EARLY TO LATE OUTCOMES FOLLOWING ACHILLES TENDON RUPTURE: CONTRIBUTORS TO CLINICAL SUCCESS

by

Jennifer A. Zellers

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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We live in this world in order always to learn industriously and to enlighten each other by means of discussion and to strive vigorously to promote the progress of science and the fine arts. - Wolfgang Amadeus Mozart

Who I am, what I am, is the culmination of a lifetime of reading, a lifetime of stories. And there are still so many more books to read. I’m a work in progress. - Sarah Addison Allen

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PREFACE

At the time of preparing this dissertation document, two of the chapters have been accepted for publication or published and reused here with copyright permission of the respective journals. I would like to take a moment to acknowledge my coauthors and clarify my contribution to these works.

Zellers JA, Cortes DH, Corrigan P, Pontiggia L, Silbernagel KG. Side-to-side differences in Achilles tendon geometry and mechanical properties following Achilles tendon rupture. *Muscles, Ligaments, Tendons J,* 2018;7(3):541-547.

The conception and study design was a joint effort amongst coauthors. I was responsible for conducting all data collections and post-processing of all data included in this manuscript, with the exception of the reliability data which was the contribution of Pat Corrigan. I contributed to the statistical analysis with assistance from Laura Pontiggia and interpretation of results with assistance of Daniel Cortes and Karin Grävare Silbernagel. I was the sole drafter of this manuscript, with editing assistance and manuscript review from the co-authors.

Zellers JA, Carmont MR, Grävare Silbernagel K. Return to play post-Achilles tendon rupture: a systematic review and meta-analysis of rate and measures of return to play. *Br J Sports Med*. 2016;50:1325-1332.

I was responsible for coordinating the efforts of the reviewing authors and was one of the two reviewers. I was responsible for conducting all data management, data analysis and statistical analysis. The conceptual framework, editing, and review of the manuscript was a joint effort amongst coauthors, however, I was largely responsible for the drafting of the manuscript with assistance from Michael Carmont.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Achilles tendon rupture has an annual incidence of 31.2-37.3/100,000 individuals per year[1–4]. The Achilles tendon is a critical component of foot and ankle function[5,6], making Achilles tendon rupture a potentially debilitating injury[7]. The purpose of this dissertation work is to look across the continuum of patient recovery to identify clinical outcome measures to evaluate recovery. Further, this work seeks to examine if outcomes measured early in recovery respond to changes during a patient's healing trajectory and relate to patient functional outcomes.

On the individual level, it seems that patients' long term prognosis relates to how well an individual recovers within the first year[8,9]. In particular, recovery of a single leg heel-rise seems to relate to patient recovery within and after the first year[9–11]. The heel-rise has limited use within the first 12 weeks of recovery due to the need for the patient to weight bear without immobilization and due to the concern that only 50% of individuals are able to perform the single-leg heel-rise at 12 weeks[10]. This points to the need for objective criteria that are sensitive to changes in the early healing trajectory of the patient that can be used to guide treatment and predict outcomes. Later in recovery, return to sport is of concern in this patient population due to the recreationally active demographic typically associated with this injury. There is large variability in return to play rates, suggesting that not only individual but also methodological influences may need consideration.

This dissertation work investigates the use of ultrasound imaging to measure structural parameters of the Achilles tendon and identify their responsiveness to change over time and the relationships of these structural changes to patient function. Ultrasound imaging techniques include B-mode ultrasound imaging as well as a novel technique, continuous shear wave elastography[12]. Functional testing includes components of a functional test battery previously used in this population[13,14] as well as similar populations[15]. The results of this work indicate that there are side to side differences in tendon structural characteristics, some of which are responsive to change over the course of early tendon healing. Further, these structural characteristics relate to components of performance on the heel-rise test and to patterns of muscle activation in the triceps surae during heel-rise and jumping tasks. The final aim of this dissertation work found that 80% of individuals after Achilles tendon rupture are able to return to play, but variability may not only be at the level of the individual but also be due to risk of bias in the available literature.

Chapter 1

INTRODUCTION

1.1 Dissertation Overview

The Achilles tendon is a critical component of foot and ankle function[5,6], making Achilles tendon rupture a potentially debilitating injury[7]. Historically, successful outcome following Achilles tendon rupture was assessed using metrics such as re-rupture rates and generalized assessment tools such as patient satisfaction and ankle/foot specific functional questionnaires[16]. With improvements in treatment techniques, re-rupture rates are now reported to be under 10% irrespective of treatment[17]. The focus of measuring successful recovery has started to shift away from re-rupture rates and towards patient outcomes with respect to Achilles tendon-specific healing and patient symptoms and functional measures.

It has been reported that damage to the Achilles tendon, such as with Achilles tendon rupture, results in significant deficits in both stance phase control as well as power generation[9,18–20]. These deficits are observed during activities from walking to more challenging tasks required for participation in sport and occupation[18,21]. While deficits are most apparent early post-rupture, studies measuring long-term outcomes following Achilles tendon rupture have identified that functional deficits persist at least up to 2-5 years post rupture[8,9,19,22], with focal deficits in calf musculature and ankle function reported 10-13 years post rupture[23–25]. Variability in patient outcomes has led to several questions regarding clinical decision-making in both the early and late phases of rehabilitation.

The purpose of this dissertation work is to look across the continuum of patient recovery to identify clinical outcome measures to evaluate recovery. Further, this work seeks to examine if outcomes measured early in recovery respond to changes during a patient's healing trajectory and relate to patient functional outcomes. The ultimate goal of this work is to provide a clinician with a set of tools that can measure patient outcomes across the continuum of recovery and provide objective information for treatment decision-making. Improving our ability to assess and track patient progress with objective measures will support future work on setting objective criteria to advance treatment progression and identify individuals at risk of long-term functional deficits.

1.2 Background

Achilles tendon rupture is a traumatic injury which leads to alterations in lower extremity function with activities such as walking[26,27], running[21], and jumping[14,19,28]. The incidence of Achilles tendon rupture is increasing[1,2], with rates as high as 31.1 per 100,000 people per year[1]. Of particular concern is the high variability of patient outcomes regardless of whether or not an individual has a surgical repair following rupture. For instance, a prior study reported some patients being unable to perform a hopping task on their injured side at one year post-injury, while other patients were able to regain 144% of their hopping capacity compared to the uninjured side[8]. Body mass index (BMI), sex[29], and pre-injury status[29,30] have been associated with patient outcomes, but much of the differences among individuals remains unaccounted for even when medical and rehabilitative treatment regimens are standardized[14].

In order to identify variables related to the clinical success of a patient, the outcome measures used to gauge patient progress must be sensitive enough to distinguish differences between individuals as well as changes over time within an individual. Furthermore, they must relate to something meaningful for the patient and their recovery. If we put outcome measures in the context of the International Classification of Functioning, Disability, and Health (ICF) model[31], we can consider a variety of outcomes spanning impairment, activity, and participation domains. At the impairment level, we can consider metrics such as re-rupture rate[17], structural measures such as tendon elongation[13,26,32,33] and gap distance[34,35], range of motion measures such as the Achilles tendon resting angle[36–39], and strength measures such as the heel-rise test[9–11,40]. At the activity level, we can consider performance with walking[26,41–47] and running gait[19,21], jumping capacity[14,19,28,48], and patient self-reported function on questionnaires such at the Achilles tendon Total Rupture Score (ATRS)[49]. At the participation level, a recent study has used wearable technology to measure patient performance in sport participation[50].

Despite the variety of tools currently available to evaluate individuals following Achilles tendon rupture, there is a limited understanding for how these tools relate to each other and how they can be used to guide treatment. Tendon elongation is one of the better studied components of tendon structure, so we can take that as an example. Tendon elongation occurs within the first 8 weeks following Achilles tendon rupture, though exact trends over time are not consistent between studies[13,32,51]. Presence of tendon elongation has been found to relate to decreased heel-rise height on the heel-rise test, indicating decreased calf function[9,13]. To take the importance of tendon elongation further, the presence of tendon elongation and heel-rise performance is also associated with alterations in muscle activity with walking[26] and increased knee loads during jogging and jumping tasks[19], respectively. These deficits are prolonged and able to be detected well after a year post-rupture, which is past the typical timeframe to return to sport activity[52]. While structural characteristics such as tendon cross-sectional area have been reported in the literature[53,54], their relationship to patient outcomes has not been described. Additionally, inferior tendon mechanical properties have been suggested to result in deficits in functional capacity, but the relationship of tendon mechanical properties to patient function has been explored in a limited number of studies[48,52,55,56] and responsiveness to change over time has only been reported in few studies with inconsistent results[27,52,55,57].

Therefore, the purpose of this dissertation work is to examine factors that contribute to the clinical success of patients after Achilles tendon rupture. Most of these factors explain variability at the level of the individual, including tendon structure and mechanical properties, muscle activation, and functional performance. In addition to the contributors at an individual level, methodological contributors to differences in reported return to play outcomes between studies will also be discussed. To accomplish this, this work encompasses the following aims:

Aim 1: Examine side-to-side differences in Achilles tendon structure (shear modulus, viscosity, tendon length, tendon thickness) and their relationship to clinical outcomes (Achilles tendon resting angle, self-reported function, and heel-rise test) within one year post-rupture.

Aim 2: Establish the relationship between weight bearing and recovery of tendon structure and functional performance (heel-rise and jump tests) within 6-months post-injury.

Aim 3: Identify adaptations at the muscle-level which accommodate for tendon dysfunction (tendon elongation or decreased viscoelastic properties) between one and three years post-injury.

Aim 4: Determine rate of and time to return to play following Achilles tendon rupture.

There are several potential clinical implications of this work. Findings from this dissertation will help improve our understanding of the structure-function relationship, timing of recovery, role of weight bearing in recovery, and muscle-tendon interaction. This will help inform future research and clinical decision-making allowing the clinician to base patient prognosis in objective findings, promote appropriate compensatory strategies, and guide patient expectations regarding recovery.

1.3 Achilles Structure and Clinical Outcome

Healthy tendon is characterized by densely packed, highly organized collagen bundles[58]. These collagen bundles, or fibrils, are connected by more elastic connective tissue, called elastin[59]. The highly aligned fibers allow the tendon to withstand high tensile forces and transfer those forces between the muscle and bone[6,60]. Because healthy Achilles tendon is able to withstand large loads, the tendon is generally considered to undergo some degenerative changes prior to rupture[58]. Following rupture, the collagen is disorganized and buckles from a microscopic standpoint[58,59] with a “mop head” appearance macroscopically. Assessments of tendon structure and mechanical properties have been suggested to be beneficial for tracking healing early following rupture[13,55,61].

From a structure standpoint, recent studies have identified gap distance between tendon ends to be predictive of patient outcomes with surgical versus non-surgical treatment[34,35]. Clinical surrogate measures available to the rehabilitation professional have been described to indirectly assess tendon length[13,36], and tendon length measured via ultrasound imaging has been found to relate to patient functional outcomes[13,26]. Tendon thickness has been found to be approximately two times greater on the ruptured compared to non-ruptured sides[62], however, the relationship between tendon thickness and patient function has not been examined.

In addition to tendons being structurally longer, injured tendons can also be functionally longer by becoming more compliant. In a study by Arya and Kulig[63], side-to-side differences in elastic modulus were observed between healthy and tendinopathic tendon, with tendinopathic tendon having lower elastic modulus. While this study provided important insight into tendon mechanical properties with injury, the technique they used to measure elastic modulus requires volitional contraction, limiting its ability to be used in the context of tendon rupture. A similar stress-strain approach was used by Schepull and colleagues[61] to measure elastic modulus in individuals with Achilles tendon rupture. In this study, tantalum beads were inserted into ruptured Achilles tendons. Beginning 7 weeks post-repair, the distance between beads during a contraction of a set force was used to estimate elastic modulus[61]. Invasiveness of this technique presents a challenge to more widespread application, and this technique still requires volitional contraction which may be problematic prior to 8 weeks post-rupture/repair.

To circumvent concerns regarding invasiveness and reliance on volitional contraction, shear wave ultrasound techniques have been developed to measure mechanical properties of soft tissues[55,64–78]. Shear wave elastography uses the speed at which vibrations propagate to estimate tendon shear elasticity. Studies in cadavers have demonstrated a relationship between shear elasticity and elasticity on tensile testing[64]. Furthermore, Zhang and colleagues[55] reported increasing shear elasticity over time in Achilles tendons following rupture with surgical repair. The benefit of this technique is that it is non-invasive, does not require active contraction, and allows for spatial resolution of tendon properties. Complications arise in very stiff, highly directional tissue as saturation becomes an issue[72]. This has likely limited comparisons between injured and healthy tendon in prior studies.

A new technique developed within our lab, continuous shear wave elastography (cSWE), is a non-invasive ultrasound technique that uses an external actuator to vibrate the tendon tissue with ultrasound imaging tracking tissue displacement[12,79]. This technique has been able to overcome concerns regarding saturation as shear wave speeds measured exceed the capacity of commercial scanners[12]. There are three output variables of interest obtained from cSWE. Shear modulus is the tendon's resistance to shear force that is independent of velocity and may relate to fibrous contents of the tissue. Viscosity is the tendon's resistance to shear force that is velocity dependent and may relate to volume of fluid content or fluid flow within the fibrous matrix of the tendon. Finally, dynamic shear modulus is a measure that combines shear modulus and viscosity at an assumed 400 Hz excitation frequency. This measure seems more comparable to other commercially available scanners and may account for both fibrous and fluid contents of the tendon. Thus, cSWE presents a unique opportunity to explore side-to-side differences in tendon viscoelastic properties following Achilles tendon rupture and has been applied to this population in one case study[52].

The purpose of Aim 1 is to establish the presence of side-to-side differences in tendon structure and the relationship to clinical outcomes in individuals following Achilles tendon rupture using quantitative, non-invasive measures.

Aim 1: Examine side-to-side differences in Achilles tendon structure (shear modulus, viscosity, tendon length, tendon thickness) and their relationship to clinical outcomes (Achilles tendon resting angle, self-reported function, and heel-rise test) within one year post-rupture.

Hypothesis 1.1: Differences will be observed between ruptured and non-ruptured sides in tendon structural outcomes.

Hypothesis 1.1a: Within the first year, tendon mechanical properties will be lower on ruptured compared to non-ruptured sides.

Hypothesis 1.1b: Within the first year, tendon length and thickness will be greater on ruptured compared to non-ruptured sides.

Hypothesis 1.2: Improved tendon structure on the ruptured side will positively relate to improved clinical outcomes

Hypothesis 1.2a: Higher tendon viscoelastic properties and lower tendon length/thickness on the ruptured side will positively relate to improved clinical outcomes.

Hypothesis 1.2b: More symmetrical values of tendon structure will positively relate to improved clinical outcomes.

