ACHILLES TENDINOPATHY: THE ROLE OF TENDON STRUCTURE IN SYMPTOM AND FUNCTIONAL RECOVERY

by

Patrick Corrigan

A dissertation submitted to the Faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Biomechanics and Movement Science

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PREFACE

Currently, chapters two and four of this dissertation have been accepted for publication. They are reused here with permission from the publishers. I would like to a take the opportunity to clarify my contribution to these studies.

Corrigan P, Zellers JA, Balascio P, Silbernagel KG, Cortes DH. Quantification of mechanical properties in healthy Achilles tendon using continuous shear wave elastography: a reliability and validation study. *Ultrasound Med Biol*, 2019, Epub Ahead of Print.

The design of this study was a joint effort amongst authors. I was responsible for data collections, post-processing, statistical analysis, and manuscript drafting. Jen Zellers and Phoebe Balascio assisted with data collections, post-processing, and drafting the validation portion of this study. Karin Silbernagel and Daniel Cortes provided technical support, assisted with data interpretation, and provided critical feedback throughout manuscript drafting.

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Karin Silbernagel and I designed this study. I was responsible for all data collections, post-processing, statistical analysis with support from Ryan Pohlig, and drafting the manuscript. Daniel Cortes provided technical support and feedback for the manuscript. Karin assisted with data interpretation and feedback throughout the drafting process.

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ABSTRACT

Achilles tendinopathy is a debilitating overuse injury that is characterized by pain during loading activities, swelling, and impaired functional performance.[1,2] The incidence rate in the adult population is 2.35 per 1000, with middle-aged adults (i.e. 30-50 years old) who are physically active being the most frequently affected.[3] Throughout rehabilitation, patient-reported symptoms are commonly used to monitor recovery and tailor treatment. However, a rehabilitation program that solely focuses on symptoms may be problematic since the resolution of symptoms does not ensure the structure or function of the tendon has normalized.[4,5] With 41% of patients continuing to have symptoms after 8 years and up to 29% undergoing surgery,[6] a more comprehensive approach to rehabilitation is needed to improve long-term patient outcomes. Measures of tendon morphology and mechanical properties may provide critical information regarding the health of the tendon that can be used to supplement patient-reported symptoms. Before these measures can be implemented in clinical practice, there is a need to determine if tendon morphology and mechanical properties relate to the patient symptoms and function. Therefore, the purpose of this dissertation work was to determine if tendon morphology and mechanical properties play a critical role in recovery for patients with Achilles tendinopathy.

The first aim of this dissertation work was to assess the reliability and validity of measuring *in vivo* mechanical properties with continuous shear wave elastography (cSWE) in healthy and degenerative Achilles tendons. Our findings support the use of cSWE for monitoring changes in tendon mechanical properties, with fair-to-excellent

intrarater reliability for all properties.[7] The second aim was to determine if tendon morphology and mechanical properties were associated with recovery of patient-reported symptoms and functional performance. This was performed by prospectively following a cohort of patients with Achilles tendinopathy for one year. The key findings were 1) greater tendon thickening was associated with worse symptoms and calf muscle function 2) patient-reported symptoms over the year depended on the initial shear modulus of the tendon and 3) worse calf muscle function was associated with lower viscosity. These results indicate that Achilles tendon morphology and mechanical properties are predictive of long-term symptoms and function in patients with Achilles tendinopathy. The goal of the third aim was to evaluate the immediate effects of laser-induced photobiomodulation therapy on Achilles tendon morphology and mechanical properties in healthy and degenerative tendons. Results demonstrated that laser therapy does not have immediate effects on the Achilles tendon,[8] which suggests that laser therapy can be administered at any time during a treatment session without influencing other treatments. Lastly, in aim 4 we explored the relationships between patient-reported outcomes, tendon morphology, mechanical properties, lower leg function, pain, and running mechanics in patients with Achilles tendinopathy. We found that pain and lower leg functional performance were associated with Achilles tendon loading patterns while running, but patient-reported outcomes, tendon morphology and mechanical properties were not.

Collectively, this dissertation work supports the use of cSWE for estimating tendon mechanical properties, identifies the importance of tendon morphology and mechanical properties in symptom and functional recovery, and elucidates aspects of

tendon health that may be critical when progressing patients with Achilles tendinopathy from return-to-sport to return-to-performance.

Chapter 1

INTRODUCTION

1.1 Background

1.1.1 Overview of Achilles tendon Anatomy and Structure

The soleus, medial gastrocnemius, and lateral gastrocnemius muscles collectively form the triceps surae (i.e. calf).[9] Proximally, the soleus originates on the posterior aspect of the tibia (central 3rd) and fibula (proximal 3rd), while the medial and lateral gastrocnemii originate on the femoral condyles.[9] Distally, these three muscles insert on the posterior aspect of the calcaneus through a common tendon, known as the Achilles tendon. This is the largest and strongest tendon in the human body.[10] Additionally, it has a unique twisted structure with soleus fascicles contributing to the medial aspect, medial gastrocnemius fascicles contributing to the posterolateral aspect, and lateral gastrocnemius fascicles contributing to the anterolateral aspect when dissected one centimeter above the osteotendinous junction.[11]

On a more basic level, the Achilles tendon is composed of tendon cells and an extracellular matrix.[12] Tenocytes and tenoblasts (immature tenocytes) make up 90-95% of the cellular content and are responsible for preserving tendon health and function by maintaining the extracellular matrix.[13] Collagen, elastin, ground substance (e.g. water, proteoglycans and glycosaminoglycans), and anorganic components (e.g. calcium, copper, manganese) form the extracellular matrix.[12] Collagen is the primary component that gives the tendon its strength, while elastic fibers are thought to

contribute to the tendon's shock-absorbing capacity (i.e. elasticity) and ability to restore the crimped pattern of collagen after being stretched.[10] Surrounding the collagen is ground substance, which is responsible for maintaining an environment that promotes collagen synthesis.[14] Lastly, anorganic components are involved in tendon growth, development, and metabolism. For example, copper plays a critical role in collagen cross-linking, manganese is required for enzymatic reactions that result in collagen synthesis, and calcium is important for the development of the osteotendinous junction.[15] Collectively, an understanding of Achilles tendon anatomy and structure is important when assessing tendon function and developing treatments aimed at improving tendon health.

1.1.2 Function and Biomechanics of the Achilles Tendon

The triceps surae produces ankle plantar flexion and knee flexion since it has attachments below the ankle and above the knee (gastrocnemii only). When the triceps surae is producing ankle plantar flexion, the Achilles tendon transfers forces to the calcaneus. If there is a rapid stretch (i.e. lengthening) of the tendon prior to ankle plantar flexion, elastic energy will be stored and released by the Achilles tendon.[10,16,17] This process is known as the stretch-shortening cycle and takes place during ballistic activities, such as hopping and running. The release of elastic energy contributes to the total work of the triceps surae and reduces the metabolic cost of the movement.[18–23] In addition to its role during dynamic tasks, the Achilles tendon also transfers forces from the soleus to the calcaneus in order to maintain balance while standing.

The function of the Achilles tendon depends on its biomechanical characteristics.[24,25] These characteristics are traditionally explained by describing the stress-strain curve, which represents the tendons response to loading.[10] When the

tendon is unloaded, collagen fibers are relatively slack and demonstrate a crimped pattern. Upon loading the tendon, the collagen fibers progressively align in parallel. This transition (i.e. uncrimping) represents the toe region of the stress-strain curve.[10,26] As more load is applied to the tendon, strain increases linearly until initial failure at approximately 4% strain.[10] This region of the stress-strain curve is known as the linear elastic region. The slope of the curve in this region represents the elastic modulus (i.e. tensile stiffness) of the tendon. If the tendon is loaded beyond 4% strain, collagen fibers will begin to rupture until complete rupture occurs at approximately 8% strain.[10]

The Achilles tendon is also viscoelastic, which means the mechanical behavior of the tendon depends on how quickly it is loaded.[27–29] Tendons are ductile when loaded slowly and brittle when loaded quickly.[10] Therefore, tendons absorb more load at lower loading rates, but are more efficient at transmitting forces at higher loading rates. The purpose of this behavior is not fully understood, yet it has been suggested that tendon viscoelasticity optimizes the force-length-velocity relationships of muscle and improves the economy of walking and running.[18–20,23,30–32]

1.1.3 Achilles Tendon Overuse Injury

Achilles tendinopathy is a debilitating overuse injury to the Achilles tendon. It is a clinical syndrome characterized by pain during loading activities, swelling (diffuse or local), and impaired functional performance.[1,2] A more specific diagnosis is commonly made by dichotomizing Achilles tendinopathy into midportion and insertional based on the region that is affected. Midportion tendinopathy occurs 2-6 cm proximal to the osteotendinous junction, while insertional tendinopathy occurs within the osteotendinous region.[1,2] Regardless of the region, ultrasound and magnetic resonance imaging are frequently used to confirm a diagnosis and determine if other

anatomical structures are involved (e.g. retrocalcaneal bursa, Kager's fat pad). If the tendon has non-uniform thickness and hypoechoic regions visualized with ultrasound imaging, then the term tendinosis is used to describe the presence of degenerative changes.[1,2] Since tendinosis simply indicates structural changes, tendinosis can be present without pain. Another term that is frequently used in the general population to describe a painful tendon injury is tendinitis. This term indicates the presence of inflammatory cells. With pivotal research showing the lack of inflammatory cells in patients with Achilles tendinopathy,[33,34] this term has been sparsely used in recent literature. Therefore, for the purposes of this dissertation, the term tendinopathy will be used to describe patients who have pain in their Achilles tendon during loading activities, altered tendon structure, and impaired triceps surae function.

1.1.4 Epidemiology of Achilles tendinopathy

Achilles tendinopathy is one of the most common overuse injuries, with an incidence rate of 2.35 per 1000 in the adult population.[3] Historically, Achilles tendinopathy was thought to affect men more often than women,[35] but a recent review of more than 180,000 patients showed equal incidence rates between sexes.[36] Overall, middle-aged adults (i.e. 30-50 years old) who are physically active are the most frequently affected population.[3,37] However, sedentary individuals,[38] adolescents,[39] and older adults (i.e. > 60 years old) are also affected.[3]

Participation in running and jumping activities seems to increase the risk of developing Achilles tendinopathy. This risk appears to be greater when participation abruptly increases (e.g. Couch-to-5K programs) or when subtle changes occur during training that increase the demand on the triceps surae (e.g. increased frequency of hill workouts).[40] Runners specifically appear to be at a risk of developing Achilles

tendinopathy, with reported annual incidence rates between 7% and 11%.[41,42] Additionally, lifetime incidence rates of former elite male distance runners have been reported to be between 52% and 57%.[43,44] Achilles tendinopathy is also more prevalent in runners who participate in longer races, with ultramarathon, 20K and 10K runners having a prevalence of 19%,[45] 9.5%,[46] and 6.2%,[47] respectively. However, the increased prevalence of Achilles tendinopathy with racing longer distances may be partially explained by older adults typically participating in longer races.

While most patients with Achilles tendinopathy have unilateral symptoms, bilateral Achilles tendinopathy is also common. The prevalence of bilateral symptoms has not been systematically reviewed, yet it appears that approximately 30% of patients with Achilles tendinopathy have bilateral symptoms.[6,35] Even more alarming, evidence suggests that 41% of patients with Achilles tendinopathy will develop similar symptoms on their previously healthy side.[6]

1.1.5 Etiology of Achilles tendinopathy

Achilles tendinopathy is generally described as a degenerative process or failed healing response.[48–50] The pathoetiology remains largely unclear, but it is considered multifactorial. Excessive loading is thought to be the main contributor to this degenerative process.[40] Yet, there are many intrinsic and extrinsic factors (reviewed in Table 1.1) that may be associated with the development of Achilles tendinopathy. An understanding of these factors is required to appreciate differences in clinical presentations, identify factors that can be addressed during rehabilitation, and establish a prognosis.

Table 1.1 Intrinsic and Extrinsic Risk Factors for Achilles tendinopathy

Intrinsic Factors	
Age	• In the general population, Achilles tendinopathy most commonly occurs between the ages of 41 and 60.[3] • Histological evidence suggests that tendon degeneration is present in 50% of older adults (mean age of 66 years) and 30% of younger adults (mean age of 38).[49] • Prospective cohort studies are conflicting.[51–53]
Body composition	• A systematic review identified obesity as a risk factor for developing Achilles tendinopathy.[54]
Alignment	• Recent systematic reviews have identified limited evidence to suggest static foot posture is associated with the development of Achilles tendinopathy.[55] • Kvist et al. found 60% of patients with Achilles tendinopathy had a predisposing malalignment[35,56]
Triceps surae weakness	• Decreased plantar flexion strength has been shown to predict the development of Achilles tendinopathy in military recruits.[57,58]
Altered tendon structure	• Increased tendon thickness and ultrasound abnormalities are predictive of developing Achilles tendinopathy[59]
Biomechanical characteristics during Running	• Greater laterally directed force under the forefoot at foot flat, decreased total anterior/posterior center of pressure displacement, longer duration of eversion and a more everted rearfoot at heel off have been identified as risk factors for Achilles tendinopathy[52,58] • A systematic review identified high braking forces as a risk factor for developing Achilles tendinopathy[60]
Flexibility	• Both increased and decreased ankle dorsiflexion has been shown to increase the risk of developing Achilles tendinopathy[57,61]
Comorbidities	• Dyslipidemia, diabetes mellitus, hypertension have been suggested to increase the risk of Achilles tendinopathy[62]
Genetics	• Variants of the TNC, COL5A1, MMP3, GDF5 and CASP8 genes, which affect the composition of the extracellular matrix, have been identified as risk factors for Achilles tendon pathology[63]

Extrinsic Factors	
Excessive loading/training errors	• More years of running and greater mileage increase the incidence of Achilles tendinopathy[64,65] • 60-80% of patients with Achilles tendinopathy increase intensity or amount of loading too quickly[35,56,66,67] • 75.2% of patients with Achilles tendinopathy were found to be overtraining[40]
Equipment	• Shock absorbing insoles in military issued combat boots led to lower incidence of Achilles tendinopathy compared to rigid insoles (4% versus 8%)[68] • Footwear may also influence the risk of Achilles tendinopathy[69,70]
Medications	• Fluoroquinolones, hormone replacement therapy, and oral contraceptives are associated with increased risk of developing Achilles tendinopathy[62,71–74]
Environmental conditions	• Cold weather training has been suggested as a risk factor for developing Achilles tendinopathy (specially involving the peritenon), based on a study that prospectively followed military recruits[70] • Running in sand and up hills appear to be associated with the development of Achilles tendinopathy, while stiffer surfaces appear protective[44]

1.1.6 Overview of Treatment for Achilles Tendinopathy

Patients with Achilles tendinopathy, in most cases, attempt to self-manage their symptoms before seeking medical advice. This period typically includes resting and icing the painful area to reduce pain, taking over-the-counter medications to reduce inflammation, and performing calf stretches to reduce stiffness. Each of these treatments may temporary reduce pain, but they do not increase the tendon's tolerance to load. In fact, rest can be detrimental to the tendon,[75] anti-inflammatories do not address the source of pain since inflammatory cells are not present in chronic tendinopathy,[33,34] and stretching may further attenuate reductions in mechanical properties.[76] Therefore, if high-load activities are resumed without receiving

treatments that improve load tolerance, pain returns. When self-management fails, patients generally become frustrated[77] and seek medical advice.

Initial medical advice for patients with midportion or insertional Achilles tendinopathy is non-surgical, non-invasive management for at least three months.[78–81] Physical therapy is the primary method of management, with the overall goal of returning the patient back to their desired physical activities with minimal symptoms and a low risk of re-injury. To accomplish this goal, many treatments have been proposed and used in clinical practice.[78,82–85] These treatments have varying amounts of supporting evidence and include, but are not limited to, patient education, activity modification, orthotics, shoe modifications, stretching, manual therapy, ultrasound, laser therapy, shockwave therapy, and exercise therapy.

Exercise therapy is the standard of care for treating patients with Achilles tendinopathy and supported by the highest levels of evidence.[82,86] Various exercise therapy protocols exist, but there is minimal evidence to suggest one protocol is superior to another.[87] The main differences between these protocols are the number of exercises performed each day and the type of muscle contraction used to load the tendon (e.g. eccentric, concentric). Irrespective of the exercise protocol used, loading the Achilles tendon appears essential for obtaining positive long-term outcomes.[88] The efficacy of exercise therapy is thought to be explained by improvements in triceps surae function, changes in tendon mechanical properties, and normalization of tendon morphology. Successful outcomes with exercise therapy may also be affected by other factors, such as age, sex, genetics, comorbidities, patient motivation, and the anatomical structures involved (i.e. peritenon vs. bursa vs. tendon vs. calcaneus).

In addition to exercise therapy, other non-invasive treatments include patient education, rest, activity modification, orthotics, shoe modifications, stretching, manual therapy, laser therapy, and shockwave therapy.[78,79] In general, patient education is of great importance for improving patient outcomes.[89] For patients with Achilles tendinopathy specifically, patient education has not been systematically evaluated in isolation, but appears to be a critical component of most treatment protocols. A period of rest is commonly recommended for most musculoskeletal injuries. For tendons, however, rest can have a detrimental effect on tendon structure and recovery.[75] Modifying physical activities, such as reducing running volume or intensity, may be better than complete rest.[90] This is further supported by a clinical trial in patients with Achilles tendinopathy that showed no negative effect of remaining active as long as a pain-monitoring model was followed.[90] Orthotics (e.g. heel lifts) and shoe modifications have also been prescribed to patients with Achilles tendinopathy. Shoes with a greater heel-to-toe drop decrease Achilles tendon forces during running[91] and are thought to decrease compression on the tendon and bursa,[92] while orthotics that control subtalar motion are thought to decrease the proposed wringing effect caused by increased pronation. However, because of inconsistent findings, the current clinical practice guidelines for Achilles tendinopathy do not provide recommendations for heel-lifts or orthotics.[82,86] Stretching and manual therapy are routinely used in clinical settings to increase flexibility of the triceps surae and range of motion of the talocrural and subtalar joints. However, both increased and decreased range of motion have been suggested as risk factors for Achilles tendinopathy[57,61] and no randomized clinical trials have assessed if adding stretching to an exercise therapy program improves outcomes. Stretching may also increase compressive forces on the anterior aspect of

the tendon and bursa, potentially leading to insertional symptoms.[92] Laser therapy, which will be reviewed in Chapter 4 of this dissertation, has been shown to have biomechanical and biochemical effects in animal models and improve clinical outcomes when supplementing an exercise therapy program.[93–96] Lastly, shockwave therapy has been shown to be an effective treatment for patients with recalcitrant symptoms, specifically patients with insertional Achilles tendinopathy.[84,97–99] Each of these treatments may be used to supplement an exercise therapy program, but no evidence exists that suggests they are superior to exercise therapy when used in isolation.

1.2 Purpose and Specific Aims of this Dissertation

Achilles tendinopathy leads to sensations of pain and stiffness, altered tendon morphology, decreased mechanical properties, and impaired functional performance.[1,2,76,100,101] Patient-reported symptoms are commonly used to gauge recovery and make treatment decisions during rehabilitation for patients with Achilles tendinopathy. A rehabilitation program that solely uses symptoms, however, may be problematic since the resolution of symptoms does not mean the structure or function of the tendon has normalized.[4,5] With 37% to 41% of patients with Achilles tendinopathy having symptoms at long-term follow-up (8-10 years)[6,102] and up to 29% undergoing surgery,[6] a more comprehensive approach that monitors symptoms, tendon morphology, tendon mechanical properties, triceps surae function, and psychological aspects of injury may be necessary for tailoring treatment and improving long-term outcomes. Before this approach can be implemented, there is a need to determine if tendon morphology and mechanical properties play a critical role in recovery. Therefore, the purpose of this dissertation work was to determine if tendon

morphology and mechanical properties play a critical role in recovery for patients with Achilles tendinopathy. This purpose was fulfilled in four specific aims, which are outlined here.

Aim 1: Assess the reliability and validity of measuring *in vivo* mechanical properties with continuous shear wave elastography (cSWE) in healthy and degenerative Achilles tendons.

Aim 2: Determine if tendon morphology and mechanical properties are associated with recovery of patient-reported symptoms and functional performance in patients with Achilles tendinopathy.

Aim 3: Evaluate the immediate effects of laser-induced photobiomodulation therapy on Achilles tendon morphology and mechanical properties in healthy and degenerative tendons.

Aim 4: Explore the relationships between patient-reported outcomes, tendon morphology, mechanical properties, lower leg function, pain, and running mechanics in patients with Achilles tendinopathy.

1.3 Measuring Achilles tendon Mechanical Properties *in vivo*

Achilles tendon morphology is routinely assessed with ultrasound and magnetic resonance imaging in clinical and research settings. Tendon thickness (anterior-posterior), cross-sectional area, length, and volume are the morphologic measurements most commonly reported in the literature. These measurements are well established, have excellent reliability,[103–105] and have been used for diagnosis,[50,106–108] predict the development of symptoms,[59,109–111] and tracking tendon healing.[5,112,113] Tendon morphology, however, does not necessarily reflect how the tendon will

respond when loaded. Therefore, tendon mechanical properties have become an additional dimension of interest for evaluating tendon health and understanding injury.

Tendon mechanical properties have primarily been estimated in research settings with two experimental techniques – real-time ultrasound imaging synchronized with plantar flexion dynamometry and elastography. Real-time ultrasound imaging with plantar flexion dynamometry estimates tendon tensile properties by measuring linear displacement of the tendon or myotendinous junction during ankle plantar flexion contractions.[76,114,115] Even though the estimated properties represent mechanical behaviors that are critical for understanding tendon function, there are several limitations of this method. Namely, this technique relies on volitional muscle contractions, places large tensile loads on the tendon that may be painful to injured populations, and assumes tissue homogeneity. Elastography, on the other hand, estimates tendon shear properties by measuring tendon displacement with ultrasound imaging when a shear wave is applied.[116,117] Shear properties represent the tendon's resistance to a shearing force, which is a different mechanical behavior compared to tensile properties. However, measuring shear properties may improve our understanding of tendon injury since non-uniform shear forces between tendon fascicles has been identified as a possible explanation of pathogenesis[118,119] and shear forces are thought to stimulate tenocytes.[120] Additionally, this technique does not rely on muscle contraction or place large loads on the tendon, and it is capable of mapping properties throughout the tendon. Various shear wave elastography techniques have been developed,[121,122] yet there are difficulties with reliably estimating tendon mechanical properties with commercial scanners.[123] Typically, the elastogram (map of mechanical properties) becomes saturated because shear wave propagate through

tendon quicker than the maximum velocity visualized by the ultrasound scanner.[124,125] Therefore, there is a need to develop elastography techniques that can reliably estimate tendon mechanical properties.

Continuous Shear Wave Elastography (cSWE) is a technique developed in our laboratory for quantifying *in vivo* tendon mechanical properties.[117] It can capture shear wave velocities up to 25 m/s (compared to 15 m/s for commercial scanners), so elastogram saturation is not a limitation of this technique. This technique has been used to evaluate individuals with healthy Achilles tendons,[7,126] Achilles tendinopathy,[8,117] and Achilles tendon rupture.[127–129] However, validation of cSWE is limited to comparisons against magnetic resonance elastography using agarose gels[117] and observations of side-to-side differences in individuals with tendon pathology.[117,129] Additionally, test-retest reliability has been assessed between trials performed consecutively,[126] but reliability and stability over time have not been evaluated. Therefore, **Aim 1** will assess the reliability and validity of measuring *in vivo* mechanical properties with cSWE in healthy and degenerative Achilles tendons.

Hypothesis 1.1 cSWE will have excellent reliability (ICC>0.75) for measuring tendon mechanical properties (static shear modulus, dynamic shear modulus, and viscosity) in healthy Achilles tendons.

Hypothesis 1.2 Achilles tendon mechanical properties (static shear modulus, dynamic shear modulus, viscosity) measured with cSWE will increase as the amount of ankle dorsiflexion increases.

Hypothesis 1.3 Achilles tendon mechanical properties (static shear modulus, dynamic shear modulus, viscosity) measured with cSWE will have a strong positive

relationship (r>0.75) to Young's modulus measured with ultrasound imaging and dynamometry in healthy and degenerative tendons.

1.4 Prognostic value of Tendon Morphology and Mechanical Properties

Traditionally, patient-reported symptoms and impairments in calf muscle function (e.g endurance, power) are evaluated throughout rehabilitation to guide treatment decisions. Patient outcomes are generally positive when returning to low-load activities (e.g. walking), yet up to 44% of patients with Achilles tendinopathy will suffer from re-injury when returning to high-load activities (e.g. running)[130] and 37-41% of patients will have symptoms for many years.[6,102] The reason for these poor outcomes is relatively unknown, but it could be partially explained by taking a treatment approach that does not consider the structural and mechanical status of the tendon. Since there is an 8-fold increase in the risk of developing symptoms when tendon morphology is altered,[59] adding tissue-level measures of tendon morphology and mechanical properties may improve long-term outcomes. However, it is currently unclear if measures of tendon morphology and mechanical properties play a critical role in obtaining full symptomatic and functional recovery. Therefore, the purpose of **Aim 2** is to determine if tendon morphology and mechanical properties are associated with recovery of patient-reported symptoms and functional performance in patients with Achilles tendinopathies.

Hypothesis 2.1 Greater tendon thickening at initial assessment will be associated with worse patient-reported symptoms and calf muscle function at 6-month and 1-year follow-up assessments.

Hypothesis 2.2 Lower tendon shear modulus at initial assessment will be associated with worse patient-reported symptoms and calf muscle function at 6-month and 1-year follow-up assessments.

Hypothesis 2.3 Lower tendon viscosity at initial assessment will be associated with worse patient-reported symptoms and calf muscle function at 6-month and 1-year follow-up assessments.

1.5 Effects of Laser therapy on Tendon Morphology and Mechanical Properties

Exercise therapy has been shown to effect tendon morphology and mechanical properties.[131–138] These effects may partially explain the positive effects of exercise therapy for treating Achilles tendinopathy. After a single loading session, however, tendon stiffness reduces.[139,140] This may temporarily influence the tendons ability to transfer loads and may increase the tendon's susceptibility to damage (i.e. more strain per unit force). Since there are several treatments that are frequently used to supplement an exercise program, there is a need to determine if they directly affect the tendon or if they only address patient pain and symptoms.

Laser-induced photobiomodulation therapy is a promising adjunct treatment that leads to greater improvements in patient pain and symptoms compared to exercise therapy only.[94,141] Reduced inflammation,[142,143] decreased cell apoptosis,[144] increased collagen synthesis,[145–147] and increased angiogenesis[148] are mechanisms that have been identified in animal and human research. These underlying mechanisms may promote tendon remodeling and influence tendon morphology and mechanical properties. However, the effects of laser therapy on tendon morphology and mechanical properties remain unknown. The first step towards understanding these effects is to determine if a single laser treatment causes immediate changes in tendon morphology

and mechanical properties. This knowledge is critical for determining if laser therapy could influence the tendon's response to exercise therapy or make the tendon more susceptible to damage if heavy loading is performed immediately after laser treatment. Therefore, **Aim 3** will evaluate the immediate effects of laser-induced photobiomodulation therapy on Achilles tendon morphology and mechanical properties in healthy and degenerative tendons.

