. Longitudinal stiffness of the PF varied along its length in healthy and plantar fasciitis groups and appears to be related

to clinical measurements of arch stiffness. Both plantar fasciitis groups exhibited increased thickness along the PF compared to controls. SWE has the potential to be a useful tool to monitor recovery and effectiveness of treatment, especially in monitoring progress in the absence of visible changes in clinical foot measures and/or PF thickness. More work is warranted to assess the potential of SWE to provide insight into the etiology of plantar fasciitis.

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Chapter 5

Relationships between Foot Structure Stiffness and Plantar Pressures in Individuals with Plantar Fasciitis

Abstract

Plantar fasciitis is a common musculoskeletal disorder that affects various populations. However, diagnosis remains heavily reliant on patient history and little is known about how plantar fasciitis affects tissue properties prior to or after the resolution of symptoms. Gait deviations have been widely studied in individuals with plantar fasciitis, including plantar pressures, with conflicting results. Exploring potential changes in tissue properties and the effects they may have on foot function may provide better understanding of plantar fasciitis etiology and improve current treatment methods. Thus, the purpose of the present study is to investigate the relationship between foot structure stiffness and plantar pressures in individuals with current plantar fasciitis symptoms and a history of plantar fasciitis symptoms. It is hypothesized that plantar pressures will negatively correlate with foot structure stiffness (i.e. higher plantar pressures will coincide with lower stiffness), suggesting that decreased stiffness is indicative of damage and/or weakening of intrinsic foot structures with a decreased ability to withstand load, thereby relating to increased plantar pressures.

Bilateral measurements of stiffness were assessed and quantified with shear modulus using ultrasound SWE for 11 individuals with active plantar fasciitis symptoms (AG) and 6 individuals with a history of plantar fasciitis symptoms, but currently asymptomatic (HxG) participated in this study (N=17). Bilateral walking plantar pressure data was collected using pressure insoles and were then analyzed using a custom 10-region mask. Plantar pressure regions of interest included the heel pad, 1st met head, and hallux.

Several relationships were found between foot structure stiffness and plantar pressures, but contrary to the hypothesis, most were positively correlated. Differential relationships were observed between symptomatic and asymptomatic individuals. Only one significant relationship was found among currently symptomatic individuals. All other significant relationships observed between stiffness and plantar pressures were found among individuals with a history of plantar fasciitis who were currently asymptomatic. Material properties of the PF were found to directly relate to plantar pressures under the foot in both groups, highlighting a need to further explore how changes in material properties influence plantar pressure distributions within the plantar fasciitis population. Future work is warranted to further investigate the role of foot structure stiffness on plantar pressures and foot function in individuals with acute and chronic plantar fasciitis.

Introduction

Plantar fasciitis is a common musculoskeletal disorder that affects various age and activity populations (Huffer et al 2017), however, the etiology of plantar fasciitis is unclear, and diagnosis relies heavily on patient history (Goff and Crawford 2011). Currently, little is known about how plantar fasciitis affects tissue properties prior to or after the resolution of symptoms and what effects these potential tissue property changes can have on foot function. Knowledge of plantar fascia (PF) and surrounding tissue properties and the effects they have on foot function in individuals with and without plantar fasciitis is needed to better understand the etiology of plantar fasciitis and improve diagnostic and treatment methods.

Structural property changes are well documented in the literature of plantar fasciitis patients with findings of increased thickness of the PF in both the symptomatic and asymptomatic limbs (Granado et al. 2018, Tsai et al. 2000, Ermutlu et al. 2018, McMillan et al. 2009) and compared to controls with no history of plantar fasciitis (Granado et al. 2018, Tsai et al. 2000, McMillan et al. 2009). However, few studies have investigated material properties of the PF in patients with plantar fasciitis. In the study outlined in Chapter 3, we found decreased stiffness of foot muscles and tendons in diabetic individuals compared to controls, which led us to the idea of damage potentially being responsible for the observed decreased stiffness. Consequently, in the study outlined in Chapter 4, we found lower stiffness of foot structures to be related to higher plantar pressures, further suggesting that these changes in material properties may be indicative of damage in the diabetic foot. Lower stiffness of the PF has been found in currently symptomatic patients than in individuals with and without a history of plantar fasciitis in studies using compression elastography (Wu et al. 2015, Lee et al. 2014, Sconfienza et al.

2013) and shear wave elastography (Gatz et al. 2019, Bell et al. 2019). It is very likely that these material property changes coincide with functional changes in the foot. Thickening of the PF has been suggested to relate to severity of heel pain, arch shape, and regional loading (Wearing et al. 2007), yet relationships between tissue material properties and overall foot function in plantar fasciitis individuals have yet to be investigated.

Gait deviations have been widely studied among patients with plantar heel pain and plantar fasciitis (Phillips & McClinton 2017), some of which include assessment of plantar pressures and the medial longitudinal arch. Our previous findings of no differences in any clinical measures between individuals with current plantar fasciitis and individuals with and without a history of plantar fasciitis from the study in the previous chapter align with previous studies finding no difference in arch index/medial longitudinal arch angle in patients with plantar fasciitis (Wearing et. al. 2004, Wearing et. al. 2007, Hsu et. al. 2013). Plantar pressure findings in individuals with plantar fasciitis are conflicting, with some studies finding no difference in peak pressure between symptomatic and control individuals (Hsu et al. 2013, Kanatli et al. 2001) while others found greater pressure in symptomatic individuals compared to controls (Kelly et al. 1995, Werner et al. 2010) using force plates or pressure platforms. This conflicting evidence makes it difficult to draw conclusions about how plantar fasciitis effects plantar pressure distributions, especially with the lack of information concerning material property changes at the tissue level and how it relates to overall foot function.

Therefore, the purpose of the present study is to investigate the relationship between foot structure stiffness and plantar pressures in individuals with current plantar fasciitis symptoms

and a history of plantar fasciitis symptoms. It is hypothesized that plantar pressures will negatively correlate with foot structure stiffness (i.e. higher plantar pressures will coincide with lower stiffness), suggesting that decreased stiffness is indicative of damage and/or weakening of foot structures with a decreased ability to withstand load, thereby relating to increased plantar pressures.

Methods

Eleven individuals with active plantar fasciitis symptoms (AG) and 6 individuals with a history of plantar fasciitis symptoms, but currently asymptomatic (HxG) participated in this study (N=17). Individuals with previous foot surgery and diagnosed osteoarthritis were excluded from study participation. Individuals were assigned to the symptomatic group (AG) based on self-reported pain within the past week prior to study participation including: plantar medial heel pain most noticeable with initial steps after a period of inactivity but also worse following prolonged weight bearing, heel pain precipitated by a recent increase in weight-bearing activity, and pain with palpation of the proximal insertion of the PF. Individuals were assigned to the asymptomatic group (HxG) based on self-reported history of the above criteria, but currently exhibiting an absence of such symptoms for more than one week prior to study participation.