1.4 Achilles Structure Over Time and Role of Weight Bearing

It is clear that the factors at play early in an individual's recovery after Achilles tendon rupture are poorly understood and contribute to late outcomes, specifically an individual's ability to return to their desired level of activity. Tendon structural characteristics associated with poor prognosis, such as tendon elongation, appear within the first 3 months after rupture and remain throughout recovery[11,80]. Prior studies have identified significant recovery of function 3 to 6 months post-injury, with smaller functional gains between 6 and 12 months[14,81]. No functional improvements and persistent side-to-side asymmetries have been reported 1 to 2 years post-injury[8]. Detecting individual differences early in recovery requires the clinician to rely on objective, measurable outcomes to identify patients at risk for poor outcome. Being able to identify patients with a poor prognosis within the first 3 months post-injury would provide the clinician the opportunity to individualize treatment and hopefully improve a patient's potential for full functional recovery. In order to achieve this clinical prognostic ability, we must first understand changes in tendon healing over time, the relationship of early tendon structure to later patient function, and the role of early rehabilitation factors (such as weight bearing) on tendon structure and patient function.

Prior studies in humans have begun to describe changes in tendon elongation and cross-sectional area over time[32,51]. Longitudinal studies have identified tendon elongation occurring prior to 12 weeks, with the greatest lengthening occurring prior to 8 weeks[32,51]. The exact trend of tendon elongation does differ slightly between studies. Tendon cross-sectional area has also been found to increase on the ruptured side[82] and has been associated with the formation of a healing callus[54]. Both tendon elongation and cross-sectional area seem to trend from values more similar to the uninjured side to much larger[32,51,82], possibly indicating a remodeling process. Values then begin to restore back toward the uninjured side[32,51,82], possibly indicating maturation of the recovering tendon.

There is also growing evidence to suggest that early tendon structure is related to patient function later in recovery. Beginning within the first few weeks following rupture, quality of tendon tissue evidenced by characteristics of tendon structure and mechanical properties contribute to regaining function in later phases[61,83]. Structurally, tendon elongation occurs within 3 months post-rupture[83] and is associated with deficits in heel rise height on the heel-rise test at 6 and 12 months post-rupture[13]. Prior studies have found higher tendon elastic modulus at 7 weeks post injury to relate to improved performance on the heel-rise test, a lower leg functional test, at 18 months[61]. Other studies using ultrasound elastography have found increasing tendon elastic modulus to be related to improved general ankle function[55].

As our understanding of mechanobiology continues to develop, questions regarding the role of weight bearing in tendon healing are becoming more and more of interest. Animal studies have shown that tendon mechanical properties are affected by loading[84], suggesting that mechanical properties are potentially recoverable with physical therapy treatments aimed at providing appropriately dosed tendon loading. Furthermore, studies in rats have reported that early tendon loading is critical in developing a healing tendon callus[54,85] as early loading – even loading bouts of short duration – have been associated with increased tendon cross-sectional area. There has been the suggestion that mechanical loading promotes signaling cascades that promote tendon formation rather than cartilage or bone formation[86] and upregulates tendon-specific genes[85]. In humans, early loading has been associated with increased tendon metabolism[87] and elastic modulus[82]. Clinically, early loading protocols have demonstrated equivalent[62,88,89] to superior[87,90] functional outcomes compared to protocols with a 4-6 week period of non-weight bearing, including earlier return to sporting activity without increased risk of rerupture or major complications[24,82,87–93]. Clinical studies have been limited, however, with a lack of non-invasive, safe measurement techniques to measure parameters such as tendon mechanical properties and objective quantification of weight bearing load.

Therefore, the purpose of Aim 2 is to investigate change over time in tendon structure (tendon geometry and mechanical properties) and functional performance in individuals with Achilles tendon rupture. Furthermore, this aim serves to establish the relationship between tendon structure, functional performance, and cumulative weight bearing days.

Aim 2: Establish the relationship between weight bearing and recovery of tendon structure and functional performance (heel-rise and jump tests) within 6-months post-injury.

Hypothesis 2.1: Tendon structure (mechanical properties, length, cross-sectional area) will increase between 4-weeks and 6-months post injury/surgery.

Hypothesis 2.2: Individuals able to perform a unilateral heel-rise at 12-weeks post injury/surgery will have a higher number of weight bearing days during the first 12-weeks compared to patients who are unable to perform a unilateral heel-rise.

Hypothesis 2.3: A higher number of weight bearing days during the first 12-weeks will positively relate to improved recovery of functional performance (heel-rise and jumping tests) at 6-months.

Hypothesis 2.4: A higher number of weight bearing days during the first 12-weeks will positively relate to greater tendon cross-sectional area and mechanical properties values, and lower tendon elongation at 12-weeks post injury/surgery.

Hypothesis 2.5: Patients who are weight bearing by 6-weeks post injury/surgery will have a smaller difference in tendon structure between the healthy and injured side at the 6-month follow-up.

1.5 Muscle-Tendon Interplay

The triceps surae is composed of both muscle and tendon. The tendon is designed to transfer muscle force to the bone to allow for movement and also plays a role in the storing and releasing of energy during rapid, repetitive movements.

There are numerous tests that assess the muscle-tendon unit as a whole, however, what these tests tell us about the individual components is a more challenging question[6]. For example, the heel-rise test for calf endurance has been shown to have clinical utility in individuals with Achilles tendon injury, but was found in a systematic review of the literature to lack information specific to what test results indicate about the underlying pathology[94]. Since the time of that review, different parameters of that test have been found to relate to different aspects of tendon health[13]. For example, maximum heel rise height has been found to relate to Achilles tendon elongation in a population of individuals following Achilles tendon rupture[13].

The relative contribution of muscle to tendon is task-dependent in healthy individuals. For example, with increasing running speeds the tendon contributes more to the overall work performed by the musculotendinous unit[95]. The way that muscle forces are transmitted through the tendon depends on the task. It has been demonstrated that the different muscles of the triceps surae (medial and lateral gastrocnemius and soleus), result in non-uniform shear stresses on the Achilles tendon in healthy individuals that is task-dependent[96]. Passive loading (stretching) has been reported to result in greater tissue displacement in the deep rather than the superficial portions of the tendon and demonstrated greater displacements than eccentric loading at specific knee positions[96]. Appreciating these components and the complexity of their interactions is critical in understanding what predisposes an individual to injury and how to optimally recover post-injury.

Understanding what aspects of performance are related to a particular target tissue may help guide rehabilitative intervention. For instance, in the context of treating the muscle-tendon unit, contraction type, intensity, and recovery time differ when targeting tendinous versus muscular components. Additionally, identifying adaptive strategies will help clinicians to understand how the body acclimates to injury in order to proactively support these strategies. Aim 3 will help to decipher which clinical tests are sensitive to tendon dysfunction as well as how different parameters of a single test may help differentiate tendon dysfunction versus lack of muscular compensation. Lastly, this study will help to identify what compensatory strategies injured individuals use to successfully accomplish a given task.

Aim 3: Identify adaptations at the muscle-level which accommodate for tendon dysfunction (tendon elongation or decreased viscoelastic properties) between one and two years post-injury.

Hypothesis 3.1: Muscle activation will occur earlier on the ruptured side compared to the uninjured side during heel-rise and jumping tasks.

Hypothesis 3.2: Earlier muscle activation onset with clinical testing will positively relate to greater tendon elongation and lower tendon mechanical properties.

1.6 Late Outcomes – Return to Play

The ability to return to play is another area of great variability in patient outcome. Some studies report return to play rates as low as 18.6%[93], while others report rates as high as 100%[97–99]. This is of particular concern given that the majority of Achilles tendon ruptures occur during recreational sport[2,100–102], and return to an active life-style is often of high priority[101]. It is unclear whether this variability can be accounted for as individual variation or whether it is due to methodological differences in experimental design in studies reporting return to play outcomes.

Return to activity, including sport-specific activity is regularly reported as an outcome in studies regarding Achilles tendon rupture treatment[103]. Understanding return to play rates and time frame is important in providing well-informed education to patients to guide expectations as well as to assist the clinician in making return to play decisions. Aim 4 seeks to determine return to sport/return to activity rates and time frame in individuals following Achilles tendon rupture, and examine whether stringency of return to play measurement affects reported return to play rates through a systematic review and meta-analysis.

Aim 4: Determine rate of and time to return to play following Achilles tendon rupture.

Hypothesis 4.1: Determine the rate of return to play following Achilles tendon rupture.

Hypothesis 4.2: Rate of return to play will be lower in studies with a reported method for return to play measurement than in studies with undescribed methods.

Hypothesis 4.3: Determine the typical time to return to play following Achilles tendon rupture.

1.7 Summary

In summary, this dissertation work seeks to assess tendon healing following Achilles tendon rupture across multiple domains of the ICF model. The goal of this approach is to identify relationships between outcomes early in rehabilitation with those late in recovery that could be used to help guide patient prognosis and treatment. Ultimately, this work seeks to lay the groundwork for future studies advancing a criterion-based rehabilitation progression for this population of individuals.

Chapter 2

SIDE TO SIDE DIFFERENCES IN ACHILLES TENDON GEOMETRY AND MECHANICAL PROPERTIES FOLLOWING ACHILLES TENDON RUPTURE

2.1 Introduction

Outcomes following Achilles tendon rupture are highly variable. For instance, a prior study reported some patients being unable to perform a hopping task on their injured side at one year post-injury, while other patients were able to regain over 100% of their hopping capacity compared to the uninjured side[8]. Body mass index (BMI) and sex[29] have been associated with patient outcomes, but much of the variability between individuals remains unaccounted for even when treatment regimens are standardized[14]. Differences in outcomes appear within the first 3 months after rupture and remain throughout recovery. Prior studies have identified significant functional recovery 3 to 6 months post-injury, with smaller functional gains between 6 and 12 months[14,81]. No functional improvements and continued side-to-side deficits have been reported 1 to 2 years post-injury[8]. Detecting individual differences early in recovery requires the clinician to rely on objective, measurable outcomes to identify patients at risk for poor outcomes. Being able to identify patients with a poor prognosis within the first 3 months post-injury would provide the healthcare professional the opportunity to intervene and hopefully improve a patient's potential for full functional recovery.

There are few objective tools to guide clinical decision-making at this key, early phase of recovery. Functional testing, such as the heel-rise test and jump testing[15] have been used in the mid to late stages (5+ months) of recovery. Performance of these tests can be problematic in the early (0-4 months) stages of rehabilitation due to floor effects as they rely on unilateral lower extremity tasks. For example, at three months post-rupture, only 50% of individuals are able to complete a single, unilateral heel-rise[11]. Assessing tendon structure – including both geometrical and mechanical properties – following rupture has been suggested to fill this void[13,55,61].

Animal studies have identified differences in tendon structure throughout the healing course[54,84]. Tendon stiffness and ultimate stress, but not elastic modulus, was found to respond to different tendon loading protocols in rats[54]. A study by Freedman, et al., identified differences in mechanical properties with regard to surgically versus non-surgically managed tendons as well as with timing of activity[84]. Tendon cross-sectional area has been found to increase with healing post-tendon transection in rats, particularly with increasing amounts of tendon load[54,84,85]. Differences in tendon geometry and mechanical properties between treatment groups points to the importance of quantifying these properties to guide clinical decision-making.

In humans, quality of tendon tissue – evidenced by characteristics of tendon structure and mechanical properties – have been found to contribute to regaining function in later phases. Structurally, tendon elongation occurs within 3 months post-rupture[83] and is associated with deficits in heel rise height on the heel-rise test at 6 and 12 months post-rupture[13]. From a mechanical property standpoint, early recovery of elastic modulus measured by Roentgen stereophotogrammetric analysis (RSA) at 7 weeks post-injury correlated with performance on the heel-rise test at 19 weeks[61]. However, assessment of mechanical properties of tendon tissue has not been without its challenges. Techniques to measure mechanical properties often require loading of the tendon with muscle contraction[104] or invasive techniques[61], limiting their clinical application particularly early post-injury.

To overcome these obstacles, non-invasive ultrasound techniques have been proposed to measure tendon mechanical properties *in vivo*. Shear wave elastography has been applied to the Achilles tendon rupture population in one study[55], and has been found to relate to elastic modulus with tensile testing[64]. Continuous shear wave elastography (cSWE) has been developed[12] and utilized in assessment of Achilles tendons in a healthy population[79], and has been applied to Achilles tendon rupture in a case study[52]. This technique uses an external actuator to generate a vibration in the tendon. As the vibration travels down the tendon, linear displacement of tendon tissue is recorded using ultrasound imaging. From this information, the speed of shear wave propagation is calculated and used in a biomechanical model to estimate tendon shear modulus and viscosity. Therefore, the purpose of this study is two-fold. First, we aim to identify side-to-side differences in tendon shear modulus and viscosity following Achilles tendon rupture using cSWE. Second, we aim to investigate the relationship of tendon mechanical properties measured using cSWE to tendon geometry as well as clinical and functional outcomes in individuals following Achilles tendon rupture.

2.2 Methods

2.2.1 Study Design and Subject Selection

This cross-sectional study included data from a subgroup of participants included in a larger, prospective study of individuals with Achilles tendon pathology between November 2014 and June 2016. Data from individuals within 12 months following unilateral Achilles tendon rupture were included. Data were excluded for participants with tendon laceration (n=2), repair complicated by deep wound infection (n=1), or history of contralateral Achilles tendon rupture (n=1). This study was conducted with approval of the University of Delaware institutional review board. This study meets the ethical standards of this journal[105].

2.2.2 Quantification of Tendon Structure

Tendon structure was measured using B-mode ultrasound imaging. The participant was positioned in prone with feet hanging off the side of a plinth in resting position. To measure Achilles tendon length, a mark was made on the skin between the medial and lateral gastrocnemius. The probe was positioned in long axis to the Achilles tendon over the midpoint of the calcaneus and then moved to the mark between gastrocnemius heads. Achilles tendon length from insertion to the gastrocnemius myotendinous junction was measured using extended field of view settings (GE LOGIQ e, GE Healthcare, Chicago, IL)[106]. Tendon thickness was measured in long axis at the region of interest – either the rupture site or the anatomical equivalent on the uninjured side – by drawing a line from the superficial to deep fascial lines. For both tendon length and thickness, an average of three measures was used for analysis.

Tendon shear modulus and viscosity were quantified using cSWE as described in detail by Cortes, et al[12,79] using an ultrasound scanner (MDP, Ultrasonix, Vancouver, Canada) with a L14-5/38 transducer and external data acquisition unit (DAQ). This technique uses an external actuator to propagate a shear wave along the length of the Achilles tendon. The participant is positioned in prone with their feet secured against a footplate set at 10 degrees dorsiflexion. An ultrasound probe is placed at the region of interest, either the rupture site or the anatomical equivalent of the rupture site on the uninjured side, and linear displacement of the tissue is captured using ultrasound imaging. From this data, speed of shear wave propagation is calculated and then used in the Voigt model to approximate tendon shear modulus and viscosity. The average values for shear modulus and viscosity within the region of interest were used in data analysis.