Hypothesis 3.1 Changes in Achilles tendon thickness and cross-sectional area will be greater in a laser-treated side compared to a placebo-treated side over a four hour time period in healthy and degenerative tendons.

Hypothesis 3.2 Changes in Achilles tendon static shear modulus and viscosity will be greater in a laser-treated side compared to a placebo-treated side over a four hour time period in healthy and degenerative tendons.

Hypothesis 3.3 Changes in Achilles tendon thickness, cross-sectional area, static shear modulus and viscosity over a four hour time period will be greater in injured tendon compared to healthy tendon when treated with laser therapy.

1.6 Return-to-Sport for patients with Achilles tendinopathy

The final phase of rehabilitation for Achilles tendinopathy is commonly referred to as the return-to-sport (RTS) phase. The main goal of this phase is to safely progress the patient back to their desired physical activities without their symptoms returning. Although no consensus exists to define the start and finish of the RTS phase, it has been suggested that the RTS phase should start when symptoms are no longer present with low load activities (e.g. walking) and finish when the patient has participated in one year of sports/recreational activity without symptoms.[149] This makes the RTS phase the longest phases of rehabilitation and attempting to shorten

this phase leads to reoccurrence of symptoms in nearly half of patients.[150] Thus, the RTS phase is a particularly critical part of the recovery process. During this phase, patients progressively return to high load activities (e.g. running, jumping). Current recommendations suggest that patient symptoms should be used to progress and tailor exposure to high load activities.[90,151] This approach protects the tendon from being exposed to too much load too quickly by monitoring symptomatic response, but it does not provide specific evidence for prescribing activities of optimal load. By taking measures that span multiple facets of the injury (i.e. patient-reported symptoms, tendon morphology, mechanical properties, and function) RTS decisions may be improved and reoccurrence rates reduced. This is comparable to how soreness rules, effusion grades, ligament stability testing, quadriceps strength, hop testing, and patient-reported outcomes are implemented for RTS decisions for patients after anterior cruciate ligament reconstruction.[152–155] However, in patients with Achilles tendinopathy, it is currently unknown if patient symptoms, tendon morphology, mechanical properties, and calf muscle function relate to how someone loads their Achilles tendon while performing functional activities. Therefore, **Aim 4** will explore the relationships between patient-reported outcomes, tendon morphology, mechanical properties, lower leg function, pain, and running mechanics for patients with Achilles tendinopathy.

Hypothesis 4.1 Side-to-side differences in pain-pressure threshold will be related to side-to-side differences in Achilles tendon loading rates during running in patients with Achilles tendinopathy.

Hypothesis 4.2 Side-to-side differences in Achilles tendon morphology and mechanical properties will be related to side-to-side differences in peak ankle joint plantar flexion power during running in patients with Achilles tendinopathy.

Hypothesis 4.3 Side-to-side differences in heel-rise test performance will be related to side-to-side differences in ankle joint plantar flexion power during running in patients with Achilles tendinopathy.

1.7 Summary

Achilles tendinopathy is an overuse injury that primarily affects middle-aged adults who are physically active. Rehabilitation aims to reduce pain with loading activities and improve functional performance. However, long-term clinical outcomes remain poor. This dissertation work will help determine if tissue-level measures of tendon morphology and mechanical properties play a critical role in obtaining symptomatic and functional recovery.

Chapter 2

QUANTIFICATION OF MECHANICAL PROPERTIES IN HEALTHY ACHILLES TENDON USING CONTINUOUS SHEAR WAVE ELASTOGRAPHY: A RELIABILITY AND VALIDATION STUDY

2.1 Introduction

The Achilles tendon is a highly-organized, densely-packed collagenous tissue that acts to transfer loads between muscle and bone. Furthermore, the Achilles tendon has a mechanical function that allows energy to be stored and released into the musculoskeletal system during dynamic activities. Achilles tendon injury is characterized by disorganization and buckling of collagen fibers, which alters the tendon's mechanical properties.[48,49] Consequently, mechanical properties (e.g. Young's modulus and shear modulus) have recently been proposed as biomarkers for tendon injury and recovery.[117,156,157]

Traditionally, real-time ultrasound imaging is synchronized with dynamometry to evaluate tendon tensile stiffness and Young's modulus.[76,158,159] Although this technique accurately measures tensile properties in healthy tendon, it relies on volitional contractions, places large tensile loads on the tendon, and assumes that the tendon is homogenous. These features may negatively affect the accuracy of measuring tensile properties in patients with Achilles tendinopathy because of tissue heterogeneity and alterations in muscle activity.[160,161] Also, because of the large tensile loads on the tendon during maximal plantar flexion contractions, dynamometry is contraindicated in patients early after Achilles tendon rupture. Therefore, there is a

need to develop valid and reliable techniques for measuring tendon mechanical properties in injured populations.

In recent years, various shear wave elastography (SWE) techniques have been developed and commercialized to estimate Achilles tendon shear properties (e.g. shear elasticity, shear modulus). These properties represent the tendon's resistance to a shear force, which is a different mechanical behavior compared to traditional tensile testing. However, measuring shear properties may improve our understanding of tendon injury since non-uniform shear forces between tendon fascicles has been identified as a possible explanation of pathogenesis[118,119] and shear forces are thought to stimulate tenocytes to promote tendon healing.[120] Additionally, these techniques put minimal tension on the tendon and allow for spatial variation of shear properties to be measured.[156,162] Although SWE techniques appear ideal for measuring tendon shear properties, there are several limitations. Saturation of the elastogram (i.e. the shear elasticity map) is a major limitation of many commercially-available elastography techniques, especially when evaluating healthy tendons.[124,125] Saturation occurs when the shear elasticity of the tendon exceeds the upper limit of the elasticity scale that is used to render the elastogram. Saturation is problematic since measurements taken from a saturated elastogram yield underestimated mechanical properties. Anisotropy is another limitation of SWE that may influence the accuracy of measuring mechanical properties. The calculations used to estimate mechanical properties with SWE assume the tendon is an isotropic material, which does not match the well-known elastic anisotropy of the tendon. However, the mechanical properties calculated represent an overall/average measurement of the elasticity of the tendon. By standardizing ultrasound probe alignment (i.e. parallel to tendon fibers based on B-

mode images), patient positioning, and the region of interest, SWE mechanical properties may be reliably measured over time. Despite these limitations, it appears that critical information about tendon injury and recovery could be gained from developing a valid and reliable elastography technique that is safe for evaluating injured populations and is capable of measuring tendon mechanical properties without saturation.

We recently developed an ultrasound elastography method named continuous Shear Wave Elastography (cSWE) to measure tendon mechanical properties (static shear modulus and viscosity) *in vivo*.[117] cSWE is a modification of the Supersonic Shear Imaging (SSI) technique that uses an external actuator to generate shear waves across a specified range of frequencies. Frequency and shear wave speed data measured with cSWE is then analyzed using the Voigt model to estimate the static shear modulus and viscosity of the tendon. Other techniques use transient shear waves, which estimate a dynamic shear modulus of the tissue.[116] cSWE has been found to measure shear wave velocities in healthy tendon above the capacity of some commercially-available scanners, which negates the concern of saturating the elastogram.[117] It has also been applied to individuals with healthy Achilles tendons,[126] Achilles tendinopathy,[117] Achilles tendon rupture,[127–129] and hamstring tendon.[163] Test-retest reliability during a single experimental session has been previously reported.[126] However, intra-rater reliability of cSWE over longer durations has not been investigated, which is critical to evaluate before measuring changes in tendon mechanical properties over time. Furthermore, criterion validity has been demonstrated by using agarose gels with known mechanical properties to compare measurements between cSWE and magnetic resonance elastography,[117] but validation

in tendon tissue is limited to observations of side-to-side differences in individuals with tendon pathology.[117,129] The use of cSWE for evaluating human tendon tissue would be further supported by demonstrating construct validity (i.e. the ability of a tool to measure the construct it was designed to measure). Additionally, since mechanical properties measured with cSWE (static shear modulus and viscosity) represent different mechanical behaviors compared to commercial elastography techniques (shear elasticity) and traditional tensile testing (Young's modulus), it is necessary to calculate an equivalent/dynamic shear modulus that more closely relates to measures obtained with the SSI technique.

The purposes of this study were to evaluate the intra-rater reliability and stability of measuring mechanical properties with cSWE in healthy Achilles tendons, propose a measure of dynamic shear modulus determined with cSWE that is equivalent to shear elasticity measured with SSI, demonstrate construct validity of cSWE, and explore relationships between shear and tensile properties. Findings from this investigation are important to ascertain prior to evaluating Achilles tendon mechanical properties with cSWE over time or exploring relationships between these properties and clinical, functional and patient-reported outcomes.

2.2 Materials and Methods

2.2.1 Study Design

The study was performed in two separate parts – reliability and validation. All individuals included were without Achilles tendon pathology, as determined through a clinical examination performed by a licensed physical therapist and showed no signs of tendon degeneration during screening with B-mode ultrasound imaging (tendon

thickening or hypoechoic areas). Both parts of the study were approved by the institutional review board at the University of Delaware and subjects provided written consent after being informed of experimental procedures.

2.2.2 Reliability

2.2.2.1 Subjects

Twenty subjects (11 males, 9 females) with a mean (SD) age of 29 (4) years, height of 177 (8) cm, and body mass of 82 (18) kg participated in the reliability portion of this study.

2.2.2.2 Experimental Procedures for Reliability Testing

Continuous shear wave elastography (cSWE) was used to estimate Achilles tendon static shear modulus and viscosity.[117] Minor differences existed between the experimental procedures for cSWE in the current study and the originally described technique.[117] The ultrasound scanner used in the current study was a SonixMDP Q+ (Ultrasonix, Vancouver, Canada), which is an upgraded model of the SonixMDP scanner used in the original study.[117] Both studies however used the same L14-5/38 ultrasound transducer. The frame rate in the current study was 6438 frames/s compared to 6450 frames/s in the original study reported by Cortes et al.[117] In order to maintain an integer fraction of frames per wave period, excitation frequencies were adjusted. Additionally, raw radiofrequency (RF) data were acquired for twelve frequencies, instead of six. The excitation frequencies were 322, 339, 358, 379, 402, 429, 460, 495, 536, 585, and 643 Hz compared to the original six frequencies of 323, 340, 358, 379, 403, and 430 Hz. RF data were post-processed as described previously, except every other frequency was used to allow for a wider range of frequencies to

better estimate viscoelastic properties. For highly compliant and stiff tendons, the first six or last six frequencies are used to keep the wavelength comparable to the size of the region of interest (ROI). However, throughout both parts of the current study, every other frequency was used. Static shear modulus and viscosity were calculated on a pixel-wise basis and averaged across each pixel within the central 50% of the ROI. The original method included all pixels within the ROI. However, inaccuracies associated with the Local Frequency Estimation (LFE) method for estimating wave speed are minimized by ignoring pixels within 25% of each lateral border. In addition to these technical modifications, ankle plantar flexion angle was altered from 0 to -10 degrees. This dorsiflexed position increased the likelihood that the tendon was within the linear elastic region (i.e. where the tendon has a constant elastic modulus). To maintain a consistent position and limit muscle activity, the subject's feet were secured against a platform with straps across the dorsum of the feet. This modification has previously been used[126] and was selected for the current study due to difficulties with designing splints that accommodate different lower leg shapes and sizes.

All 20 subjects completed two experimental sessions with two weeks between sessions. During the first session, data was collected at four time points, which can be described as baseline, 30 minutes after baseline, 2 hours after baseline, and 4 hours after baseline. The second session was a single time point. During each time point, three trials of cSWE were performed by a single experienced evaluator to one Achilles tendon and the average static shear modulus and viscosity were used for analysis. A computer-generated randomization scheme was used to select which Achilles tendon (right or left side) would be used throughout testing. Data was not collected bilaterally since Suydam et al.[126] showed there are no side-to-side differences in Achilles tendon

mechanical properties estimated with cSWE. The randomization led to cSWE being performed on the dominant leg for 11 individuals and non-dominant leg for 9 individuals. Leg dominance was determined by subject-reported preferred kicking leg. To reduce the effects of activities performed between the four time points, subjects were allowed to perform everyday tasks (e.g. walking, sitting) between time points, but were asked to refrain from activities thought to impact the mechanical properties of the tendon (e.g. stretching, jumping, weightlifting, running). Additionally, since regional differences exist in mechanical properties along the length of the Achilles tendon,[125] all measurements were taken at a location in the midportion of the tendon just distal to the myotendinous junction of the soleus. This location was reproduced during each session by recording the distance from the proximal calcaneal insertion to the region of interest.[104]

2.2.2.3 Dynamic Shear Modulus

As stated above, cSWE uses a series of continuous shear waves ranging from 322 Hz to 643 Hz. By analyzing the change of wave speed in that frequency range, two viscoelastic properties are calculated: static shear modulus and viscosity. The SSI technique measures the group velocity of a broadband shear wave traveling through the tissue. Dispersion analysis of the transient shear wave generated by SSI in the Achilles tendon shows that shear wave has an approximately frequency range from 300 Hz to 700 Hz, and a stronger intensity at about 400 Hz.[164] Consequently, we define a dynamic shear modulus, from cSWE measurements, using the static shear modulus, viscosity and the Voigt model as follows:

$$\mu(f) = \frac{2(\mu_1^2 + (2\pi f)^2\mu_2^2)}{(\mu_1 + \sqrt{\mu_1^2 + (2\pi f)^2\mu_2^2})}$$

where μ is the dynamic shear modulus at a frequency *f*, μ_1 is the static shear modulus, and μ_2 is the viscosity. In order to have a dynamic shear modulus comparable to that obtained by SSI, a frequency of 400 Hz was selected. Intra-rater reliability of this new measure of dynamic shear modulus was evaluated using data obtained from the reliability portion of this study. Additionally, using data from the validation portion of this study, the relationship between dynamic shear modulus and Young's modulus was explored.

2.2.3 Validation

2.2.3.1 Subjects

Six subjects (3 males, 3 females) with a mean (SD) age of 21 (1) years, height of 170 (11) cm, and body mass of 62 (12) kg participated in the validation portion of this study. These subjects did not participate in the reliability portion of this study.

2.2.3.2 Experimental Procedures for Validation

Subjects were positioned in prone with their knee fully extended and foot secured in a KinCom dynamometer (Model 500H, Isokinetic International, Chattanooga, TN, USA) at four ankle joint angles, which included 20°, 10°, 0°, and -10° of ankle plantarflexion (Figure 2.1). The order of foot positions was randomized and subjects were given a 2-minute break between foot positions to walk around the room. Only right legs were tested, which led to procedures being performed on 5 dominant legs and 1 non-dominant leg. Static shear modulus, viscosity, and dynamic shear modulus were determined as described in the reliability portion of this study.

The only difference was that the technique was performed in the four different ankle positions.

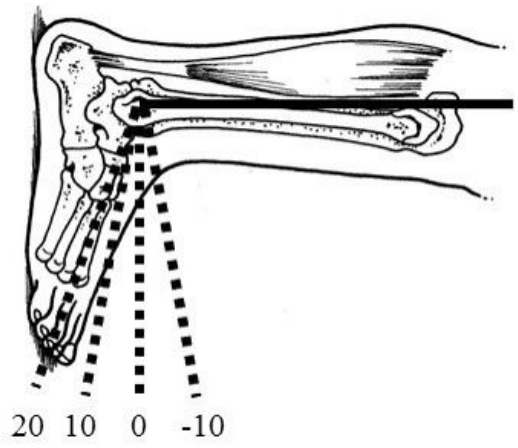

Figure 2.1 Foot position naming convention

Young's modulus of the Achilles tendon was estimated in the four foot positions using data obtained from ultrasound imaging and a KinCom dynamometer during three 5-second maximal voluntary isometric contractions (MVIC). The experimental procedures used in the current study were modified from previously described techniques (Arya and Kulig 2010; Kongsgaard et al. 2011).[76,165] All ultrasound images were gathered with a LOGIQ *e* Ultrasound system (GE Healthcare, Chicago, IL, USA) with a wide-band linear array probe (5.0-13.0MHz). Achilles tendon length and cross-sectional area were obtained while the subject was prone with their foot hanging naturally over the end of the table. Tendon length was measured as the distance from the calcaneal osteotendinous junction to the myotendinous junction of the medial gastrocnemius using extended field of view settings.[103,104] Tendon cross-

sectional area was measured with short-axis ultrasound images immediately distal to the myotendinous junction of the soleus. Linear displacement of the tendon during each MVIC was measured with cine-loop ultrasound recordings. Peak displacement between a tape shadow positioned at rest and the myotendinous junction of the medial gastrocnemius during MVIC was measured (Figure 2.2).

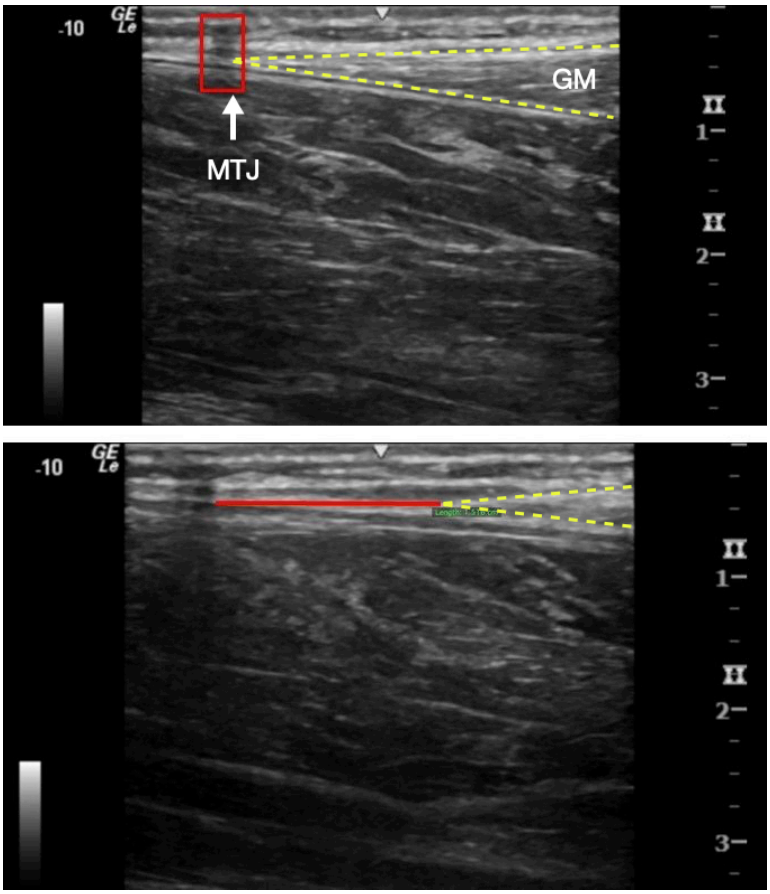

Figure 2.2 Medial gastrocnemius (GM) myotendinous junction (MTJ) displacement measured during the current study. A. Prior to maximal isometric plantar flexion contraction B. During maximal isometric plantar flexion contraction. The tape shadow was aligned with the GM MJT at rest.

Peak plantar flexion force was measured during each MVIC using a KinCom dynamometer. Peak plantar flexion force was multiplied by the external moment arm of the load cell to calculate the external plantar flexion moment. The external moment arm was fixed to 19.5 cm for all subjects, which was measured as the distance between the load cell and the axes of the dynamometer and ankle joint. Peak plantar flexion force created by the triceps surae was then estimated by dividing the measured external plantar flexion moment by the Achilles tendon moment arm. The Achilles tendon moment arm was measured from the midpoint of the lateral malleolus to the most posterior aspect of the tendon with a tape measure. Three MVICs were performed with strong verbal encouragement in each foot position after performing two practice trials. The average peak displacement of the myotendinous junction of the medial gastrocnemius and average peak plantarflexion torque from three trials were used to estimate the Young's Modulus.

Young's Modulus was calculated using the following equation:

$$\frac{\left(\left(\frac{\tau}{MA}\right)(L_0)\right)}{A\Delta L}$$

Where τ is peak plantarflexion torque at the load cell, *MA* is moment arm of the Achilles tendon, L_o is tendon length at rest, *A* is tendon cross-sectional area at rest, and ΔL is the peak displacement of the myotendinous junction of the medial gastrocnemius during MVIC.

2.2.4 Statistical Analysis

2.2.4.1 Intra-rater Reliability

Descriptive data are reported as mean (SD). Reliability analyses were performed using recommendations from Denegar and Ball.[166] Briefly, intra-rater reliability was assessed for each viscoelastic property during the first session using intraclass correlation coefficients ($ICC_{2,3}$).[166] Values are reported as ICC (95% CI) and interpreted as poor (<0.40), fair-to-good (0.40-0.75), and excellent (>0.75) reliability as suggested by Shrout and Fleiss.[167]

2.2.4.2 Stability

Although an ICC provides an estimate of the reliability of a measurement, it does not necessarily reflect the stability of what is being measured over time. Therefore, to evaluate the stability of viscoelastic properties, standard error of measurement (SEM) and minimal detectable change (MDC95%) were calculated using data from the first session. A one-way repeated measures ANOVA was performed for each variable to analyze stability within the first session (i.e. baseline, 30 minutes, 2 hours and, 4 hours). A Greenhouse-Geisser correction was applied when assumptions of ANOVA were violated. Partial eta-squared effect sizes are reported and interpreted as suggested by Cohen[168] as no effect (<0.01), small effect (<0.06), medium effect (<0.14), and large effect (≥0.14). Paired t-tests were performed using baseline data from the first session and data from the second session to evaluate stability over a two week period. Cohen's d effect sizes are reported and interpreted as no effect (<0.2), small effect (<0.5), medium effect (<0.8), large effect (≥0.8).[168]

2.2.4.3 Validation

To demonstrate the construct validity of cSWE for measuring viscoelastic properties, values were compared across the four different foot positions. As the foot is moved from a plantarflexed position to a dorsiflexed position, the passive tension within the Achilles tendon increases. Since tension is directly related to wave speed propagation, viscoelastic properties are expected to increase with increased dorsiflexion. To demonstrate the capability of cSWE to detect this relationship, viscoelastic properties were compared across the four different foot positions using a one-way repeated measures ANOVA. In order to determine the sample size needed, a power analysis was performed using data obtained from the first five participants. With an effect size of $\eta^2_{partial}=0.497$ for static shear modulus, $\beta=0.8$, and $\alpha=0.05$, it was determined the analysis would be adequately powered with 6 participants.

2.2.4.4 Relationships of mechanical properties

To explore the relationships between viscoelastic properties measured with cSWE and Young's modulus measured with ultrasound and dynamometry, group averages at each foot position were calculated, plotted and investigated using Pearson product-moment correlations. All statistical procedures were performed using IBM SPSS v24 (Chicago, IL, USA) at a significance level of $p<0.05$.

2.3 Results

2.3.1 Intra-rater Reliability

The mean (SD) static shear modulus, viscosity, and dynamic shear modulus for each time point are shown in Table 2.1. Shear modulus had fair-to-good reliability with an ICC of 0.697 (0.392-0.868), viscosity had excellent reliability with an ICC of

0.856 (0.717-0.937), and dynamic shear modulus had excellent reliability with an ICC of 0.855 (0.715-0.936).

Table 2.1: Viscoelastic properties measured with cSWE for both experimental sessions.

	Baseline	30 Minutes	2 Hours	4 Hours	2 Weeks
Static Shear Modulus (kPa)	95.0 (16.0)	94.6 (15.8)	94.8 (15.4)	94.0 (13.0)	95.7 (13.9)
Viscosity (Pa*s)	57.4 (13.4)	55.5 (12.4)	58.4 (13.3)	58.5 (11.5)	56.8 (11.3)
Dynamic Shear Modulus (kPa)	226.8 (49.4)	218.0 (46.2)	230.7 (49.0)	230.6 (42.2)	224.8 (39.6)

2.3.2 Stability

For static shear modulus, the SEM was 8.284 kPa, individual level $MDC_{95\%}$ was 22.948 kPa, and the group level $MDC_{95\%}$ was 5.131 kPa. Viscosity had a SEM of 4.797 Pa*s, an individual level $MDC_{95\%}$ of 13.286 Pa*s, and a group level $MDC_{95\%}$ of 2.971 Pa*s. Dynamic shear modulus had a SEM of 46.718 kPa, individual level $MDC_{95\%}$ of 49.277 kPa, and group level $MDC_{95\%}$ of 11.019 kPa.

During the first session, there were no significant differences between time points for static shear modulus ($p=0.978$; $\eta^2_{partial}=0.001$), viscosity ($p=0.623$; $\eta^2_{partial}=0.030$), and dynamic shear modulus ($p=0.502$; $\eta^2_{partial}=0.040$). Additionally, there were no differences for static shear modulus ($p=0.854$; $d=0.050$), viscosity ($p=0.828$; $d=0.049$), and dynamic shear modulus ($p=0.844$; $d=0.043$) between the baseline session and the 2-week follow up session.

2.3.3 Construct Validity

Mean (SD) tendon length to the medial gastrocnemius was 19.4 (3.4) cm and cross-sectional area distal to the myotendinous junction of the soleus was 0.406 (0.075) cm^2. Static shear modulus, viscosity, dynamic shear modulus, and Young's modulus increased with increasing amounts of dorsiflexion. There was a significant main effect of foot position on static shear modulus, viscosity, and dynamic shear modulus, but not on Young's modulus (Table 2.2, Figure 2.3-2.6).

Table 2.2 Tendon Mechanical Properties at different Foot Positions.