Participants completed a Foot and Ankle Ability Measure (FAAM) questionnaire (Martin et al. 2005) to self-report foot and ankle function in addition to assessment of clinical foot measures including navicular drop (Menz & Munteanu 2006), arch stiffness (Menz & Munteanu 2006), longitudinal arch angle (Jonson & Gross 1997), arch index (Williams et al. 2000), and gastrocnemius and soleus flexibility (Rabin & Kozol 2010) by a licensed physical therapist

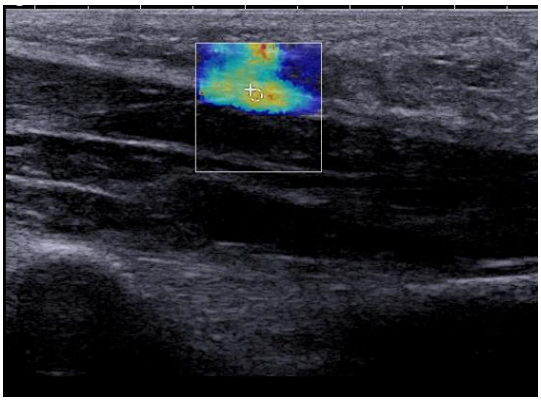
(Table 5.1). Participants lay prone, in a relaxed position, on an examination table with their feet hanging just slightly off the end for the entirety of the scanning protocol. All images were taken in the longitudinal view. Since tissue property changes are reported in both the symptomatic and asymptomatic limbs in patients with plantar fasciitis (Granado et al. 2018, Tsai et al. 2000, Ermutlu et al. 2018, McMillan et al. 2009), we measured both feet in all groups. However, only the symptomatic foot or foot with history of plantar fasciitis symptoms was included in the analyses performed in the study (AG n=17 feet, HxG n=10 feet). All participants provided written informed consent and all procedures were approved by the East Carolina University Institutional Review Board.

Table 5.1 Plantar fasciitis group demographics including IPAQ scores. Significance indicated by bold font and * ($p \leq 0.05$). Trending indicated by † ($0.05 < p \leq 0.10$).

Demographics	**AG**	**HxG**	**p**
N	11	6	-
Sex	3M/8F	1M/5F	-
Age	**50.9 (6.9**	**42.5 (8.5)**	**0.041***
Height (cm)	171.7 (12.6)	166.6 (9.8)	0.41
Weight (kg)	92.2 (24.8)	78.7 (17.7)	0.26
BMI (kg/m^2)	31.0 (5.7)	28.3 (4.5)	0.34
Years with plantar fasciitis	2.9 (2.8)	4.3 (4.1)	0.45
Clinical Foot Measures			
Navicular drop (cm)	0.68 (0.23)	0.61 (0.37)	0.71
Arch stiffness (N/cm)	1439.9 (519.8)	1839.5 (1131.8)	0.53
Gastrocnemius (°)	37.0 (5.0)	34.7 (12.1)	0.64
Soleus (°)	45.6 (5.6)	43.9 (7.1)	0.79
FAAM Self-Function Scores			
Normal	2	3	-
Nearly Normal	5	2	-
Abnormal	4	1	-

Longitudinal material stiffness was assessed and quantified with shear modulus using SWE taken on an Aixplorer ultrasound system (SuperSonic Imagine, Aix-en-Provence, France). The PF was assessed in two regions because of previous findings of inhomogeneous stiffness in healthy and plantar fasciitis participants by Putz et al. (2017) and Gatz et al. (2019). The PF was measured at a proximal and distal site, located at ~40% and ~75% of foot length from the most posterior aspect of the heel, respectively. Shear modulus was determined in a 1 mm circular region of interest placed in the middle of the tissue at each measurement site (Figure 5.1). The mean shear modulus of three measurements were averaged and reported as longitudinal stiffness for each site.

Figure 5.1 Example elastogram with circular region of interest used to quantify stiffness for the proximal PF.



Structures measured included the PF, flexor hallucis brevis muscle (FHB), abductor hallucis muscle (AHB) and tendon (AHT), and the Achilles tendon (AchT). The FHB has been shown to be a substantial contributor to foot posture (Angin et al. 2018) and increase medial longitudinal arch height along with other intrinsic flexor muscles following a strengthening intervention (Hashimoto & Sakuraba 2014). The AHB has previously been shown to act as a dynamic elevator (Wong 2007), support the medial longitudinal arch (Fiolkowski et al. 2003)

and help maintain medio-lateral balance in quiet and single leg standing (Kelly et al. 2012). Due to the contributions of these structures to the function of the longitudinal arch and ease of measurement, these structures were examined as the tissue properties of these structures may be altered in addition to the PF due to changes induced by plantar fasciitis. The AchT was also examined because it is typically evaluated and included in treatment of plantar fasciitis (DiGiovanni et al. 2003), and its anatomical relationship with the PF (Stecco et al. 2013).

Bilateral walking plantar pressure data was collected using a Novel Pedar pressure measurement system (novel gmbh, Munich, Germany) which utilizes 2 mm thick sensor insoles that contain a matrix of 99 sensors to directly measure the pressure at the foot interface at a rate of 50 Hz or 100 Hz per foot. All participants wore standardized footwear to ensure against shoe design influence on plantar pressures and walking biomechanics. These data were then analyzed using a custom 10-region mask with Novel software. The 10 regions were: medial and lateral heel, medial and lateral arch, 1st metatarsal (met) head, 2nd met head, 3rd-5th met heads, hallux, 2nd toe, and lesser toes. Commonly susceptible ulcer sites include the heel pad, 1st met head, and hallux (Pai & Ledoux 2010), thus in the present study, plantar pressure distributions were analyzed only at these locations. Variables calculated included peak pressure and pressure-time integral (PTI) at both a self-selected (average of 1.11m/s) and standardized walking speed (1.30m/s).

Regression analysis was used to assess relationships between stiffness and plantar pressures at a self-selected and standard speed. Plantar pressure regions of interest included the

medial heel, 1st metatarsal head (1st met head), and hallux. Feet were treated as independent observations for all analyses in the present study.

Results

Group subject demographics are shown in Table 5.1, including clinical foot measures and FAAM scores. No statistically significant differences in height, weight, BMI, or years with plantar fasciitis were observed between AG and HxG individuals, but age differences did exist between the groups (p=0.041). Years with plantar fasciitis ranged from 6 months to 10 years in both plantar fasciitis groups, with the majority (8 out of 11) of AG participants reporting plantar fasciitis symptoms for 3 years or less. No statistically significant differences were observed between groups for any of the clinical foot measures (Table 5.1). Self-reported foot and ankle function on the FAAM was less than normal in 82% of AG participants and in 50% of HxG participants. Mean plantar pressure values are reported in table 5.2 for both groups.

Table 5.2 Comparison of mean plantar pressure values between groups.

	Self-Selected Speed				**Standard Speed (1.3m/s)**			
	AG		**HxG**		**AG**		**HxG**	
	Peak Pr. (kPa)	**PTI (kPa*s)**	**Peak Pr. (kPa)**	**PTI (kPa*s)**	**Peak Pr. (kPa)**	**PTI (kPa*s)**	**Peak Pr. (kPa)**	**PTI (kPa*s)**
Medial Heel	117.9 (28.9)	28.1 (9.3)	119.4 (39.8)	23.8 (9.2)	138.8 (26.8)	27.2 (7.4)	144.14 (21.5)	28.31 (4.8)
1st Met Head	118.6 (69.8)	36.4 (27.9)	100.0 (38.1)	22.7 (12.1)	129.2 (73.1)	35.2 (25.8)	110.82 (37.0)	23.68 (8.0)
Hallux	96.4 (94.5)	24.6 (26.0)	76.5 (61.5)	14.7 (16.7)	108.1 (102.0)	23.9 (25.6)	90.68 (59.9)	16.36 (14.0)

Stiffness vs Peak Pressure

Several relationships were observed between stiffness and peak pressure at both the self-selected and standard speeds for various structures the medial heel (Table 5.3), 1st met head (Table 5.4), and hallux (Table 5.5). However, relationships only reached significance in the HxG for peak pressure. Select correlations between stiffness and plantar pressure variables are displayed in Figure 5.2.