2.2.3 cSWE Test-retest Reliability Study

Nineteen individuals with healthy Achilles tendons were included in this test-retest reliability study. Three trials of cSWE were performed for both the test and re-test conditions and the average of these measures was used for data analysis. For the re-test condition, cSWE was repeated at the same location on the tendon after a break of no longer than 10 minutes. The mean(SD) for shear modulus was 94.8(16.4) kPa for the test and 95.0(16.1) kPa for the re-test condition. The mean(SD) for viscosity was 57.8(13.6) Pa*s for the test and 55.4(12.7) Pa*s for the re-test condition. Intraclass correlation coefficients (ICC) and standard error of measurement (SEM) were calculated[107]. The ICC was found to be 0.67 for shear modulus and 0.80 for viscosity. The SEM was found to be 9.4 kPa for shear modulus and 6.04 Pa*s for viscosity.

2.2.4 Measurement of Clinical Outcomes

Achilles tendon resting angle was measured using an inclinometer on the plantar aspect of the participant's foot, with the knee flexed to 90 degrees[36]. Maximum calf circumference was measured using a tape measure. Lower leg function was assessed using the heel-rise test as described by Silbernagel, et al[40]. In this test, unilateral heel-rises are performed at a rate of 30 per minute on a 10 degree incline until fatigue (Figure 2.1). Participant self-reported level of function was evaluated using the Achilles tendon total rupture score (ATRS)[49], the Foot and Ankle Outcome Score – quality of life subscale[108], and activity level was assessed using the Physical Activity Scale (PAS)[109].

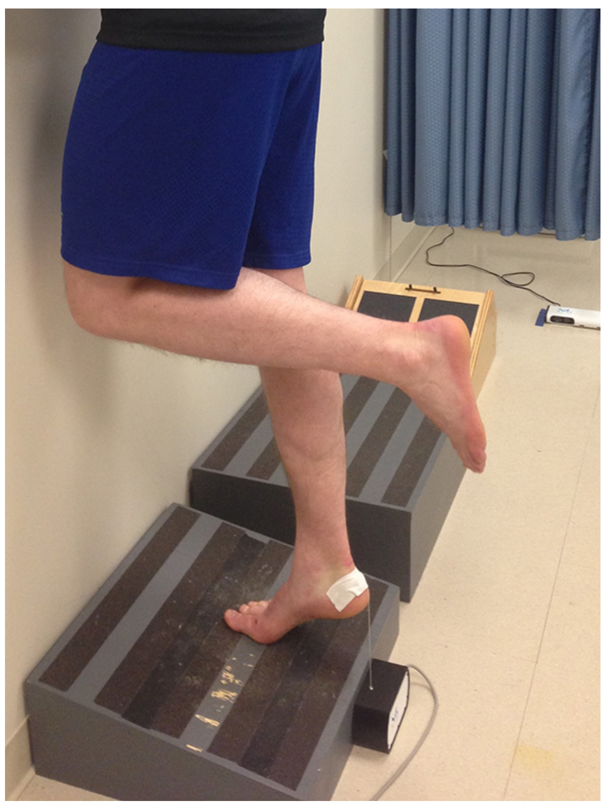

Figure 2.1: Set-up for the heel-rise test.

2.2.5 Statistical Analysis

Due to the nonparametric nature of the data and small sample size, statistical analysis was performed using nonparametric tests. For quantitative variables, the median and interquartile range (IQR) are reported. The Spearman correlation coefficient was used for correlation analyses. The difference between rupture and non-rupture sides and the difference between pre and post activity levels were evaluated with Wilcoxon Signed Rank test. Effect sizes were calculated by dividing the Z-score from the Wilcoxon Signed Rank test by the square root of the number of samples. To determine the difference in time since injury and thickness for participants grouped by nominal variable, an independent samples Mann-Whitney U Test was used. Limb symmetry indexes (LSI) were calculated by dividing the value for the ruptured side by the value of the non-ruptured side (ruptured side/non-ruptured side * 100).

2.3 Results

2.3.1 Subject Demographics

Data from twenty participants (15 male, 5 female) were included. Participants were a mean (SD) age of 42.7 (13.6) years with the left side injured in 16 and the right side injured in 4 participants. All participants were between 2 and 12 months post complete Achilles tendon rupture (median (IQR) of 4.6 (3.1-6.6) months). Seven participants had non-surgical and 13 had surgical treatment. Participants rated their activity prior to injury as a median(IQR) of 5.5(4.5-6.0) prior to injury and 3.5(3.0-4.5) on the Physical Activity Scale at the time of evaluation. There were no statistically significant differences between surgically and non-surgically managed participants for any measurement on the ruptured side or any change score.

2.3.2 Tendon Structure

Tendon thickness was significantly greater on the ruptured side ($p < 0.001$) with a median (IQR) of 1.38(1.21-1.56) cm on ruptured and 0.49 (0.40-0.52) cm on healthy sides (Figure 2.2). Tendon length to the gastrocnemius myotendinous junction was also significantly longer ($p < 0.001$) on ruptured (median (IQR) 22.85 (21.71-24.31) cm) than non-ruptured (21.66 (20.74-23.62) cm) sides.

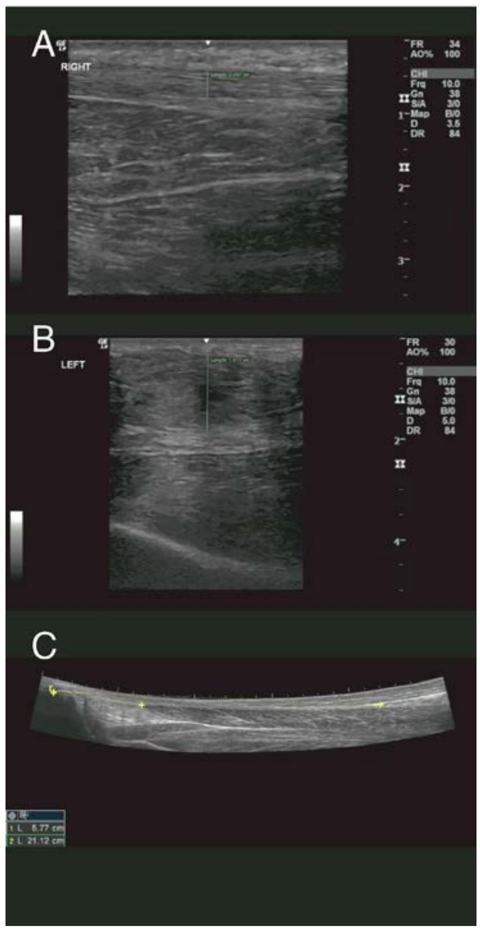

Figure 2.2: B-mode ultrasound images with measurement lines for A. tendon thickness in a non-ruptured tendon, B. tendon thickness in a ruptured tendon, and C. tendon length to gastrocnemius myotendinous junction.

Viscosity was significantly lower on the ruptured side (p = 0.001), with a median (IQR) of 37.7 (30.6-43.3) Pa*s on ruptured and 53.5 (48.4-59.6) Pa*s on non-ruptured sides, with a large effect size of 0.691. The difference in viscosity between sides surpassed the SEM in 17 individuals, with the ruptured side being lower than the non-ruptured side in 15 of the 17 cases. Shear modulus was not significantly different between sides with a median (IQR) of 94.3 (82.4-106.1) kPa on ruptured and 94.2 (90.6-113.2) kPa on non-ruptured sides, with a small effect size of 0.042. The difference in shear modulus between sides surpassed the SEM in 15 of 20 individuals. In 8 individuals (40% of total participants), shear modulus was lower on the ruptured side, and in 7 individuals (35% of total participants), the shear modulus was higher on the ruptured side.

2.3.3 Clinical Outcomes

The participants demonstrated significantly smaller calf circumference, increased tendon length, decreased Achilles tendon resting angle, and decreased heel-rise performance on the ruptured versus non-ruptured side (Table 2.1). Two participants were not permitted to perform the heel-rise test on their ruptured side due to early phase of healing, and five participants were unable to complete a unilateral heel-rise on their ruptured side. Heel-rise test performance was the only clinical or structural measurement that related to time since injury. With increasing time from injury, participants demonstrated improved heel-rise height LSI (rho=0.487, p=0.04), repetitions LSI (rho=0.515, p=0.003), and total work LSI (rho=0.493, p=0.04). Participants' current physical activity level (median [IQR] 3.5 [3-4.5]) was significantly lower compared to before injury (median [IQR] 5.5 [4.5-6.0]) (p <0.001).

Participants scored a median (IQR) of 65.5 (29.5-75.5) of 100 total points on the ATRS.

Clinical Measure	Ruptured Side	Non-ruptured Side	p-value
Calf circumference (cm)	37.2 (35.0-39.5)	38.5 (36.2-41.0)	0.003**
Achilles tendon length to gastrocnemius (cm)	22.85 (21.71-24.31)	21.66 (20.74-23.62)	< 0.001*
Achilles tendon resting angle	4.90 (2.60-12.30)	16.0 (12.4-21.0)	< 0.001**
Heel-rise Test			
Maximum heel-rise height (cm)	6.65 (0-8.10)	12.30 (11.40-13.00)	< 0.001*
Number repetitions	13.5 (0-25)	24 (20-31)	< 0.001*
Total work (Joules)	593 (0-1294)	2049 (1556-2517)	< 0.001*

Table 2.1: Results of clinical measures. Displayed values are Median (IQR) * p-value from Wilcoxon Signed Rank test (test for a median difference significantly different from 0) ** p-value from Wilcoxon Signed Rank test (test for a median limb symmetry index significantly different from 100%)

2.3.4 Relationship Between Tendon Structure and Clinical Tests

Shear modulus correlated with age on the ruptured side only (rho = -0.481, p = 0.037). Shear modulus LSI correlated with side-to-side difference in tendon thickness (rho = 0.492, p = 0.028). Tendon thickness on the ruptured side was found to relate to ATRS score (rho=0.488, p=0.029) and FAOS score (rho = 0.536, p = 0.018). The relative difference in thickness was also significantly related to ATRS score (rho=0.498, p=0.025) and FAOS score (rho=0.561, p=0.013).

In all individuals who were able to attempt the heel-rise test (n=18), tendon thickness on the ruptured side was related to heel-rise test repetitions (rho = 0.684, p =

0.002), maximum height (rho = 0.616, p = 0.007), and total work (rho = 0.675, p = 0.002). Furthermore, tendon thickness was significantly larger in individuals who were compared with those who were not able to complete a unilateral heel-rise on the ruptured side (p = 0.014). When looking at individuals able to complete the heel-rise test (n = 13), shear modulus on the ruptured side was found to inversely relate to heel-rise test repetitions (rho = -0.798, p = 0.001), maximum height (rho = -0.564, p = 0.045), and total work (rho = -0.791, p = 0.001) (Figure 2.3). The difference in tendon length to the gastrocnemius on ruptured compared to healthy sides was found to relate to heel-rise test repetitions LSI (rho = -0.567, p = 0.043). There was no significant relationship between viscoelastic properties and heel-rise test performance on the healthy side. Viscosity did not relate to self-reported function or heel-rise test performance.

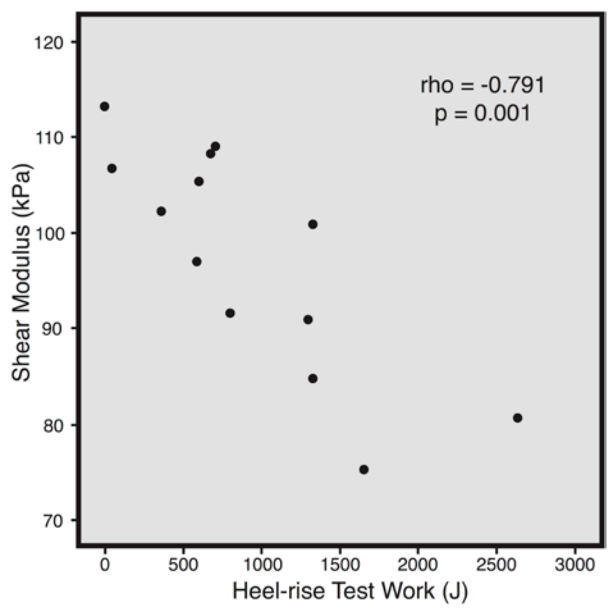

Figure 2.3: The inverse relationship between total work performed on the heel-rise test (J) and shear modulus (kPa).

2.4 Discussion

The results of this study show side-to-side differences in tendon geometry and viscosity in individuals following Achilles tendon rupture. Achilles tendon geometry, but not viscosity, was also found to significantly relate to clinical outcomes. While no significant differences between ruptured and non-ruptured sides was observed, shear modulus was found to relate to clinical outcomes on the ruptured side.

Side-to-side differences in tendon mechanical properties have been identified in prior studies using advanced ultrasound imaging[65,75]. Shear modulus, measured by supersonic shear wave imaging, was found to be lower in damaged porcine tendons (tendons treated with collagenase) compared to healthy tendons and was also found to strongly relate to Young's modulus[65]. Similarly, shear modulus was found to be lower in individuals with tendon pain compared to the asymptomatic side[75]. When looking over time using shear wave elastography, shear modulus has been reported to increase following Achilles tendon repair, however, side-to-side comparisons have not been reported[55]. The lack of side-to-side comparison may be due to concerns regarding saturation of stiff tissue using commercially available shear wave elastography. Saturation does not appear to be an issue with use of cSWE, allowing for side-to-side comparison between limbs. A prior study in individuals with healthy Achilles tendons demonstrated no side-to-side differences in shear modulus or viscosity when measured with cSWE[79]. When applied to the Achilles tendon rupture population, cSWE was able to detect side-to-side differences in tendon viscosity, however, we did not identify differences in shear modulus at the group level. There are several reasons why prior studies using similar ultrasound techniques identified differences in shear modulus and we did not. First, cSWE and supersonic shear-wave imaging (SSI) measure different mechanical properties. cSWE separates the mechanical response of the tendon into a ‘static’ shear modulus and a viscosity parameter characterizing the loading rate dependency. In the case of SSI, both static and rate dependent effects are combined into a single measurement of shear modulus. Therefore, the changes in viscosity reported in this study may be related to the changes in shear modulus reported in other studies using SSI. Second, it is possible that due to a relatively small sample size included in this study, we were not powered to see differences in shear modulus. Third, participants in this study were placed in a standardized foot position with their foot against a foot plate. This is different than the above studies, which placed the foot in a resting position. Finally, participants included individuals at varied stages of healing, which may have resulted in differences in shear modulus between sides going in different directions. Future studies in a more homogenous population (controlled for variables such as surgical/non-surgical management, rehabilitation, and time from injury) may help in identifying differences between sides with regard to shear modulus.

Increased tendon cross-sectional area following Achilles tendon rupture has been reported previously in animal and human studies[54,57,84,110]. Furthermore, level of activity and surgical versus non-surgical intervention has been found to affect tendon cross-sectional area[84]. Prior studies in rats have reported a relationship between increased tendon cross-sectional area and lower elastic modulus, which was suggested to relate to formation of a tendon callus[54]. In the present study, a moderate relationship was seen between shear modulus and tendon thickness. The underlying cause of the observed relationships between tendon geometry and mechanical properties warrants further study[111], however, based on animal studies investigating the role of tendon loading[84], these parameters seem potentially modifiable.