	Foot Angle					
	20 degrees	10 degrees	0 degrees	-10 degrees	p-value	Effect size
Static Shear Modulus (kPa)	88.0 (12.2)	92.7 (12.5)	104.4 (15.4)	106.6 (14.6)	0.036*	0.425
Viscosity (Pa*s)	29.7 (6.9)	35.1 (11.5)	41.7 (6.0)	41.9 (9.5)	0.019*	0.476
Dynamic Shear Modulus (kPa)	131.3 (24.6)	149.9 (38.2)	174.1 (22.7)	176.2 (32.4)	0.013*	0.502
Young's Modulus (GPa)	0.20 (0.11)	0.23 (0.12)	0.27 (0.16)	0.28 (0.09)	0.118	0.316

*Indicates $p<0.05$
PF= Plantar flexion

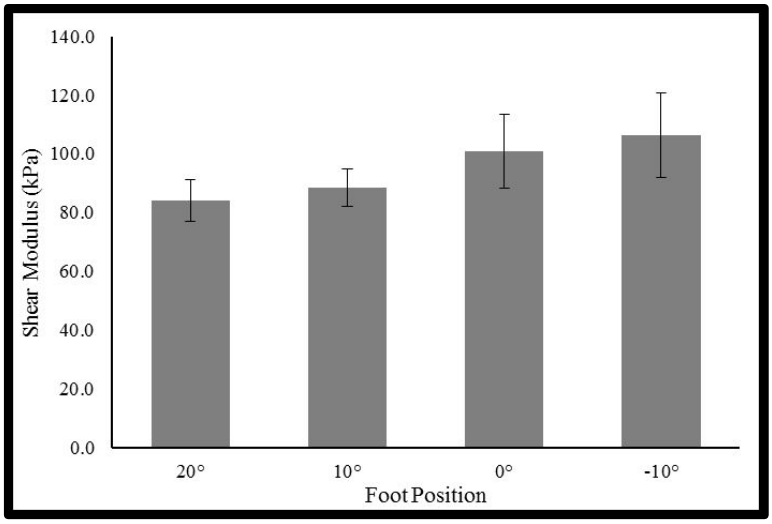

Figure 2.3 Change in Shear Modulus with Foot position. There was a significant effect of foot position on Shear Modulus (p=0.036; η^2_p=0.497)

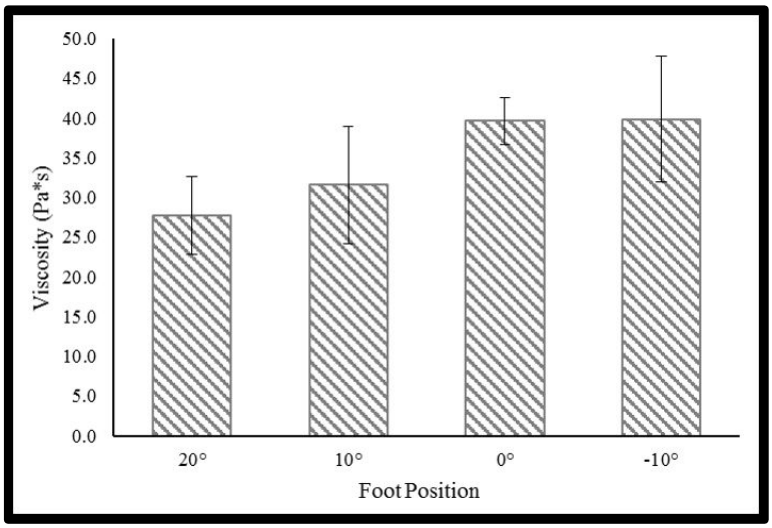

Figure 2.4 Change in Viscosity with Foot Position. No significant effect of foot position on Viscosity (p=0.051; η^2_p=0.464) was observed.

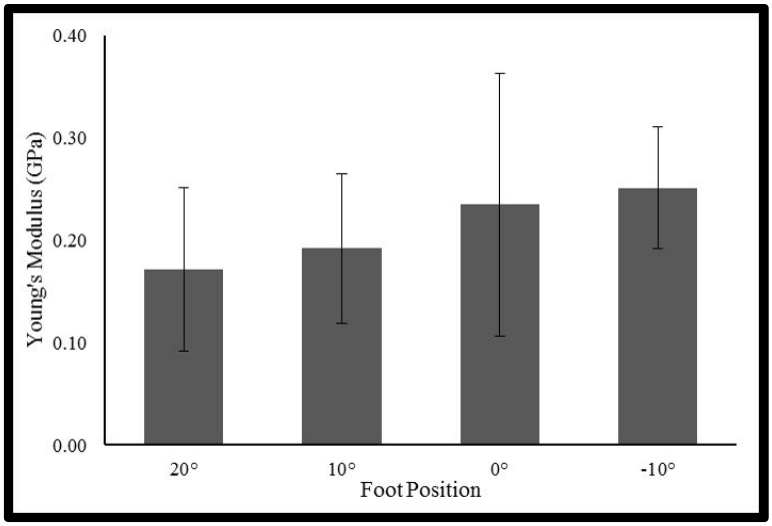

Figure 2.5 Change in Young's Modulus with Foot Position. No significant effect of foot position on Young's Modulus (p=0.246; η^2_p=0.308) was observed.

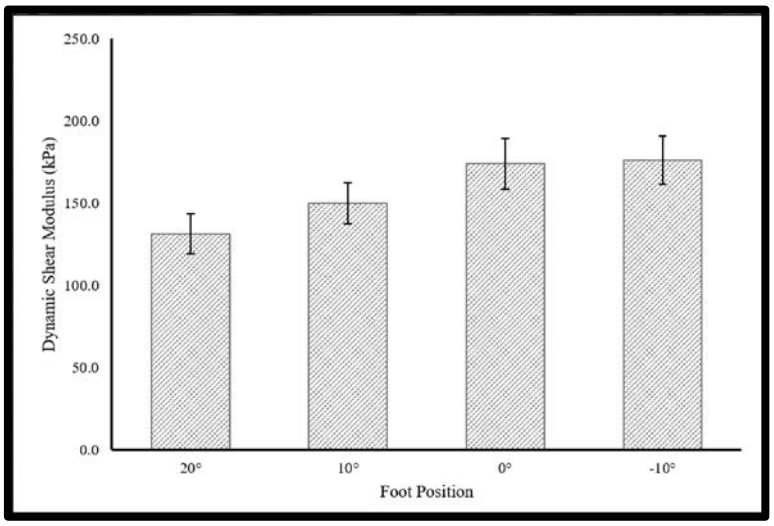

Figure 2.6 Change in Dynamic Shear Modulus (400Hz) with Foot Position. A significant effect of foot position on Dynamic Shear Modulus was observed (p=0.034; η^2_p=0.501).

2.3.4 Relationships of Mechanical Properties

A linear relationship was found between Young's modulus and static shear modulus (r=0.992, p=0.008), viscosity (r=0.994, p=0.006), and the proposed dynamic shear modulus (r=0.997, p=0.003) (Figures 2.7-2.9).

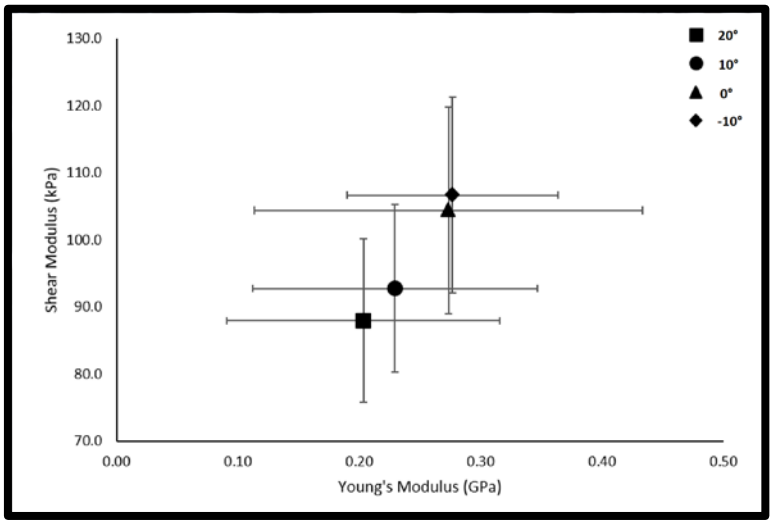

Figure 2.7 Relationship of shear modulus and Young's modulus at the group level. Data points represent group means at the different foot positions. Error bars represent ±1 SD.

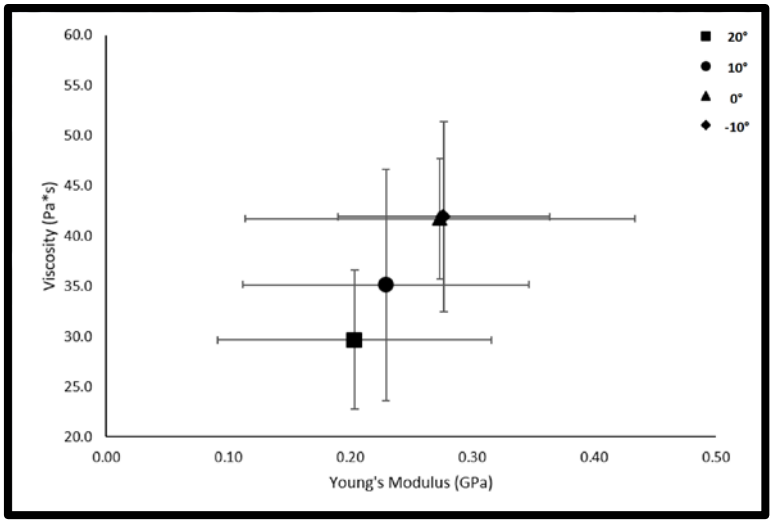

Figure 2.8 Relationship of viscosity and Young's modulus at the group level. Data points represent group means at the different foot positions. Error bars represent ±1 SD.

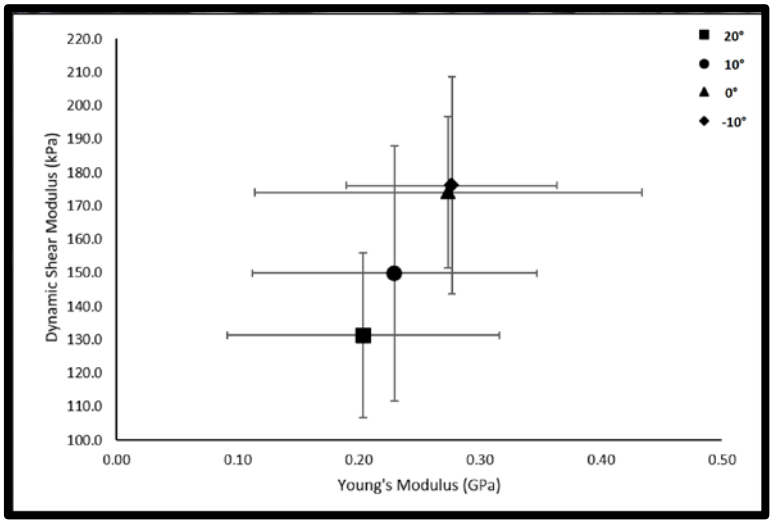

Figure 2.9 Relationship of Dynamic Shear Modulus and Young's Modulus at the group level. Data points represent group means at the different foot positions. Error bars represent ±1 SD.

2.4 Discussion

We found fair-to-excellent intra-rater reliability for measuring static shear modulus, viscosity, and dynamic shear modulus in healthy Achilles tendons with cSWE. Additionally, these viscoelastic properties appear to be stable over a 4-hour and 2-week period in healthy Achilles tendons. We also further validated cSWE by demonstrating that greater degrees of dorsiflexion lead to increases in viscoelastic properties. Furthermore, the dynamic shear modulus proposed in this study was more comparable to values reported using SSI[124] than previous reports of static shear modulus.[117,126] Taken together, these findings provide support for the use of cSWE in quantifying Achilles tendon viscoelastic properties over time and using dynamic shear modulus as a new parameter to track these properties.

2.4.1 Reliability of Elastography

Recent evidence has shown that ultrasound elastography can be a useful tool in measuring tendon mechanical properties and appears to be more sensitive in detecting pathologic changes than structural measures obtained from conventional ultrasound.[156,169,170] These properties have further been suggested as possible biomarkers for diagnosis and tracking structural recovery in the presence of tendon pathology.[117,156,157] Despite the potential usefulness of elastography, methodological and computational differences exist between the different elastography techniques (i.e. cSWE, SSI, Compression elastography), which directly impacts the ability to compare results between studies and calls into question the reliability and validity of each technique.

Intra-rater reliability of SSI, cSWE, and compression elastography have been reported for measuring Achilles tendon mechanical properties.[123,126,171,172] SSI was

found to have fair-to-good (ICC=0.42) intra-rater reliability after pooling data from both right and left tendons, but reliability was poor (ICC=0.17) on the right and fair-to-good (ICC=0.62) on the left.[172] Intra-rater reliability of static shear modulus (ICC=0.875) and viscosity (ICC=0.876) measured via cSWE has been shown to be excellent when analyzing three trials performed consecutively.[126] Poor intra-rater reliability has been reported for compression elastography when five trials are performed consecutively (ICC=0.11) and when a single trial is performed over five days (ICC=0.01).[123] Conversely, Drakonaki et al.[171] found good-to-excellent (ICC=0.66-0.78) intra-rater reliability for compression elastography when five trials are performed. These results suggest that cSWE may have superior reliability compared to other elastography methods, as demonstrated by the higher intra-class correlation coefficient.

In the current study, we found fair-to-excellent intra-rater reliability for measuring viscoelastic properties over a 4-hour period and determined that these measures are stable in healthy Achilles tendons during a 4-hour and 2-week period. We speculate that these findings may be due to the standardization of experimental procedures (e.g. ultrasound probe alignment, subject positioning, and locating the ROI), minimization of operator-dependent factors (e.g. no pressure application or qualitative grading systems), and performing the study in a healthy population. It is difficult however to compare our findings to the reliability of other elastography techniques since our study used the average of three trials across multiple time points rather than multiple measures at a single time point. Future research is needed to compare the reliability of different elastography techniques for measuring tendon mechanical properties.

2.4.2 Evaluating Construct Validity of Continuous Shear Wave Elastography

During the development of cSWE, mechanical properties of agarose gels were compared between cSWE and magnetic resonance elastography. The mechanical properties obtained with these two techniques were similar and cSWE was capable of detecting spatial variations in mechanical properties. Further validation of cSWE has included identifying side-to-side differences in tendon mechanical properties in patients with Achilles tendinopathy and Achilles tendon rupture. Collectively, these findings support the use of cSWE for estimating mechanical properties and comparing injured to uninjured tendons, but further testing is needed to determine if cSWE is actually capturing tendon mechanical properties when applied to human tendon. Therefore, in the current study, we aimed to demonstrate that cSWE captures the construct it was intended to measure (i.e. *in vivo* tendon mechanical properties). To demonstrate this, we evaluated tendon mechanical properties with cSWE in different ankle joint angles. Because the Achilles tendon crosses posterior to the ankle joint, Achilles tendon mechanical properties are expected to increase when the ankle joint is passively moved from a plantarflexed to a dorsiflexed position. Our results confirmed that Achilles tendon mechanical properties estimated with cSWE increase with increasing ankle dorsiflexion. Additionally, it appears that the gradual increase in tendon mechanical properties from 20 to 0 degrees of plantar flexion may represent the toe region of the stress-strain curve, while the minimal change from 0 to -10 degrees of plantar flexion may represent the transition into the linear elastic region of the stress-strain curve. Taken together, these findings suggest that cSWE is capturing tendon mechanical properties.

cSWE has now been validated in several ways, yet it remains unknown if cSWE accurately measures *in vivo* tendon mechanical properties. In other words, if the

same tendon was evaluated with cSWE and bench-top testing (gold standard for mechanical testing), the values obtained for each mechanical property may differ greatly. In many circumstances the accuracy of measuring mechanical properties would be critical. However, the purpose of developing cSWE was to estimate tendon mechanical properties that could be used as biomarkers of tendon health and recovery. Therefore, the accuracy of the tendon's mechanical properties is not as critical as having good reliability and sensitivity to changes within the tendon.

2.4.3 Comparison to Supersonic Shear Imaging (SSI)

The average dynamic shear modulus of the Achilles tendon at baseline was 226.8 kPa for the 20 healthy individuals included in the reliability portion of this study. This value represents the estimated modulus at 400 Hz instead of 0 Hz, which is proposed to be more comparable to measures obtained with SSI. Healthy human Achilles tendons have an average reported modulus ranging from 51.5 kPa and 779.5 kPa when measured with SSI.[124,173–175] These values are difficult to compare to cSWE since there is no consensus on foot position or calculations used to estimate modulus. Using data from a study that compared mechanical properties between ruptured and non-ruptured sides in patients within 1 year of Achilles tendon rupture,[129] dynamic shear modulus was determined to be 155 kPa on the ruptured side and 207 kPa on the non-ruptured side. In a study that tracked mechanical properties with SSI over a 48-week post-operative period in patients post-Achilles tendon rupture,[162] the average modulus increased from 187.7 kPa at 12 weeks to 289.6 kPa at 48 weeks. Taken together, dynamic shear modulus calculated from cSWE appears more comparable to SSI than static shear modulus. The current study found that estimating dynamic shear modulus with cSWE in healthy Achilles tendons has adequate intra-rater reliability

and is stable over time. Therefore, it appears that dynamic shear modulus estimated with cSWE can be used to monitor Achilles tendon mechanical properties over time. Further research is needed to better understand if there is physiological or histological rationale for continuing to look at static shear modulus and viscosity independently.

2.4.4 Relationship between Elastography and Traditional *in vivo* Mechanical Testing

Validation of cSWE has been limited to comparisons to magnetic resonance elastography using agarose gels and observations of side-to-side differences in patients with tendon injury.[117,127,129] Similarly, detection of side-to-side differences in Achilles tendinopathy and rupture has also been reported with axial-strain elastography[176,177] and shear wave elastography(Aubry et al. 2015; Chen et al. 2013).[124,178] Despite the clinical usefulness of detecting side-to-side differences, limited studies have validated measures obtained with elastography to bench-top testing[179,180] and only one study has investigated the ability of elastography to identify histological changes.[169] Haen et al.[179] found a strong relationship between shear modulus measured with ultrasound elastography and elastic modulus from bench-top testing in human cadaveric tendons, while Yeh et al.[180] found a strong relationship between shear wave speed and elastic modulus in a porcine model. Klauser et al.[169] showed that axial-strain elastography identified 100% of tendon samples with histologyical degeneration, which was superior to the 86% identified with B-mode ultrasound imaging. In the current study, we found a strong relationship between Young's modulus and viscoelastic properties obtained with cSWE. For the elastography portion of this study, shear modulus was used rather than wave speed since much of the literature reports modulus and the two variables are directly related.[164,181] Additionally, in our study there was a significant

effect of foot position on shear modulus, which agrees with what is reported in the literature.[174,179,182] This finding reflects the ability of cSWE to detect the linear nature of tendon that occurs with different amounts of strain. These findings further validate cSWE for quantifying Achilles tendon viscoelastic properties *in vivo* and supports its use when mechanical testing is not feasible.

2.4.5 Advantages and Pitfalls of Continuous Shear Wave Elastography (cSWE)

There are many advantages of measuring tendon mechanical properties with cSWE compared to other elastography and *in vivo* techniques (e.g. ultrasound synchronized with dynamometry). One of the main advantages is that it can be safely completed throughout all stages of injury, including immediately after tendon rupture. This is because cSWE does not rely on muscle contractions that place large tensile loads on the tendon. Another advantage of cSWE is the ability to measure variations of mechanical properties within healthy and injured tendons without concerns of saturating the elastogram. This enhances the validity of cSWE and may provide future insights into tendon healing and pathogenesis. Contrary to these advantages, cSWE requires additional hardware (e.g. external actuator) and two testers to perform data collection. Another pitfall is that cSWE requires offline processing, which is time consuming compared to commercially-available elastography techniques that have processing in real time. Taking these advantages and disadvantages into consideration, it appears that cSWE is well-situated for measuring tendon viscoelastic properties, especially when conventional mechanical testing is not feasible.

2.4.6 Study Limitations

The current study is not without its limitations. A relatively small sample of only young, healthy Achilles tendons were included throughout both parts of this study. Although a healthy sample is critical for establishing reliability, uncertainty remains if the relationships between Young's modulus and measures of viscoelastic properties differ in the presence of tendon injury. Additionally, the relationships between mechanical properties violate the assumption of Pearson product-moment correlation that data points are independent of each other. However, it was necessary to use the same subjects throughout testing due to large individual variability. Therefore, reported R- and p-values should be interpreted with caution. Another limitation is that measures of shear modulus and viscosity from this study cannot be directly compared to values previously reported with cSWE[117,126] due to procedural and computational modifications that are outlined in the material and methods section. It is unknown if the values obtained with cSWE are representative of the true shear modulus and viscosity of the tissue. However, the purpose of quantifying these values is to establish biomarkers that can be used to track structural integrity of tendon. Lastly, all testing procedures were performed by a single experienced investigator. Results may represent the reliability of cSWE performed by this individual and not accurately reflect the reliability if performed by another evaluator.

2.5 Conclusion

This study showed fair-to-excellent intra-rater reliability of cSWE for measuring tendon viscoelastic properties, demonstrated construct validity of cSWE by detecting differences in viscoelastic properties with changes in ankle position, and found strong relationships between mechanical properties obtained with cSWE and

traditional mechanical testing. Additionally, as expected in healthy tendon, measurements of static shear modulus, viscosity, and dynamic shear modulus were stable over time. Collectively, findings suggest that cSWE can be used for measuring changes in Achilles tendon viscoelastic properties.

2.6 Relationship of Young's modulus and Shear Properties in patients with Achilles tendinopathy

The contents of sections 2.1 through 2.5 of this dissertation are published in the Journal of Ultrasound in Medicine and Biology.[7] We found significant relationships between viscoelastic properties measured with cSWE and Young's modulus measured with ultrasound and dynamometry in healthy tendon. It remains unclear, however, if these relationships are similar in tendinopathic tendons. Therefore, we performed an additional analysis with the purpose of exploring the relationship between Young's modulus, shear modulus, and viscosity in patients with Achilles tendinopathy. We hypothesized that Achilles tendon mechanical properties (static shear modulus, dynamic shear modulus, viscosity) measured with cSWE would have a strong positive relationship ($r>0.75$) to Young's modulus measured with ultrasound imaging and dynamometry in degenerative tendons.

Young's modulus was estimated with ultrasound and dynamometry with the ankle in neutral. Static shear modulus, viscosity, and dynamic shear modulus were estimated with cSWE while the ankle was positioned in 10 degrees of dorsiflexion. These methods are detailed in section 5.2.7 of this dissertation. The patients with Achilles tendinopathy who participated in Aim 4 of this dissertation (see section 5.2.2) and completed cSWE were included in this analysis (n=19). Additionally, a secondary analysis was performed with only patients who have midportion Achilles tendinopathy

(n=12). Pearson's correlations were used to analyze the relationships between viscoelastic properties and Young's modulus.

In the full cohort, Young's modulus was not associated with static shear modulus (r=-0.083; p=0.736), viscosity (r=-0.264; p=0.275), or dynamic shear modulus (r=-0.249; p=0.303). Similarly, in the patients with midportion tendinopathy, Young's modulus was not associated with static shear modulus (r=0.219; p=0.494), viscosity (r=-0.390; p=0.210), or dynamic shear modulus (r=-0.332; p=0.292).

This analysis suggests that viscoelastic properties estimated with cSWE are not related to tensile properties in tendinopathic tendon. This lack of association may be a result of measuring different aspects of the musculotendinous unit. For example, since tensile testing relies on muscle contraction, measurements may reflect the overall functional status of the muscle-tendon unit. On the other hand, viscoelastic properties estimated with cSWE may specifically reflect the tendon component of the muscle-tendon unit. It can therefore be speculated that the relationships between viscoelastic properties and tensile properties would become stronger throughout recovery while calf muscle function and tendon mechanical properties are improving. Further research is needed to confirm this speculation and determine if specific mechanical properties relate to the recovery of patient symptoms and lower leg function.

Chapter 3

TENDON MORPHOLOGY AND MECHANICAL PROPERTIES PREDICT RECOVERY FOR PATIENTS WITH ACHILLES TENDINOPATHY

3.1 Introduction

Achilles tendinopathy is a debilitating overuse injury that is characterized by pain, impaired functional performance, and altered Achilles tendon morphology.[1,2] The clinical diagnosis of Achilles tendinopathy is based mainly on patient history and clinical examination. Ultrasound and magnetic resonance imaging (MRI) are routinely used to confirm the diagnosis and measure morphologic features of the tendon (e.g. thickness, cross-sectional area). Yet, the clinical usefulness of evaluating tendon morphology has been questioned since structural changes can exist without symptoms.[183–185] On the other hand, altered tendon structure has been shown to be predictive of developing symptoms.[59,109–111] In order to improve the clinical care of patients with Achilles tendinopathy, there is a need to determine if tendon morphology plays a critical role in patient recovery.

While traditional measures of tendon morphology reflect the size and/or shape of the tendon, they do not necessarily represent the tendon's ability to absorb and transfer loads during functional activities. Tendon mechanical properties reflect the structural integrity of the tendon and have become of interest to supplement measures of tendon morphology. In the context of Achilles tendinopathy, research has focused on developing techniques for measuring mechanical properties, comparing properties of healthy and tendinopathic tendons,[76,114] and determining if mechanical properties

can assist with diagnosis.[178,186,187] We have developed a valid and reliable technique known as continuous shear wave elastography (cSWE) for measuring shear modulus (resistance to a shearing force) and viscosity (rate dependent resistance to a shearing force).[7,117] cSWE has been used to evaluate these properties in healthy,[7,117,126] tendinopathic[8,117] and ruptured Achilles tendons.[127–129] Still, it remains unclear if mechanical properties are related to symptomatic and functional recovery. A better understanding of Achilles tendon injury and recovery may be gained by exploring associations between tendon mechanical properties and patient outcomes.

It is currently recommended that patients with Achilles tendinopathy are treated conservatively for at least three months before invasive treatments are considered.[80,85] This recommendation is typically made regardless of symptom severity, alterations in tendon morphology, functional status, or patient characteristics (e.g. age, BMI, activity levels). Although findings on diagnostic imaging may help guide treatment decisions, they are rarely used to determine treatment dosages or adjusting treatment expectations. One of the speculated benefits of measuring tendon morphology and mechanical properties is the ability to better predict patient outcomes, therefore resulting in more realistic treatment expectations. However, it is currently unknown if these measures have this predictive value. Therefore, this study aimed to understand the associations between tendon morphology, mechanical properties, and the recovery of patient outcomes by prospectively following a cohort of individuals with Achilles tendinopathy. We hypothesized that greater tendon thickening, lower shear modulus, and lower viscosity at initial assessment would relate to worse symptoms and calf muscle function at 6-month and 1-year follow-up assessments.

3.2 Materials and Methods

3.2.1 Study Design

This was an observational study that followed patients with various Achilles tendon injuries prospectively for a year (Level 2 evidence). Participants were recruited from November 2014 to January 2018. Treatment was not provided as part of the study and the participants treatment, or lack of treatment, was not controlled or documented. This design allowed for the natural sequela of the injury to be observed. Participants were asked to complete an initial visit and 6-month and a 1-year follow-up visits. At the initial visit, patient-reported symptoms, calf muscle function, tendon morphology, and tendon mechanical properties were evaluated. At the follow-up visits, patient-reported symptoms and calf muscle function were evaluated. Prior to data collection, participants were informed of the study procedures and provided written consent. The study protocol was approved by the Institutional Review Board at the University of Delaware.

3.2.2 Participants

Participants who had a clinical diagnosis of midportion or insertional Achilles tendinopathy, as defined by van Dijk et al.,[1] were included in the current study. A clinical examination was performed by a licensed physical therapist to confirm diagnosis. Participants with a history of surgery to the Achilles tendon, comorbidity that affects pain perception (e.g. multiple sclerosis, fibromyalgia), or minimal symptoms at their initial visit (i.e. VISA-A score > 90) were excluded. Additionally, participants were excluded if they did not complete both follow-up visits or undergo the structural evaluation. Demographics, anthropometrics, injury characteristics, and physical activity levels were recorded. The Physical Activity Scale (PAS) originally

described by Grimby[188] was used. This is an ordinal scale from one to six, with higher values indicating greater amounts of physical activity.

3.2.3 Patient-Reported Symptoms

The Victorian Institute of Sports Assessment – Achilles (VISA–A) questionnaire was used to quantify symptom severity at each visit. The VISA–A is a questionnaire designed for patients with Achilles tendinopathy that is valid, reliable, and commonly used in clinical practice.[82,189] The questionnaire is scored from 0 to 100, with higher scores indicating less symptoms. Ideally, participants complete all eight questions, with the first seven questions worth 10 points each and the eighth question worth 30 points. However, patients occasionally skip questions six and eight, which are related to pain during hopping and sports participation. In this study, the questionnaire was not scored when the eighth question was skipped. If only the sixth question was skipped, the average score of questions one through five was used to fill in the missing response.