At the medial heel, peak pressure displayed strong relationships in the HxG with proximal PF stiffness at the self-selected speed (r=-0.74, p=0.015) and with AchT at the standard speed (r=0.63, p=0.049). A trend existed in the AG for AchT stiffness (r=0.44, p=0.076) at the standard speed. No other relationships were observed for stiffness of any structure with medial heel peak pressure at either speed (Table 5.3).

Table 5.3 R and p values for correlations between stiffness and peak plantar pressure at the medial heel. Significance indicated by bold font and * ($p<.05$). Trends indicated by † ($.10 \leq p \geq .05$).

Medial Heel	**Self-selected Speed**				**Standard Speed (1.3m/s)**			
	AG		**HxG**		**AG**		**HxG**	
	r	p	r	p	r	p	r	p
Proximal PF	0.41	0.11	**-0.74**	**0.015***	-0.06	0.82	-0.16	0.66
Distal PF	0.07	0.79	0.38	0.27	0.12	0.66	-0.05	0.89
AHT	0.19	0.46	0.40	0.26	-0.07	0.78	0.43	0.21
AchT	0.25	0.33	0.50	0.14	0.44	0.076†	**0.63**	**0.049***
FHB	-0.09	0.73	0.20	0.57	-0.32	0.21	-0.13	0.73
AHB	0.13	0.61	-0.18	0.61	-0.16	0.55	0.24	0.51
HP	0.29	0.25	0.01	0.98	0.40	0.12	-0.08	0.83

At the 1st met head, a strong positive relationship was observed with distal PF stiffness (r=0.65, p=0.043) in the HxG at the self-selected speed, as well as a trend for proximal PF stiffness at the standard speed (r=0.55, p=0.099). Trends existed in the AG for negative

relationships with AHB stiffness at both the self-selected (r=-0.43, p=0.085) and standard speeds (r=-0.44, p=0.078). Trends also existed in the AG for relationships with FHB stiffness (r=-0.41, p=0.098) and HP stiffness (r=0.46, p=0.062) at the standard speed. No other relationships were observed for stiffness for any structure with the 1st met head pressure at either speed (Table 5.4).

Table 5.4 R and p values for correlations between stiffness and peak plantar pressure at the 1st met head. Significance indicated by bold font and * ($p<.05$). Trends indicated by † ($.10 \leq p \geq .05$).

1st Met Head	**Self-selected Speed**				**Standard Speed (1.3m/s)**			
	AG		**HxG**		**AG**		**HxG**	
	r	p	r	p	r	p	r	p
Proximal PF	-0.34	0.19	-0.21	0.56	-0.33	0.19	0.55	0.099†
Distal PF	0.37	0.15	**0.65**	**0.043***	0.30	0.24	0.36	0.31
AHT	-0.38	0.13	0.39	0.27	-0.31	0.23	0.37	0.29
AchT	0.13	0.62	0.28	0.44	0.23	0.38	0.18	0.61
FHB	-0.40	0.11	-0.06	0.88	-0.41	0.098†	-0.39	0.27
AHB	-0.43	0.085†	0.00	1.00	-0.44	0.078†	0.30	0.40
HP	0.37	0.15	-0.16	0.65	0.46	0.062†	0.01	0.98

At the hallux, peak pressure displayed strong positive relationships in HxG with proximal PF stiffness (r=0.87, p=0.001) and with AHB stiffness (r=0.65, p=0.043) at the standard speed. A trend existed in HxG for distal PF stiffness (r=0.58, p=0.081) at the self-selected speed. In the AG, a trend existed for HP stiffness at the standard speed (r=0.47, p=0.057). No other relationships were observed for stiffness for any structure with hallux peak pressure at either speed (Table 5.5).

Table 5.5 R and p values for correlations between stiffness and peak plantar pressure at the hallux. Significance indicated by bold font and * ($p<.05$). Trends indicated by † ($.10 \leq p \geq .05$).

Hallux	**Self-selected Speed**				**Standard Speed (1.3m/s)**			
	AG		**HxG**		**AG**		**HxG**	
	r	**p**	**r**	**p**	**r**	**p**	**r**	**p**
Proximal PF	-0.17	0.53	0.16	0.67	-0.23	0.39	**0.87**	**0.001***
Distal PF	0.17	0.52	0.58	0.081†	0.13	0.63	0.34	0.33
AHT	-0.18	0.49	0.43	0.22	-0.16	0.54	0.38	0.28
AchT	0.09	0.72	0.34	0.33	0.25	0.34	0.16	0.66
FHB	-0.28	0.27	0.00	1.00	-0.35	0.17	-0.13	0.73
AHB	-0.29	0.25	0.52	0.13	-0.32	0.21	**0.65**	**0.043***
HP	0.35	0.17	-0.39	0.27	0.47	0.057†	-0.50	0.15

Stiffness vs Pressure-Time Integral

Several relationships were observed between stiffness and pressure-time integral at both the self-selected and standard speeds for various structures the medial heel (Table 5.6), 1st met head (Table 5.7), and hallux (Table 5.8). A strong positive relationship was observed in the HxG with AHT stiffness at the standard speed ($r=0.69$, $p=0.026$). Trends were observed in the HxG with proximal PF stiffness ($r=-0.60$, $p=0.066$) and AHT stiffness ($r=0.56$, $p=0.091$) at the self-selected speed. No relationships were observed in the AG between stiffness and pressure-time integral at the medial heel for any of the examined structures at either speed (Table 5.6).

Table 5.6. R and p values for correlations between stiffness and pressure-time integral at the medial heel. Significance indicated by bold font and * ($p<.05$). Trends indicated by † ($.10 \leq p \geq .05$).

Medial Heel PTI	**Self-selected Speed**				**Standard Speed (1.3m/s)**			
	AG		**HxG**		**AG**		**HxG**	
	r	p	r	p	r	p	r	p
Proximal PF	-0.06	0.82	-0.60	0.066†	-0.10	0.70	0.42	0.22
Distal PF	0.13	0.61	0.33	0.34	0.21	0.42	-0.12	0.74
AHT	-0.04	0.88	0.56	0.091†	-0.06	0.82	**0.69**	**0.026***
AchT	0.27	0.30	0.20	0.59	0.31	0.23	-0.33	0.35
FHB	-0.34	0.18	0.20	0.58	-0.30	0.25	-0.40	0.25
AHB	-0.19	0.47	-0.12	0.75	-0.17	0.52	0.51	0.13
HP	0.23	0.38	-0.06	0.86	0.25	0.34	0.13	0.72

At the 1st met head, strong negative relationships were observed in the AG with AHB stiffness at both the self-selected (r=-0.51, p=0.038) and standard speed (r=-0.52, p=0.034). Trends were observed in the AG with FHB stiffness at both the self-selected (r=-0.42, p=0.093) and standard speed (r=-0.44, p=0.079). At the self-selected speed, trends were observed in the AG with AHT stiffness (r=-0.42, p=0.092) and in the HxG with distal PF stiffness (r=0.57, p=0.086). No other relationships were observed between stiffness and pressure-time integral at the 1st met head at either speed for either group (Table 5.7).

Table 5.7 R and p values for correlations between stiffness and pressure-time integral at the 1st met head. Significance indicated by bold font and * ($p<.05$). Trends indicated by † ($.10 \leq p \geq .05$).