Previous studies have related clinical outcomes to tendon structural characteristics. Heel rise height has been associated with Achilles tendon length in the context of tendon elongation following rupture[13]. In the present study, heel-rise height was found to relate to repetitions completed during the heel-rise test but not maximum heel-rise height. The results of this study suggest that in addition to considering tendon length with these tests, tendon mechanical properties also seem to contribute to these outcomes. Prior studies using cSWE in individuals with healthy Achilles tendons found no relationship between tendon mechanical properties and strength[79]. Our findings in a population of individuals following Achilles tendon rupture support prior findings as we did not see a relationship between mechanical properties and clinical outcomes in relatively healthy tendons (non-ruptured side), however, these relationships are observed with pathology (ruptured side). It may be that in a healthy condition there is a ceiling effect; with a highly efficient tendon, muscular contributions are so great that tendon contribution is indistinguishable.

Several animal studies have reported a relationship between age and tendon mechanical properties, suggesting that tendon mechanical properties decline with increasing age[112–114]. In humans, age has further been reported to change the mechanical properties of healthy tendons in response to loading[115]. In the present study, age was found to be inversely related to shear modulus only in ruptured tendons. While this relationship was not seen on the healthy side, lower values with increasing age fits the trends previously reported in the literature[113–116].

There are several limitations to this study. First, it utilizes a cross-sectional study design, so the effect of time from injury cannot be well-discerned and would be better addressed in future, longitudinal studies. The participants in this study were heterogeneous in medical management (included individuals managed with and without surgery) as well as in rehabilitation protocol. Group heterogeneity, combined with small sample size, may make relationships between tendon structural and patient functional outcomes difficult to detect. The benefit of a heterogeneous group, however, lies in increasing the generalizability of study findings.

The strength and novelty of this study is the use of advanced imaging techniques along with well-established, Achilles tendon-specific patient outcomes to evaluate the relationship between tendon structure and clinical outcomes. Future, longitudinal studies will help elucidate the responsiveness of these properties to changes in the tendon as well as whether cSWE findings early following Achilles tendon rupture are predictive of long-term outcomes. The findings of this study indicate that tendon mechanical properties measured within the first 12 months following Achilles tendon rupture relate both to presence of pathology as well as clinical outcomes. This supports the continued investigation of the early recovery of mechanical properties following tendon injury in a research setting to better understand the process of tendon healing as well to potentially guide patient treatment in the future.

Chapter 3

CHANGES IN TENDON STRUCTURE DURING 6 MONTHS FOLLOWING ACHILLES TENDON RUPTURE

3.1 Introduction

Achilles tendon rupture causes focal, longstanding plantar flexor deficits[23,24] that result in altered biomechanics with running and jumping several years after injury[9,19]. A growing body of evidence is suggesting that tendon elongation, typically occurring within the first 12 weeks following injury[32,51], underlies gastrocnemius and soleus atrophy[117], impaired performance on calf strength and endurance testing[9,13,117], altered muscle function during gait[26], and altered ankle biomechanics during running and jumping tasks[9]. Given the continuing ramifications of poor tendon healing early in recovery, optimizing tendon structural recovery during the first 12 weeks has become a prime target to improve patient outcomes in the long term. From a rehabilitative standpoint, there has been great interest in better understanding the role of immobilization and timing of weight bearing onset following Achilles tendon rupture both in the context of surgical and non-surgical management.

Animal studies investigating the mechanical and biochemical impact of weight bearing have shown that loading the tendon in tension is important throughout the course of recovery[54,84–86,110]. In early phases, loading provides the signals necessary for tendon callus development[54,85,110] and loading later in recovery is important in the upregulation of tendon-specific genes[85] and down-regulation of pathways leading to cartilage and bone formation[86,110]. Furthermore, early tendon loading in a rat model was found to result in improved tendon mechanical properties[84]. In humans, early tendon loading has been found to be associated with differences in tendon metabolism[87] and mechanical properties[82] indicating improved tendon healing in early phases of recovery. Later functional outcomes at 6 and 12 months have been found to be comparable or superior in groups treated with early tendon loading[24,82,87–93]. It is important to note, however, that weight bearing in a walking boot with wedges may not actually relate to tensioning of the tendon[118].

Despite literature suggesting that early weight bearing is not detrimental and may be beneficial to tendon healing[24,82,87–93], there is no agreed upon definition of what constitutes "early" weight bearing[16]. Definitions rely on time-based criteria, which can be arbitrary and not account for individual variation in healing course. As rehabilitation of these individuals moves from time-based to criterion-based progression, a comprehensive understanding of biomarkers will be needed to track tendon healing within the first 12 weeks following injury. Tendon structural characteristics – such as tendon geometry and mechanical properties – may provide important information to the clinician regarding tendon response to weight bearing load and help fill this need for early biomarkers of tendon recovery.

Measurement of tendon structure has presented with its own set of unique challenges. For example, prior studies investigating tendon mechanical properties have often depended on voluntary muscle contraction[27,48,57,61]. In these techniques, the subject is required to plantar flex the foot and ankle to get a measure of force. An imaging modality is then used to look at lengthening and other geometric properties of the tendon. Using the combination of these two measures, tendon stiffness and Young's modulus can be estimated[27,48,57,61]. The assumption with these techniques is that the muscles in the deep compartment of the leg are at a poor mechanical advantage to contribute to plantar flexion force, so the total force generated is then attributed to the triceps surae. This assumption may be acceptable in healthy populations, however, is likely flawed in the context of tendon injury. Finni et al[119], showed using cine phase-contrast magnetic resonance imaging that the relative contribution of the soleus compared to the flexor hallucis longus (FHL) decreases substantially in patients with Achilles tendon rupture. In the healthy cohort, the soleus/FHL muscle displacement ratio was 3.5 compared to 0.2 in individuals following Achilles tendon rupture[119]. Heikkinen et al[117], similarly show overdevelopment of the FHL in patients with Achilles tendon rupture, likely compensating for atrophy of the gastrocnemius and soelus muscles. Techniques requiring voluntary contraction likely overestimate the force output of the triceps surae and consequently overestimate values for tendon stiffness and Young's modulus in unhealthy tendons.

Recently, shear wave elastography techniques have been developed and applied to individuals following Achilles tendon rupture[52,55,120]. These techniques are passive and do not require volitional contraction, making them safe to use early following rupture and potentially less prone to overestimation of tendon mechanical properties. With the development of extended field of view ultrasound imaging[106,121], tendon length measurement has become cheaper and more clinically viable than its MRI[117,122,123] and ultrasound-with-motion-capture[13] predecessors. Therefore, the purpose of this study is to establish the relationship between weight bearing and recovery of tendon structure and functional performance (heel-rise and jump tests) within 6-months post-injury using non-invasive, ultrasound-based assessment of tendon structure. Specifically, we hypothesized that tendon structure (mechanical properties and geometry) would increase between 4-weeks and 6-months post injury/surgery. We also hypothesized that individuals with greater weight bearing days would perform better during heel-rise and jump tasks and show greater tendon cross-sectional area and mechanical properties (i.e. shear modulus, viscosity, and dynamic shear modulus) and less tendon elongation at 12-weeks post injury/surgery. Finally, we hypothesized that individuals who were weight bearing by 6-weeks post injury/surgery would have a smaller difference in tendon structure between the healthy and injured side at the 6-month follow-up.

3.2 Methods

Participants within the first month following unilateral Achilles tendon rupture were recruited for this study from local orthopaedic practices. Individuals were excluded if they were under the age of 18 or had a history of collagen vascular disorders, peripheral neuropathy, or peripheral vascular disorders. This study was performed with the permission of the University of Delaware Institutional Review Board and all participants gave their informed consent. Participants were followed longitudinally, with assessments at 4, 8, 12, and 24 weeks after time of injury if managed non-surgically or after surgery if managed surgically. All assessments and ultrasound measurements were performed by a single examiner.

Tendon structure and mechanical properties as well as self-reported outcome measures were assessed at all time points. Participant weight bearing was assessed via participant interview for the first 12 weeks. For functional performance, the heel-rise test was assessed at 12 and 24 weeks and jump testing was performed at 24 weeks.

3.2.1 Assessment of weight-bearing

Onset of weight-bearing was assessed by patient interview. Participants self-reported when they began putting their full body weight on their injured limb for activities such as walking. Weight-bearing days was defined as the number of days between when the participant began weight-bearing and the 12-week time point. Participants were also divided into two groups based on the time that they initiated weight bearing. The group of individuals that initiated weight bearing by 6 weeks post injury/surgery was classified as "typical." The group of individuals that initiated weight bearing after 6 weeks post injury/surgery was classified as "delayed." This time frame was a conservative standard based on a systematic review regarding early weight bearing, which defined a typical weight bearing control group as a group that began weight bearing after 4 weeks[124].

3.2.2 Measurement of tendon structure

Tendon structure was measured using B-mode ultrasound imaging at 10 MHz. Tendon length from the calcaneus to the gastrocnemius myotendinous junction was measured using extended field of view settings (GE Logiq e, GE Healthcare, WI, USA)[106,121]. Tendon cross-sectional area was measured by placing the ultrasound probe at the site of rupture in short axis. On the healthy side, cross-sectional area was measured in the free tendon at a location as similar to the injured side as possible. (Due to tendon lengthening, there were instances that the same exact location was not able to be used on the injured as the uninjured side as it was no longer in the area of the free tendon on the uninjured side.) In order to ensure the same site was assessed over time, the distance between the calcaneal notch and the region of interest both marked on the skin was taken using a tape measure. At follow-up visits, the calcaneal notch was identified using B-mode ultrasound and marked on the skin. A tape measure was then used to identify the appropriate region of interest.

3.2.3 Quantification of tendon mechanical properties

Tendon mechanical properties were quantified using continuous shear wave elastography (cSWE) as described by Cortes, et al[12]. cSWE is an ultrasound technique which uses an external actuator to propagate a shear wave along the length of the tendon. An ultrasound probe placed at the region of interest then images the linear displacement of the tissue, allowing the speed of wave propagation to be calculated. Using a biomechanical model, shear modulus and shear viscosity are estimated. The average of three trials was used in data analysis. This technique has been previously validated[12] and shown to be reliable[79,120].

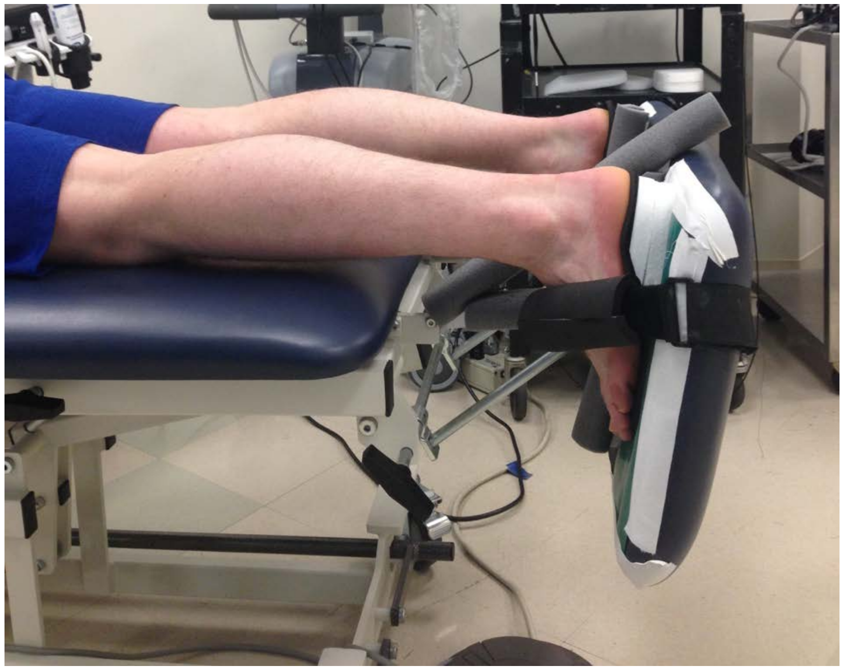

Figure 3.1: Participant positioning for continuous shear wave elastography with wedges.

Prior studies using cSWE have applied the technique to Achilles tendons following rupture[52,120], however, this is the first study to use cSWE in ruptured tendons in individuals that are still immobilized. Therefore, we did need to modify the foot position of the participant for safety purposes. At the 4-week time point, the participant was positioned in prone with wedging that approximated the amount of wedging used in their walking boot (Fig. 3.1). This same foot position was repeated at all following time points. Once the participant was able to safely position their foot in a plantigrade position, cSWE was repeated in both the wedged position as well as the standardized, neutral foot position as previously described[120]. To improve the comparison to other work using shear wave elastography, a combined measure of dynamic shear modulus at 400 Hz (shear $modulus_{400}$) was calculated from the shear modulus and viscosity using the following equation:

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

Where $\mu(\omega)$ is dynamic shear modulus, μ_1 is shear modulus, μ_2 is viscosity, and f is the frequency (400Hz in this case).

3.2.4 Assessment of functional performance

At all time points, participant self-reported outcome was measured using the Achilles tendon Total Rupture Score (ATRS)[49]. This is a 0 to 100 scale score where higher self-reported function is indicated by a higher score. The ATRS was used for descriptive purposes and is included along with participant age, sex, and side of injury.

All functional testing was performed on the right leg first in order to quasi-randomize injured sides. Beginning at the 12-week time point, calf strength and endurance was assessed using a heel-rise test as described by Silbernagel, et al[13,40]. In this test, participants stand on a 10 degree slant box and perform unilateral heel-rises at a cadence of 30 per minute until fatigue. A linear encoder (MuscleLab™, Ergotest Technology, Norway) taped to the participant's heel was used to measure the maximum heel-rise height, number of repetitions, and total heel-rise work (= total linear displacement * body weight). Performance on the heel-rise test has been found to relate to improved functional prognosis[9]. Prior work by Olsson et al., has found that at 12 weeks post injury, only 50% of individuals are able to complete a single leg heel-rise[10]. Therefore, individuals were classified as being either "able" or "unable" to perform a single leg heel-rise at the 12-week time point.

Jumping ability was assessed at the 24-week time point[14]. Participants completed three jumping tasks. The first was a unilateral jump for height, called a counter movement jump (CMJ). Participants were instructed to stand on one leg with hands behind their back and jump as high as possible. A light mat (MuscleLab™, Ergotest Technology, Norway) was used to measure flight time, which was converted to jump height. The average jump height of three trials on each side were included in data analysis, testing was completed alternating legs to avoid fatigue.

Participants were then asked to complete a repetitive jumping task, called hopping. In this task, participants were to rhythmically jump at a self-selected pace "like jumping rope." Jump height, frequency, and plyometric quotient (= flight/contact time) averaged across two trials was used for data analysis.

Finally, participants completed a drop counter movement jump (drop CMJ). In this task, participants were asked to stand on a 20 cm box on one leg and with hands behind their back. They were then instructed to drop off of the box and, upon landing, perform a single jump for height. The average jump height of three trials was used for data analysis.