3.2.4 Calf Muscle Function

Participants performed the heel-rise endurance test to quantify the functional status of the calf musculature at each visit. The heel-rise endurance test is valid and reliable[190] and has been used to detect functional deficits in patients with Achilles tendinopathy.[101] For this test, participants perform as many single-leg heel-rises on a 10° incline box as possible while keeping their knee straight and following a metronome (30 repetitions/minute). Testing was terminated when the participant was unable to perform any more repetitions or maintain the testing parameters. A linear encoder (MuscleLab®, Ergotest Innovations, Porsgrunn, Norway) was attached to the

heel of the participant to determine the total mechanical work (Work= ∑displacement x mass). A zero was recorded when a participant could not complete a single-leg heel-rise.

3.2.5 Tendon Morphology

Achilles tendon morphology was evaluated with ultrasound imaging at each visit. Participants were prone with their feet hanging naturally over the edge of the treatment table. Three extended field of view images were obtained with a LOGIQ *e* ultrasound system (GE Healthcare, Chicago, IL, USA) equipped with a wide-band linear array probe (5.0-13.0MHz). Tendon thickness was measured at the thickest part of the tendon and at a standardized reference location. By taking the difference of these measurements, tendon thickening was calculated (Figure 3.1). The reference location reported in the literature[191] for patients with midportion Achilles tendinopathy is 2 centimeters proximal to the osteotendinous junction. Therefore, this location was used for these participants. The same reference location could not be used for participants with insertional Achilles tendinopathy because this region's morphology is affected. Thus, immediately distal to the soleus myotendinous junction was used for participants with insertional tendinopathy. This reference location was also used for the participants who presented with equal symptoms in both regions. Although the reference location differs between the participants, each location reflects a region of the tendon that is unaffected for each subgroup.

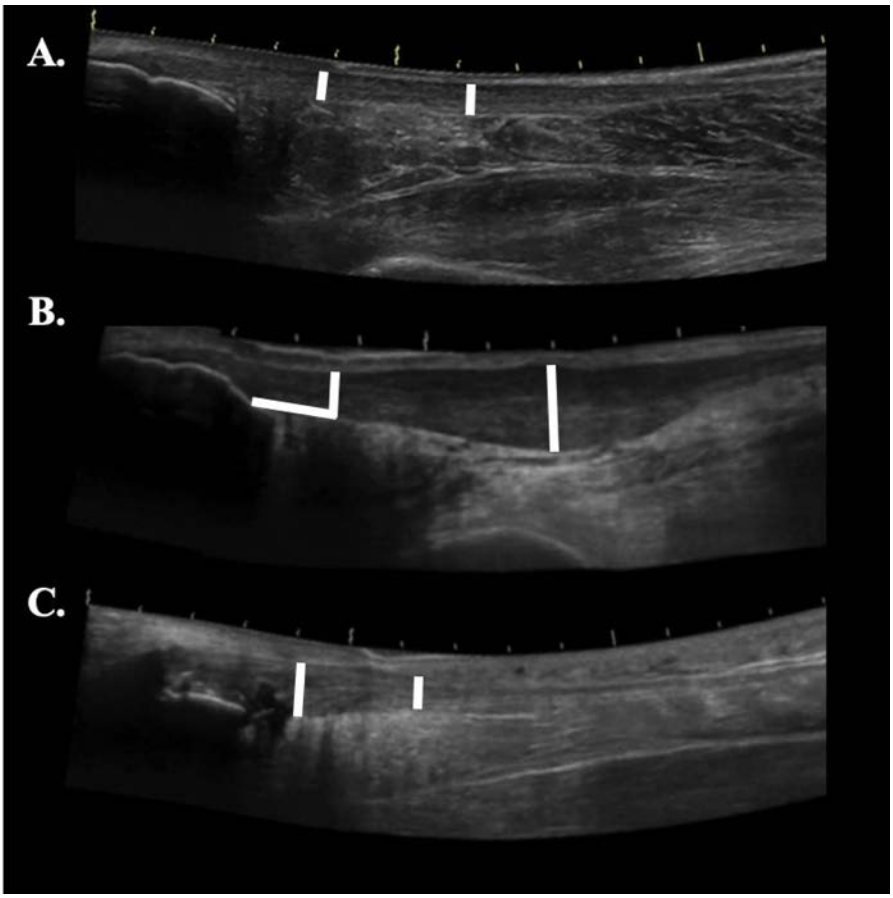

Figure 3.1 Representative ultrasound images for measuring Achilles tendon thickening. A. represents a healthy Achilles tendon. Notice that thickening is zero. B. represents midportion Achilles tendinopathy. Thickening = Thickness at thickest location – Thickness 2 cm distal to osteotendinous junction. C. represents insertional Achilles tendinopathy. Thickening = Thickness at thickest location – Thickness immediately distal to soleus myotendinous junction.

3.2.6 Tendon Mechanical Properties

Achilles tendon mechanical properties were quantified with cSWE.[7,117] Briefly, participants were prone with their feet secured to a platform in 10° of ankle dorsiflexion. This positioning ensured that the tendon was within the linear region of the stress-stiffness curve. Shear waves were generated with an external actuator (Mini-

Shaker Type 4810, Bruel & Kjaer, Norcross, GA, USA) that propagated along the length of the Achilles tendon at eleven known frequencies (Range: 322-643Hz). While the waves were propagating, a SonixMDP Q+ ultrasound system (Ultrasonix, Vancouver, Canada) with a L14-5/38 probe and a 128-channel data acquisition device sampled raw radiofrequency data (frame rate=6438 frames/s). Viscoelastic modeling was then used to estimate the tendon's shear modulus and viscosity. These mechanical properties were obtained from the thickest region of the free tendon (i.e. between the calcaneus and soleus myotendinous junction).

3.2.7 Statistical Analysis

Associations between patient symptoms (VISA-A) and calf muscle function (heel-rise work) with tendon morphology and mechanical properties were analyzed using two General Linear Mixed Models. All assumptions of the mixed models, including the absence of outliers at each time point, were evaluated using residual plots and Shapiro-Wilk tests for normality. If a single data point for an individual was identified as an outlier for that visit, it was removed from the analysis. A first-order autoregressive (AR1) correlation structure of the residuals was selected based on comparing Akaike and Bayesian information criterions for model fit. Fixed effects in the model included, tendon thickening, shear modulus, and viscosity at the initial visit and time (initial, 6-month, and 1-year). Lastly the interaction of time with tendon thickening, shear and viscosity were evaluated. Significant interactions were post-hoc probed by comparing the simple slopes for structural measures for each visit following the suggestions of Aiken & West.[192] In other words, if VISA-A scores or calf muscle function over time depended on a structural variable, the interaction was visualized by plotting the simple slopes when the structural variable was set to the mean and one

standard deviation above and below the mean. For all analyses, the significance level was set to $p<0.05$.

3.3 Results

3.3.1 Participants

The inclusion and exclusion criteria resulted in 59 eligible participants. Their demographics, anthropometrics, injury characteristics, physical activity levels and initial measures of morphology and mechanical properties are reported in Table 3.1. Additionally, the flow of participants is depicted in Figure 3.2.

Table 3.1 Initial Characteristics of Patients with Achilles tendinopathy.

	Mean (SD), Min-Max
Age (years)	52 (15), 19-79
Height (cm)	174 (11), 140-195
Weight (kg) (n=58)[a]	84 (21), 56-164
Duration of Symptoms (months) (n=55)[b]	25.4 (57.5), 0.4-396.3
Physical Activity Scale (n=58)[a]	4.1 (1.4), 1-6
VISA-A Score[a,c]	55 (21), 18-88
Tendon Thickening (mm)	2.88 (1.9), 0.1-7.5
Shear Modulus (kPa)	100.7 (17.5), 63.2-139.4
Viscosity (Pa*s)	50.8 (12.9), 20-80
	Frequencies
Sex (males: females)	33:26
Location of Injury (midportion: insertion: both)	28:25:6

[a] One participant did not complete
[b] Four participants did not report
[c] Raw Victorian Institute of Sports Assessments- Achilles questionnaire scores at baseline

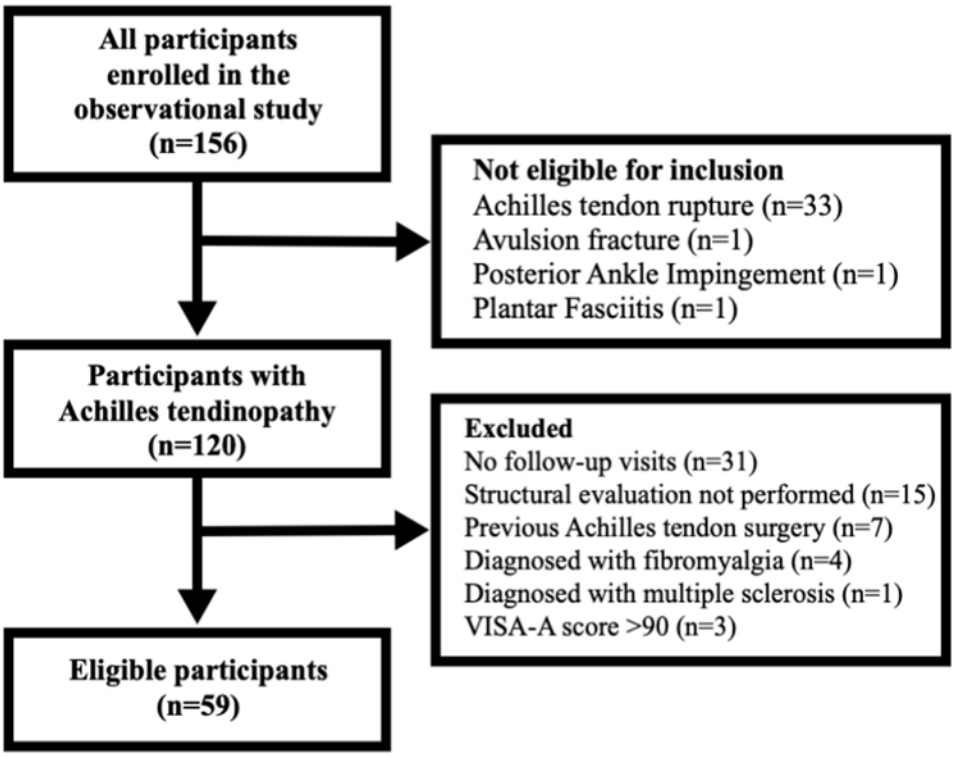

Figure 3.2 Participant Flow Diagram

3.3.2 Patient-Reported Symptoms

When analyzing the associations between VISA–A scores over time and tendon morphology and mechanical properties at the initial visit, two outliers were identified at the 1-year follow-up and removed from the final model. This resulted in data for 58 patients at baseline, 49 at 6-month follow-up, and 46 at 1-year follow-up.

Adjusted mean (95% CI) VISA–A scores were 54 (50-60) at baseline, 72 (67-77) at 6-month follow-up, and 78 (72-83) at 1-year follow-up with a significant fixed effect of time (p=0.016). Tendon thickening was significantly associated with VISA–A scores consistently across all time points (p=0.001). The model showed for every 1 millimeter increase in tendon thickening, VISA–A scores decreased by 4 points.

Additionally, the relationship between VISA–A scores and time significantly depended on the tendon's shear modulus (p=0.009). The effect of low (i.e. one standard deviation below the mean), moderate (i.e. the mean), and high (i.e. one standard deviation above the mean) shear modulus on VISA–A scores over time was post-hoc probed and plotted in Figure 3.3. VISA–A scores were not associated with tendon viscosity (fixed effect: p=0.221; interaction time with viscosity: p=0.270).

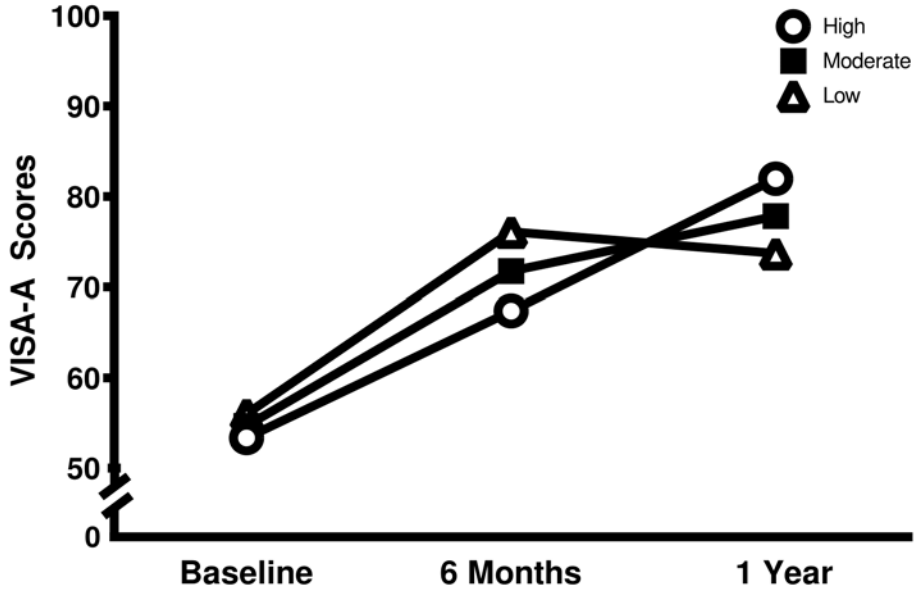

Figure 3.3 Effect of low, moderate and high Achilles tendon shear modulus at initial evaluation on the recovery of patient symptoms (VISA–A scores). Low group was determined at 1 standard deviation below the mean. Moderate group was set at the mean. High group was determined at 1 standard deviation above the mean.

3.3.3 Calf Muscle Function

When analyzing the associations between heel-rise work over time and tendon morphology and mechanical properties at the initial visit, three outliers were identified (one participant at all time points) and removed from the final model. Additionally, another participant was removed because they did not complete the heel-rise endurance test at all visits. This resulted in data for 54 patients at baseline, 47 at 6-month follow-up, and 44 at 1-year follow-up.

The adjusted means (95% CI) for heel-rise work were 1180 (984-1376) J at baseline, 1601 (1399-1803) J at 6-month follow-up, and 1598 (1387-1809) J at 1-year follow-up with a non-significant fixed effect of time ($p=0.282$). Tendon thickening was significantly associated with heel-rise work consistently across all time points ($p<0.001$). The model showed for every 1 millimeter increase in tendon thickening, heel-rise work decreased by 179 J. Tendon viscosity was also significantly associated with heel-rise work consistently across all time points ($p=0.001$), with the model showing for every 1 Pa*s increase in viscosity, heel-rise work improved by 20 J. Change in heel-rise work over time did not depend on viscosity ($p=0.053$). Finally, heel-rise work was not associated with tendon shear modulus (fixed effect: $p=0.132$; interaction time with shear modulus: $p=0.430$).

3.4 Discussion

The purpose of this study was to understand the associations between tendon morphology, mechanical properties, and the recovery of symptoms and function in patients with Achilles tendinopathy. We hypothesized that greater tendon thickening, lower shear modulus, and lower viscosity at initial assessment would relate to worse symptoms (VISA–A scores) and calf muscle function (heel-rise work) at 6-month and

1-year follow-up assessments. We found that greater tendon thickening at the initial visit was consistently associated with worse symptoms and calf muscle function at each visit. Additionally, patient symptoms over the year depended on the initial shear modulus. Lastly, a lower initial viscosity was consistently associated with worse calf muscle function at each visit. These findings suggest that tendon morphology and mechanical properties matter for the recovery of symptoms and function in patients with Achilles tendinopathy.

Tendon morphology is evaluated in clinical and research settings with ultrasound imaging or MRI. In addition to confirming a diagnosis of Achilles tendinopathy, these techniques have been used to monitor the tendon's response to treatment[5,112,113] and predict the development of symptoms.[59,109–111] A recent cross-sectional study showed that tendon thickening was related to current symptoms and physical activity levels.[191] Additionally, a systematic review by McAuliffe et al[59] found that the risk of developing symptoms was seven times greater in people who had structural abnormalities. However, it remains unclear if tendon thickening can predict outcomes of patients with Achilles tendinopathy. In the current study, we showed that a greater degree of tendon thickening at the initial evaluation was associated with worse symptoms and calf muscle function at 6 months and 1 year. This suggests that the degree of alteration in tendon morphology plays a critical role in patient recovery. Future clinical research should incorporate measures of tendon thickening in order to track recovery and identify treatments that improve tendon morphology.

In patients with Achilles tendinopathy, reduced mechanical properties accompany changes in tendon morphology.[76,114] This reduction negatively affects the

tendon's ability to efficiently store and release elastic energy during locomotor and explosive (e.g. jumping) activities.[29,193–195] Consequently, mechanical properties have been proposed as biomarkers for tendon health and recovery. In the current study, we found that changes in patient symptoms (VISA–A) by 6 months and 1 year depended on the tendon's initial shear modulus (Figure 3.3). Overall, it appears that patient symptoms are relatively the same at their initial visit regardless of their shear modulus. However, patients with lower shear modulus have the greatest improvement in symptoms after 6 months, but slightly regress by 1 year. Patients with higher shear modulus, on the other hand, are the least improved by 6-months but end with the best outcomes by 1 year. Collectively, it appears that a higher initial shear modulus is desirable because it is predictive of greatest long-term improvements in symptoms. Further study is needed to determine if measures of mechanical properties during rehabilitation can help with treatment decisions, such as dosages and return-to-sport.

Limited research has investigated tendon viscosity because of the technical inability to separate dampening behaviors from elastic behaviors *in vivo*. With the development of cSWE, we are able to reliably estimate tendon viscosity.[7,117] This parameter may have large clinical implications since it describes the tendon's ability to resist strain at different loading rates. In the current study, we found that lower tendon viscosity initially was associated with consistently lower heel-rise endurance. This suggests that tendon viscosity may be an important determinant of calf muscle function. Further research is needed to determine if tendon viscosity changes with treatment and if it is related to improvements in function.

For patients with Achilles tendinopathy, rehabilitation aims to alleviate symptoms, improve function, and allow for a safe return to recreational activities. In

many cases, symptoms are the primary factor patients and clinicians use to assess recovery. Although symptoms are an important part of the clinical picture, a treatment approach that mainly focuses on symptoms to guide clinical decisions may partially explain high re-injury rates and poor long-term outcomes.[6,88,130] This is because symptom resolution does not ensure full structural or functional recovery.[4,5] In the current study, we showed that tendon structure plays a critical role in symptomatic and functional recovery. Therefore, a more comprehensive approach that takes symptoms, structure and function into consideration may improve long-term outcomes for patients with Achilles tendinopathy. Before this comprehensive approach to tendon health can be fully implemented, research is needed to further understand the effects of treatment on symptoms, structure and function.

This study has several limitations. Patient demographics, anthropometrics, medications, comorbidities, and biopsychosocial variables were not considered in the analysis. Although this limits the ability to identify subgroups of patients who will respond favorably to conservative treatments, it improves the generalizability of the results. Current and previous treatments were not controlled or recorded. The lack of controlled treatment, however, allowed us to investigate the natural sequela of Achilles tendinopathy. Another limitation is that patients with midportion and insertional Achilles tendinopathy were collapsed into a single cohort. Thus, it remains unclear if tendon morphology and mechanical properties play a more critical role in one pathology versus the other. Conversely, tendon thickening, shear modulus and viscosity were related to long-term symptoms and function even with the heterogeneous population.

This is the first study to identify tendon morphology and mechanical properties as prognostic biomarkers for the recovery of patients with Achilles tendinopathy. Clinically, this suggests that treatments that improve tendon mechanical properties will improve long-term patient outcomes. This may explain why exercise therapy, which improves mechanical properties through mechanotransduction,[196,197] is an effective treatment for patients with Achilles tendinopathy.[82] However, research is needed to determine how tendon morphology and mechanical properties change over time and in response to different treatments.

In conclusion, Achilles tendon morphology and mechanical properties are predictive of long-term symptoms and function in patients with Achilles tendinopathy. This suggests that measures of tendon structure are clinically useful at the time of diagnosis. Future research is needed to determine if measures of tendon structure can be used to inform treatment and return-to-sport decisions.

Chapter 4

IMMEDIATE EFFECT OF PHOTOBIOMODULATION THERAPY ON ACHILLES TENDON MORPHOLOGY AND MECHANICAL PROPERTIES: AN EXPLORATORY STUDY

4.1 Introduction

The Achilles tendon is a collagenous tissue that is designed to efficiently store and release elastic energy during locomotor activities. The efficiency of this energy transfer relies on many factors, including the integrity of the Achilles tendon.[21,23,31,198–200] Achilles tendinopathy is an overuse injury that reduces the integrity of the tendon.[48,49] This manifests as fusiform thickening of the tendon and reduced mechanical properties.[1,76,100,114,201] Pain during loading activities and functional impairments accompany these structural changes and lead patients to seek treatment.

Exercise therapy is currently the standard of care for treating Achilles tendinopathy.[82] Throughout a long-term exercise program, the mechanical properties (e.g. strength and stiffness) of the Achilles tendon increase.[133,136] Interestingly though, there appears to be immediate (within 30 minutes) and short-term (within 7 days) reductions in mechanical properties after a single bout of exercise.[139,140] Taken together, these findings illustrate that the Achilles tendon is a metabolically active tissue and undergoes complex remodeling in response to exercise. There are, however, other treatments (e.g. injection therapies, shock-wave therapy, laser therapy) that are commonly used as adjuncts to exercise that may influence the remodeling process. In order to improve outcomes and tailor treatments for patients with Achilles

tendinopathy, the mechanisms that explain the effectiveness of each adjunct treatment need elucidated.

Laser therapy has been investigated for the treatment of tendinopathies, with mixed outcomes in human-subjects research.[96] For Achilles tendinopathy specifically, Tumilty et al[94] found that after 12 weeks of treatment patients who receive exercise plus laser therapy have better outcomes than patients who receive only exercise therapy. Furthermore, Stergioulas et al[93] noted that patients who are treated with only exercise therapy for 12 weeks have similar outcomes to patients who are treated with exercise plus laser therapy for 4 weeks. These positive outcomes may be attributed to the physiologic effects of laser therapy, which include reducing inflammation,[142,143] and cell apoptosis,[144] inhibiting activity of matrix metalloproteinases,[145] and increasing collagen synthesis[146,147] and angiogenesis.[148] However, changes in patient-reported symptoms (e.g. pain) have been the primary focus for evaluating the efficacy of laser therapy rather than also considering tissue-level changes.[93,95,96,202–204] This is problematic since full symptomatic recovery does not ensure full structural or functional recovery of the musculotendinous unit.[4,5] In order to optimize clinical outcomes for patients with Achilles tendinopathy, there is a need to further evaluate the physiological effects of laser therapy on human tendon.

Laser therapy, similar to exercise therapy, may induce temporary changes to the tendon's morphology and mechanical properties. This would affect the efficiency of the muscle-tendon unit and potentially increase the tendon's susceptibility to further tissue damage. Additionally, laser therapy may affect the tendon's response to exercise therapy if administered beforehand. Therefore, the purpose of this exploratory study is to evaluate the immediate (within 4 hours) effects of a laser-induced

photobiomodulation (PBM) treatment on Achilles tendon morphology and mechanical properties in healthy and degenerative tendons. We hypothesize that changes in tendon morphology and mechanical properties will be greater in a laser-treated side compared to a placebo-treated side in people with healthy Achilles tendons and people with Achilles tendinopathy. Additionally, we hypothesize that changes in tendon morphology and mechanical properties would be greater in tendinopathic Achilles tendons compared to healthy Achilles tendons when treated with PBM.

4.2 Materials and Methods

4.2.1 Study Design

Two cohorts of participants were enrolled in this study. The first cohort included participants with healthy Achilles tendons and the second cohort included participants with Achilles tendinopathy. After determining each participant's eligibility, demographics, anthropometrics, and a subjective history of current and previous lower body injuries were gathered. Achilles tendon morphology and mechanical properties were acquired bilaterally at baseline. PBM treatment was then administered to one Achilles tendon following an established protocol[94] and a placebo treatment was administered to the other Achilles tendon. Tendon morphology and mechanical properties were measured bilaterally immediately after the PBM treatment, 2 hours after the PBM treatment, and 4 hours after the PBM treatment. To reduce the effects of loading between measurements, participants were asked to refrain from performing activities thought to influence mechanical properties (e.g. running, jumping, and stretching). A single, experienced evaluator performed all experimental procedures. Prior to data collection, each participant provided written consent after

being thoroughly introduced to the study procedures and potential risks. This study was approved by the Institutional Review Board at the University of Delaware.

4.2.2 Participants

Twenty participants with healthy Achilles tendons were enrolled and their descriptive information are reported in Table 4.1. Healthy participants were at least 18 years old with no history of Achilles tendon injury or pain. To ensure the healthy participants had no underlying Achilles tendon pathology or tissue degeneration (i.e. asymptomatic Achilles tendon degeneration), they were screened with ultrasound imaging, a clinical evaluation performed by a licensed physical therapist, and the Victorian Institute of Sports Assessment - Achilles (VISA-A) questionnaire.[189] If there were clinical signs of Achilles tendon pathology (e.g. pain to palpation, palpable tendon thickening) or tissue degeneration (e.g. fusiform thickening or hypoechoic regions visualized with ultrasound) during the screening procedures, the potential participant was excluded.

Twelve participants with midportion Achilles tendinopathy were enrolled and their descriptive information are reported in Table 4.1. Participants were included in this cohort if they were at least 18 years old, had a clinical diagnosis of midportion Achilles tendinopathy, and had ultrasound-confirmed tendinosis.[205] Achilles tendinosis was defined as a minimum of 2 mm of midportion tendon thickening as previously reported in the literature.[114,191,206] Briefly, tendon thickening is measured by taking the difference in tendon thickness at the thickest part of the tendon and the tendon's thickness 2 cm proximal to the osteotendinous junction.[191] Participants were excluded from the tendinopathic cohort if they presented with pathology in addition to midportion Achilles tendinopathy (e.g. insertional Achilles tendinopathy,

retrocalcaneal bursitis, history of Achilles tendon rupture). These diagnoses were ruled out by screening with ultrasound imaging and a clinical evaluation. Exclusion criteria for both cohorts included currently taking heat or light sensitive medications, an open wound in the treatment area, a diagnosis of peripheral neuropathy, or previously received laser therapy to either Achilles tendon.

Table 4.1 Demographics for healthy and tendinopathy cohorts

		Healthy Cohort (n=20)	Tendinopathy Cohort (n=12)
Age (years)		29 (4)	59 (8)
Height (cm)		177 (8)	173 (11)
Weight (kg)		82 (18)	78 (12)
Sex (Male: Female) (n)		11: 9	8: 4
Duration of Symptoms (months)		N/A	29 (23) Range: 11-98
Pain to palpation (NPRS)	Placebo	N/A	1.4 (1.8) Range: 0-8
	Laser	N/A	3.7 (2.6) Range: 0-5
VISA-A Score	Placebo	100 (0.2) Range: 99-100	85 (11) Range: 63-100
	Laser	100 (0.2) Range: 99-100	79 (11) Range: 63-100

Data presented as mean (SD), unless otherwise noted
VISA-A– Victorian Institute of Sports Assessment – Achilles Questionnaire
NPRS– Numeric Pain Rating Scale
N/A– Not Applicable

4.2.3 Laser Treatment

Laser-induced PBM treatment was administered to one Achilles tendon and a placebo treatment to the other Achilles tendon. The order of treatment was randomized. The placebo treatment was identical to the actual treatment, except the finger-trigger that activates the laser was not depressed. Participants were blinded to treatment. Blinding was maintained during the treatment by positioning participants in prone and having them wear noise-cancelling headphones with white noise playing. These procedures ensured that the participant could not see when the finger-trigger was depressed or hear the beeping that occurs when the laser is active.