1st Met Head PTI	**Self-selected Speed**				**Standard Speed (1.3m/s)**			
	AG		**HxG**		**AG**		**HxG**	
	r	p	r	p	r	p	r	p
Proximal PF	-0.41	0.11	-0.19	0.60	-0.39	0.12	0.41	0.23
Distal PF	0.36	0.15	0.57	0.086†	0.34	0.18	0.38	0.28
AHT	-0.42	0.092†	0.45	0.19	-0.39	0.12	0.24	0.50
AchT	0.04	0.89	0.01	0.99	0.06	0.82	-0.09	0.80
FHB	-0.42	0.093†	0.09	0.80	-0.44	0.079†	-0.34	0.34
AHB	**-0.51**	**0.038***	-0.03	0.93	**-0.52**	**0.034***	0.08	0.82
HP	0.25	0.33	-0.17	0.64	0.31	0.23	0.35	0.32

At the hallux, strong positive relationships were observed in the HxG with proximal PF stiffness (r=0.92, p=0.0002) and AHB stiffness (r=0.68, p=0.032), but only at the standard speed. Trending relationships were observed in the HXG with AHT stiffness (r=0.56, p=0.089) and AHB stiffness (r=0.61, p=0.059) at the self-selected speed. No significant relationships were observed in the AG between stiffness and pressure-time integral at the hallux for any of the examined structures at either speed (Table 5.8). However, trends were observed with FHB

stiffness (r=-0.42, p=0.096) and HP stiffness (r=0.44, p=0.076) in the AG, but only at the standard speed.

Table 5.8 R and p values for correlations between stiffness and pressure-time integral at the hallux. Significance indicated by bold font and * (p<.05). Trends indicated by † (.10 ≤p≥ .05).

Hallux PTI	**Self-selected Speed**				**Standard Speed (1.3m/s)**			
	AG		HxG		AG		HxG	
	r	p	r	p	r	p	r	p
Proximal PF	-0.26	0.32	0.29	0.42	-0.28	0.28	**0.92**	**0.0002***
Distal PF	0.19	0.48	0.45	0.19	0.12	0.64	0.24	0.50
AHT	-0.22	0.40	0.56	0.089†	-0.19	0.48	0.46	0.18
AchT	0.20	0.43	0.24	0.51	0.26	0.32	0.10	0.79
FHB	-0.36	0.16	-0.03	0.93	-0.42	0.096†	-0.14	0.70
AHB	-0.36	0.16	0.61	0.059†	-0.40	0.11	**0.68**	**0.032***
HP	0.39	0.13	-0.39	0.26	0.44	0.076†	-0.47	0.17

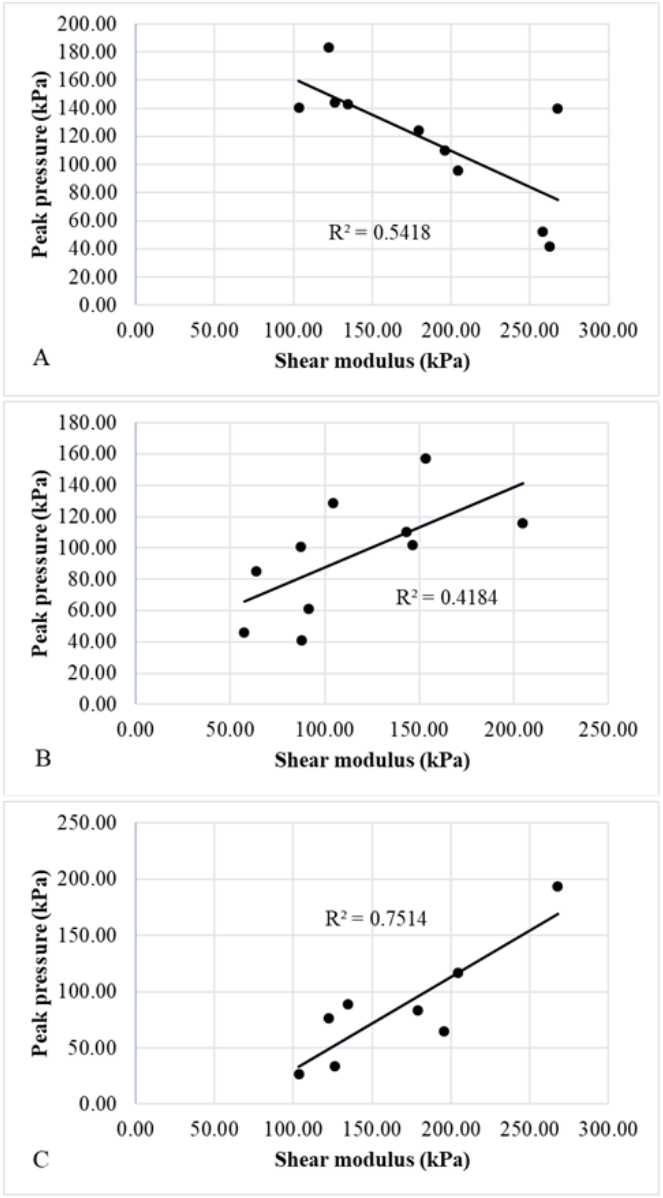
Discussion

The purpose of the present study is to investigate the relationship between foot structure stiffness and plantar pressures in individuals with current plantar fasciitis symptoms and a history of plantar fasciitis symptoms. The results partially supported the hypothesis as foot structure stiffness negatively correlated with plantar pressures for some, but not all structures, and the presence of these relationships seemed to be dependent on walking speed and pressure site.

The present study found several relationships between foot structure stiffness and peak plantar pressure. Interestingly, all significant relationships between stiffness and peak plantar pressure were found among individuals with a history of plantar fasciitis who were currently asymptomatic (HxG), while only trending relationships were found in currently symptomatic individuals (AG). The HxG exhibited strong relationships between proximal PF stiffness and

peak plantar pressure at both the medial heel and the hallux, as well as a strong relationship between distal PF stiffness and peak pressure at the 1st met head (Figure 5.2). Of these relationships, only the relationship between proximal PF stiffness and the medial heel was negative. Thus, the proximal PF exhibited relationships with multiple pressure sites, yet the direction of the relationship differed based on the site, as it was negative at the medial heel ($r=-0.74$), yet positive at the hallux ($r=0.87$). Because the PF spans the length of the foot, these results may indicate functional differences of the PF that are dependent on the region of the foot with which the PF is interacting. In addition, stiffness of the proximal and distal PF, as well as the AchT displayed relationships with the region of the foot directly in its proximity. Effectively, the proximal PF and AchT affected peak pressure at the heel and the distal PF affected peak pressure at the 1st met head. Evidence that PF properties are breaking down foot function in individuals with plantar fasciitis shows the importance of needing to specifically target the PF in treatment. Stretching is the standard treatment recommended in general practice to individuals who are diagnosed with plantar fasciitis (Chew et al. 2013), yet most stretching interventions place an emphasis on stretching of the AchT without specifically addressing the PF (DiGiovanni et al. 2003). Our results suggest that individuals with plantar fasciitis may stand to benefit from treatment interventions designed to directly target the PF, or specific regions of the PF, to more effectively reduce pressure under the foot than a generic stretching intervention.

Figure 5.2 Select regression analyses observed in the HxG between peak pressure and select structures: proximal PF with medial heel at self-selected speed (a), distal PF with 1st met head at self-selected speed (b), and proximal PF with hallux at standard speed (c).