3.2.5 Statistical analysis

Descriptive statistics were calculated for all variables of interest. Data was inspected to ensure it fit the assumptions of parametric statistical testing. To determine change in mechanical properties over time, a within subject analysis of variance (ANOVA) was used with post hoc pairwise comparisons using a Bonferroni correction. To identify whether higher amounts of weight bearing days at the 12-week time point improves functional performance, an independent samples t-test was used to compare the number of weight bearing days during the first 12 weeks following injury/surgery between those participants able versus unable to perform a single leg heel-rise at the 12-week time point. To determine the strength of the relationship between number of weight bearing days and patient limb symmetry indexes (LSI = ruptured value/uninjured value * 100%) on the heel-rise test and jumping tests at the 24-week time point, a pearson's correlation was used. Pearson's correlation was also used to determine the strength of the relationship between weight bearing days and tendon cross-sectional area, shear modulus, viscosity, and shear $modulus_{400}$ on the injured side as well as tendon elongation at the 12-week time point. Finally, an independent samples t-test was used to identify differences in tendon structure at the 24-week time point between participants in typical versus delayed weight bearing groups.

Effect sizes were also calculated. For change over time, partial eta squared was used to estimate effect size. As there are no currently accepted guidelines within rehabilitative medicine for interpretation of partial eta squared, the suggestions for interpretation reported by Morris & Fritz[125] were used as they are more conservative than those originally reported by Cohen[126]. A partial eta squared of at least 0.08 indicates a small effect, at least 0.18 a moderate effect, and at least 0.41 a large effect. For correlation analysis, the r value was used to determine effect size with values greater than or equal to 0.10 indicating a small effect, greater than or equal to 0.30 indicating a moderate effect, and greater than or equal to 0.50 indicating a large effect[127]. For t-tests, Cohen's d is reported, with values of at least 0.2 indicating a small effect, 0.5 indicating a moderate effect, and 0.8 indicating a large effect[125,127].

3.3 Results

Twenty-three participants (19 male, 3 female) with a mean(SD) age of 39(11) years were included in this study. Eleven participants had ruptured their right Achilles tendon, 12 had ruptured their left. Eighteen participants had been managed surgically, 5 were managed non-surgically. Participants demonstrated a mean(SD) of 60(21) weight bearing days by the 12-week time pint. By the 24-week time point, participants reported a mean(SD) score of 82(15) out of 100 possible points on the ATRS. The 4-week time point was completed a mean(SD) of 31(5) days; the 8-week, 60(6) days; the 12-week, 90(7) days; and the 24-week, 180(14) days following injury/surgery. Seven participants were recruited for the study having missed the 4-week time point. One participant dropped out of the study due to geographic reasons after the 12-week time point, a second participant was not able to attend the 24-week time point. Therefore, data from 18 participants is included in the 4-week time point, 23 participants in the 8 and 12-week time points, and 21 participants in the 24-week time point.

3.3.1 Tendon structural changes over time

Descriptive statistics for tendon structure and results of the ANOVA are displayed in Table 1. Complete cSWE datasets were available for 13 participants as there was a hardware concern with the ultrasound scanner, which took one month to resolve due to awaiting part delivery. Ruptured tendons had lower shear modulus and viscosity at all time points ($p<0.001$) with a small effect size for time (shear modulus partial η^2= 0.120; viscosity partial η^2= 0.100) and a non-significant interaction term (Table 3.1). Differences between sides exceeded measurement error for both shear modulus and viscosity at all time points.

	4 weeks		8 weeks		12 weeks		24 weeks		P-values and effect size (partial eta squared) for main effects		
	Injured	Uninjured	Injured	Uninjured	Injured	Uninjured	Injured	Uninjured	Time point	Side	Time*side
Shear Modulus (kPa)	65.3(14.0) n=16	89.8(20.1) n=16	76.6(18.2) n=21	98.8(19.3) n=21	72.1(19.3) n=22	95.4(17.6) n=22	84.0(19.5) n=21	97.9(18.1) n=21	0.196 η_p^2=0.120	<0.001* η_p^2=0.671	0.984 η_p^2=0.004
Viscosity (Pa*s)	23.9(10.6) n=16	46.7(8.5) n=16	25.9(11.6) n=21	46.7(14.5) n=21	29.5(16.5) n=22	47.6(3.0) n=22	27.9(9.3) n=21	46.0(12.1) n=21	0.278 η_p^2=0.100	<0.001* η_p^2=0.723	0.731 η_p^2=0.035
Shear $Modulus_{400}$ (kPa)	105.7(34.5) n=16	185.0(33.3) n=16	116.3(39.3) n=21	190.4(49.1) n=21	142.8(39.0) n=22	209.8(30.8) n=22	125.3(33.4) n=21	186.6(43.7) n=21	0.003* η_p^2=0.321	<0.001* η_p^2=0.830	0.824 η_p^2=0.024
Cross-sectional area (cm^2)	2.12(0.91) n=16	0.65(0.15) n=16	2.27(1.19) n=22	0.60(0.11) n=22	3.21(1.17) n=23	0.61(0.13) n=23	3.41(0.94) n=21	0.62(1.12) n=21	<0.001* η_p^2=0.585	<0.001* η_p^2=0.825	<0.001* η_p^2=0.615
Length to gastrocnemius (cm)	21.89(2.90) n=18	20.85(2.24) n=18	22.09(3.34) n=23	20.87(2.60) n=23	22.37(2.87) n=23	20.88(2.36) n=23	22.51(2.91) n=21	21.12(2.36) n=21	0.064 η_p^2=0.147	0.009* η_p^2=0.374	0.723 η_p^2=0.029

Table 3.1: Tendon structural changes over time. * Indicates a p-value < 0.05

When considering these two properties combined in the shear $modulus_{400}$ measure, ruptured tendons had significantly lower shear $modulus_{400}$ at all time points ($p<0.001$), with shear $modulus_{400}$ increasing over time ($p=0.003$) (Figure 3.2). There was no significant interaction between injured/uninjured side and time. Side to side differences exceeded measurement error at all time points and change in shear $modulus_{400}$ between 8-12 and 12-24 week time points exceeded the MDC on both sides. Ruptured tendons also had a larger cross-sectional area than uninjured tendons which increased over time ($p<0.001$ for main effect of injured/uninjured side and time and for interaction term), with statistically significant changes in tendon cross sectional area occurring between 8 and 12-weeks post-rupture ($p<0.01$) (Figure 3.3). Side to side differences exceeded measurement error at all time points, and change in tendon cross sectional area exceeds the MDC on the ruptured side between each follow-up time point. Ruptured tendons were longer than uninjured tendons ($p=0.009$), which exceeded measurement error, with a small effect size for time ($\eta^2 = 0.147$) and a non-significant interaction term (Figure 3.4).

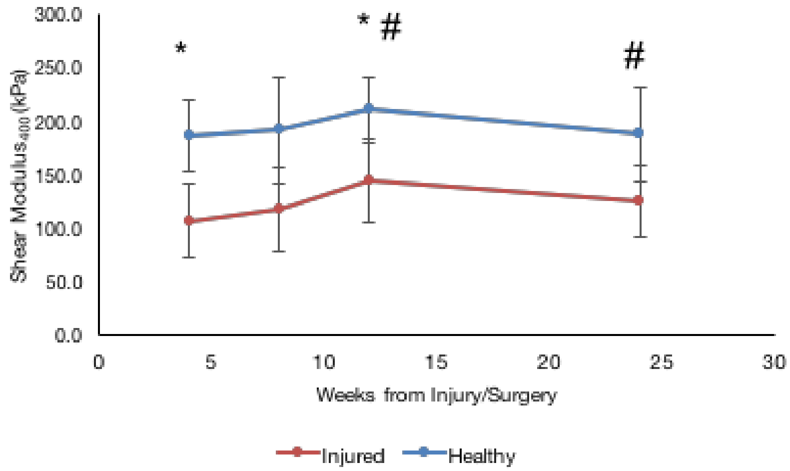

Figure 3.2: Changes in shear modulus400 (μ_{400}) over time. Symbols indicate pairwise comparisons with $p<0.05$.

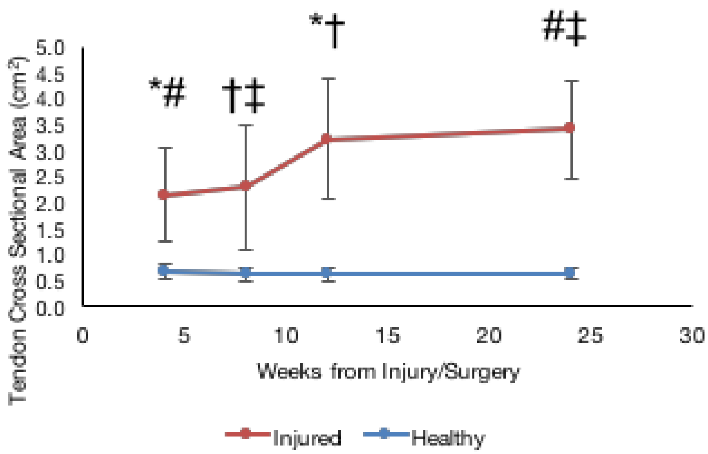

Figure 3.3: Changes in tendon cross-sectional area over time. Symbols indicate pairwise comparisons with $p<0.05$.

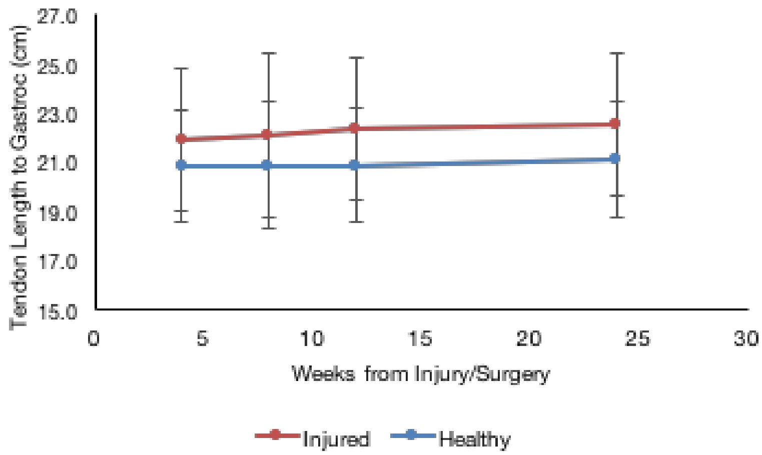

Figure 3.4: Changes in tendon length over time. Gastroc – gastrocnemius myotendinous junction.

3.3.2 Association of weight bearing with patient function

There were 4 participants of the 23 who were able to perform a unilateral heel-rise at the 12-week time point. By the 12-week time point (time point when the heel-rise test was assessed), participants able to perform a unilateral heel-rise had a mean(SD) of 55.0(28.6) weight bearing days, and participants unable to perform a unilateral heel-rise had a mean(SD) of 61.0(20.2) weight bearing days. There were no differences in number of weight bearing days between participants able versus unable to complete a unilateral heel-rise at 12 weeks (p=0.62). There was no relationship between number of weight bearing days at 12 weeks and total work limb symmetry index at 24 weeks (r=-0.095, n=20).

Descriptive statistics for patient performance with functional testing is included in Table 3.2. There were no statistically significant relationships between weight bearing days and LSI for CMJ height (r=0.149, n=19) or hopping plyometric quotient (r=0.243, n=18). Greater weight bearing days was associated with improved drop CMJ height LSI (r=0.502, p=0.034, n=18).

	Injured	Uninjured	LSI (%)	p-value
Heel-rise Test Total Work (J) (n=20)	1204(862)	2383(855)	47.8(25.7)	<0.001*
CMJ height (cm) (n=19)	8.1(4.8)	11.1(5.1)	70.5(18.9)	<0.001*
Hopping PQ (n=18)	0.34(0.15)	0.45(0.14)	79.0(34.3)	0.021*
Drop CMJ height (cm) (n=18)	7.2(4.9)	9.4(4.5)	76.4(37.9)	0.030*

Table 3.2: Participant functional performance on clinical testing at 24-weeks. Values indicate mean(SD). LSI – limb symmetry index, CMJ – counter movement jump, PQ – plyometric quotient. *Indicates a p-value < 0.05

3.3.3 Association of weight bearing with tendon structure

There were no statistically significant relationships between weight bearing days at 12 weeks and tendon elongation (r=0.015) or shear $modulus_{400}$ LSI (r=0.074) at 12 weeks. Participants with higher weight bearing days at the 12-week time point demonstrated smaller tendon cross-sectional area LSI (r=-0.427, p=0.042) at 12 weeks. There were no differences between typical and delayed weight bearing groups at 24 weeks with regard to shear $modulus_{400}$ LSI (p=0.395), elongation (p=0.270), or cross-sectional area LSI (p=0.234) (Table 3.3).

	Typical (n=13)	Delayed (n=8)	p-value	Cohen's d
Shear $modulus_{400}$ LSI (%) (n=21)	73.9(22.4)	64.9(24.4)	0.395	0.384

Cross-sectional area LSI (%) (n=21)	526.0(177.8)	609.8(91.4)	0.234	0.381
Elongation (cm) (n=21)	1.76(1.27)	0.79(2.63)	0.270	0.470

Table 3.3: Tendon structural characteristics at 24-weeks in typical compared to delayed weight bearing groups. Values indicate mean(SD). LSI – limb symmetry index.

3.3.4 Surgical subgroup analysis

When comparing surgically versus non-surgically managed patients, statistically significant differences between groups were observed for tendon cross sectional area LSI at 4 (surgical mean(SD): 3.77(1.43), non-surgical: 2.17(0.35), p = 0.002), 8 (surgical: 4.06(1.39), non-surgical: 2.42(0.96), p = 0.015), and 12 weeks (surgical: 6.16(1.16), non-surgical: 3.73(1.06), p = 0.001). There were also statistically significant differences in number of weight bearing days (surgical: 53.0(18.5), non-surgical: 84.8(5.5), p < 0.001). There were no differences between patients managed surgically compared with non-surgically with regard to tendon mechanical properties, elongation, or functional performance LSI. In order to ensure that the combining of both surgically and non-surgically managed participants did not affect the outcome of this study, a survival analysis was performed including only the surgically managed patients with regard to cross-sectional area change over time and weight bearing analyses.

Similar to the total group, there were statistically significant main effects for time ($p < 0.001$, η^2=0.638) and side ($p < 0.001$, η^2=0.908), with a significant interaction term ($p < 0.001$, η^2=0.665). Pairwise comparisons again showed an increase in tendon cross sectional area between 8 and 12 weeks.

There were no significant differences in weight bearing days between those able compared to those unable to perform a heel-rise at 12 weeks in patients managed surgically (able mean(SD): 55.0(28.6) days, unable: 52.4(16.0) days, p-value = 0.815). There were no statistically significant relationships between weight bearing days and performance on functional testing at 24 weeks (Pearson's r range: -0.009-0.34; p-value range: 0.223-0.973). The drop CMJ had the strongest relationship to weight bearing days, but this was not statistically significant (r = 0.34, p = 0.223).