For the healthy cohort, the side that received treatment (i.e. right or left) was determined with a computer-generated randomization scheme. This resulted in 11 dominant and 9 non-dominant limbs being treated. Limb dominance was defined as the participants reported preferred kicking leg. For the tendinopathic cohort, the side that received treatment was the side with greater local tendon thickening, which is also typically the side of worse symptoms. This resulted in 4 dominant and 8 non-dominant limbs being treated in the tendinopathic cohort.

PBM treatment was delivered following a previously reported protocol.[94] This protocol was selected since it has been shown to improve clinical outcomes for patients with Achilles tendinopathy.[94] Briefly, a LightForce EX unit (LiteCure LLC, Newark, DE, USA) was used for treatment. The tendon was irradiated with an in-contact, constant scanning motion (2.5-5 cm/second per manufacturer) from the osteotendinous junction of the Achilles tendon to 10 cm proximal. Ultrasound imaging was used to locate the osteotendinous junction and a tape measure was used to measure 10 cm proximal. Marks were made on the skin to visualize the treatment area.

The medial, lateral, and posterior aspects of the Achilles tendon were each treated for 30 seconds (i.e. total treatment time of 1 minute and 30 seconds).

The PBM treatment was administered with a 3 cm^2 ball applicator. A blend of 810:980 nm laser light in a 20:80 power ratio was used. The total treatment area was 67.5 cm^2, which was calculated from the length of the treatment area (10 cm), beam diameter (1.95 cm), and the area of the laser end caps (3.0 cm^2 for each aspect). The power output was 10 W pulsed at a frequency of 100 Hz, resulting in an average power output of 5 W. This led to an average power density of 74.07 mW/cm^2. Applying the treatment for 1 minute and 30 seconds resulted in a total dose of 450 Joules (150 Joules per aspect) at 6.66 J/cm^2.

4.2.4 Tendon Morphology

Achilles tendon morphology was evaluated with B-mode ultrasound imaging using a LOGIQ *e* ultrasound system (GE Healthcare, Chicago, IL, USA) with a wide-band linear array probe (5.0-13.0 MHz). Participants were positioned prone with their feet hanging naturally over the edge of a treatment table. Images were taken at the same location along the length of the Achilles tendon at each time point by marking and recording the distance from the osteotendinous junction of the Achilles tendon to the center of the treatment area. For the healthy cohort, images were acquired immediately distal to the myotendinous junction of the soleus. For the tendinopathic cohort, the location of greatest tendon thickness was used on the PBM-treated side and an anatomically matched location was used on the placebo-treated side.

Three long- and short-axis images of each Achilles tendon were taken at each time point to measure Achilles tendon thickness and cross-sectional area. Ultrasound images were exported from the ultrasound scanner to an external computer where

measurements were made with OsiriX imaging software (Pixmeo SARL, Bernex, Switzerland). Measurements were taken in a random order by a single assessor who was blinded to treatment. Intra-rater reliability for measuring Achilles tendon thickness and cross-sectional area using ultrasound imaging has been found to be excellent.[105]

4.2.5 Tendon Mechanical Properties

Achilles tendon mechanical properties were quantified with continuous shear wave elastography (cSWE) bilaterally at the same location of morphologic measurements. cSWE has been shown to be a valid and reliable method for quantifying Achilles tendon mechanical properties and is described in detail elsewhere.[7,117] Briefly, an external actuator (Mini-Shaker Type 4810, Bruel & Kjaer, Norcross, GA, USA) generates a series of continuous shear waves that propagate along the length of the Achilles tendon at six known frequencies (322, 358, 402, 460, 536, 643Hz). While these waves propagate, a SonixMDP Q+ ultrasound system (Ultrasonix, Vancouver, Canada) with a L14-5/38 probe and a 128-channel data acquisition device collect raw radiofrequency data (frame rate=6438 frames/s). These data are used to track tendon displacement and estimate wave speed. Static shear modulus and viscosity of the tendon are then calculated on a pixel-wise basis using viscoelastic modeling. Static shear modulus and viscosity is then averaged for the selected region of interest (i.e. the Achilles tendon), which is identified on a B-mode ultrasound image. Lastly, a dynamic shear modulus at a frequency of 400 Hz was calculated using static shear modulus, viscosity and the Voigt model. Dynamic shear modulus is calculated since it is more comparable to elastography techniques that

estimate tendon mechanical properties by measuring the group velocity of a broadband shear wave (e.g. Supersonic Shear Imaging).

During cSWE procedures, participants were secured to a platform in 10° of ankle dorsiflexion. The dorsiflexed angle ensured that the tendon was within the linear elastic region (i.e. constant elastic modulus). The feet were secured to minimize muscle activity and movement. Three trials on each tendon were performed at each time point and the average was used for analysis.

4.2.6 Statistical Analysis

Descriptive data are reported as means and standard deviations (SD). The variables of interest were tendon thickness, cross-sectional area, static shear modulus, viscosity, and dynamic shear modulus. The immediate (within 4 hours) effects between laser- and placebo-treated sides were compared with 2 (laser-treated side vs. placebo-treated side) x 4 (time) repeated measures ANOVA for each variable of interest. This analysis was performed separately for each cohort (i.e. tendinopathic and healthy). The immediate effects between healthy and tendinopathic tendons treated with laser were compared with a 2 (laser-treated side tendinopathic cohort vs. laser-treated side healthy cohort) x 4 (time) mixed model ANOVA for each variable of interest. For all analyses, Greenhouse-Geisser corrections were applied when assumptions of ANOVA were violated. In addition to raw values, changes in tendon morphology and mechanical properties were calculated as the difference between baseline and each follow-up time point. Changes were compared against the minimal detectible change ($MDC_{95\%}$) for each variable of interest. $MDC_{95\%}$ for each variable are as follows: Static shear modulus= 5.1 kPa; Viscosity= 3.0 Pa*s; Dynamic shear modulus= 11.0 kPa; Tendon Thickness= 0.089 mm; Cross-sectional area= 0.009 cm^2.

4.3 Results

For the healthy cohort, descriptive data obtained at baseline and each post-treatment time point are presented in Table 4.2. There were no significant treatment by time interactions for measures of tendon morphology or mechanical properties ($p=0.273\text{-}0.922$; $\eta^2_{partial}=0.008\text{-}0.066$) for the healthy cohort. On the placebo-treated side, there were no changes in tendon morphology or mechanical properties greater than the $MDC_{95\%}$ (Figure 4.1-4.5). On the laser-treated side, there was an increase in tendon thickness and a decrease in cross-sectional area detected 2-hours after treatment and a decrease in tendon thickness 4-hours after treatment that exceeded the $MDC_{95\%}$. There were however no changes in mechanical properties greater than the $MDC_{95\%}$ on the laser-treated side.

Table 4.2 Achilles tendon morphology and mechanical properties at baseline and after photobiomodulation therapy in participants with healthy Achilles tendons.

	Side	Baseline	Immediate	2 hours	4 hours	p-value	Effect ($\eta^2_{partial}$)
Thickness (mm)	P	4.645 (0.551)	4.646 (0.607)	4.628 (0.563)	4.627 (0.601)	0.273	0.066
	L	4.731 (0.661)	4.704 (0.673)	4.842 (0.610)	4.625 (0.586)		
Tendon CSA (cm^2)	P	0.553 (0.128)	0.556 (0.129)	0.549 (0.115)	0.552 (0.112)	0.922	0.008
	L	0.562 (0.132)	0.558 (0.129)	0.552 (0.123)	0.556 (0.123)		
Static Shear Modulus (kPa)	P	95.0 (16.0)	94.6 (15.8)	94.8 (15.4)	94.0 (13.0)	0.819	0.013
	L	90.9 (14.7)	90.4 (14.9)	94.1 (10.7)	93.0 (12.5)		
Viscosity (Pa*s)	P	57.4 (13.4)	55.5 (12.4)	58.4 (13.3)	58.5 (11.5)	0.886	0.011
	L	57.1 (10.7)	57.8 (13.1)	58.5 (10.1)	57.3 (8.9)		
Dynamic Shear Modulus (kPa)	P	226.8 (49.4)	218.0 (46.2)	230.7 (49.0)	230.6 (42.2)	0.812	0.017
	L	224.4 (39.0)	227.6 (49.2)	229.2 (37.4)	225.0 (32.2)		

Data presented as mean (SD)
P – Placebo side
L – Laser side
CSA– Cross-sectional area

For the tendinopathic cohort, descriptive data obtained at baseline and each post-treatment time point are presented in Table 4.3. There were no significant treatment by time interactions for measures of tendon morphology or mechanical properties (p=0.316-0.752; $\eta^2_{partial}$=0.035-0.100) for the tendinopathic cohort. On the placebo-treated side, there was a decrease in tendon thickness 2-hours and 4-hours after treatment (Figure 4.1) and a decrease in cross-sectional area immediately after treatment and 4-hours after treatment (Figure 4.2). There were no changes in

mechanical properties greater than the $MDC_{95\%}$ on the placebo side (Figure 4.3-4.5). On the laser-treated side, there was a decrease in cross-sectional area at all time points after treatment that exceeded the $MDC_{95\%}$ (Figure 4.2) and a decrease in static shear modulus 4-hours after treatment that exceeded the $MDC_{95\%}$ (Figure 4.3). There were no changes in tendon thickness, viscosity, or dynamic shear modulus greater than the $MDC_{95\%}$ on the laser-treated side (Figure 4.1, 4.4, and 4.5).

Table 4.3 Achilles tendon morphology and mechanical properties at baseline and after photobiomodulation therapy in participants with Achilles tendinopathy.

	Side	Baseline	Immediate	2 hours	4 hours	p-value	Effect ($\eta^2_{partial}$)
Thickness (mm)	P	6.531 (1.301)	6.487 (1.206)	6.366 (1.210)	6.390 (1.514)	0.455	0.070
	L	8.585 (2.364)	8.548 (2.391)	8.657 (2.634)	8.611 (2.504)		
Tendon CSA (cm^2)	P	0.757 (0.234)	0.745 (0.224)	0.752 (0.219)	0.740 (0.206)	0.316	0.100
	L	1.102 (0.445)	1.048 (0.418)	1.062 (0.440)	1.049 (0.431)		
Static Shear Modulus (kPa)	P	95.5 (19.7)	99.9 (16.8)	97.6 (12.6)	95.5 (19.4)	0.381	0.088
	L	103.2 (21.5)	98.6 (16.5)	102.6 (18.4)	95.4 (19.7)		
Viscosity (Pa*s)	P	54.7 (10.7)	54.9 (12.1)	54.3 (14.3)	54.9 (13.7)	0.729	0.038
	L	53.6 (10.6)	52.6 (10.3)	51.3 (12.0)	56.5 (10.9)		
Dynamic Shear Modulus (kPa)	P	216.7 (38.1)	217.5 (42.8)	215.7 (49.8)	217.5 (50.9)	0.752	0.035
	L	212.9 (41.1)	209.0 (37.9)	204.8 (44.2)	221.7 (42.1)		

Data presented as mean (SD)
P – Placebo side
L – Laser side
CSA– Cross-sectional area

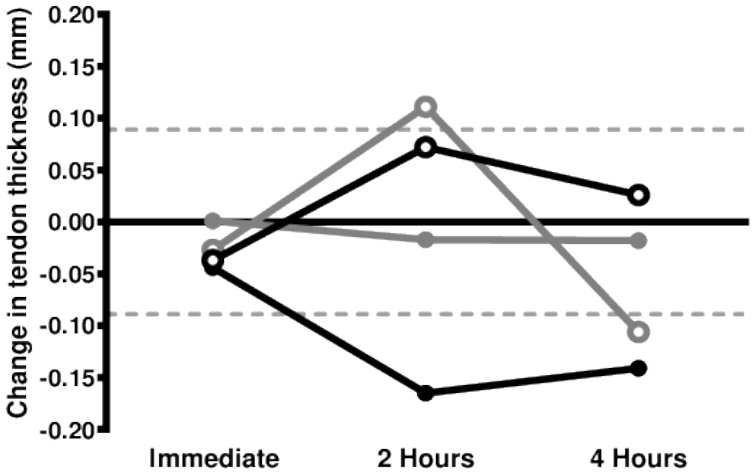

Figure 4.1 Change in Achilles tendon thickness in the four-hour period following photobiomodulation therapy. Black lines represent the tendinopathy cohort and gray lines represent the healthy cohort. Open circles represent the laser-treated side and closed circles represent the placebo-treated side. Horizontal dashed lines depict the $MDC_{95\%}$.

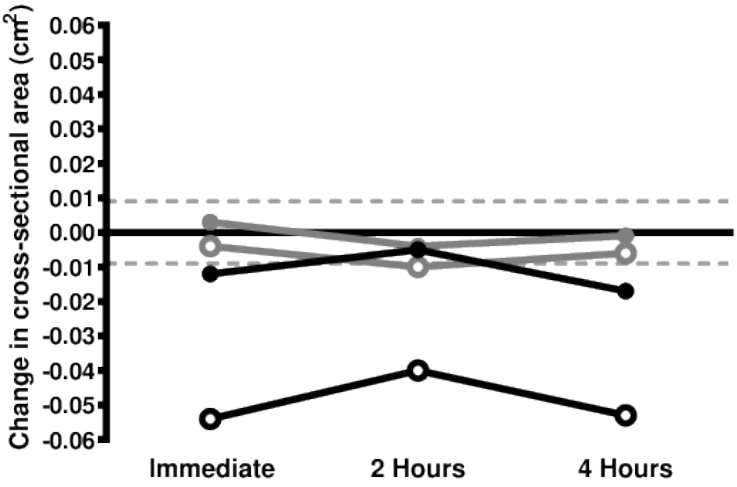

Figure 4.2 Change in Achilles tendon cross-sectional area in the four-hour period following photobiomodulation therapy. Black lines represent the tendinopathy cohort and gray lines represent the healthy cohort. Open circles represent the laser-treated side and closed circles represent the placebo-treated side. Horizontal dashed lines depict the MDC95%.

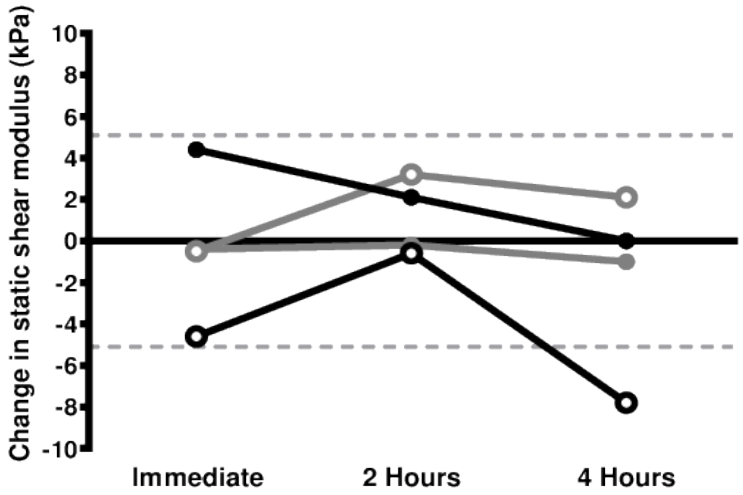

Figure 4.3 Change in Achilles tendon static shear modulus in the four-hour period following photobiomodulation therapy. Black lines represent the tendinopathy cohort and gray lines represent the healthy cohort. Open circles represent the laser-treated side and closed circles represent the placebo-treated side. Horizontal dashed lines depict the $MDC_{95\%}$.

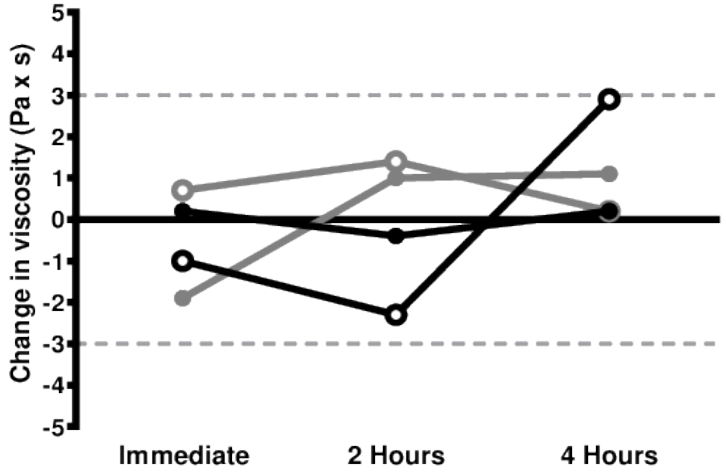

Figure 4.4 Change in Achilles tendon viscosity in the four-hour period following photobiomodulation therapy. Black lines represent the tendinopathy cohort and gray lines represent the healthy cohort. Open circles represent the laser-treated side and closed circles represent the placebo-treated side. Horizontal dashed lines depict the $MDC_{95\%}$.

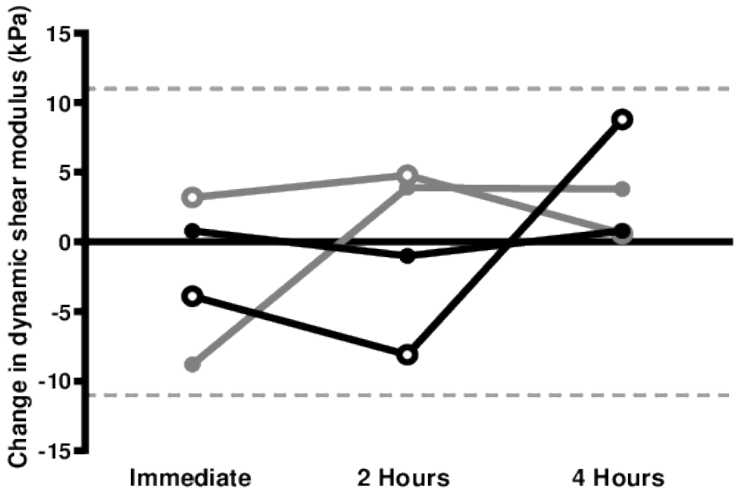

Figure 4.5 Change in Achilles tendon dynamic shear modulus in the four-hour period following photobiomodulation therapy. Black lines represent the tendinopathy cohort and gray lines represent the healthy cohort. Open circles represent the laser-treated side and closed circles represent the placebo-treated side. Horizontal dashed lines depict the $MDC_{95\%}$.

When comparing the immediate effects between healthy and tendinopathic tendons treated with laser, there were no significant group by time interaction effects for mechanical properties (Dynamic shear modulus: $p=0.586$; $\eta^2_{partial}=0.021$, Static shear modulus: $p=0.461$; $\eta^2_{partial}=0.028$, Viscosity: $p=0.514$; $\eta^2_{partial}=0.025$). Additionally, there were no significant group by time interaction effects for measures of tendon morphology (tendon thickness: $p=0.673$; $\eta^2_{partial}=0.016$, cross-sectional area: $p=0.062$; $\eta^2_{partial}=0.084$).

4.4 Discussion

This exploratory study aimed to evaluate the immediate (within 4 hours) effects of a laser-induced PBM treatment on Achilles tendon morphology and mechanical properties. The main finding was that for both healthy and tendinopathy

cohorts there were no differences between the laser-treated and placebo-treated sides over time. Additionally, the effects of PBM treatment did not differ between healthy and tendinopathic Achilles tendons. However, since there was a reduction in tendon cross-sectional area that exceeded the $MDC_{95\%}$ following PBM that was not seen with the placebo treatment, the effect of PBM on tendon cross-sectional area warrants further investigation.

Research on laser therapy is currently limited to basic research that use animal models and clinical research that does not necessarily investigate the physiologic mechanisms responsible for positive outcomes. Since increased collagen synthesis[146,147] and decreased cell apoptosis[144] are proposed physiologic effects of laser therapy, measuring changes in tendon mechanical properties following laser treatment may be critical to improve dosage guidelines and elucidate mechanisms responsible for clinical outcomes. The current study used cSWE to evaluate the immediate (within 4 hours) effects of a single laser treatment on human Achilles tendon mechanical properties. This was the first step to evaluate the physiologic effects of laser therapy on tendon mechanical properties. Future research is needed to understand how tendon mechanical properties respond throughout a typical laser therapy program since positive clinical outcomes are commonly reported with longer follow-up periods (e.g. 12 weeks) and programs that involve multiple treatments (e.g. 2 treatments per week for 4 weeks).[94,95,204]

Tendon morphology is frequently evaluated with ultrasound and magnetic resonance imaging in clinical research and relates to symptom severity and physical activity levels in patients with Achilles tendinopathy.[191] Clinical trials have reported positive changes in tendon morphology (i.e. reduction in tendon size) and pain when

treated with exercise therapy.[112,113] Additionally, Tumilty et al.[94] found reductions in tendon thickness following a treatment program that incorporated both exercise and laser therapy. Findings from these studies [94,112,113] suggest that treatment of Achilles tendinopathy should focus on normalizing tendon structure, yet a previous systematic review concluded that improvements in symptoms and function cannot be explained by changes in tendon structure.[5] Similar to Tumilty et al., the current study found that laser treatment led to reductions in tendon cross-sectional area that exceeded measurement error in participants with Achilles tendinopathy. This indicates that tendon cross-sectional area may be a variable of interest for monitoring treatment response in patients with Achilles tendinopathy.

In addition to changes in tendon morphology, laser therapy has previously been shown to reduce short- and long-term pain following treatment.[93,94,202] Reductions in pain may be due to the anti-inflammatory effects of laser therapy or remodeling of the tendon's structure. Evidence also suggests that laser therapy may increase pain-pressure threshold.[142] Collectively, it appears advantageous to administer laser treatment early in a treatment session to reduce pain so that more loading exercises can be performed. To investigate this notion further, we performed a secondary analysis evaluating the immediate effects of PBM on pain. We hypothesized that pain to palpation would decrease on the laser-treated side in patients who presented with palpatory pain (n=10). At each of the four time points a single examiner palpated the midportion of the Achilles tendon using a highly standardized pinch-grip technique moving up the tendon from distal to proximal. Participants were prone and asked to report the greatest amount of pain experienced during palpation. Pain was reported using the Numeric Pain Rating Scale (NPRS), which is an eleven-

point scale ranging from 0 (no pain) to 10 (worst imaginable pain).[207] This technique has been previously reported in Achilles tendinopathy literature and has good intra-rater reliability.[208] The immediate effects of PBM on pain to palpation was analyzed with a one-way repeated measures ANOVA. Changes in pain to palpation were also calculated and compared against a minimal clinically important difference (MCID) of two points on the NPRS.[209] We found no immediate effects of PBM on pain to palpation (Baseline: 4.4(2.1), Immediate: 3.9(2.2), 2-hours: 3.3(1.9), 4-hours: 3.4(1.8); $p=0.07$; $\eta^2_{partial}=0.22$). Additionally, reductions in pain were smaller than the MCID. These results suggest that a single PBM treatment does not lead to clinically meaningful reductions in pain to palpation in patients with Achilles tendinopathy. This contradicts Bjordal et al[142] who showed an immediate increase in pain-pressure threshold following a low-level laser treatment. However, comparing our findings is difficult since there were major differences in study designs (i.e. subjects who participated in Bjordal et al[142] performed pain inducing activity before treatment), laser treatment parameters, and methods for assessing pain. Further research is needed to investigate the analgesic effects of laser therapy.

There are several limitations to this study. One limitation is how power density was calculated for the laser treatment. The World Association of Laser Therapy recommends a power density of less than 100mW/cm^2 for irradiating the Achilles tendon,[46] but it is unclear if this should be calculated over the spot size of the laser or over the treatment area. A power density of 74.07 mW/cm^2, which was calculated over the entire treatment area, was used for the PBM treatment in the current study. This calculation however neglects to consider that the laser treatment targeted the same tissue from three different directions (i.e. medial, lateral and posterior) and therefore

could be considered to have a power density of 222mW/cm^2. Regardless of how power density was calculated, the PBM treatment parameters were based on Tumilty et al.[94], who demonstrated positive clinical outcomes in patients with Achilles tendinopathy. A second limitation is heterogeneity within the tendinopathic cohort. Participants with and without pain to palpation were included in the tendinopathic cohort and there was large variability in the patient's duration of symptoms. This may partially explain why the short-term effects of PBM treatment did not differ from the effects of a placebo treatment. However, the relatively high VISA-A scores indicate a conservative sample was used (i.e. greater changes might be expected in a sample with more severe pathology). A third limitation is that the tendinopathic cohort had a relatively small sample size and an a priori power analysis was not completed. A post-hoc power analysis was performed using the determined interaction effect for tendon cross-sectional area in the tendinopathic cohort ($\eta^2_{partial}$=0.1) with α=0.05 and 80% power. This showed that a sample size of 36 subjects would be needed to detect differences between PBM and placebo treatments in the tendinopathic cohort. This study was however the first study to explore the immediate effects of laser therapy with innovative techniques and therefore an a priori power analysis was not feasible. Lastly, the healthy and tendinopathic cohorts were not matched for possible covariates (e.g. age, sex). Therefore, the comparison between healthy and tendinopathic tendon treated with PBM treatment should be interpreted with caution.

4.5 Conclusion

Laser therapy does not have immediate (within 4 hours) effects on Achilles tendon morphology or mechanical properties when administered with the presented laser parameters. This was found in both healthy and degenerative Achilles tendons.

Findings suggest that tendon cross-sectional area may be a variable of interest for monitoring treatment response in future research and that laser therapy can be administered at any time during a clinical treatment session without influencing other treatments.

Chapter 5

RUNNING MECHANICS RELATE TO PAIN AND FUNCTION FOR RUNNERS WITH ACHILLES TENDINOPATHY DURING RETURN-TO-SPORT

5.1 Introduction

Achilles tendinopathy is an overuse injury characterized by pain with loading activities, swelling, and impaired functional performance.[1,2] It frequently affects runners, with annual incidence rates between 7% and 11%[41,42] and lifetime incidence rates between 52% and 57% in former elite male runners.[43,44] Even more concerning, 41% of patients with Achilles tendinopathy will continue to have symptoms after 8 years, 41% will develop similar symptoms on contralateral side, and 29% will undergo surgery.[6] These poor outcomes can have long-term effects on physical activity levels and quality of life.[210]

Mechanical loading is a critical part of rehabilitation for patients with Achilles tendinopathy. Loading stimulates a cellular response that leads to improved tendon mechanical properties, normalization of tendon morphology, and reductions in symptoms.[88,185,196,197,211,212] Underloading and overloading, however, have detrimental effects on tendon health.[75] It, therefore, appears essential to properly control and progress loading in order to optimize tendon remodeling and recovery. Improvements during rehabilitation have been seen in patients with Achilles tendinopathy who continued to participate in recreational activities.[211] Yet, Visnes et al.[213] found no improvements when elite athletes with patellar tendinopathy were treated in season.