Several relationships were also found between foot structure stiffness and PTI. All but one of the significant relationships between stiffness and PTI were found among individuals with a history of plantar fasciitis who were currently asymptomatic (HxG). In the HxG, proximal PF and AHB stiffness exhibited relationships with PTI at the hallux, and AHT stiffness exhibited a relationship with PTI at the medial heel. In the AG, only AHB stiffness displayed a relationship

with PTI at the 1st met head. In the previous chapter, relationships between AHT stiffness and pressure were also observed in diabetic individuals. In the present study, both the HxG and the AG displayed relationships with either the AHB or AHT. The AHB has been shown to effect calcaneal and metatarsal center of pressure and segment angles in response to load (Kelly et al. 2013). Based on results from the present study, the AHB muscle-tendon unit influences plantar pressure (PTI) across the span of the foot, at all three of the measured pressure sites, which seems intuitive given that the AHB attaches proximally to the calcaneus and distally to the 1st met head (Cameron et al. 2008). The observed relationships indicate that there is something differential occurring in each group in respect to the AHB muscle-tendon unit that is influencing foot function. Because the AHB has previously been shown to play a role in elevating (Wong 2007) and supporting the medial longitudinal arch (Fiolkowski et al. 2003), it could potentially serve as another structure to target in treatment interventions to help decrease plantar pressures and improve foot function in individuals with active plantar fasciitis and with a history of plantar fasciitis.

Plantar pressure distributions have been widely used as a risk assessment tool for development of diabetic foot ulcers, although it has been previously suggested that peak pressure alone is not enough to predict injury risk (Lavery et al. 2003?). Evidence of relationships between foot structure stiffness and PTI in the present study suggests that contact time may play an important role in loading characteristics and injury risk for regions under the foot in addition to absolute pressure values. Thus, results of the present study, although conducted on a different clinical population, suggest that it may be important to consider other plantar pressure variables, like PTI, when using plantar pressure data to evaluate injury risk.

A limitation of the present study is that it is unknown whether stiffness and thickness were once similar between groups before injury occurred or how long the individuals in the HxG had been asymptomatic since their last episode of plantar fasciitis. However, based on results from the present study, it is evident that changes in material properties in the PF are directly affecting plantar pressures under the foot in individuals with acute and chronic plantar fasciitis. Thus, longitudinal studies assessing changes in stiffness in response to current treatment interventions (i.e. stretching, collagen injection, orthotics, corticosteroid injection) as well the ability of SWE to monitor recovery and effectiveness of treatment are warranted. Additionally, investigating how changes in stiffness relate to and/or modify plantar pressures in individuals with plantar fasciitis would provide further insight into the recovery process at the local tissue level. For comparison purposes to a previous chapter (Chapter 3), plantar pressure relationships were only analyzed at the medial heel, 1st met head, and hallux. Excessive pronation and arch collapse are well documented in the literature in individuals with plantar fasciitis (Barrett & O'Malley 1999, Young et al. 2001, Crosby & Humble 2001), and likely leads to increased plantar pressure under the arch. Thus, it may be beneficial to assess relationships between foot structure stiffness and plantar pressure at other relevant sites under the foot, such as the medial and lateral arch, in future studies involving individuals with plantar fasciitis.

In conclusion, the present study found several relationships between foot structure stiffness and plantar pressures, but most were positively correlated, suggesting that stiffness is related to pressures in individuals with plantar fasciitis. The presence and direction of these relationships seemed to be dependent on walking speed and pressure site, as well as symptom

status. With one exception, all significant relationships observed between stiffness and plantar pressures were found among individuals with a history of plantar fasciitis who were currently asymptomatic (HxG), while mostly trending relationships were found in currently symptomatic individuals (AG). More work is warranted to further investigate the role of foot structure stiffness on plantar pressures and foot function in individuals with acute and chronic plantar fasciitis.

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Chapter 6

Integrated Discussion

Main Findings

The ultimate purpose of this dissertation was to investigate the relationship between foot structure stiffness (material properties) and plantar pressures during gait in diabetic individuals. The four studies reported within this body of work served to experimentally investigate the existence of altered material and architectural properties of individual foot structures and assess variables believed to be relevant to explain the relation of these observed altered properties to plantar pressure distributions in diabetic individuals. The first study provided information as to the existence of altered material and architectural properties in individual foot structures in diabetic individuals compared to controls, which had yet to be conducted in current literature. The second study directly explored the overall hypothesis that altered material properties are related to plantar pressure distributions in diabetic individuals. The third and fourth studies provided a unique opportunity to explore and compare material properties observed in diabetic individuals with another clinical population that exhibits known similar architectural property changes upon injury in hopes of providing further insight into clinical applications of these findings. Thus, the third study explored the existence of altered material and architectural properties in individuals with plantar fasciitis compared to controls using shear wave elastography (SWE), one of few recent studies in current literature to do so. The fourth study examined potential relationships between altered material properties and plantar pressures in individuals with plantar fasciitis to help give further insight into the effect of altered material properties on plantar pressure distributions.

The purpose of the first study was to measure material and structural properties of foot structures in diabetic and non-diabetic individuals. In this study, it was important to establish a

detectable difference in properties between individuals from diabetic and non-diabetic populations. It was found that foot structure stiffness in diabetic individuals was not significantly different from controls, however, diabetic individuals displayed large variability in material properties, evidenced by large standard deviations and percent differences. Structurally, diabetic individuals had a thicker heel pad than controls, but muscles and tendons were thinner than controls. Additionally, no relationships were observed between stiffness and glycemic control (HbA1c) across all participants or within groups, but differential relationships were found within the diabetic group when accounting for Type 1 or Type 2 status. The results of this study provided evidence, for the first time, that altered material and structural properties of individual foot structures are detectable in diabetic individuals using ultrasound SWE, despite the lack of significance observed in some structures, and that these altered properties are not as simply related to glycemic control as previously assumed. Evidence of altered properties in diabetic individuals led to the second study to investigate how these altered properties influence foot function.

The purpose of the second study was to investigate the relationship between foot structure stiffness and plantar pressures in diabetic individuals. Several significant relationships were observed, but interestingly, all but one of the measured structures exhibited negative relationships. This suggests that decreased stiffness of foot structures is related to increased plantar pressures. Additionally, no significant relationships were observed between glycemic control and stiffness, nor between glycemic control and plantar pressures. The observation of negative relationships between stiffness and plantar pressures could be indicative of damage or

weakened structures that have a decreased ability to withstand load, leading to increased pressures under the foot.

A musculoskeletal clinical population may more readily exhibit changes in soft tissue than a control population for comparison purposes. Plantar fasciitis is a common musculoskeletal disorder that, like diabetes, is associated with thickening of the PF. Some studies have attempted to address PF stiffness with compression elastography, finding decreased stiffness in individuals with active plantar fasciitis symptoms compared to controls. Other studies have attempted to examine plantar pressures in plantar fasciitis populations, but results have been conflicting. Some report increased plantar pressures compared to controls (Hsu et al. 2013, Kanatli et al. 2001), while others support decreases (Kelly et al. 1995, Werner et al. 2010). It is possible that, in addition to thickening of the PF, plantar fasciitis populations may also exhibit material property changes of the PF and other arch supporting structures that contribute to the plantar fasciitis injury mechanism that are similar to the material property changes observed in structures in the diabetic foot. Furthermore, the plantar fasciitis population may also exhibit relationships between foot structure stiffness and plantar pressures, which could give further insight into the relationship between foot structure stiffness and foot function in order to aid in developing better treatment options for both diabetics and plantar fasciitis populations.