With regard to early versus late weight bearing groups in surgically managed patients only, there were no relationships between weight bearing days and tendon structure at 12-weeks (Pearson's r range: -0.046-0.279, p-value range: 0.241-0.855). Additionally, there were no significant differences between early and late weight bearing groups with regard to any tendon structural property at 24-weeks (p-value range: 0.373-0.848).

3.4 Discussion

The results of this study suggest that after Achilles tendon rupture, the healing tendon has structural alterations that change over time. The most robust measures to track patient progress within the first 24 weeks may be tendon cross-sectional area this measure shows between limb differences and increases over time only on the ruptured side. Shear $modulus_{400}$ does show side-to-side differences and change over time, however, it seems that both the ruptured and uninjured side change similarly over time. In this study, tendon length shows between limb differences, with a small effect size for change over time. We found moderate to large relationships between weight bearing days early in recovery and tendon structure or patient function at 24 weeks, with higher amounts of weight bearing days being associated with a smaller relative tendon cross-sectional area and improved drop counter movement jump performance.

Interestingly, pairwise comparisons between time points showed significant changes in tendon cross-sectional area between the 8 and 12-week time point, which captures a period when participants were initiating weight bearing and also discontinuing use of the walking boot. It may be, therefore, that discontinuing the walking boot in addition to initiation of weight bearing is what results in the cross-sectional area changes associated with formation of a healing callus. Prior animal studies have related weight bearing to callus formation[54], so it would seem counterintuitive to not see the same trend in humans. The results of a study by Sandberg and colleagues[118], however, suggest that the forefoot, and consequently the Achilles tendon, is loaded very little in a walking boot with wedges. Putting this together with the findings of the current study, it may be reasonable to conclude that the tendon is loaded very little with weight bearing in a boot with wedges and so there were limited associations with weight bearing onset and structural or functional outcomes, however, if we were to control for the time of discontinuation of the walking boot, these relationships may be stronger.

With regard to performance on the heel-rise test (total work), CMJ, and hopping, no relationship was observed between weight bearing days at 12 weeks and function at 24 weeks. It may be either that similar concerns regarding the use of weight bearing rather than discontinuation of immobilization may be at play here as well. Alternatively, it may be that the effect of weight bearing in the first 12 weeks washes out by 24 weeks. The only functional task that did not fit this trend was the drop counter movement jump, as participants who had greater weight bearing days by

12 weeks were able to jump at a height more similar to their uninjured side at 24 weeks. Prior studies have pointed out that this particular task is one that is challenging to this population[20], and anecdotally it seems that participants are hesitant to perform this task. It may be that participants with a greater amount of weight bearing experience may or may not have better function of their musculotendinous unit, but may also be less hesitant to perform this particular task. Further investigation into this relationship may provide interesting insight into the complex relationships between patient perception of a task and functional performance. Additionally, it does seem that non-surgically managed participants may have been driving the relationship between weight bearing days and drop CMJ performance, so this finding needs to be interpreted with caution.

From a technical standpoint, this study does provide support for the use of ultrasound based measures in the assessment of patient progress after Achilles tendon rupture. Tendon cross-sectional area[82] at the site of rupture as well as tendon length[32,51] seem to be responsive to change over time and have previously been shown to relate to patient function[9,13,26], respectively.

With regard to the use of elastography, it seems that using shear modulus and viscosity measured via cSWE may be very sensitive to subtle changes in the tendon, increasing variability and decreasing the robustness of this measure. However, when taken together in combination, we may have a more robust measure that could potentially be used to track the early healing trajectory. This measure is considered to be more comparable to the shear elasticity measure provided by commercially available shear wave elastography scanners, and the results of this study provide similar values and change over time in ruptured Achilles tendons reported by Zhang, et al[55]. The use of cSWE to calculate shear $modulus_{400}$ did allow for measurement of shear $modulus_{400}$ on the uninjured side. We did find similar changes in shear $modulus_{400}$ on both ruptured and uninjured sides, however. It may be that as individuals are changing weight bearing status and beginning strength training in rehabilitation that both sides respond to these changes in tendon loading.

This study is limited by small sample size, which is compounded with concerns regarding missing data. Additionally, the population studied is heterogeneous with regard to sex, age, and treatment strategy. While this may result in large variability, it does make the findings more generalizable to the population of individuals with Achilles tendon rupture. This study did rely on participant self-report for weight bearing onset and did not record wedge height or gait symmetry at the time of weight bearing onset. These limitations may have impacted our ability to observe the effect of weight bearing on tendon structure and functional performance. Despite these limitations, this study does provide novel, preliminary data in an immerging body of literature regarding the clinical usage of ultrasound to track soft tissue healing and supports further study.

Clinically, the results of this study suggest that weight bearing within the first 6 weeks following injury/surgery is not detrimental to tendon healing from a tendon structure or patient function standpoint. It is possible that weight bearing within this time frame may provide some small clinical benefit within the first 6 months of recovery with regards to jumping performance. It does seem like discontinuing immobilization and its effect on the loads placed on the Achilles tendon may play a role in tendon structural changes, but additional studies supporting this suggestion are warranted before incorporating ultrasonographic findings into the clinical decision making process.

Chapter 4

TIMING OF MUSCLE ACTIVATION ONSET DIFFERS BY MUSCLE AND TASK IN INDIVIDUALS WITH ACHILLES TENDON REPAIR

4.1 Introduction

Achilles tendon rupture is a traumatic injury which leads to long term deficits in plantar flexor function[23,24]. As re-rupture rates are reported to be less than 10%[17], patient functional outcomes are becoming more of a focus when assessing patient success following injury. It is concerning that deficits in plantar flexor function seem to improve significantly within the first year after injury, but deficits in strength, heel-rise performance, and plantar flexor power during dynamic tasks have the tendency to become permanent[8,23,24]. In fact, studies have identified focal deficits in plantar flexor strength at 10 or more years following rupture[23,24]. Furthermore, recent studies have identified altered ankle kinetics and kinematics as well as a shift of lower extremity power generation during running and jumping tasks from the ankle to the knee in individuals an average of 6 years following rupture[9,19].

There have been a few suggested mechanisms underlying these deficits in plantar flexor function, both at the tendon and the muscle level. Lengthening of the Achilles tendon, which typically occurs within the first 12 weeks following injury, has been found to relate to poor performance on isolated calf strength testing[9,13,128], altered biomechanics with jogging and jumping 6 years following injury[9], and poor patient outcomes[11,32]. Also at the tendon level, tendon mechanical properties have been found be altered following rupture[27,55,57] and to relate to performance on strength testing[61,120].

From a muscular standpoint, lower muscle volumes in the triceps surae[117,122,129] and fatty infiltration of the soleus muscle has been found to relate to decreases in plantar flexor strength[129].

The musculotendinous unit is a dynamic system in which a delicate interplay between components, so with advancements in assessing the structure of both the healing tendon and muscle, it is of interest to identify the relationship of tendon structure to muscle function. Prior work has noted changes in muscle fascicle length and pennation angle in individuals following Achilles tendon rupture, which may be a structural compensation at the muscle level for tendon lengthening[130]. Furthermore, tendon elongation has been found to relate to atrophy of the medial gastrocnemius and soleus[117]. Healing Achilles tendon also seems to respond to larger muscle torques, with increased tendon cross-sectional area relating to larger triceps surae muscle cross-sectional area[131].

From a functional standpoint, is seems that the triceps surae musculature are consistently more metabolically active following Achilles tendon rupture[87,132,133]. Given this increase in metabolic activity, it is not surprising that studies using electromyography have found differences in muscle activity in individuals with Achilles tendon injury. In individuals with Achilles tendon rupture, the gastrocnemius has been found to increase activity during the stance phase of gait suggested to be in response to tendon lengthening[26]. Medial gastrocnemius activity has also been suggested to relate to tendon mechanical properties during a bilateral jumping task[48]. There is also evidence to suggest temporal modulation of muscle activity in response to tendon dysfunction. In a study of individuals with Achilles tendinopathy, Chang and Kulig[56] identified earlier muscle onset in individuals as a compensation for decreased tendon mechanical properties during a hopping task.

Taken together, it seems that there are two primary mechanisms by which an individual can accommodate for tendon dysfunction following Achilles tendon rupture. The first is to offload power generation from the ankle joint to more proximal joints. The second is to allow the triceps surae muscle to adapt from both a structural and functional standpoint to accommodate for tendon dysfunction. In tandem, these adaptations allow for successful completion of a given task.

Despite these findings, there are limitations innate in the methodologies used in the available literature. In particular, there are significant concerns regarding the quantification of tendon mechanical properties in the context of Achilles tendon rupture. Young's Modulus of the tendon is commonly quantified by measuring linear displacement of the tissue during a voluntary contraction against a given load. This technique assumes the plantar flexion torque is coming from the Achilles and the torque produced by the deep compartment of the lower leg is negligible. While this may be a valid assumption in healthy individuals, in the context of Achilles tendon rupture there is growing evidence that the flexor hallucis longus compensates for gastrocsoleal atrophy or inhibition, which would artificially inflate Young's Modulus values[117,119]. Recent work using shear wave elastography techniques as allowed for the quantification of Achilles tendon viscoelastic properties[55,64,72]. Specifically, continuous shear wave elastography has been developed[12,79] and applied to a population of individuals following Achilles tendon rupture[52,120].

In addition to concerns regarding measurement of tendon mechanical properties, the relative contribution of tendon mechanical properties and tendon structural characteristics, such as tendon length, to patient performance with dynamic tasks is unclear. It has been suggested in modelling studies that tendon length rather than tendon mechanical properties would have greater implications on tendon stress[33], but this has not been assessed in injured individuals. Therefore, the purpose of this study is to identify adaptations at the muscle-level which accommodate for tendon dysfunction (tendon elongation or decreased viscoelastic properties) between one and three years post-injury.

4.2 Methods

Two groups of individuals were included in this study – those with a history of unilateral Achilles tendon rupture and those with healthy tendons. Participants without Achilles tendon pain or injury were included in the healthy group. Participants were excluded from the healthy group if they had current Achilles tendinopathy, signs of tendinosis (defined as thickening of the Achilles tendon on ultrasound imaging), or had a current injury limiting their ability to comfortably jump unilaterally. Participants were included in the rupture group if they were 1-3 years post unilateral Achilles tendon rupture with surgical repair. Participants were excluded from the rupture group if they had a history of post-operative complications (deep wound infection) and if their ability to comfortably jump unilaterally was limited by pain or injury aside from their Achilles tendon rupture.

All participants attended a single assessment session in which all testing procedures were completed. For the purposes of describing participant self-reported symptoms/function, the rupture group completed the Achilles tendon Total Rupture Score (ATRS)[49], and the healthy group completed the Victorian Institute of Sport Assessment – Achilles Questionnaire (VISA-A)[134]. In order to describe participant activity level, all participants completed the Physical Activity Scale (PAS)[109,135], which is a 6-point scale with higher scores indicating higher activity levels. This study was conducted with the approval of the University of Delaware Institutional Review Board and all participants gave their informed consent prior to participating.

4.2.1 Measurement of tendon geometry and mechanical properties

Tendon geometry was assessed using B-mode ultrasound imaging at 10 MHz. Tendon length was measured from the calcaneal notch to the gastrocnemius myotendinous junction using extended field of view settings (GE Logiq e, GE Healthcare, Wisconson, USA)[106,121]. Tendon cross-sectional area was measured in short axis using a standoff pad for improved visualization. Cross-sectional area was measured at the approximate rupture site on injured limbs and at a point on the free tendon immediately distal to the soleus myotendinous junction in healthy limbs[120]. The average of three measures was used in analysis for tendon length and cross-sectional area.

Tendon mechanical properties were assessed using continuous shear wave elastography as described by Cortes, et al[12]. This technique uses an external actuator to propagate a shear wave along the length of the tendon. High frequency ultrasound is used distally to track linear displacement of the tendon tissue. Wave speed is calculated and tendon shear modulus and viscosity is estimated using the Voigt model[12]. This technique has been previously found to be valid and reliable[79,120] and has been used in individuals with Achilles tendon rupture[52,120]. It is possible to calculate dynamic shear modulus at 400Hz (shear modulus_{400}), which combines shear modulus and viscosity values and has yielded values similar to those reported in the literature from commercially available shear wave scanners. Therefore, to improve comparison to the available literature, the average shear modulus$_{400}$ of three trials for each tendon was used in analysis.

4.2.2 Dynamic functional testing

The test battery to evaluate lower leg function included a single leg heel-rise strength test as well as three jump tests – the drop counter movement jump (drop CMJ), counter movement jump (CMJ), and hopping. The jump tests have been utilized previously in the literature[14] and have been found to be valid and reliable for assessment of lower leg function in people with Achilles tendinopathy and Achilles tendon rupture[14,15,40]. The right leg was tested first in all participants, with repetitions during jumping tasks performed alternating sides.

For the heel-rise strength test, a modification of the heel-rise test as described by Silbernagel, et al.[9,13,40,136] was used for this study. Participants stood on a 10 degree slant board with 2 fingers touching a PVC pipe structure for balance (Figure 4.1). They then performed 5 unilateral heel-rises at a rate of 30 per minute, of which the middle 3 repetitions were used for data analysis. Auditory cues were provided for pacing using a metronome.

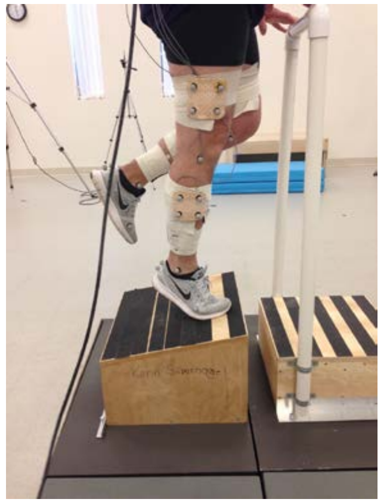

Figure 4.1: Heel-rise task.

Following heel-rise testing, participants performed three jump tests – first the drop CMJ, then the CMJ, and finally hopping. For the drop CMJ, participants stood on top of a 20 cm box with hands across their chest. Standing on a single leg, participants jumped off of the box onto a force plate and then performed a single maximum jump for height. For the CMJ, participants started standing unilaterally on a force plate and performed a single leg, maximum jump for height with arms across the chest. For both the drop CMJ and CMJ, participants completed 3 trials on each leg. For hopping, participants stood on a force plate with and performed rhythmic hopping like jumping rope on one leg for 25 repetitions. The middle 10 hops were used for analysis. Participants performed 2 trials on each leg. For all jumping tasks, participants were instructed to try and take off and land in the same place.

To synchronize EMG with participant movement as well as to evaluate performance on the lower leg functional test battery, motion capture was used. Retro-reflective markers were placed on the pelvis, hip, knee, ankle, and foot[137] (Figure 4.2).