These studies suggest that patients with tendinopathy can participate in recreational activities during rehabilitation, but there is likely an upper limit.

Progressive loading programs are recommended for treating patients with Achilles tendinopathy and supported by the highest level of evidence.[78,214] These programs are effective at reducing symptoms and improving calf muscle function, but up to 44% of patients will have symptoms reoccur when returning to high-load activities.[130] Furthermore, the risk of reoccurrence increases with shorter rehabilitation and an accelerated return-to-sport (RTS).[150] This highlights the importance of a RTS phase of rehabilitation where loading exercises are continued and sport-specific loads are progressively introduced. Recently, a RTS program was proposed for patients with Achilles tendinopathy that uses pain and rate of perceived exertion to guide loading volume and frequency.[151] Although this program protects the tendon from being exposed to too much load too quickly, it does not consider how the tendon is actually loaded during high-load activities, such as running. Since aberrant loading patterns during RTS activities may influence return-to-performance and risk of recurrence, there is a need to determine what aspects of tendon health are related to tendon loading patterns during RTS.

The purpose of this study was to explore the associations between running mechanics and patient-reported outcomes, tendon structural properties, lower leg function, and pain in patients with Achilles tendinopathy who are in the RTS phase. We hypothesized that side-to-side differences in patient-reported outcomes, tendon morphology, tendon mechanical properties, lower leg function, and pain would relate to side-to-side differences in Achilles tendon loading patterns and ankle joint powers while running.

5.2 Materials and Methods

5.2.1 Study Design

Prior to conducting the study, the protocol was approved by the University of Delaware Institutional Review Board. Participants were recruited through local running and triathlon clubs, the university's physical therapy clinic, and posted advertisements at local athletic clubs, on the University of Delaware campus, and social media. All participants provided verbal and written consent after thoroughly reviewing the study procedures and risks. Data collection was performed in two visits that were separated by 2 weeks. To accommodate participant schedules, visits were scheduled up to 6 weeks apart. Data collection was split into two visits to reduce the burden on participants (i.e. an 8-hour data collection was deemed burdensome) and to negate the effect of performing one experimental method before another. During the first visit, patient-reported outcomes, anthropometrics, relevant injury history, and running experience were recorded. Additionally, a clinical examination that included ultrasound imaging, pain sensitivity testing, and functional testing was performed. During the second visit, tendon mechanical properties and running mechanics were evaluated. Participants were asked to refrain from running and "hard" lower extremity exercise (e.g. lifting weights, biking) within 48 hours of the second visit. This brief period of relative inactivity was to reduce the potential influence of muscle and tendon fatigue on tendon mechanical properties and running mechanics.

5.2.2 Inclusion/Exclusion

To qualify for the study, all participants were required to be a runner diagnosed with Achilles tendinopathy, currently in the RTS phase, and at least 18 years old. A runner was defined as someone who identifies themselves as a runner and runs at least

30 minutes two times per week without walking or stopping. Achilles tendinopathy was defined based on the literature[1,2] and confirmed with a clinical examination and ultrasound screening performed by a licensed physical therapist. The RTS phase was defined as the period from when no symptoms were experienced with daily activities (e.g. walking, stair negotiation) until one year of running without symptoms.[149] Participants were excluded if they had a history of surgery to either lower extremity or if they had a lower body injury (besides Achilles tendinopathy) within the past year that limited the ability to run for longer than 1 month.

5.2.3 Participant Characteristics

Demographics and anthropometrics, including age, sex, height, weight, and limb dominance were recorded. Limb dominance was determined by self-reported kicking leg. Information about the participants' current Achilles tendon injury and running were also reported. This included the side of the injury, location of injury, duration of symptoms, running distance per week, number of runs per week, average pace while running, years of running experience, and treadmill comfort. If a participant had bilateral symptoms, they reported which side was more symptomatic. For reporting running volume and pace, participants were asked about their current running (at time of evaluation) and running before becoming injured. Treadmill comfort was determined by rating comfort with treadmill running on a scale from 0 to 10, with 0 indicating completely uncomfortable and 10 indicating completely comfortable.[215]

5.2.4 Patient-Reported Outcomes

Participants completed a Physical Activity Scale (PAS),[188] Victorian Institute of Sports Assessment – Achilles (VISA–A) questionnaire,[189] and the Tampa Scale for Kinesiophobia (TSK).[216] The PAS, as originally described by Grimby,[188] was used to quantify physical activity levels currently and before injury. This scale ranges from 1 to 6, with higher scores representing more physical activity. The VISA–A quantified symptom severity and was completed for both sides (i.e. right and left) because of the large proportion of patients with Achilles tendinopathy that have bilateral symptoms. This is an 8-item questionnaire that is scored from 0 to100, with higher scores representing less symptoms. Participants also completed bilateral VISA–A questionnaires at the beginning of their second visit to ensure symptoms were stable between visits. Lastly, TSK quantified the participants' degree of kinesiophobia (i.e. fear of movement). The TSK is a 17-item questionnaire scored from 17 to 68, with higher scores representing a greater degree of kinesiophobia.

5.2.5 Tendon Morphology

Achilles tendon morphology was evaluated with ultrasound imaging. Participants were prone with their feet hanging freely over the edge of a treatment table. A LOGIQ *e* ultrasound system (GE Healthcare, Chicago, IL, USA) with a wide-band linear array probe (5.0-13.0 MHz) was used to obtain three short-axis, long-axis, and extended field of view images of each tendon. All images were exported to an external computer and measurements were made in OsiriX imaging software (Pixmeo SARL, Bernex, Switzerland). A single experienced evaluator performed all imaging and measurements. The variables of interest were tendon thickness and cross-sectional area, which were calculated as the average of three measurements. On the most

symptomatic side, measurements were made in the thickest portion of the tendon. If the contralateral tendon was healthy (i.e. pain-free and no thickening), an anatomically matched location was used. If the contralateral side was pathologic, the thickest portion of the tendon was used.

5.2.6 Tendon Mechanical Properties

Achilles tendon viscoelastic properties were estimated with continuous shear wave elastography (cSWE).[7,117] This technique has been validated[7,117] and used to monitor patients with Achilles tendinopathy[8,117] and Achilles tendon rupture.[127–129] Participants were prone with their feet secured in 10º of ankle dorsiflexion. This angle ensured the tendon was within the linear elastic region of the stress-strain curve. Continuous shear waves of 11 different frequencies (ranging from 322 to 643) were applied to the tendon with a mechanical actuator (Mini-Shaker Type 4810, Bruel & Kjaer, Norcross, GA, USA). A SonixMDP Q+ ultrasound system (Ultrasonix, Vancouver, Canada) with a L14-5/38 and 128-channel data acquisition device collected raw radiofrequency data (Frequency = 6438 frames/s). These data tracked tendon displacement and were used to estimate wave speed. Static shear modulus (the tendon's resistance to a shearing force at 0 Hz) and viscosity (the tendon's rate-dependent resistance to a shearing force) were calculated on a pixel-wise basis with viscoelastic modeling.

Achilles tendon Young's modulus was estimated for each participant using ultrasound imaging and dynamometry during maximal voluntary isometric contractions (MVIC) of ankle plantar flexion. These procedures were based on previously reported techniques by Arya & Kulig[76] and Chang & Kulig.[114] Participants were prone with their upper body firmly secured to the table with a Velcro strap across

the top to their pelvis. The foot was firmly secured to a KinCom Dynamometer (Model 500H, Isokinetic International, Chattanooga, TN, USA) with two industrial strength velcro straps. The first strap pulled the forefoot against the foot pedal by applying it over the dorsum of the foot in line with the 1st and 5th metatarsal heads. The second strap secured the hindfoot into the heel cup of the dynamometer attachment by placing it around the anterior aspect of ankle and firmly pulling it into the heel cup. The hip and knee were in 0 degrees of flexion and the ankle was in 0 degrees of plantar flexion (i.e. foot perpendicular to the lower leg) throughout MVIC testing. During positioning, the axis of the dynamometer was aligned with the lateral malleolus and joint angles were visually checked. Once the participant was properly positioned, the medial gastrocnemius myotendinous junction was located with ultrasound imaging and marked on the skin. A thin piece of rubber tape was placed perpendicular to the long-axis of the lower leg on the participant's skin immediately distal to the mark of the myotendinous junction. To reduce the chances of the rubber tape moving during MVIC, two additional pieces of athletic tape secured the ends of the rubber tape. Participants were instructed that they were going to perform three 5-second maximal voluntary isometric contractions of ankle plantar flexion after performing two practice trials. A member of the research team demonstrated ankle plantar flexion prior to testing. One practice trial was performed at 50% of the participants perceived maximal plantar flexion strength and the other was performed at 75%. The purposes of the practice trials were to ensure the participant understood the testing procedures and for the research team to identify the optimal position of the ultrasound transducer. For the MVICs, participants were instructed to push down as hard as possible until told to stop. Rate of force development was not controlled.

Strong verbal encouragement was given during each trial by yelling “push” repetitively for 5 seconds. Participants were not allowed to anchor their arms or hands into the dynamometer table during testing. A 2-minute break was given between trials and a 5-minute break was given when switching the leg being tested. Three valid trials were collected on each leg. A trial was discarded if the displacement of the medial gastrocnemius myotendinous junction was not fully visualized throughout the trial. The most common reason for poor visualization of the myotendinous junction was inadequate amounts of ultrasound gel. A trial was also discarded if the ankle plantar flexion torque did not plateau during the trial, which indicated a submaximal effort. The ultrasound image was visually checked after each trial and the plantar flexion torque curve was checked by plotting the plantar flexion torque over time with a custom LabVIEW Program (National Instruments, Austin, TX). If a trial was discarded, an additional trial was performed. However, no participants required more than five trials on a single leg.

Achilles tendon strain was calculated by dividing the linear displacement of the medial gastrocnemius myotendinous junction during MVIC by the initial resting length of the Achilles tendon. Cine-loop ultrasound recordings of the myotendinous junction were collected during each MVIC (Frame rate = 33 frames/s). Images were exported as DICOM files to an external computer where measurements were taken using OsiriX (Pixmeo SARL) imaging software. The position of the myotendinous junction and tape shadow created by the rubber tape were recorded at rest and during the MVIC (Figure 5.1). Peak displacement of the medial gastrocnemius myotendinous junction was calculated after adjusting for movement of the ultrasound probe (i.e. change in shadow position). The initial resting length of the Achilles tendon was

measured with extended field of view ultrasound images as described in the literature.[103,104] This measurement is taken from the proximal aspect of the osteotendinous junction of the Achilles tendon to the medial gastrocnemius myotendinous junction. The techniques for obtaining and measuring the resting length of the Achilles tendon in the current study were different from the techniques used by Arya & Kulig[76] and Chang & Kulig.[114] In their studies, a motion capture system was used to measure Achilles tendon length as the distance between a retroreflective marker on the heel and the myotendinous junction located with ultrasound imaging.

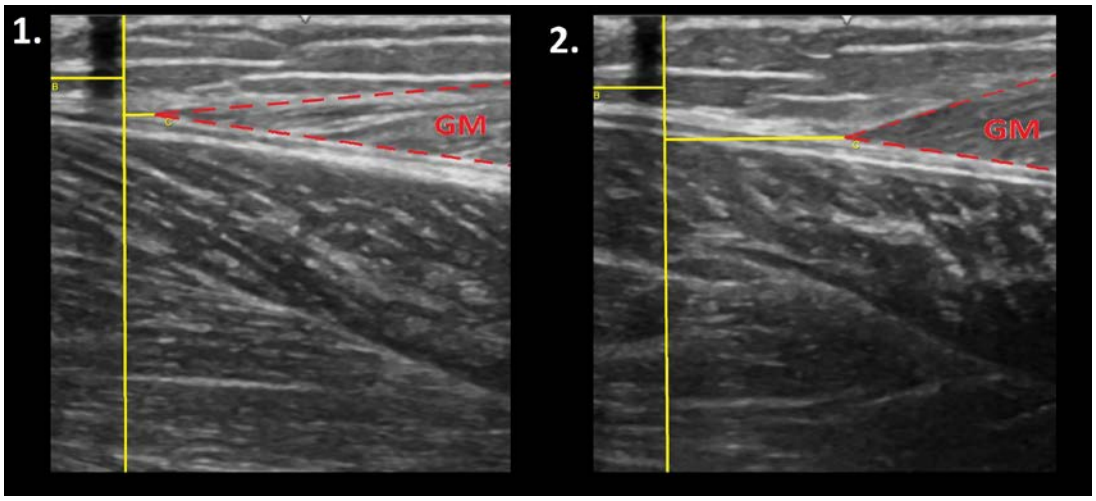

Figure 5.1 Position of the medial gastrocnemius (GM) myotendinous junction was recorded at rest (1) and during ankle plantar flexion maximal voluntary isometric contractions (2). Line B was used to adjust for movement of the ultrasound probe and Line C was used to measure linear displacement of the medial gastrocnemius.

Achilles tendon stress was calculated by dividing the force on the tendon by the cross-sectional area of the tendon. To determine the force on the tendon, the external plantar flexion moment recorded by the dynamometer was divided by the Achilles tendon moment arm. The tendon excursion method was used to determine the Achilles tendon moment arm when the ankle was in neutral.[159,217] Briefly, the ankle was passively moved by the dynamometer from 15º of plantar flexion to 15º of dorsiflexion at a rate of 10º/s while cine-loop ultrasound recordings were obtained. This ankle range of motion differed from Arya & Kulig[76] and Chang & Kulig,[114] which was 5º of plantar flexion to 5º of dorsiflexion. However, other studies have used 15º of plantar flexion to 15º of dorsiflexion.[218,219] The displacement of the medial gastrocnemius myotendinous junction during three passive trials was measured using the same method described for obtaining tendon strain during MVICs. This displacement was divided by 30º in radians (i.e. 0.5236) to calculate the Achilles tendon moment arm. The cross-sectional area of the tendon was measured during the ultrasound evaluation with three short-axis images. Since non-uniform tendon thickness is a characteristic of tendinopathy, cross-sectional area measurements were taken 2, 4, and 6 cm proximal to the osteotendinous junction and averaged.

Young's modulus was calculated as follows:

$$YM = \frac{Stress}{Strain} = \left(\frac{\frac{F}{A}}{\frac{\Delta L}{L_0}} \right)$$

Where *YM* is Young's modulus in pascals, *F* is force on the Achilles tendon during MVIC in newtons, *A* is the cross-sectional area of the tendon in meters squared, ΔL is the linear displacement of the medial gastrocnemius myotendinous junction during

MVIC in meters, and L_0 is the resting length of the Achilles tendon in meters. For reporting *YM*, pascals were converted to megapascals (MPa).

5.2.7 Functional Evaluation

A functional test battery was performed to evaluate lower extremity and triceps surae function. This test battery has previously been used to evaluate patients with Achilles tendinopathy and includes three countermovement jumps (CMJ), three drop countermovement jumps (drop CMJ), two bouts of hopping, and one heel-rise endurance test on each leg.[101] For each CMJ, participants attempted a maximal single-leg vertical jump from flat ground with their arms behind their back. Using a light mat (MuscleLab measurement system, Ergotest Innovation, Porsgrunn, Norway) jump height was calculated from flight time (max height = $\frac{1}{8}gt^2$; g=gravity, t= flight time in seconds). Drop CMJ was similar to CMJ, except the participant dropped from a 20 cm box prior to jumping. Hopping performance was assessed by having the participant repetitively hop 25 times on a single leg. After removing the first 3 and last 2 hops, average hop height and plyometric quotient $\left(\frac{Flight\ Time}{Contact\ Time}\right)$ were determined. The heel-rise endurance test was performed on a single leg while standing on a 10º incline box and following a metronome (30 repetitions/minute). A linear encoder was attached to the heel (MuscleLab) to track the number of repetitions performed and height of each repetition. Total work was then calculated (Σ displacement x body mass x gravity). Participants wore standardized shoes (Glycerin 15, Brooks Sports Inc., Seattle, WA, USA) for functional testing, except the heel-rise test was performed barefoot. For each variable of interest during the jumping tasks, an average was calculated and used for analysis.

5.2.8 Pain Assessment

Mechanical algometry was used to standardize and analyze pain on palpation. Pain-pressure thresholds were determined for each Achilles tendon. Participants were positioned in prone with their feet hanging freely over the edge of a treatment table. Pressure was applied as a squeeze with 1 cm^2 probe tips to the medial and lateral aspects of the tendon with an algometer (Somedic SenseLab AB, Sösdala, Sweden) (Figure 5.2). This pressure was applied at a rate of 30 kPa/s and maintained by monitoring a scale on the algometer. Participants used a response button to indicate when the mechanical stimulus became painful. The testing sites matched the locations where tendon thickness and cross-sectional area were measured with ultrasound. In all cases, three trials were performed on each side and the average was used for analysis. This testing was completed before functional testing to reduce the influence that loading may have on pain sensitivity.

Pain was also evaluated throughout functional testing with the Numeric Pain Rating Scale (NPRS), which ranges from 0 (no pain) to 10 (worst pain imaginable). Immediately after performing each CMJ, drop CMJ, bout of hopping, or heel-rise test, participants were asked to report their pain during the task. The maximum pain was recorded for each task and used for analysis. Additionally, pain was reported during the running analysis.

Figure 5.2 Pain-pressure threshold testing of the Achilles tendon with a mechanical algometer.

5.2.9 Running Biomechanics

5.2.9.1 Data Collection

Forty-seven retroreflective markers were affixed to the pelvis and lower extremities (Figure 5.3), including marker clusters attached to the posterior pelvis, posterolateral thighs and lower legs, and heels. The marker set was modified from Willy et al [220] and placed by the same evaluator for every participant. A 10-second static calibration trial was collected prior to the dynamic trial with the participant standing erect, feet positioned shoulder-width apart, arms crossed with hands resting on the contralateral shoulders, and the y-axes (i.e. axis that goes anterior-posterior) of each segment closely aligned with the y-axis of the global coordinate system. The static trial was visually checked for the presence of all markers, little to no movement

of the participant, and proper alignment. If the static trial did not fulfill these criteria, the trial was repeated. Anatomical markers were removed from the participant when a valid static trial was obtained, which left only marker clusters for tracking during the dynamic trial.

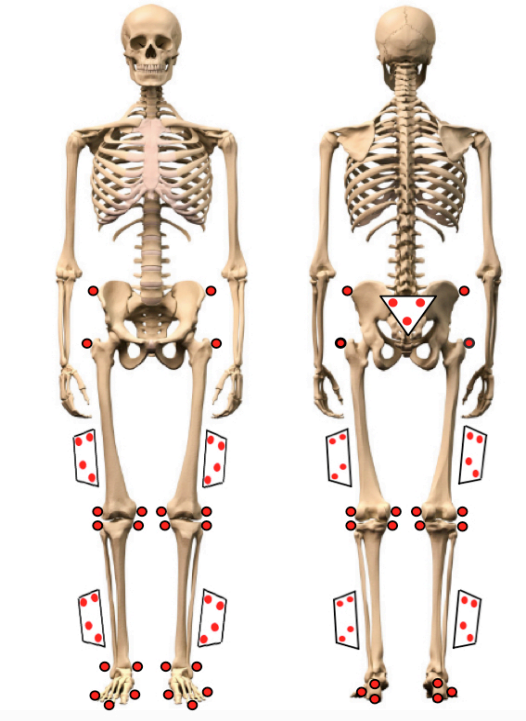

Figure 5.3 Marker set used during 3-D motion capture.

Participants ran at their self-selected endurance pace (mean (SD): 2.93 (0.29) m/s) for 7 minutes on a treadmill with standardized shoes (Glycerin 15, Brooks Sports Inc., Seattle, WA, USA). Endurance pace was defined as the participants self-reported pace during the middle of a long run. This definition of endurance pace has been used previously in the literature.[221] The first 6 minutes were used for familiarization and

fine-tuning the pace of the run based on the participant's feedback.[222] During the 7th minute, ground reaction forces were sampled (2000 Hz) with an instrumented treadmill (Bertec Corp. Worthington, OH, USA) and marker trajectories were sampled (100 Hz) with an 8-camera motion capture system (Motion Analysis Corp. Santa Rosa, CA, USA).

5.2.9.2 Biomechanical Model from Static Calibration

Marker trajectory data from the twenty-eight retroreflective markers affixed to the lower legs and feet were needed for the purposes of this dissertation. Therefore, the additional nineteen markers attached to the pelvis and thighs were ignored for this study. Marker trajectory data obtained during the 10-second static calibration was trimmed to a 1-second clip. The first second of the static calibration trial was used unless noticeable movement was detected (i.e. markers or ground reaction force vector moved) or if any marker was not present throughout the entire clip. If the first second contained movement or marker drop-out, the entire 10-second trial was visually scanned for a 1-second clip that did not have movement or marker drop-out. Markers were labeled for every frame in Cortex software (Version 8, Motion Analysis Corp. Santa Rosa, CA, USA) and exported as a c3d file.

Using Visual3D (Version 6, C-motion Inc. Germantown, MD, USA) a subject-specific model of the lower legs and feet was constructed. The lower legs were defined proximally by the medial and lateral tibial plateaus and distally by the medial and lateral malleoli. The feet were defined proximally by the malleoli and distally by the first and fifth metatarsal heads. Both lower legs and feet were modeled as frustum of a right cone (i.e. a truncated cone). The distance between markers at the ends of each segment were used to define the proximal and distal diameters as well as construct the

change in diameter from one end of the frustum to the other end. The distance between the centroids of the proximal and distal markers was used to determine the length of the frusta. The mass of each lower leg was estimated as 4.65% of the participants' body mass, while each foot was estimated as 1.45%.[223] Segmental coordinate systems were created with their origin at the proximal end of the segment. A vector from the segments distal endpoint to the segments proximal endpoint defined the z-axis. A vector perpendicular to the segments x-z plane (i.e. a plane created from the segments four anatomical markers using a least squares approach) defined the y-axis. Lastly, the resulting vector from the cross-product of the z and y axes defined the x-axis. The ankle joint center was defined by the centroid of the malleoli.

Virtual coordinate systems were also created for each foot to accurately reflect ankle joint angles. A vector from the distal heel marker to the toe marker defined the y-axis. During data collection, the positions of these markers were closely inspected during the static calibration trial to ensure they were the same distance from the ground. The x-axis was defined by a unit vector perpendicular to the y-z plane, which was created by markers on the toe, proximal heel and distal heel. The resulting vector from the cross-product of the x and y axes defined the z-axis.

5.2.9.3 Biomechanical Data Processing for Dynamic Trial

Ground reaction forces and marker trajectories sampled during the 7th minute of the run were reduced to 10 gait cycles bilaterally. The first 20 complete gait cycles of the trial were used for every participant. Five frames of data before and after the gait cycles were included to improve gait event detection of initial contact for the first gait cycle and toe-off for the last gait cycle. Marker clusters on the lower legs and feet were labeled in Cortex software (Version 8, Motion Analysis Corp. Santa Rosa, CA,

USA). If a gap existed in a marker's trajectory data that was less than six frames, data was interpolated with a cubic spline. If a gap was greater than five frames, virtual marker data filled the gap based on positioning of other markers in the same marker cluster. With both types of gap filling, marker xyz position plots were checked in real-time for similar and realistic trajectories. Once each marker was labeled for every frame of the dynamic trial, the file was exported as a c3d.

In Visual3D (C-motion inc., Germantown, MD, USA), ground reaction forces and marker trajectories were filtered with a fourth-order, low-pass Butterworth filter with a cutoff frequency of 15 Hz. An identical cutoff frequency was used to minimize nonphysiologic signal artifacts that occur during inverse dynamic routines with high-impact activities (e.g. running).[224,225] A 20 N vertical ground reaction force threshold detected initial contact and toe-off events. Ankle joint angles were calculated with an XYZ Cardan angle sequence and resolved in the lower legs coordinate system. Ankle joint moments and powers were derived from inverse dynamic routines and resolved in the lower legs coordinate system using published segmental inertial parameters.[226] The sagittal plane ankle plantar flexion moment throughout the stance phase was divided by the predicted instantaneous Achilles tendon moment arm (AT_{ma}) to estimate Achilles tendon force. The predicted instantaneous AT_{ma} was based on the sagittal plane ankle joint angle at each frame using an equation derived from Rugg et al[227] ($AT_{ma} = -0.5910 + 0.08297\theta_a - 0.0002606\theta_a$; where θ_a is the sagittal plane ankle joint angle in degrees and 90° represents when the foot and lower leg are perpendicular). Achilles tendon force was normalized to body weight by dividing the raw Achilles tendon force by the participant's body mass in newtons.

The discrete variables of interest for the running analysis were peak Achilles tendon force, average and peak Achilles tendon loading rates, Achilles tendon impulse and peak concentric and eccentric ankle power. These variables were selected since they pertain to energy storage and release (eccentric and concentric power), how much the Achilles tendon is loaded (peak force and impulse), and how quickly the tendon is loaded (peak and average loading rate). All discrete analyses were performed in Visual3D (C-motion inc., Germantown, MD, USA). Peak Achilles tendon force was detected as the maximum force during stance. To determine peak and average Achilles tendon loading rates, gait events were created at initial contact and peak Achilles tendon force. The middle 60% of the time from initial contact and peak Achilles tendon force was determined by creating events at 20% and 80% of the duration from initial contact to peak Achilles tendon force. Taking the average 1st derivative between the 20% and 80% events yield the average Achilles tendon loading rate. The peak Achilles tendon loading rate was detected as the maximum of the 1st derivative between the 20% and 80% events. Achilles tendon impulse was calculated as the time integral (i.e. the area under the Achilles tendon force-time curve) from initial contact to toe-off. Peak concentric ankle power was detected as the maximum of the sagittal plane ankle joint power-time curve during stance. Peak eccentric ankle power was detected as the minimum of the sagittal plane ankle joint power-time curve during stance.

5.2.10 Statistical Analysis

The variables of interest were side-to-side differences in patient-reported outcomes, tendon morphology, tendon mechanical properties, lower leg function, pain, and running mechanics. Most and least symptomatic sides were compared with paired

t-tests, except patient-reported pain was compared with Wilcoxon signed-rank tests. Paired t-tests were also performed on VISA-A scores from each visit to ensure symptoms remained stable between evaluations. Side-to-side differences were then calculated for all bilateral variables by subtracting the most symptomatic side from the least symptomatic side. Normality was checked with Shapiro-Wilk tests and visual inspection of histograms and box-and-whisker plots. If all assumptions were met, Pearson's correlations were used to analyze the associations between side-to-side differences in running mechanics and side-to-side differences in patient-reported outcomes, tendon morphology, tendon mechanical properties, lower leg function, and pain. If the assumption of normality was violated or if outliers were identified, Spearman's correlations were performed. All correlation coefficients were interpreted as no relationship (<0.26), fair relationship (0.26-0.50), moderate relationship (0.51-0.75), and strong relationship (>0.75), as suggested by Portney and Watkins.[228] The association between TSK scores and side-to-side differences in running mechanics were also explored with Pearson's correlations. Side-to-side differences in running mechanics were also compared between participants with and without differences in pain with hopping with Mann-Whitney U tests. These analyses were performed since kinesiophobia may affect return-to-performance for patients with Achilles tendinopathy and pain during hopping has been suggested as a variable that clinicians can use to make RTS decisions.[151,211] All statistical analyses were performed in SPSS (Version 25, IBM Corp., Armonk, NY, USA) and significance level was set to $p<0.05$.