Thus, the purpose of the third study was two-fold: 1) to assess stiffness of the PF and foot structures supporting the longitudinal arch in individuals with and without plantar fasciitis, and 2) to assess thickness of the PF and foot structures supporting the longitudinal arch in individuals with and without plantar fasciitis. Decreased stiffness of the PF was found in individuals with

active plantar fasciitis symptoms compared to individuals without (controls) and with a history of plantar fasciitis (currently asymptomatic). Increased thickness of the PF was found in individuals with active plantar fasciitis symptoms compared to controls, but not compared to currently asymptomatic individuals. These results could indicate a weakening of the PF and other arch supporting structures which may contribute to or further exacerbate symptoms of plantar fasciitis. Therefore, it was important to explore how these altered material properties relate to plantar pressures and foot function in individuals with plantar fasciitis, as they may exhibit similar relationships to those observed in diabetic individuals in the previous study.

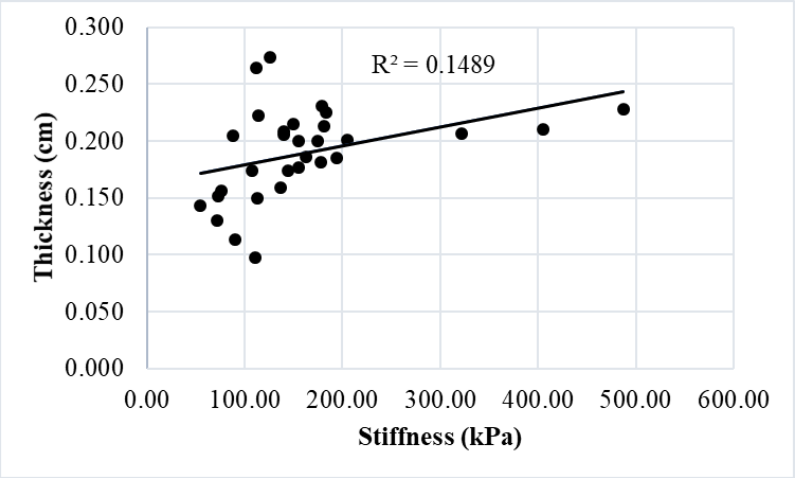
The purpose of the fourth study was to investigate the relationship between foot structure stiffness and plantar pressures in individuals with current plantar fasciitis symptoms and a history of plantar fasciitis symptoms. Several relationships were found between foot structure stiffness and plantar pressures, but most were positively correlated, suggesting that stiffness is related to pressures in individuals with plantar fasciitis. However, the presence and direction of these relationships seemed to be dependent on walking speed and pressure site, as well as symptom status. Only one significant relationship found among currently symptomatic individuals. All other significant relationships observed between stiffness and plantar pressures were found among individuals with a history of plantar fasciitis who were currently asymptomatic. Finding such differential relationships between symptomatic and asymptomatic individuals suggests that something is occurring to change material properties during the recovery process in individuals with plantar fasciitis. Stiffness seemed to be related to clinical foot measures, but opposite relationships observed between currently symptomatic individuals

and those with chronic plantar fasciitis (currently asymptomatic) may indicate some important functional differences that exist between these groups.

Future Directions

The results of the study outlined in Chapter 2 showed altered material and structural properties in diabetic individuals compared to non-diabetic individuals. Despite stiffness differences not reaching statistical significance for any of the examined structures, findings of increased stiffness in diabetic individuals still clearly illustrated the proposed ideas in literature and the original hypothesis that diabetic individuals exhibit increased stiffness compared to controls. Thickness alone was not enough to explain the observed differences in stiffness as only the proximal PF had a significant relationship between stiffness and thickness (Figure 1), but this relationship was only moderate ($r=0.39$, $p=0.035$). Few studies have examined properties like muscle density and intramuscular fatty infiltration of muscle and tendons in diabetic feet, (Cheuy et al. 2013, Robertson et al. 2002). Future studies should investigate the compositional nature of individual foot structures in conjunction with stiffness and structural measures to give further insight into potential explanations for the observed changes of stiffness and thickness in structures in the diabetic foot.

Figure 6.1 Correlation between stiffness and thickness of the proximal PF in diabetic individuals. (p=0.035)



The study outlined in Chapter 2 is the first to use ultrasound SWE to measure material properties of multiple individual foot structures in diabetic individuals. The lack of relationship between stiffness and HbA1c levels may be confounded by medications being used by diabetic individuals for glycemic control. Future studies should investigate the effects of medications on HbA1c levels and foot structure stiffness, perhaps longitudinally at onset (diagnosis) of diabetic status until glycemic levels are well-regulated. Evidence of differential relationships between stiffness and HbA1c levels observed among Type 1 and Type 2 diabetic individuals within the diabetic group suggest a need to further investigate stiffness differences between Type 1 and Type 2 individuals and how stiffness relates to glycemic control in each of these groups. Studies have also shown differences in plantar soft tissue stiffness between diabetic individuals with and without peripheral neuropathy (Jan et al. 2013, Klaesner et al. 2002, Zheng et al. 2000). Although neuropathic individuals were included in the study outlined in Chapter 2, not enough were recruited to make these comparisons between neuropathic and non-neuropathic diabetic individuals for the observed foot structures, thus more work is warranted on this topic. Additionally, the finding of relationships between stiffness and physical activity in controls that

was lacking in diabetic individuals suggests some alteration in foot function is occurring in diabetic individuals that is limiting their ability to respond to physical activity compared to controls. Longitudinal training studies should be conducted to investigate how material properties and strength of structures in the foot respond to physical activity in diabetic individuals.

The results outlined in Chapter 3 showed that stiffness of foot structures is related to plantar pressures, but contrary to the proposed hypothesis and suggestions in previous literature, as all significant relationships were negative except those at the heel pad. Several studies have proposed a link between increased stiffness of muscles and tendons in the diabetic foot and increased plantar pressures (Caravaggi et al. 2016, Fernando et al. 1991, Francia et al. 2015, Giacomozzi et al. 2008, Mueller et al. 1989, Veves et al. 1992, Zimny et al. 2004) due to observed limited joint mobility. However, our findings of decreased stiffness of foot structures relating to increased plantar pressures indicate that a potential mechanism of foot ulcer development is not as simple as increased stiffness leading to increased pressures. Future studies should include gait analysis along with plantar pressure measurements to assess whether gait deviations or specific gait patterns/variables are present that are contributing to altered pressures (i.e. metatarsal-phalangeal joint power, center of pressure excursion, ground reaction forces). Investigating the relationship of stiffness with plantar pressures in diabetics with peripheral neuropathy, as well as those with a history of ulcers would further elucidate these relationships and how they potentially contribute to ulcer development.

Hba1c levels were not found to be significantly related to stiffness or plantar pressures, once again suggesting that glycemic control alone may not indicative of these observed alterations. It is evident that damage is occurring, but as previously stated, medications used by diabetic individuals may have confounded the ability to accurately assess relationships between stiffness and HbA1c levels. Conducting longitudinal studies that examine how medications influence HbA1c levels and intrinsic foot stiffness are warranted. Studies using tissue specific measures of glycation that can be compared to ultrasound SWE measures of material properties could also provide valuable insight into how physiological changes at the tissue level are being reflected in ultrasound measurements of stiffness and give better interpretation to ultrasound SWE measurements of tissue material properties. Additionally, investigating how tissue glycation relates to plantar pressures in diabetic individuals would allow a more direct comparison of how physiological changes at the tissue level are affecting plantar pressure distributions.