Eight infrared-based, high-speed motion capture cameras recorded participant movement (Nexus, Vicon, United Kingdom) at 120 Hz. Ground reaction forces were measured using an in-ground force plate (Bertec Corporation, Ohio, USA) at a rate of 1080 Hz. Inverse dynamics was used to estimate ankle joint powers (Visual 3D, C-Motion, Maryland, USA). Biomechanical variables of interest included peak ankle plantar flexion angle for the heel-rise, peak concentric ankle power for the CMJ, and peak eccentric ankle power for the drop CMJ and hopping tasks.

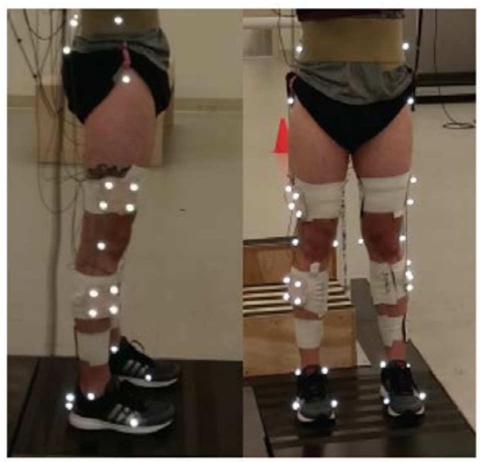

Figure 4.2: Marker placement

4.2.3 Assessment of muscle activity

To measure muscle activity, bipolar, wired, surface electrodes (Motion Systems, New Jersey, USA) were placed on the soleus and medial and lateral gastrocnemius following SENIAM guidelines[138,139]. Electromyography (EMG) was collected at 1080 Hz. The EMG signal was pre-amplified at the pick-up site. The signal was then filtered using a 30 Hz highpass and 350 Hz lowpass Butterworth filter.

The signal was then rectified and a 4 Hz Butterworth filter was used to create a linear envelope.

Onset times were determined using an automated Visual3D script. To determine the resting baseline of the signal, the average signal from a 100 ms portion of EMG signal was taken for each muscle with the patient standing statically. Thresholds and windows for onset were optimized in a small pilot group of individuals. For the heel-rise task, onset was defined as 3 times resting baseline within a window 500ms prior to the start of each heel-rise through the start of the heel-rise. For the CMJ and drop CMJ tasks, onset was also defined as 3 times the resting baseline. To account for the speed of the task but also anticipating that participants in the rupture group may have an electromechanical delay (EMD) exceeding that typically observed in healthy individuals, the window for activation was 450ms prior to peak knee flexion through toe off for the CMJ and 300ms prior to initial contact through initial contact for the drop CMJ. Muscle onset for the hopping task was defined as 2 times the resting baseline within 250ms prior to initial contact through initial contact. Electromechanical delay was defined as the time from onset of activation to the biomechanical even of interest.

4.2.4 Statistical analysis

Descriptive statistics were calculated for all variables in each group. Data was checked to ensure it met parametric assumptions using a Shapiro-Wilk test and Levene’s test for equality of variances. An independent samples t-test was used to compare values between the groups and paired samples t-test was used to compare values between limbs in the ruptured group. For tendon structural characteristics, values for the rupture relative to the uninjured side were calculated. For tendon length, tendon elongation was calculated by subtracting the value of the uninjured side from the ruptured side. For tendon shear modulus$_{400,}$ a limb symmetry index (LSI) was calculated (LSI=value of ruptured side/value of uninjured side *100%). Pearson's correlation was used to determine the relationship between tendon elongation and shear modulus$_{400}$LSI and EMD for each muscle with each of the tasks.

In order to compare groups regarding task performance, limb symmetries were calculated for biomechanical variables of interest. LSIs were calculated for the ruptured group as described above. For the healthy group, LSIs were calculated as (LSI = value of right side/value of left side *100%) for the first 5 participants and flipping the ratio with the value of the left side in the numerator for the second 5 participants. This was done to mitigate concerns regard learning effects as the right side was consistently tested first. An independent t-test was performed to compare LSIs between the ruptured and healthy groups. Effect size interpretation was reported with Cohen's d – 0.2 indicating a small effect, 0.5 a medium effect, and 0.8 a large effect[127].

4.3 Results

Ten individuals (5 male, 5 female) with a mean(SD) age of 35(7) were included in the healthy group and 11 individuals (10 male, 1 female) with a mean(SD) age of 44(9) were included in the rupture group. Participants in the rupture group were significantly older than those in the healthy group (p=0.02), however, groups were not significantly different with regard to body mass index (ruptured group: 25.9(3.2) kg/m^2, healthy group: 23.7(3.0) kg/m^2) or physical activity level on the PAS (ruptured group: 5.0(1.4), healthy group: 4.8(0.88)). Participants in the ruptured group had a mean(SD) ATRS score of 88.8(14.3), participants in the healthy group had a mean(SD) VISA-A score of 94.7(9.1).

Participants in the healthy group did not demonstrate any statistically significant differences between sides for tendon length to gastrocnemius (right: 18.7(2.6) cm, left:18.2(1.8) cm) or shear $modulus_{400}$ (right: 211.8(38.3) kPa, left: 222.5(36.4) kPa). Participants in the rupture group had significantly longer tendons on the ruptured side with a mean(SD) elongation of 1.8(0.73) cm and lower shear $modulus_{400}$ on the ruptured side with a mean(SD) LSI of 87.6(17.4)% (Table 4.1). Ensemble curves for biomechanical and EMG data are shown in Figure 4.3.

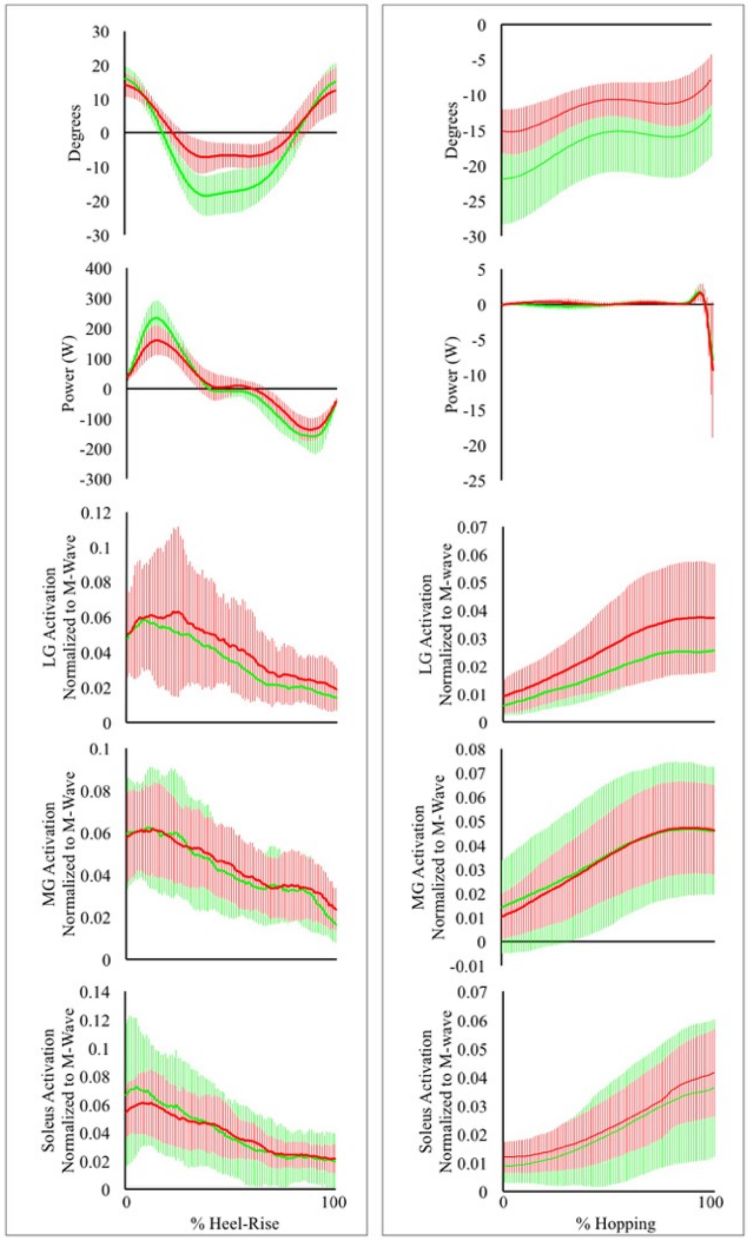

Figure 4.3: Ensemble curves for biomechanical and electromyography signals on injured and uninjured sides of the rupture group for the heel-rise and hopping tasks. Line indicates group mean and shaded area indicates standard deviation. Red indicates ruptured and green indicates uninjured sides. From top to bottom: ankle angle, ankle power, muscle activation for the lateral gastrocnemius (LG), muscle activation for the medial gastrocnemius (MG), and muscle activation for the soleus.

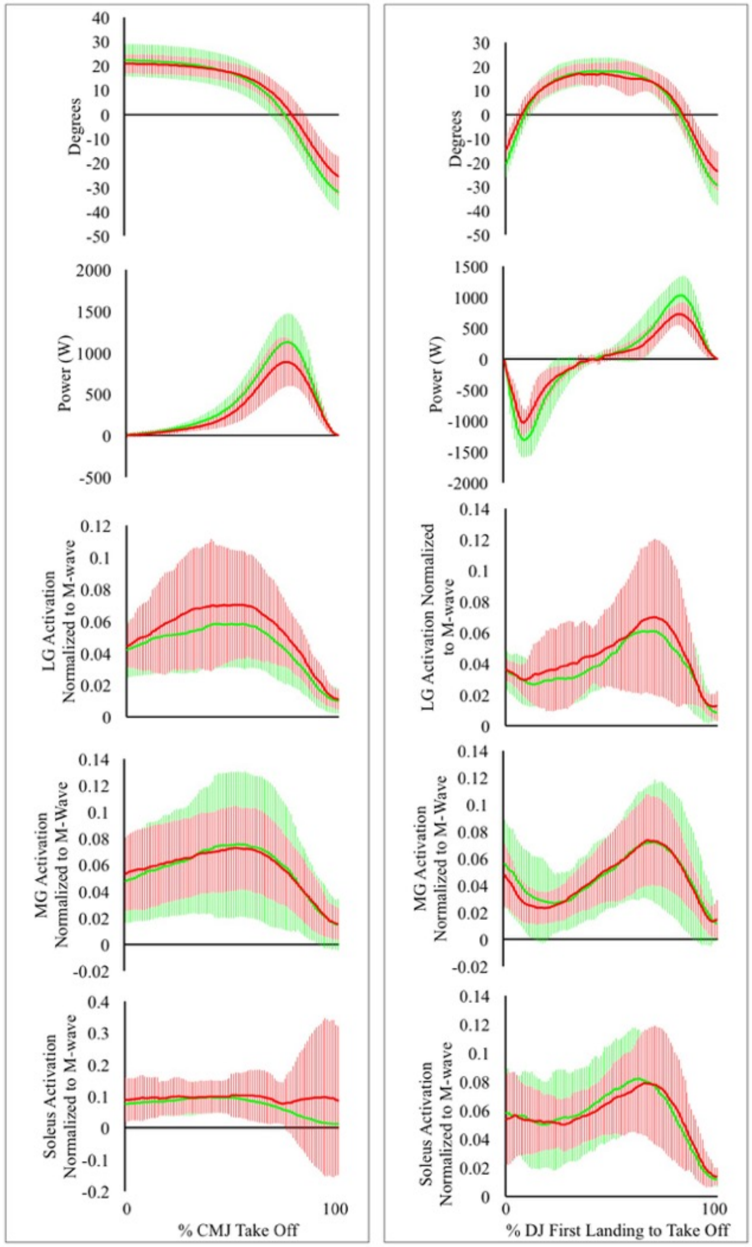

Figure 4.4: Ensemble curves for biomechanical and electromyography signals on injured and uninjured sides of the rupture group for the counter movement jump (CMJ) and drop counter movement jump (DJ). Line indicates group mean and shaded area indicates standard deviation. Red indicates ruptured and green indicates uninjured sides. From top to bottom: ankle angle, ankle power, muscle activation for the lateral gastrocnemius (LG), muscle activation for the medial gastrocnemius (MG), and muscle activation for the soleus.

	Ruptured (n=11)	Non-ruptured side (n=11)	Healthy group (n=10)	p-value†	Cohen's d†
Tendon length to gastrocnemius (cm)	22.4(1.3)	20.5(1.5)	18.2(1.8)	<0.001*	2.52
Tendon μ_{400} (kPa)	192.0(46.4)	222.8(49.9)	222.5(36.4)	0.024*	0.80

Table 4.1: Mean(SD) for tendon structural properties. * indicates p-value < 0.05. † indicates comparisons between ruptured and non-ruptured side in the injured group; ** comparisons between ruptured side in the injured group and the healthy group. μ_{400} – instantaneous shear modulus at 400Hz.

For the heel-rise task, EMG data was unable to be used in 2 of the participants in the ruptured group for the lateral gastrocnemius and in an additional participant for the medial gastrocnemius. There were no statistically significant within subject differences in EMD in the rupture group or when comparing the ruptured side to the healthy group in either the heel-rise or drop CMJ tasks (Table 4.2).

For the CMJ task, there were no statistically significant differences between ruptured and uninjured sides in the ruptured group (Table 4.2). However, when comparing the ruptured side to a healthy group, there were statistically significant differences in EMD in the medial gastrocnemius and soleus with the ruptured side demonstrating greater EMD in the medial gastrocnemius and shorter EMD in the soleus.

For the hopping task, participants in the ruptured group demonstrated longer EMD in the medial gastrocnemius on the ruptured side (Table 4.2). Longer EMD was also observed in the medial gastrocnemius as well as the lateral gastrocnemius when comparing the ruptured side to a healthy group.

	Ruptured (n=11)	Non-ruptured side (n=11)	Healthy group (n=10)	p-value†	Cohen's d†	p-value**	Cohen's d**
Heel-Rise Task							
LG	215.6(112.2) n=9	268.2(100.6)	236.4(92.7)	0.116	0.59	0.664	0.20
MG	282.6(88.2) n=8	262.5(59.2)	243.2(69.1)	0.654	0.17	0.302	0.50
Sol	155.1(80.2)	212.4(80.1)	181.4(59.4)	0.069	0.62	0.407	0.37
Counter Movement Jump							
LG	577.3(92.9)	590.2(87.4)	631.5(82.0)	0.640	0.15	0.174	0.49
MG	559.2(69.7)	509.6(101.4)	474.4(57.1)	0.134	0.49	0.007*	1.33
Sol	500.5(75.2)	573.5(62.9	605.4(104.3)	0.060	0.64	0.015*	1.15
Drop Counter Movement Jump							
LG	179.4(26.4)	190.3(30.3)	174.2(26.8)	0.302	0.33	0.656	0.20
MG	202.0(27.4)	196.6(24.8)	185.4(30.4)	0.314	0.32	0.204	0.57
Sol	127.5(45.8)	155.8(42.3)	147.5(57.9)	0.053	0.66	0.389	0.38
Hopping							
LG	125.5(13.7)	117.3(25.1)	90.6(27.3)	0.277	0.35	0.001*	1.62
MG	139.3(13.0)	125.8(13.3)	120.0(24.1)	0.004*	1.20	0.039*	1.00
Sol	71.1(34.0)	67.6(24.3)	50.1(23.5)	0.743	0.10	0.121	0.72

Table 4.2: Mean(SD) from time between muscle activation onset and biomechanical event (electromechanical delay). * indicates p-value < 0.05. † indicates comparisons between ruptured and non-ruptured side in the injured group; ** comparisons between ruptured side in the injured group and the healthy group. Number of participants is indicated by column, exceptions are listed within the cell.