5.3 Results

5.3.1 Participants

Twenty-four participants were enrolled in the study. Two participants withdrew from the study because of sustaining other injuries between visits. One injury was diagnosed as a knee sprain and the other a metatarsal stress fracture. Two additional participants were excluded from analysis because of unusable biomechanical data. These data were unusable because one participant was not running (i.e. no flight phase) and ground reaction forces were erroneously not collected for the other participant. This resulted in twenty participants included in the study. Their characteristics are reported in Table 5.1.

There was no significant change in VISA-A scores between visits for the most (mean (SD) 1st visit: 75 (13); 2nd visit: 78 (15); p=0.21) or least symptomatic sides (1st visit: 90 (9); 2nd visit: 91 (9); p=0.37).

Table 5.1 Participant Characteristics

Demographics & Anthropometrics	
Age (years)	44 (13), 21-65
Height (cm)	174.1 (9.1), 151.8-188.0
Weight (kg)	75.4 (12.8), 48.4-100.9
Sex (male:female)*	14:6
Limb dominance (right:left)*	16:4
Injury Information	
Laterality (unilateral:bilateral)*	11:9
Most symptomatic side (right:left)*	10:10
Injury location (midportion:insertion)*	13:7
Duration of symptoms (months)	40.8 (52.6), 0.4-216.6
Running History	
Current Volume (miles/week)	22.5 (14.6), 4-60
Current Pace (min/mile)	9.04 (1.55), 7.3-14.0
Current Frequency (runs/week)	3.5 (1.5), 2-6

Volume Before Injury (miles/week) (n=19)†	24.7 (12.5), 8-60
Pace Before Injury (min/mile) (n=19)†	8.54 (1.02), 6.66-10.0
Frequency Before Injury (runs/week) (n=19)†	4.1(1.5), 2-7
Running Experience (years)	15.9 (12.3), 4-40
Treadmill Comfort (0-10)	8.9 (1.4), 6-10
Physical Activity	
PAS Current	5.6 (0.7), 4-6
PAS Before Injury	5.7 (0.8), 3-6
Kinesiophobia	
TSK Score	29.9 (6.6), 20-41

Data presented as mean (SD), min-max, unless otherwise noted
* Indicates data presented as frequencies
† One participant did not complete
PAS—Physical Activity Scale
VISA-A—Victorian Institute of Sports Assessment- Achilles questionnaire
TSK—Tampa Scale for Kinesiophobia

5.3.2 Side-to-side Comparisons

Descriptive data for the most and least symptomatic sides for all bilateral variables are reported in Table 5.2. VISA-A scores were significantly ($p<0.001$) lower on the most symptomatic side. The most symptomatic tendon was significantly ($p=0.027$) thicker than the least symptomatic tendon. Drop CMJ height, average hopping height, and plyometric quotient while hopping were significantly lower on the most symptomatic side compared to the least symptomatic side. Pain during drop CMJ, hopping, and running were significantly higher on the most symptomatic side compared to the least symptomatic side. All remaining side-to-side comparisons were non-significant (Table 5.2).

Table 5.2 Side-to-side differences in patient-reported outcomes, tendon morphology, tendon mechanical properties, lower leg function, pain and running mechanics for patients with Achilles tendinopathy who are in the return to sport phase.

	Most Symptomatic	**Least Symptomatic**	**Mean (SD) Difference**	**p-value**
Patient-Reported Outcomes				
VISA-A	75 (13), 51-98	90 (10), 72-100	15 (14)	**<0.001***
Tendon Morphology				
Thickness (mm)	6.24 (1.68), 3.91-9.37	5.52 (1.92), 3.44-11.03	-0.71 (1.33)	**0.027***
Cross-sectional Area (cm^2)	0.763 (0.278), 0.388-1.542	0.693 (0.365), 0.369-1.953	-0.070 (0.194)	0.125
Tendon Mechanical Properties				
Shear Modulus (kPa) (n=19)	94.6 (18.2), 66.8-125.1	92.4 (19.0), 69.0-126.7	-2.2 (32.9)	0.770
Viscosity (Pa*s) (n=19)	58.2 (9.8), 35.0-72.3	53.5 (16.4), 22.8-81.2	-4.7 (17.8)	0.271
Young's Modulus (MPa)	605 (299), 202-1406	691 (315), 279-1521	86 (297)	0.210
Lower Leg Function				
Heel-Rise Reps	31 (8), 16-48	30 (8), 15-44	-1 (4)	0.428
Heel-Rise Height (cm)	12.2 (3.0), 6.3-17.2	12.8 (2.3), 8.6-17.6	0.6 (1.4)	0.112
Heel-Rise Work (J)	2103 (746), 1027-3943	2090 (726), 1219-3652	-13 (485)	0.910
CMJ Height (cm)	8.8 (2.4), 5.6-13.8	9.3 (2.4), 5.0-13.6	0.5 (1.3)	0.058
Drop CMJ Height (cm)	8.1 (2.9), 1.8-13.5	9.1 (2.7), 3.5-14.4	1.0 (1.8)	**0.017***
Average Hopping Height (cm)	3.1 (1.1), 1.4-5.3	3.7 (1.5), 1.4-6.9	0.6 (0.8)	**0.004***
Hopping Plyometric Quotient	0.43 (0.08), 0.32-0.58	0.49 (0.09), 0.31-0.69	0.06 (0.07)	**0.002***
Pain				
Pain-Pressure Threshold (kPa)	266 (120), 104-628	252 (101), 102-498	-14 (80)	0.453
Heel-Rise Pain	0 (0), 0-3	0 (0), 0-0	0 (0)	0.066

(0-10)†				
CMJ Pain (0-10)†	0 (1), 0-5	0 (0), 0-2	0 (1)	0.115
Drop CMJ Pain (0-10)†	0 (1), 0-6	0 (0), 0-0	0 (1)	**0.026***
Hopping Pain (0-10)†	1 (3), 0-8	0 (0), 0-1	-1 (3)	**0.003***
Running Pain (0-10)†	2 (3), 0-4	0 (0), 0-3	-2 (3)	**0.003***
Running Mechanics				
Peak Achilles Tendon Force (BW)	4.49 (0.57), 3.05-5.72	4.53 (0.49), 3.71-5.71	0.04 (0.42)	0.676
Achilles tendon Impulse (BW*s)	0.611 (0.092), 0.393-0.793	0.616 (0.078), 0.518-0.796	0.005 (0.070)	0.773
Peak Achilles tendon Loading Rate (BW/s)	60.69 (8.30), 49.82-78.29	61.52 (11.11), 47.08-94.78	0.83 (5.24)	0.488
Average Achilles tendon Loading Rate (BW/s)	43.84 (6.92), 30.66-56.88	44.64 (7.15), 34.98-57.33	0.80 (4.17)	0.397
Peak Concentric Ankle Power (W/kg*m)	5.58 (1.18), 4.38-8.37	5.68 (1.36), 3.77-9.21	0.10 (0.63)	0.463
Peak Eccentric Ankle Power (W/kg*m)	3.20 (0.84), 2.25-5.71	3.37 (1.10), 2.1-6.91	0.17 (0.58)	0.207

Data presented for each side as mean (SD), min-max, unless otherwise noted
* $p<0.05$
† indicates reported as median (IQR), min-max for each side, median difference (IQR), and p-value results from Wilcoxon-signed rank test
‡ Sample size needed to adequately power the analysis. Only performed if p-value <0.3.
BW— Body weight

5.3.3 Relationships with Side-to-side Differences in Running Mechanics

Side-to-side differences in drop CMJ height were significantly ($\rho=0.598$; $p=0.005$) associated with side-to-side differences in peak eccentric ankle power (Figure 5.4). Additionally, side-to-side differences in pain-pressure threshold were significantly associated with side-to-side differences in average Achilles tendon loading rates (Figure 5.5). All other relationships were non-significant (Table 5.3).

Table 5.3 Associations of side-to-side differences in patient-reported outcomes, tendon morphology, tendon mechanical properties, lower leg function, and pain with side-to-side differences in running mechanics for patients with Achilles tendinopathy who are in the return to sport phase.

	Peak Achilles Force	Achilles tendon Impulse	Peak Achilles tendon loading rates†	Average Achilles tendon loading rates	Peak Concentric Ankle Power	Peak Eccentric Ankle Power
Patient-Reported Outcomes						
VISA-A Scores	0.152 (0.522)	0.107 (0.653)	-0.052 (0.828)	0.173 (0.466)	0.172 (0.469)	0.149 (0.530)
TSK Score ‡	0.222 (0.348)	0.308 (0.186)	-0.015 (0.949)	0.146 (0.539)	-0.103 (0.665)	-0.174 (0.463)
Tendon Morphology						
Thickness†	-0.215 (0.363)	-0.272 (0.246)	0.038 (0.875)	-0.248 (0.292)	0.080 (0.738)	-0.195 (0.409)
Cross-sectional area†	-0.200 (0.398)	-0.263 (0.262)	-0.002 (0.995)	-0.095 (0.691)	0.024 (0.920)	-0.135 (0.569)
Tendon Mechanical Properties						
Shear Modulus (n=19)	-0.220 (0.365)	-0.124 (0.614)	-0.261 (0.280)	-0.321 (0.181)	-0.250 (0.301)	-0.094 (0.703)
Viscosity (n=19)	0.086 (0.727)	0.044 (0.858)	0.070 (0.775)	0.111 (0.652)	-0.179 (0.465)	-0.050 (0.839)
Young's Modulus†	0.323 (0.164)	0.355 (0.125)	0.371 (0.107)	0.266 (0.257)	0.280 (0.232)	0.033 (0.890)
Lower Leg Function						
Heel-rise Reps	0.134 (0.572)	0.083 (0.727)	0.372 (0.106)	0.205 (0.386)	0.104 (0.661)	0.355 (0.124)
Heel-rise Height	-0.123 (0.605)	-0.202 (0.393)	-0.098 (0.682)	-0.170 (0.474)	0.054 (0.822)	-0.058 (0.808)
Heel-rise Work†	-0.017 (0.945)	-0.074 (0.758)	0.029 (0.905)	-0.060 (0.801)	-0.143 (0.548)	0.275 (0.240)
CMJ Height†	-0.144 (0.544)	-0.194 (0.413)	0.149 (0.531)	-0.026 (0.915)	-0.056 (0.816)	0.195 (0.409)
Drop CMJ Height†	0.433 (0.056)	0.430 (0.058)	0.164 (0.490)	0.362 (0.116)	0.232 (0.326)	**0.598 (0.005)***
Average Hopping Height	0.201 (0.395)	0.244 (0.300)	0.394 (0.086)	0.266 (0.257)	-0.117 (0.624)	0.171 (0.470)
Hopping PQ	0.250	0.273	0.442	0.295	0.007	0.147

	(0.287)	(0.245)	(0.051)	(0.206)	(0.977)	(0.537)
Pain						
Pain-pressure threshold†	0.389 (0.09)	0.329 (0.156)	0.155 (0.514)	**0.453 (0.045)**	0.206 (0.384)	0.230 (0.329)

Data presented as Pearson's r (p-value), unless otherwise noted
* $p<0.05$
† Spearman's Correlations reported as ρ (p-value)
‡ Association of single value to side-to-side differences in running mechanics
PQ—Plyometric Quotient
TSK—Tampa Scale for Kinesiophobia

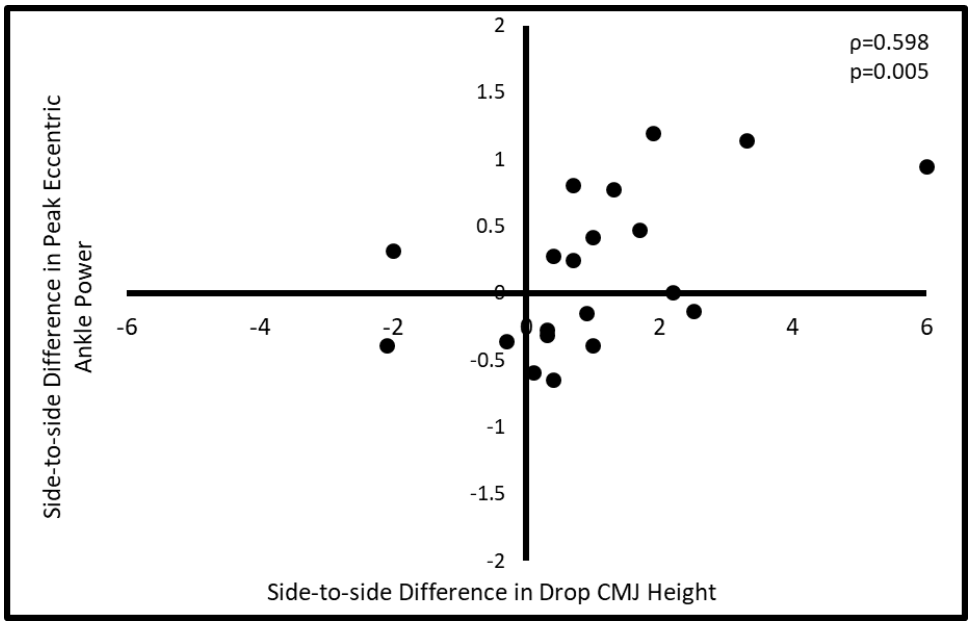

Figure 5.4 Relationship of side-to-side differences in drop countermovement jump (CMJ) height and side-to-side differences in peak eccentric ankle power. Positive x-axis values represent lower drop CMJ height on the most symptomatic side compared to the least symptomatic side. Positive y-axis values represent lower peak eccentric ankle power on the most symptomatic side compared to the least symptomatic side while running.

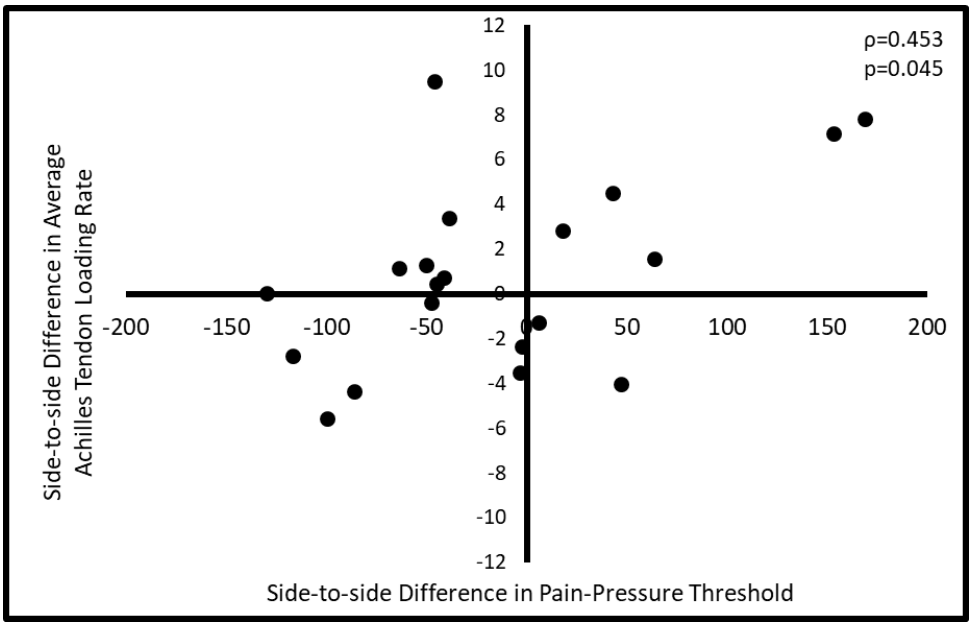

Figure 5.5 Relationship of side-to-side differences in pain-pressure threshold and side-to-side differences in average Achilles tendon loading rate. Positive x-axis values represent the most symptomatic side is more sensitive to a mechanical stimulus than the least symptomatic side. Positive y-axis values represent lower average Achilles tendon loading rates on the most symptomatic side compared to the least symptomatic side while running.

5.3.4 Comparing Running Mechanics in Patients with and without side-to-side differences in Hopping Pain

Seven participants had no side-to-side difference in hopping pain, while the other thirteen participants did. Side-to-side differences in peak (p=0.006) and average (p=0.004) Achilles tendon loading rates were significantly different between groups. Side-to-side differences in peak Achilles tendon loading rates were median (IQR)1.35 (5.43) for the group with side-to-side differences in hopping pain and -3.95 (2.79) for the group without side-to-side differences in hopping pain. The side-to-side differences in average Achilles tendon loading rates were median (IQR) 1.30 (5.61) for the group with side-to-side differences in hopping pain and -3.53 (2.02) for the

group without side-to-side differences in hopping pain. Side-to-side differences in peak Achilles tendon force, Achilles impulse, peak concentric ankle power and peak eccentric ankle power did not differ between groups (p=0.052-0.721).

5.4 Discussion

In this study we explored the associations between running mechanics and patient-reported outcomes, tendon morphology, tendon mechanical properties, lower leg function, and pain in patients with Achilles tendinopathy who are in the RTS phase. We found that side-to-side differences in drop CMJ height were associated with side-to-side differences in peak eccentric ankle power during running. Additionally, side-to-side differences in tendon pain-pressure thresholds were associated with side-to-side differences in average Achilles tendon loading rates while running. These findings suggest that plyometric ability during a drop CMJ and the tendon's sensitivity to a mechanical stimulus are associated with the amount of energy absorbed over time by the ankle and how quickly the tendon is loaded during running.

Patient-reported outcome measures are commonly used in clinical practice to monitor recovery and identify aspects of an injury that need addressed. For Achilles tendinopathy specifically, the VISA-A questionnaire is extensively used in clinical research and recommended by the American Physical Therapy Association's clinical practice guidelines for clinical use.[82] Since this questionnaire quantifies the clinical severity of the injury across domains of symptoms, function, and physical activity participation,[189] it can be speculated that VISA-A scores would relate to functional performance. In the current study, we found no association between side-to-side differences in VISA-A scores and side-to-side differences in running mechanics for patients with Achilles tendinopathy who are in the RTS phase of rehabilitation.

Interestingly, VISA-A scores were significantly different between the most and least symptomatic sides, but running mechanics were on average symmetrical. This lack of association, however, may be a consequence of including patients with bilateral symptoms or having participants run at a conservative speed. Further research is needed to determine if the VISA-A scores can be used to progress patients with Achilles tendinopathy from RTS to return-to-performance.

The TSK is an additional patient-reported outcome measure that has been used in clinical research to quantify a patient's fear of movement.[216,229,230] Kinesiophobia has been implicated as a factor that affects patient recovery and the efficacy of exercise therapy for treating patients with Achilles tendinopathy.[88,231] In a 5-year follow-up study of patients with Achilles tendinopathy who were treated with exercise alone, 35% of the recovery of heel-rise endurance was explained by TSK scores at the time of enrollment.[88] This highlights the role that kinesiophobia plays in responding to exercise treatment, but it does not necessarily mean that kinesiophobia relates to aberrant loading patterns during functional activities. In the current study, we found no associations between TSK scores and running mechanics for patients with Achilles tendinopathy who are in the RTS phase. Possible explanations for these findings may be that kinesiophobia is more relevant during early stages of rehabilitation, the running assessment was not strenuous enough to detect the effects of kinesiophobia, or kinesiophobia alters running mechanics throughout a run.

Achilles tendon morphology and mechanical properties are altered in patients with Achilles tendinopathy.[1,76,114] Namely, the size of the tendon increases and stiffness reduces. Evidence suggests that these aspects of tendon health can normalize over time with exercise therapy.[232] This normalization may be critical for return-to-

performance, since Achilles tendon mechanical properties have been associated with running efficiency[23,195,233] and hopping performance.[193,234] In the current study, we found that side-to-side differences in tendon morphology and mechanical properties were not associated with side-to-side differences in Achilles tendon loading behaviors in patients who were in the RTS phase of rehabilitation. Although non-significant, it appears that Young's modulus has the strongest association with Achilles tendon loading behaviors. We speculate this relationship is the strongest because Young's modulus reflects the tendon's mechanical behavior to a tensile load, which is the principle type of load the tendon is exposed to during running. On the other hand, we found that tendon thickness was significantly different between the most and least symptomatic sides, but cross-sectional area and mechanical properties were not. The lack of differences between sides for cross-sectional area, viscosity, and Young's modulus appears to be a result of the small sample size in this study. Further research is needed to determine if measures of tendon morphology and mechanical properties can be used to prescribe runs of optimal load and monitor the tendon's response to RTS activities.

Functional performance measures are used in clinical research and practice to identify dysfunction and monitor recovery. These types of measures have also been incorporated in RTS criteria for various injuries. For Achilles tendinopathy, specific RTS criteria do not exist, although a RTS program that uses pain and rate of perceived has been proposed.[151] Functional testing may be a critical part of a RTS program, since deficits in muscle-tendon function exist after symptoms have resolved.[4] In this exploratory study, we found that side-to-side differences in drop CMJ height were associated with side-to-side differences in peak eccentric ankle power while running in

patients with Achilles tendinopathy who are in the RTS phase. This suggests that the ankle joint on the most symptomatic side absorbs less energy over time while running compared to the least symptomatic side, when drop CMJ height is lower on the most symptomatic side. Furthermore, it appears that drop CMJ height is also related to peak Achilles tendon force, Achilles tendon impulse, and average loading rates, but this study was not adequately powered to detect these associations. In addition to drop CMJ, there were significant side-to-side differences in hopping height and plyometric quotient, but they were not associated with Achilles tendon loading patterns or ankle joint powers. Collectively, these findings suggest that drop CMJ and repetitive hopping performance differ between sides for patient with Achilles tendinopathy during RTS and that in drop CMJ height relates to energy absorption while running. Interestingly, these side-to-side differences and associations with running mechanics were only found for functional tests that utilize the stretch-shortening function of the tendon. Therefore, functional testing that challenges the tendon's stretch-shortening cycle may provide critical information that could be used for progressing patients through RTS.

Pain in the Achilles tendon while performing activities that involve running and jumping is a hallmark sign of Achilles tendinopathy.[1,2] Additionally, pain is used clinically to monitor recovery, gauge response to treatment, and make RTS decisions. Although positive outcomes are seen when pain is used to guide the amount of loading,[211] it remains unclear if pain is associated with how the tendon is actually loaded during RTS activities. In the current study, we found that side-to-side differences in pain-pressure threshold were associated with side-to-side differences in average Achilles tendon loading rates while running in patients with Achilles

tendinopathy who are in the RTS phase. This finding suggests that if the most symptomatic side is more sensitive to pain compared to the least symptomatic side, the average rate that the tendon is loaded during running is lower on the most symptomatic side. Whether or not this a learned behavior or protective mechanism is unknown. Interestingly, we also found significant side-to-side differences in pain during drop CMJ and hopping tasks. These are the same functional tests that showed significant side-to-side differences in performance. This further supports the use of tests that challenge the stretch-shortening cycle of the tendon during RTS testing. Lastly, when comparing participants with and without side-to-side differences in hopping pain, we found significant differences in peak and average Achilles tendon loading rates. The median difference in loading rates suggest that patients with side-to-side differences hopping pain have lower loading rates on their more symptomatic side while patients without side-to-side differences have higher loading rates on their more symptomatic side. Based on these findings, it appears that pain with hopping may be related to Achilles tendon loading patterns in patients with Achilles tendinopathy. Further research is needed to determine if changes in pain are associated with changes in running mechanics.

There are several limitations of this study. The inclusion of patients with bilateral injury may have affected the side-to-side differences detected in our variables of interest. However, the sample is probably more representative of what is seen in clinical practice since bilateral symptoms and asymptomatic structural changes are common in this population. Another limitation of this study is that patients could be at any point in the RTS phase. Meaning, some participants were close to a year of running without symptoms, while others still had minor symptoms with running (max

pain was 4 out of 10 while running). Despite this limitation, we still found significant side-to-side differences in several aspects of tendon health, which helps identify factors that could be critical for a successful transition from RTS to return-to-performance. The small sample size is a limitation of this study. However, given the exploratory nature of this study, an a priori power analysis could not be performed. After the first 10 participants, a power analysis was completed to determine the number of participants needed to detect an association between peak Achilles tendon loading rate and pain-pressure threshold on the most symptomatic side. With an alpha of 0.05, beta of 0.2, and a correlation coefficient (r) of 0.60, it was determined that 19 participants would adequately power the study.

5.5 Conclusion

Side-to-side differences in drop CMJ height and pain-pressure threshold are associated with peak Ankle eccentric power and average Achilles tendon loading rates while running, respectively. Patients with Achilles tendinopathy who are in the RTS phase have significant side-to-side differences in patient-reported outcomes, functional performance on tasks that involve stretch-shortening function, and pain with these same tasks. Taken together, these results suggest that lower leg function and pain may play a critical role as clinical measures to aid in clinical decision making relating to loading during RTS. Future research is needed to develop RTS criteria that optimizes loading and improves patient outcomes.

Chapter 6

CONCLUSION

6.1 Aim 1 – Measuring Achilles tendon Mechanical Properties in vivo

Continuous shear wave elastography (cSWE) been used to evaluate individuals with healthy Achilles tendons,[7,126] Achilles tendinopathy,[8,117] and Achilles tendon rupture.[127–129] However, validation of is limited to comparisons against magnetic resonance elastography using agarose gels and observations of side-to-side differences in individuals with tendon pathology. Additionally, test-retest reliability has been assessed between trials performed consecutively,[126] but intrarater reliability and stability over time have not been evaluated. In order to further support the use of cSWE for monitoring tendon mechanical properties over time, there was a need for further validation and reliability testing. Therefore, the purpose of this aim was to assess the reliability and validity of measuring in vivo mechanical properties with cSWE in healthy and degenerative Achilles tendons.

6.1.1 *Hypothesis 1.1* – cSWE will have excellent reliability (ICC>0.75) for measuring tendon mechanical properties (static shear modulus, dynamic shear modulus, and viscosity) in healthy Achilles tendons.

This hypothesis was partially supported. Shear modulus had fair-to-good intrarater reliability with an ICC of 0.697 (0.392-0.868), viscosity had excellent reliability with an ICC of 0.856 (0.717-0.937), and dynamic shear modulus had excellent reliability with an ICC of 0.855 (0.715-0.936).

6.1.2 *Hypothesis 1.2* – Achilles tendon mechanical properties (static shear modulus, dynamic shear modulus, viscosity) measured with cSWE will increase as the amount of ankle dorsiflexion increases.

This hypothesis was confirmed. There was a significant main effect of ankle angle on static shear modulus (p=0.036, η^2_p=0.425), viscosity (p=0.019, η^2_p=0.476), and dynamic shear modulus (p=0.013, η^2_p=0.502).

6.1.3 *Hypothesis 1.3* – Achilles tendon mechanical properties (static shear modulus, dynamic shear modulus, viscosity) measured with cSWE will have a strong positive relationship (r>0.75) to Young's modulus measured with ultrasound imaging and dynamometry in healthy and degenerative tendons.

This hypothesis was partially supported. In healthy tendon, the relationship of mechanical properties measured with cSWE across different ankle angles was strongly associated with Young's modulus measured with ultrasound and dynamometry in the same ankle angles (r=0.992, p=0.008). However, for tendinopathic tendons (n=19), there was no relationship between viscoelastic properties (measured in 10 degrees of dorsiflexion) and Young's modulus (measured in neutral).