The results of the study outlined in Chapter 4 showed that individuals with active plantar fasciitis symptoms have decreased PF stiffness compared to controls and to individuals with a history of plantar fasciitis that are currently asymptomatic. Although plantar fascia stiffness was lower in the active plantar fasciitis group and higher in diabetic individuals compared to controls, no statistically significant differences were observed between these patient groups (Table 1). Muscles and tendons also appear to have decreased stiffness in the active plantar fasciitis group, but diabetic individuals seem to exhibit even lower stiffness of muscles and tendons in comparison to individuals with active plantar fasciitis and a history of plantar fasciitis (Table 1). In the study outlined in Chapter 3, we found decreased muscle and tendons stiffness in diabetic

individuals coincided with higher pressures. Because individuals with active plantar fasciitis also display this decreased stiffness in these structures, it was important to assess the relationship between stiffness and plantar pressures in individuals with plantar fasciitis. This could give further insight into the etiology of plantar fasciitis development, as well as a better understanding and comparison of potential injury mechanism in diabetic and plantar fasciitis populations. Damage to the PF seems reversible in plantar fasciitis, but the question remains whether it is possible to assess what is actually happening at the tissue level that leads to this "recovery" of material properties in individuals with chronic plantar fasciitis.

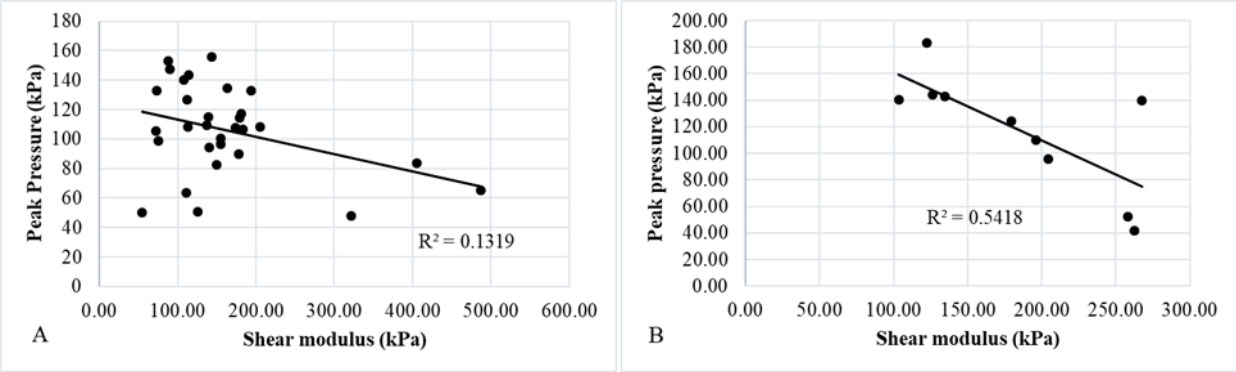
Table 6.1 Comparison of shear modulus between patient groups. Statistical significance indicated by * for difference from symptomatic, [a] for difference from asymptomatic ($p<0.05$).

	Diabetic	**Symptomatic**	**Asymptomatic**
Proximal PF	160.98 (94.09)	114.08 (74.15)	185.40 (62.54)
Distal PF	97.25 (56.72)	92.03 (31.05)	113.97 (46.38)
AbHT	282.43 (74.31)[a]	306.95 (102.05)	348.03 (72.24)
AchT	313.95 (119.74)*	417.70 (134.24)	392.67 (81.25)
FHBM	25.54 (8.42)	22.46 (8.00)	27.01 (7.51)
AbHM	27.72 (9.51)	26.04 (6.53)	28.60 (11.41)
Heel Pad	24.84 (25.78)	19.02 (15.26)	11.68 (4.07)

The results of the final study outlined in Chapter 5 is the first to assess relationships between material properties measured by SWE and plantar pressures in individuals with plantar fasciitis. Our results show that stiffness of foot structures is related to plantar pressures, but mostly contrary to the proposed hypothesis based on results from Chapter 3, as most relationships observed were positive. However, there were a few relationships that were similar in direction in both the diabetic and plantar fasciitis populations. Notably, proximal PF stiffness exhibited a relationship with medial heel peak pressure that was moderately negative in the diabetic group (r=-0.36) and strongly negative in the asymptomatic plantar fasciitis group (r=-0.74) (Figure 2). Table 1 shows that there was no difference in proximal PF stiffness among any

of the diabetic or plantar fasciitis groups, and the mean value for the diabetic and asymptomatic groups were actually quite similar. Both of these relationships indicate that decreased stiffness of the PF leads to increased plantar pressures under the heel within these groups. As it is known that the PF plays a key role in foot function and that damage to the PF is a root cause of pain and injury in individuals with plantar fasciitis (Crosby & Humble 2001), these results suggest that damage to the PF may be a critical factor in the observed anomalies in plantar pressure distributions and foot function in diabetic individual.

Figure 6.2 Proximal PF stiffness correlations with medial heel peak pressure at self-selected speeds for individuals with diabetes (a) and asymptomatic plantar fasciitis (b).



Stretching is the standard treatment recommended in general practice to individuals who are diagnosed with plantar fasciitis (Chew et al. 2013). If diabetic and plantar fasciitis populations display relationships between lower stiffness and high pressures, investigating responses of material properties to stretching and other interventions are warranted for both diabetic and plantar fasciitis populations, as these may potentially increase strength and stiffness of foot structures, and thereby decrease plantar pressures. The evidence of relationships between stiffness and clinical foot measures of diabetic and active plantar fasciitis groups that are

opposite to controls and individuals with a history of plantar fasciitis suggest a potential shift that may occur in recovery or that is unique to individuals within these populations (Table 2).

Table 6.2 R and p values for proximal PF correlations with clinical foot measures in control, diabetic, and plantar fasciitis populations. Statistical significance indicated by * and bold font. Trending indicated by †.

	Navicular Drop (cm)		**Arch Stiffness (N/cm)**	
	r	p	r	p
Control	0.33	0.15	-0.22	0.34
Diabetic	-0.29	0.12	**0.40**	**0.028***
Symptomatic	-0.49	0.065†	0.21	0.46
Asymptomatic	0.60	0.065†	**-0.65**	**0.041***

One study has shown that three months following collagen injection as a plantar fasciitis treatment, the plantar fascia exhibited increased stiffness with minimal change in thickness (Kim et al. 2016), thus it is possible to induce and detect material property changes and symptom resolution even in the absence of noticeable structural property changes. Longitudinal studies examining response of material properties to current and novel treatment interventions and how altering material properties of the PF impacts resolution of symptoms, recurrence and frequency of recurrence of symptoms are warranted to potentially monitor recovery and response to treatment interventions. This is especially important due to our findings of differential relationships between stiffness and plantar pressures in symptomatic and asymptomatic individuals with plantar fasciitis. It is apparent that something is occurring to change material properties during the recovery process, that seems to be unaccompanied by changes in thickness, thus conducting studies that investigate material property and thickness changes in the PF in response to different types of treatment is warranted to provide a better understanding of what is occurring at the tissue level to induce these property changes in the PF.

Regarding thickness results observed in Chapter 4, individuals with active plantar fasciitis and a history of plantar fasciitis exhibit greater thickness at multiple sites along the length of the PF compared to controls, with trends of decreased muscle and tendon thickness. In Chapter 2, diabetic individuals also displayed greater thickness of the PF and a thinner muscle (FHB) than controls. Results from Chapter 2 of increased PF thickness in diabetic individuals, supports similar findings in several previous studies in Type 1 (Duffin et al. 2002, Craig et al. 2008) and Type 2 diabetics (Ursini et al. 2017), as well as in diabetic individuals with and without peripheral neuropathy (Ursini et al. 2017, D'Ambrogi et al. 2003). Additional data from the study outlined in Chapter 3 shows several structures had positive relationships between thickness and peak plantar pressures in diabetic individuals, suggesting that increased thickness is related to higher plantar pressures (Table 3).