6.2 Prognostic value of Tendon Morphology and Mechanical Properties

One of the speculated benefits of measuring tendon morphology and mechanical properties is the ability to predict patient outcomes, resulting in more realistic treatment expectations. However, it is currently unknown if these measures have this predictive value. Therefore, the purpose of this aim was to determine if tendon morphology and mechanical properties are associated with recovery of patient-reported symptoms and functional performance in patients with Achilles tendinopathy.

6.2.1 *Hypothesis 2.1* – Greater tendon thickening at initial assessment will be associated with worse patient-reported symptoms and calf muscle function at 6-month and 1-year follow-up assessments.

This hypothesis was supported by findings that greater tendon thickening was consistently associated with lower VISA-A scores and heel-rise endurance at 6-month and 1-year follow-up. It was determined that VISA-A scores reduced by 4 points and heel-rise endurance decreased by 179 J for every 1 millimeter increase in tendon thickening.

6.2.2 *Hypothesis 2.2* – Lower tendon shear modulus at initial assessment will be associated with worse patient-reported symptoms and calf muscle function at 6-month and 1-year follow-up assessments.

This hypothesis was partially supported. VISA-A scores over the year depended on the tendon's initial shear modulus, with patients who have higher initial values of shear modulus improving the most over the year. Shear modulus was not associated with calf muscle function over the year or at each visit.

6.2.3 *Hypothesis 2.3* – Lower tendon viscosity at initial assessment will be associated with worse patient-reported symptoms and calf muscle function at 6-month and 1-year follow-up assessments.

This hypothesis was partially supported. Viscosity was consistently associated with heel-rise endurance across all time points. For every 1 Pa*s decrease in viscosity at the initial visit, heel-rise work reduced by 20 J. Viscosity was not associated with patient-reported symptoms over the year or at each visit.

6.3 Effects of Laser therapy on Tendon Morphology and Mechanical Properties

Laser therapy is an adjunct treatment that has been shown to improve patient outcomes when added to an exercise therapy program.[94,95,204] Similar to exercise, laser therapy may induce temporary changes to tendon morphology and mechanical

properties. These changes could negatively affect the efficiency of the muscle-tendon unit and potentially increase the tendon's susceptibility to further tissue damage. Therefore, the purpose of this aim was to evaluate the immediate effects of laser-induced photobiomodulation therapy on Achilles tendon morphology and mechanical properties in healthy and degenerative tendons.

6.3.1 *Hypothesis 3.1* – Changes in Achilles tendon thickness and cross-sectional area will be greater in a laser-treated side compared to a placebo-treated side over a four hour time period in healthy and degenerative tendons.

This hypothesis was not supported. Changes in Achilles tendon thickness and cross-sectional area did not differ between laser-treated and placebo-treated sides for both healthy and degenerative tendons.

6.3.2 *Hypothesis 3.2* – Changes in Achilles tendon static shear modulus and viscosity will be greater in a laser-treated side compared to a placebo-treated side over a four hour time period in healthy and degenerative tendons.

This hypothesis was not supported. Changes in Achilles tendon shear modulus and viscosity did not differ between laser-treated and placebo-treated sides for both healthy and degenerative tendons.

6.3.3 *Hypothesis 3.3* – Changes in Achilles tendon thickness, cross-sectional area, static shear modulus and viscosity over a four hour time period will be greater in injured tendon compared to healthy tendon when treated with laser therapy.

This hypothesis was not supported. Changes in Achilles tendon thickness, cross-sectional area, shear modulus, and viscosity did not differ between healthy and degenerative tendons when treated with laser-induced photobiomodoulation therapy.

6.4 Return-to-Sport for patients with Achilles tendinopathy

A return-to-sport (RTS) program has been proposed for patients with Achilles tendinopathy that uses pain and rate of perceived exertion to guide loading volume and frequency.[151] Although this program protects the tendon from being exposed to too much load too quickly, it does not consider how the tendon is actually loaded during high-load activities, such as running. Since aberrant loading patterns during RTS activities may influence return-to-performance and risk of recurrence, there is a need to determine what aspects of tendon health are related to tendon loading patterns during RTS activities. Therefore, the purpose of this aim was to explore the relationships between patient-reported outcomes, tendon morphology, mechanical properties, lower leg function, pain, and running mechanics in patients with Achilles tendinopathy.

6.4.1 *Hypothesis 4.1* – Side-to-side differences in pain-pressure threshold will be related to side-to-side differences in Achilles tendon loading rates during running in patients with Achilles tendinopathy.

This hypothesis was supported. Side-to-side differences in pain-pressure threshold were significantly associated with side-to-side differences in average Achilles tendon loading rates (ρ=0.453; p=0.045). The direction of this relationship showed that average Achilles tendon loading rates are lower on the more symptomatic side compared to the least symptomatic side, when the more symptomatic side is more sensitive to a mechanical stimulus.

6.4.2 *Hypothesis 4.2* – Side-to-side differences in Achilles tendon morphology and mechanical properties will be related to side-to-side differences in peak ankle joint plantar flexion power during running in patients with Achilles tendinopathy.

This hypothesis was not supported. Achilles tendon morphology and mechanical properties were not related to ankle joint powers or Achilles tendon loading patterns during running for patients with Achilles tendinopathy who are in the RTS phase of rehabilitation.

6.4.3 *Hypothesis 4.3* – Side-to-side differences in heel-rise test performance will be related to side-to-side differences in ankle joint plantar flexion power during running in patients with Achilles tendinopathy.

This hypothesis was not supported. Heel-rise test performance (endurance) was not associated with side-to-side differences in ankle joint powers or Achilles tendon loading patterns during running for patients with Achilles tendinopathy who are in the RTS phase of rehabilitation. Side-to-side differences in drop countermovement jump height was the functional measure found to be associated with side-to-side differences in ankle joint eccentric power while running.

6.5 Limitations

Most of the limitations of this work stem from the exploratory methods used (all aims) and the heterogeneous populations included (aims 2-4). Although aim 1 further validated cSWE and demonstrated adequate reliably for estimating Achilles tendon mechanical properties, this study only included healthy tendons of young adults. This calls to question the techniques ability to reliably measure mechanical properties in older populations and in the presence of pathology. Since the other three aims included tendinopathic tendons, results need to be interpreted with caution. One of the major limitations of aim 2 is the heterogenous population included without the

necessary sample size to control for possible confounding factors or perform subgroup analyses. Possible confounding factors of this study include the duration of patient symptoms, location of injury (insertional vs midportion), age, sex, medications and types of treatments received. Conversely, the generalizability these results may be improved by not controlling for these factors. For both aim 3 and 4, besides similar confounding factors that make interpretation difficult, the small sample sizes were a major limitation. However, both of these aims elucidated foundational knowledge that is critical for future hypothesis-driven research on laser therapy and RTS for patients with Achilles tendinopathy.

6.6 Conclusions and Clinical Significance

The overall purpose of this dissertation work was to determine if tendon morphology and mechanical properties play a critical role in recovery for patients with Achilles tendinopathy. This investigation began by further validating a technique known as continuous shear wave elastography (cSWE) and assessing its ability to reliably estimate Achilles tendon mechanical properties over time. Although the direct clinical translation of this first study is minimal, it was a necessary step towards potentially identifying biomarkers of tendon health that can be used for prognosis (aim 2), determining treatment efficacy (aim 3), and tailoring rehabilitation (aim 4). Using this experimental technique in addition to traditional ultrasound imaging, we identified that initial measures of tendon morphology and mechanical properties were predictive of patient-reported symptoms and calf muscle functional performance over the course of a year for patients with Achilles tendinopathy. These findings demonstrate that clinical expectations may need to be adjusted based on initial structure of the tendon. Additionally, with these measures, we aimed to determine if laser-induced

photobiomodulation therapy has immediate effects on the tendon. With laser therapy being used as an adjunctive treatment to exercise therapy, a better understanding of the mechanisms that explain positive clinical outcomes is needed to optimize treatment. In this study, there were no changes in tendon morphology or mechanical properties, which suggests that laser therapy can be administered at any time during a treatment session without influencing other treatments. In the last part of this dissertation, we explored the associations between Achilles tendon loading patterns during running and measures of tendon morphology, mechanical properties, patient-reported outcomes, lower leg function and pain. Loading patterns were not associated with tendon morphology or mechanical properties. However, we identified functional tests and measures of pain that may be used to make clinical decisions when a patient with Achilles tendinopathy is returning to sports. Collectively, it appears that tendon morphology and mechanical properties play a critical role in recovery for patients with Achilles tendinopathy.

6.7 Future Directions

This dissertation work further supports the use of cSWE for measuring tendon mechanical properties, but there is a critical need for establishing the reliability of these measurements in pathologic tendon (i.e. both Achilles tendinopathy and Achilles tendon rupture).

This work also demonstrated prognostic value of measuring morphology and mechanical properties, yet it remains unknown if and how these features change throughout rehabilitation. Additionally, it may be particularly informative to prospectively following healthy individuals who are at risk of developing Achilles tendinopathy.

For laser therapy, there is a large gap in evidence. Animal models have primarily been used to understand mechanism while human-subjects research has jumped to randomized clinical trials without supporting evidence. This lack of mechanistic, translational research may explain the mixed results found in clinical trials.[96,203] Possible next steps for understanding laser therapy include evaluating the effect of multiple treatments, investigating interactions between laser and exercise, and exploring possible factors that affect its efficacy (e.g. age, sex, genetics, physical activity level, metabolic disorders, medications).

Specific return-to-sport criteria are lacking for patients with Achilles tendinopathy, which may explain high reoccurrence rates. Additionally, despite Achilles tendinopathy being an overuse injury, no research has been performed in patients with Achilles tendinopathy that evaluates Achilles tendon loading behaviors during recreational activities. The final aim of this dissertation starts laying foundational knowledge that can be used for future research, with to goal of developing comprehensive return-to-sport criteria that reduces reoccurrence and gets patients back to participation and high levels of performance. Some of the next steps in furthering our understanding of return-to-sport activities are investigating changes in Achilles tendon loading patterns throughout a run, comparing laboratory based running to real-world running, and determining if changes in clinical variables effect running mechanics. Additionally, comparisons to matched healthy individuals would help elucidate critical factors for successful return to performance.

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Appendix A

INSTITUTIONAL REVIEW BOARD APPROVALS FOR INCLUDED STUDIES

IRB approvals for specific aims 1 and 3.

UNIVERSITY OF DELAWARE
RESEARCH OFFICE
210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE:	April 5, 2016
TO:	Karin Silbernagel, PT, ATC, PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[880856-1] The effect of photobiomodulation on tendon
SUBMISSION TYPE:	New Project
ACTION:	APPROVED
APPROVAL DATE:	April 5, 2016
EXPIRATION DATE:	April 4, 2017
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review category # *(4,7)*

Thank you for your submission of New Project materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Expedited Review based on the applicable federal regulation.

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Please report all NON-COMPLIANCE issues or COMPLAINTS regarding this study to this office.

Please note that all research records must be retained for a minimum of three years.

Based on the risks, this project requires Continuing Review by this office on an annual basis. Please use the appropriate renewal forms for this procedure.

RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE: May 13, 2016

TO: Karin Silbernagel, PT, ATC, PhD
FROM: University of Delaware IRB

STUDY TITLE: [880856-2] The effect of photobiomodulation on tendon

SUBMISSION TYPE: Amendment/Modification

ACTION: APPROVED
APPROVAL DATE: May 13, 2016
EXPIRATION DATE: April 4, 2017
REVIEW TYPE: Expedited Review

REVIEW CATEGORY: Expedited review category # *(4,7)*

Thank you for your submission of Amendment/Modification materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

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Based on the risks, this project requires Continuing Review by this office on an annual basis. Please use the appropriate renewal forms for this procedure.

RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE: September 15, 2016

TO: Karin Silbernagel, PT, ATC, PhD
FROM: University of Delaware IRB

STUDY TITLE: [880856-3] The effect of photobiomodulation on tendon

SUBMISSION TYPE: Amendment/Modification

ACTION: APPROVED
APPROVAL DATE: September 15, 2016
EXPIRATION DATE: April 4, 2017
REVIEW TYPE: Expedited Review

REVIEW CATEGORY: Expedited review category # (4), *(7)*

Thank you for your submission of Amendment/Modification materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

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Based on the risks, this project requires Continuing Review by this office on an annual basis. Please use the appropriate renewal forms for this procedure.

RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE: April 5, 2017

TO: Karin Silbernagel, PT, ATC, PhD
FROM: University of Delaware IRB

STUDY TITLE: [880856-4] The effect of photobiomodulation on tendon

SUBMISSION TYPE: Continuing Review/Progress Report

ACTION: APPROVED
APPROVAL DATE: April 5, 2017
EXPIRATION DATE: April 4, 2018
REVIEW TYPE: Expedited Review

REVIEW CATEGORY: Expedited review category # *(4,7)*

Thank you for your submission of Continuing Review/Progress Report materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Expedited Review based on the applicable federal regulation.

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Based on the risks, this project requires Continuing Review by this office on an annual basis. Please use the appropriate renewal forms for this procedure.

RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE: March 23, 2018

TO: Karin Silbernagel, PT, ATC, PhD
FROM: University of Delaware IRB

STUDY TITLE: [880856-5] The effect of photobiomodulation on tendon

SUBMISSION TYPE: Continuing Review/Progress Report

ACTION: APPROVED
APPROVAL DATE: March 23, 2018
EXPIRATION DATE: April 4, 2019
REVIEW TYPE: Expedited Review

REVIEW CATEGORY: Expedited review category # *(4,7)*

Thank you for your submission of Continuing Review/Progress Report materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Expedited Review based on the applicable federal regulation.

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Based on the risks, this project requires Continuing Review by this office on an annual basis. Please use the appropriate renewal forms for this procedure.

RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE: April 3, 2019

TO: Karin Silbernagel, PT, ATC, PhD
FROM: University of Delaware IRB

STUDY TITLE: [880856-6] The effect of photobiomodulation on tendon

SUBMISSION TYPE: Closure/Final Report

ACTION: CLOSED
EFFECTIVE DATE: April 3, 2019

The University of Delaware IRB has CLOSED this project. No further action on submission 880856-6 is required at this time.

Please remember that in compliance with 45 CFR 46, all records associated with this project, including data and consent forms, must be retained for three (3) years from the closure date. Records must be retained in a manner consistent with your approved protocol.

If you leave the University of Delaware prior to the end of the retention requirement, study records must remain at the University. If you need assistance arranging for the secure storage of the records, the IRB office is able to assist you. If you have any questions, please contact Renee Stewart at (302) 831-2137 or stewartr@udel.edu. Please include your study title and reference number in all correspondence with this office.

IRB approvals for specific aim 2

UNIVERSITY OF DELAWARE
RESEARCH OFFICE
210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE:	December 9, 2014
TO:	Karin Silbernagel, PT, ATC, PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[670923-1] Achilles tendinopathy and tendon rupture function, clinical and structural outcomes
SUBMISSION TYPE:	New Project
ACTION:	APPROVED
APPROVAL DATE:	December 9, 2014
EXPIRATION DATE:	December 8, 2015
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review category # *(4,7)*

Thank you for your submission of New Project materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Expedited Review based on the applicable federal regulation.

Please remember that informed consent is a process beginning with a description of the study and insurance of participant understanding followed by a signed consent form. Informed consent must continue throughout the study via a dialogue between the researcher and research participant. Federal regulations require each participant receive a copy of the signed consent document.

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Please note that all research records must be retained for a minimum of three years.

RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE: February 9, 2015

TO: Karin Silbernagel, PT, ATC, PhD
FROM: University of Delaware IRB

STUDY TITLE: [670923-2] Achilles tendinopathy and tendon rupture function, clinical and structural outcomes

SUBMISSION TYPE: Amendment/Modification

ACTION: APPROVED
APPROVAL DATE: February 9, 2015
EXPIRATION DATE: December 8, 2015
REVIEW TYPE: Expedited Review

REVIEW CATEGORY: Expedited review category # *(4,7)*

Thank you for your submission of Amendment/Modification materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

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RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE: May 6, 2015

TO: Karin Silbernagel, PT, ATC, PhD
FROM: University of Delaware IRB

STUDY TITLE: [670923-3] Achilles tendinopathy and tendon rupture function, clinical and structural outcomes

IRB REFERENCE #:
SUBMISSION TYPE: Amendment/Modification

ACTION: APPROVED
APPROVAL DATE: May 6, 2015
EXPIRATION DATE: December 8, 2015
REVIEW TYPE: Expedited Review

REVIEW CATEGORY: Expedited review category # *(4,7)*

Thank you for your submission of Amendment/Modification materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Expedited Review based on the applicable federal regulation.

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RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE:	September 15, 2015
TO:	Karin Silbernagel, PT, ATC, PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[670923-4] Achilles tendinopathy and tendon rupture function, clinical and structural outcomes
SUBMISSION TYPE:	Amendment/Modification
ACTION:	APPROVED
APPROVAL DATE:	September 15, 2015
EXPIRATION DATE:	December 8, 2016
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review category # *(4,(7)*

Thank you for your submission of Amendment/Modification materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

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Please note that all research records must be retained for a minimum of three years.

RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE: February 29, 2016

TO: Karin Silbernagel, PT, ATC, PhD
FROM: University of Delaware IRB

STUDY TITLE: [670923-5] Achilles tendinopathy and tendon rupture function, clinical and structural outcomes

SUBMISSION TYPE: Amendment/Modification

ACTION: APPROVED
APPROVAL DATE: February 29, 2016
EXPIRATION DATE: December 8, 2016
REVIEW TYPE: Expedited Review

REVIEW CATEGORY: Expedited review category # *(4,7)*

Thank you for your submission of Amendment/Modification materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

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RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE: April 8, 2016

TO: Karin Silbernagel, PT, ATC, PhD
FROM: University of Delaware IRB

STUDY TITLE: [670923-7] Achilles tendinopathy and tendon rupture function, clinical and structural outcomes

SUBMISSION TYPE: Amendment/Modification

ACTION: APPROVED
APPROVAL DATE: April 8, 2016
EXPIRATION DATE: December 8, 2016
REVIEW TYPE: Expedited Review

REVIEW CATEGORY: Expedited review category # *(4,7)*

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UNIVERSITY OF DELAWARE
RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE:	May 13, 2016
TO:	Karin Silbernagel, PT, ATC, PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[670923-8] Achilles tendinopathy and tendon rupture function, clinical and structural outcomes
SUBMISSION TYPE:	Amendment/Modification
ACTION:	APPROVED
APPROVAL DATE:	May 13, 2016
EXPIRATION DATE:	December 8, 2016
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review category # *(4,7)*

Thank you for your submission of Amendment/Modification materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

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RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE:	September 15, 2016
TO:	Karin Silbernagel, PT, ATC, PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[670923-9] Achilles tendinopathy and tendon rupture function, clinical and structural outcomes
SUBMISSION TYPE:	Amendment/Modification
ACTION:	APPROVED
APPROVAL DATE:	September 15, 2016
EXPIRATION DATE:	December 8, 2016
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review category # *(4),(7)*

Thank you for your submission of Amendment/Modification materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

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RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE:	November 29, 2016
TO:	Karin Silbernagel, PT, ATC, PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[670923-10] Achilles tendinopathy and tendon rupture function, clinical and structural outcomes
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED
APPROVAL DATE:	November 29, 2016
EXPIRATION DATE:	December 8, 2017
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review category # *(4,7)*

Thank you for your submission of Continuing Review/Progress Report materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Expedited Review based on the applicable federal regulation.

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UNIVERSITY OF DELAWARE
RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE:	May 25, 2017
TO:	Karin Silbernagel, PT, ATC, PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[670923-11] Achilles tendinopathy and tendon rupture function, clinical and structural outcomes
SUBMISSION TYPE:	Amendment/Modification
ACTION:	APPROVED
APPROVAL DATE:	May 25, 2017
EXPIRATION DATE:	December 8, 2017
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review category # *(4,7)*

Thank you for your submission of Amendment/Modification materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Expedited Review based on the applicable federal regulation.

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Please note that all research records must be retained for a minimum of three years.

RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE: December 6, 2017

TO: Karin Silbernagel, PT, ATC, PhD
FROM: University of Delaware IRB

STUDY TITLE: [670923-12] Achilles tendinopathy and tendon rupture function, clinical and structural outcomes

SUBMISSION TYPE: Continuing Review/Progress Report

ACTION: APPROVED
APPROVAL DATE: December 6, 2017
EXPIRATION DATE: December 8, 2018
REVIEW TYPE: Expedited Review

REVIEW CATEGORY: Expedited review category # *(4,7)*

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Please report all NON-COMPLIANCE issues or COMPLAINTS regarding this study to this office.

Please note that all research records must be retained for a minimum of three years.

UNIVERSITY OF DELAWARE
RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE:	August 31, 2018
TO:	Karin Silbernagel, PT, ATC, PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[670923-13] Achilles tendinopathy and tendon rupture function, clinical and structural outcomes
SUBMISSION TYPE:	Amendment/Modification
ACTION:	APPROVED
APPROVAL DATE:	August 31, 2018
EXPIRATION DATE:	December 8, 2018
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review categories 4,7

Thank you for your submission of Amendment/Modification materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

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RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE:	November 30, 2018
TO:	Karin Silbernagel, PT, ATC, PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[670923-14] Achilles tendinopathy and tendon rupture function, clinical and structural outcomes
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED
APPROVAL DATE:	November 30, 2018
EXPIRATION DATE:	December 8, 2019
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review category # *(4,7)*

Thank you for your submission of Continuing Review/Progress Report materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

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IRB approvals for specific aim 4

UNIVERSITY OF DELAWARE
RESEARCH OFFICE
210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE:	May 16, 2017
TO:	Karin Silbernagel, PT, ATC,PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[1063764-1] Structural and Biomechanical Analysis of Patients with Achilles Tendinopathy
SUBMISSION TYPE:	New Project
ACTION:	APPROVED
APPROVAL DATE:	May 16, 2017
EXPIRATION DATE:	May 15, 2018
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review categories 4 and 7

Thank you for your submission of New Project materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Expedited Review based on the applicable federal regulation.

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Please report all NON-COMPLIANCE issues or COMPLAINTS regarding this study to this office.

Please note that all research records must be retained for a minimum of three years.

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RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE:	September 26, 2017
TO:	Karin Silbernagel, PT, ATC,PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[1063764-3] Structural and Biomechanical Analysis of Patients with Achilles Tendinopathy
SUBMISSION TYPE:	Amendment/Modification
ACTION:	APPROVED
APPROVAL DATE:	September 26, 2017
EXPIRATION DATE:	May 15, 2018
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review category # *(4,7)*

Thank you for your submission of Amendment/Modification materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

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Please report all NON-COMPLIANCE issues or COMPLAINTS regarding this study to this office.

Please note that all research records must be retained for a minimum of three years.

UNIVERSITY OF DELAWARE
RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE:	May 8, 2018
TO:	Karin Silbernagel, PT, ATC,PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[1063764-4] Structural and Biomechanical Analysis of Patients with Achilles Tendinopathy
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED
APPROVAL DATE:	May 8, 2018
EXPIRATION DATE:	May 15, 2019
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review category # *(4,7)*

Thank you for your submission of Continuing Review/Progress Report materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Expedited Review based on the applicable federal regulation.

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Please note that all research records must be retained for a minimum of three years.

RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE:	August 28, 2018
TO:	Karin Silbernagel, PT, ATC,PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[1063764-6] Structural and Biomechanical Analysis of Patients with Achilles Tendinopathy
SUBMISSION TYPE:	Amendment/Modification
ACTION:	APPROVED
APPROVAL DATE:	August 28, 2018
EXPIRATION DATE:	May 15, 2019
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review category # *(4,7)*

Thank you for your submission of Amendment/Modification materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Expedited Review based on the applicable federal regulation.

Please remember that informed consent is a process beginning with a description of the study and insurance of participant understanding followed by a signed consent form. Informed consent must continue throughout the study via a dialogue between the researcher and research participant. Federal regulations require each participant receive a copy of the signed consent document.

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RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE: March 11, 2019

TO: Karin Silbernagel, PT, ATC,PhD
FROM: University of Delaware IRB

STUDY TITLE: [1063764-10] Structural and Biomechanical Analysis of Patients with Achilles Tendinopathy

SUBMISSION TYPE: Amendment/Modification

ACTION: APPROVED
APPROVAL DATE: March 11, 2019
EXPIRATION DATE: May 15, 2019
REVIEW TYPE: Expedited Review

REVIEW CATEGORY: Expedited review category # *(4,7)*

Thank you for your submission of Amendment/Modification materials for this research study. The University of Delaware IRB has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Expedited Review based on the applicable federal regulation.

Please remember that informed consent is a process beginning with a description of the study and insurance of participant understanding followed by a signed consent form. Informed consent must continue throughout the study via a dialogue between the researcher and research participant. Federal regulations require each participant receive a copy of the signed consent document.

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Please report all NON-COMPLIANCE issues or COMPLAINTS regarding this study to this office.

Please note that all research records must be retained for a minimum of three years.

Institutional Review Board
210H Hullihen Hall
Newark, DE 19716
Phone: 302-831-2137
Fax: 302-831-2828

DATE:	May 7, 2019
TO:	Karin Silbernagel, PT, ATC, PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[1063764-11] Structural and Biomechanical Analysis of Patients with Achilles Tendinopathy
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED
APPROVAL DATE:	May 7, 2019
EXPIRATION DATE:	May 15, 2020
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review category # *(4,7)*

Thank you for your Continuing Review/Progress Report submission to the University of Delaware Institutional Review Board (UD IRB). The UD IRB has reviewed and APPROVED the proposed research and submitted documents via Expedited Review in compliance with the pertinent federal regulations.

As the Principal Investigator for this study, you are responsible for and agree that:

- All research must be conducted in accordance with the protocol and all other study forms as approved in this submission. Any revisions to the approved study procedures or documents must be reviewed and approved by the IRB prior to their implementation. Please use the UD amendment form to request the review of any changes to approved study procedures or documents.
- Informed consent is a process that must allow prospective participants sufficient opportunity to discuss and consider whether to participate. IRB-approved and stamped consent documents must be used when enrolling participants and a written copy shall be given to the person signing the informed consent form.
- Unanticipated problems, serious adverse events involving risk to participants, and all non-compliance issues must be reported to this office in a timely fashion according with the UD requirements for reportable events. All sponsor reporting requirements must also be followed.

Oversight of this study by the UD IRB REQUIRES the submission of a CONTINUING REVIEW seeking the renewal of this IRB approval, which will expire on May 15, 2020. A continuing review/progress report form and up-to-date copies of the protocol form and all other approved study materials must be submitted to the UD IRB at least 45 days prior to the expiration date to allow for the required IRB review of that report.

If you have any questions, please contact the UD IRB Office at (302) 831-2137 or via email at hsrb-research@udel.edu. Please include the study title and reference number in all correspondence with this office.

Appendix B

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Title: Quantification of Mechanical Properties in Healthy Achilles Tendon Using Continuous Shear Wave Elastography: A Reliability and Validation Study

Author: Patrick Corrigan,Jennifer A. Zellers,Phoebe Balascio,Karin Grävare Silbernagel,Daniel H. Cortes

Publication: Ultrasound in Medicine & Biology

Publisher: Elsevier

Date: July 2019

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