Table 6.3 R and p values for correlations between thickness and peak plantar pressures in diabetic individuals at standardized speed of 1.3 m/s. Significance indicated by bold font and * ($p<.05$).

	Medial Heel		**1st Met Head**		**Hallux**	
	r	p	r	p	r	p
Proximal PF	-0.09	0.65	**-0.46**	**0.011***	-0.35	0.06
Distal PF	**0.51**	**0.004***	-0.08	0.68	0.22	0.25
PF Insert	**-0.40**	**0.029***	0.28	0.14	-0.03	0.86
AHT	-0.08	0.66	0.18	0.35	0.22	0.25
AchT	-0.05	0.80	-0.24	0.20	0.05	0.78
FHB	0.17	0.38	0.09	0.65	0.20	0.29
AHB	0.23	0.23	0.19	0.31	0.52	**0.003***
HP	**0.53**	**0.003***	0.17	0.38	0.39	**0.031***

These results are consistent with previous findings of increased tissue thickness relating to increased vertical ground reaction forces under metatarsal heads in diabetic individuals (D'Ambrogi et al. 2003) and increased PF thickness to be associated with higher plantar pressures in Type 1 diabetics (Craig et al. 2008). Future studies should seek to address how

thickness relates to plantar pressures in both Type 1 and Type 2, as well as diabetics with and without peripheral neuropathy. In a long-term (5- to 15-year) follow-up study of 174 patients with plantar fasciitis, Hansen et al. (2018) found PF thickness to decrease overtime regardless of symptoms, but only 24% of asymptomatic patients returned to "normal" values (below 4mm). It is possible that with the recurring nature of plantar fasciitis in the plantar fasciitis population and ulcers in the diabetic population, thickness of intrinsic foot structures may be a chronic adaptation after initial injury. Thus, future studies should investigate the effect of current and novel treatments on thickness of the PF and the potential implications that changes in thickness can have on material properties, plantar pressure distributions, and development of ulceration in diabetic populations. Similarly, conducting studies examining response of PF thickness to current and novel treatment interventions and how altering thickness of the PF impacts resolution of symptoms, recurrence and frequency of recurrence of symptoms, and plantar pressure distributions in plantar fasciitis populations is warranted.

Overall Conclusions

The research presented in this dissertation supports the overall hypothesis that a relationship exists between foot structure stiffness and plantar pressures. In diabetic individuals, these relationships are negative (i.e. lower stiffness correlates with higher pressures), contrary to the proposed idea of increased stiffness relating to higher pressures. Interestingly, individuals with plantar fasciitis exhibit relationships in both directions, but majority are positive relationships, which supports the overall hypothesis of this dissertation that increased stiffness relates to higher pressures. Diabetic individuals exhibit increased stiffness of connective tissue (i.e. PF), but similar to individuals with active plantar fasciitis, exhibit decreased stiffness of foot

muscles and tendons compared to controls. Individuals with a history of plantar fasciitis who are currently asymptomatic display more relationships with foot structure stiffness than currently symptomatic individuals. In addition, diabetic individuals and individuals with a history of plantar fasciitis exhibit similar values for proximal PF stiffness and negative relationships between proximal PF stiffness and medial heel peak pressure. Structurally, diabetic individuals exhibit increased thickness of the heel pad, yet decreased thickness of muscles and tendons similar to individuals with active plantar fasciitis and with a history of plantar fasciitis. Taken together, these results suggest that damage to the PF may be a critical factor in the observed anomalies in plantar pressure distributions and foot function in diabetic individuals, and that decreased stiffness and thickness of foot muscles and tendons may be indicative of damage and/or weakened structures that lead to the observed increased plantar pressures in diabetic individuals.

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Appendix A: IRB Approval Letters

EAST CAROLINA UNIVERSITY
University & Medical Center Institutional Review Board
4N-64 Brody Medical Sciences Building· Mail Stop 682
600 Moye Boulevard · Greenville, NC 27834
Office 252-744-2914 · Fax 252-744-2284 ·
www.ecu.edu/ORIC/irb

Notification of Continuing Review Approval: Expedited

From: Biomedical IRB
To: Erica Bell
CC: Zachary Domire
Patrick Rider
Date: 4/2/2019
Re: CR00007668
UMCIRB 15-000939
Diabetic Stiffness and Pressures in Gait

The continuing review of your expedited study was approved. Approval of the study and any consent form(s) is for the period of 4/1/2019 to 3/31/2020. This research study is eligible for review under expedited category #2,4. The Chairperson (or designee) deemed this study no more than minimal risk.

Changes to this approved research may not be initiated without UMCIRB review except when necessary to eliminate an apparent immediate hazard to the participant. All unanticipated problems involving risks to participants and others must be promptly reported to the UMCIRB. The investigator must submit a continuing review/closure application to the UMCIRB prior to the date of study expiration. The Investigator must adhere to all reporting requirements for this study.

Approved consent documents with the IRB approval date stamped on the document should be used to consent participants (consent documents with the IRB approval date stamp are found under the Documents tab in the study workspace).

The approval includes the following items:

Document	Description
DFSG_Email_Recruitment.docx(0.01)	Recruitment Documents/Scripts
DFSG_Flyer.pub(0.01)	Recruitment Documents/Scripts
DFSG_Informed_Consent_6.8.18.doc(0.04)	Consent Forms
DFSG_Protocol_6.8.18.docx(0.03)	Study Protocol or Grant Application
DSFG_Foot and Ankle Ability Measure(0.01)	Surveys and Questionnaires
IPAQ_Short_Form(0.01)	Surveys and Questionnaires

The Chairperson (or designee) does not have a potential for conflict of interest on this study.

IRB00000705 East Carolina U IRB #1 (Biomedical) IORG0000418
IRB00003781 East Carolina U IRB #2 (Behavioral/SS) IORG0000418

EAST CAROLINA UNIVERSITY
University & Medical Center Institutional Review Board
4N-64 Brody Medical Sciences Building· Mail Stop 682
600 Moye Boulevard · Greenville, NC 27834
Office 252-744-2914 · Fax 252-744-2284 ·
www.ecu.edu/ORIC/irb

Notification of Continuing Review Approval: Expedited

From: Biomedical IRB
To: Zachary Domire
CC:

Date: 3/15/2019
Re: CR00007633
UMCIRB 18-000436
Understanding the Relationship Between Plantar Pressures, Foot Tissue Stiffness, and Foot Structure in healthy feet and feet with plantar fasciitis

The continuing review of your expedited study was approved. Approval of the study and any consent form(s) is for the period of 3/14/2019 to 3/13/2020. This research study is eligible for review under expedited category #4,7. The Chairperson (or designee) deemed this study no more than minimal risk.

Changes to this approved research may not be initiated without UMCIRB review except when necessary to eliminate an apparent immediate hazard to the participant. All unanticipated problems involving risks to participants and others must be promptly reported to the UMCIRB. The investigator must submit a continuing review/closure application to the UMCIRB prior to the date of study expiration. The Investigator must adhere to all reporting requirements for this study.

Approved consent documents with the IRB approval date stamped on the document should be used to consent participants (consent documents with the IRB approval date stamp are found under the Documents tab in the study workspace).

The approval includes the following items:

Document	Description
4.3.18 protocol modification(0.01)	Study Protocol or Grant Application
Foot and Ankle Ability Measure(0.01)	Surveys and Questionnaires
PF IRB protocol 2.27.18.docx(0.02)	Study Protocol or Grant Application
recruitment flier update(0.02)	Recruitment Documents/Scripts
updated consent form 4.13.18(0.01)	Consent Forms

The Chairperson (or designee) does not have a potential for conflict of interest on this study.