Higher amounts of tendon elongation had a statistically significant, moderate relationship to greater EMD in the lateral gastrocnemius with a hopping task (Figure 4.4). There were also small to moderate relationships observed with the medial gastrocnemius and soleus in the hopping task, but these relationships were not statistically significant. A moderate inverse relationship was observed in the CMJ between both the lateral gastrocnemius and tendon elongation, though, this relationship was not statistically significant (Table 4.3). Greater limb symmetry for tendon shear modulus$_{400}$ was related to longer EMD for the soleus in the heel-rise task (Figure 4.5). There was also a moderate relationship between tendon shear modulus$_{400}$ LSI and longer soleus EMD in the CMJ.

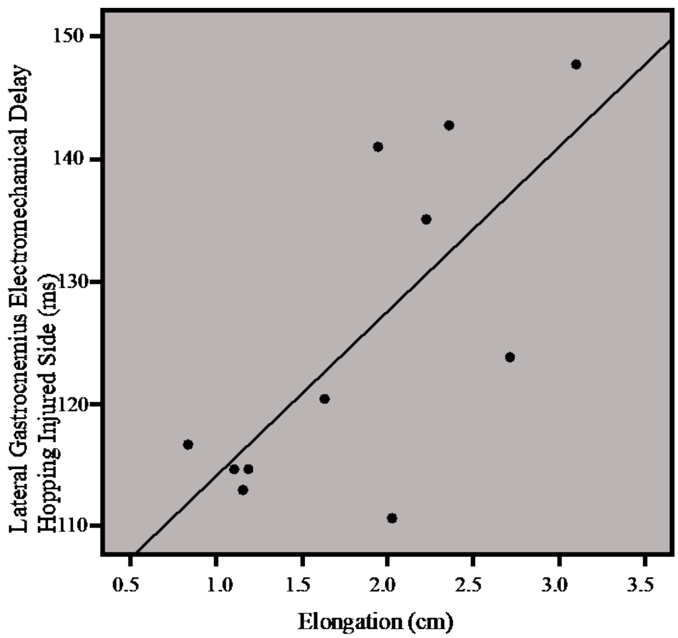

Figure 4.4: Relationship between tendon elongation and electromechanical delay in the lateral gastrocnemius, injured side during hopping task.

	Elongation	μ_{400} LSI
Heel-Rise Task		
LG	-0.237 N=9	0.004 N=9
MG	-0.252 N=8	-0.485 N=8
Sol	0.007	0.683*
Counter Movement Jump		
LG	-0.508	-0.145

MG	-0.442	-0.021
Sol	0.035	0.550
Drop Counter Movement Jump		
LG	0.321	-0.037
MG	-0.151	0.097
Sol	0.484	0.398
Hopping		
LG	0.723*	-0.267
MG	0.550	0.276
Sol	0.485	0.339

Table 4.3: Pearson's correlation *r* values between muscle electromechanical delay and tendon elongation, dynamic shear modulus at 400Hz limb symmetry index (μ_{400} LSI). N =11 unless otherwise noted. * indicates $p < 0.05$

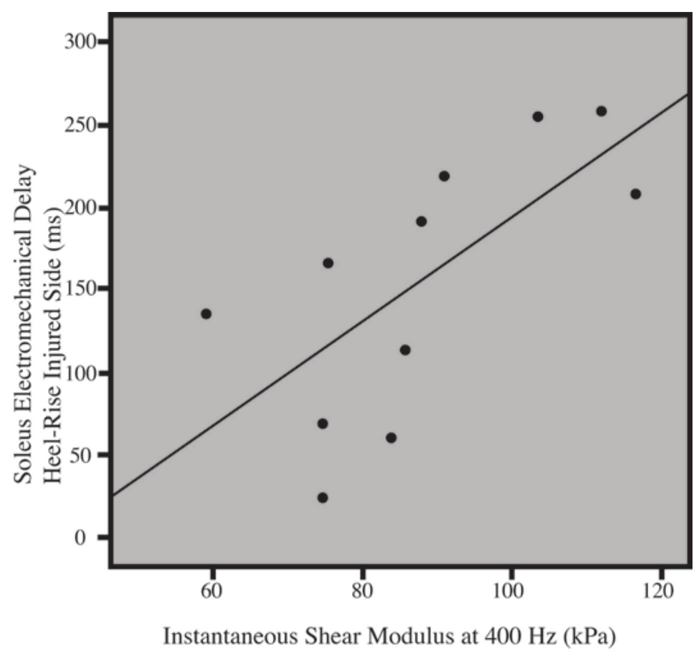

Figure 4.5: Relationship between dynamic shear modulus at 400Hz (μ_{400}) and electromechanical delay in the soleus, injured side during a heel-rise task.

There were statistically significant differences in peak plantar flexion angle LSI with the heel-rise task between the ruptured and healthy groups (p=0.014, mean(SD): ruptured group 99.8(2.5)%, healthy group 107.3(8.8)%). There were no statistically significant differences in peak concentric ankle plantar flexion power in the CMJ task between groups (p=0.895, mean(SD): ruptured group 99.0(4.4)%, healthy group 99.3(3.7)%). There were statistically significant differences in peak eccentric plantar flexion power in the drop CMJ task (p=0.046, mean(SD): ruptured group 98.7(3.0)%, healthy group 104.1(7.7)%) but not in the hopping task (p=0.435, mean(SD): ruptured group 103.3(29.1)%, healthy group 92.7(31.4)%).

4.4 Discussion

The results of this study suggest that there are changes in triceps surae activation following Achilles tendon rupture that differ with task and by muscle. Differences in EMD were most pronounced when comparing the ruptured side to the healthy group, and achieved statistical significance only in the CMJ and hopping tasks. Muscle onset of the lateral gastrocnemius related to tendon elongation in the hopping task, and muscle onset of the soleus with tendon mechanical properties in the heel-rise task.

In a study by Chang and Kulig, more pronounced differences were observed between injured and healthy groups as opposed to within subject in a group of individuals with Achilles tendinosis[56]. A similar trend was observed in the present study with the effect of rupture on muscle EMD ranges from none to moderate when comparing the ruptured to uninjured side within subject. When comparing to a healthy group, however, these differences are more pronounced with a small to large effect size.

When comparing EMD of the ruptured side to a healthy group, the medial gastrocnemius was found to consistently demonstrate a longer EMD on the ruptured side compared to the healthy group with effect sizes ranging from moderate to large (0.50-1.33) depending on the task. The medial gastrocnemius was the only muscle where there was a consistent trend towards increased EMD across all tasks. Prior work by Oda, et al.[48] has also investigated medial gastrocnemius activity, but during a bilateral hopping task. The results of the Oda, et al. study found no differences in pre-activation of the medial gastrocnemius when comparing the ruptured to the uninjured side[48]. Interestingly, we found the hopping task to be the only task where there was a statistically significant EMD (or earlier onset) of the medial gastrocnemius both within subject and between groups. Taken together, these findings suggest that neuromuscular strategies may differ when a task is performed bilaterally as opposed to unilaterally in the context of Achilles tendon rupture.

We had hypothesized that greater EMD would relate to increasing tendon elongation and lower LSI for tendon mechanical properties with the rationale that the triceps surae would pre-activate in order to pretension the tendon. Given that ankle kinetics have been reported to decrease after Achilles tendon rupture, shifting power generation to more proximal joints[19], it is not surprising that we did not find these relationships in tasks that do not isolate the plantar flexors, such as the CMJ and drop CMJ. We did see the hypothesized relationship between EMD of the lateral gastrocnemius and tendon elongation in the hopping task. With regard to tendon mechanical properties, a relationship to soleus EMD was observed, however, the direction of this relationship was opposite of predicted. Due to the viscoelastic nature of the Achilles tendon, it is reasonable that the relationship between EMD and tendon mechanical properties would be most observable at slower speeds in tasks that isolate the plantar flexors. It may be that individuals that have adopted earlier activation of the soleus have loaded the tendon more resulting in more symmetrical tendon mechanical properties. Alternatively, the reverse could also be the case, that individuals with more symmetrical tendon properties have a better ability to recruit the soleus muscle during a heel-rise task. Despite the differences in medial gastrocnemius EMD between ruptured and healthy groups, increased EMD of the medial gastrocnemius did not relate to tendon structural properties. A prior studies have reported that the medial gastrocnemius has an altered pennation angle on the ruptured side when standing compared to the uninjured side[48,140]. It may be that the medial gastrocnemius may not be situated well to pretension the tendon, however, continues to pre-activate as a compensation for structural changes in the muscle.

This study is the first to report muscle activity in all of the triceps surae musculature across a range of tasks in individuals following Achilles tendon rupture. The results of this study point to the need to use caution when generalizing the currently available literature as findings from one of the triceps surae muscles do not necessarily apply to the other muscles and the activity of the triceps surae appears to be task-dependent. This points to a need to continue to study the muscles comprising the triceps surae separately, as each muscle may have a unique contribution to the myotendinous unit.

While novel, this study does have several limitations. This is a cross-sectional study in a group of individuals that did not have a standardized treatment protocol following rupture, so it is possible that participants are in various stages of healing or have treatment-related covariates that are not accounted for. Based on prior work reporting few functional changes between 1-2 years following Achilles tendon rupture[8], we have tried to mitigate concerns regarding heterogeneity by limiting inclusion to participants based on time from rupture and with surgical repair without augmentation. Therefore, the results of this study may not be generalizable to individuals at other time points or who have had non-surgical treatment. There is also likely some selection bias, as we excluded individuals from both rupture and healthy groups who reported being unable to perform unilateral jumping tasks. When comparing our rupture group to another group published by Brorsson et al.[9], it seems from the biomechanical data gathered in our study that these participants may represent the upper quartile of patients following Achilles tendon rupture. This may underestimate the observed side-to-side differences and relationships between muscle activity and tendon structural variables. Finally, we did have group differences with regard to age and sex. Prior work has suggested that age related changes are likely mitigated in the presence of similar activity levels and healthy body mass index[6,141–144]. Taken together with a mean difference in age of 9 years in two groups of individuals with similar reported activity level and BMI, age related differences between groups are less concerning. To address concerns regarding sex differences between groups, we reanalyzed a previously published dataset[79] from our research group to identify whether sex differences were present in healthy controls, and found no differences between males and females with regard to dynamic shear modulus (p-value = 0.748, Cohen's d = 0.12).

Clinically, the results of this study provide insight into the interpretation of clinical testing. It may be that the unilateral heel-rise provides important information not only about tendon recovery[13] but also regarding recovery of soleus function.

Furthermore, unilateral hopping may provide an indication of gastrocnemius function. Moving forward, studies investigating these relationships may help to decipher treatment strategies aimed at promoting appropriate compensatory strategies for the triceps surae to maximize functional recovery.

Chapter 5

RETURN TO PLAY POST ACHILLES TENDON RUPTURE: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RATE AND MEASURES OF RETURN TO PLAY

5.1 Introduction

The Achilles tendon passes from the gastrocsoleus muscles to the calcaneus, transmitting muscle contraction into ankle plantar flexion[145]. It also retains and releases energy during the gait cycle, promoting propulsion and conserving energy. In addition, the tendon assists with balance through proprioceptive feedback[146]. A rupture of the Achilles tendon predominantly occurs in middle-aged males during sports activity[100,102,147–152], with increasing incidence rates of as much as 69 per 100,000[2,100]. The greatest increases in incidence occur in the 40-60 and over 60 age groups[1,100,101].

The majority of patients suffering from an Achilles tendon rupture are recreationally competitive or involved in social sport[3,153] at the time of injury and report a desire to return to same activity[154]. The resumption of sports and physical activity is also an essential factor for the maintenance of health and prevention of morbidities following injury[155]. Despite this explicit goal, there are reports that only half of patients return to play one year after injury[36,154].

Performance of higher-level activities, such as those required for return to play (RTP), demonstrate large variations between individuals[8]. In a study by Olsson et al.[8], limb symmetry indexes between injured and non-injured sides ranged from 84-102% with standard deviations ranging from 15-26% during two jumping tasks. This variability may be due to any number of factors – gender, method of management, plyometric strength deficits, psychological components, and other physical changes indirectly related to injury and recovery course[29,149,156,157]. Patients may be physically able to return to sports activities[158], but the fear of re-rupture may cause an individual to avoid the sports activity during which injury occurred[154]. Additionally, rupture of the Achilles tendon leads to muscle weakness[8] and decreased endurance[159], which persists to 10 years following injury[23–25,160]. Patients may also develop additional musculoskeletal problems related to changes in gait biomechanics[21,161,162] such as knee injury or contra-lateral Achilles tendinopathy (25%) and rupture (6%)[163].

In order to appreciate the impact of Achilles tendon rupture on the ability for an individual to RTP, it is important to understand what the RTP rates are following injury and how RTP is currently evaluated. This will allow for standardization of determining RTP across studies, providing a solid basis for comparisons to be made between studies and informing treatment and rehabilitative guidelines.

The aim of this study was to perform a systematic review and meta-analysis of RTP rates following Achilles tendon rupture and evaluate what measures are used to determine RTP.

5.2 Methods

5.2.1 Search Strategy

Potentially relevant articles were identified via a search of PubMed, CINAHL, Web of Science, and Scopus databases. Search terms included two strings linked by an AND modifier. The first search string included (Achilles tendon AND injur*) OR (Achilles tendon AND rupture). The second string was designated as (Recovery of function OR performance outcome* OR athletic performance* OR treatment outcome*). The terms tendinopathy and review were linked with NOT modifiers. Results were filtered to English language, human studies, and adults. Databases were searched with no restriction of timeframe through March 1, 2016. Results of the database search were exported to a reference management database for review. Preliminary searches included terms such as “return to play” and “return to sport,” however, these searches yielded less studies, and studies known to the authors as reporting return to play following Achilles tendon rupture were missing. Therefore, the more general, inclusive terminology was utilized. Articles were identified through electronic database searching; no hand searching, citation tracking, or reference scanning was performed. The initial search and search strategy was performed by a reference librarian with input from the authors.

5.2.2 Selection Criteria

To be included, articles needed to describe patients with closed, acute Achilles tendon rupture and be of randomized control trial, cohort study, or case series study design. Due to the demographics of typical patients with Achilles tendon rupture, inclusion was limited to adults (at least age 18). Finally, an outcome measure regarding return to activity, sport, or play needed to be included within the abstract or body of the article. Articles were excluded based on the following criteria: case studies, chronic/delayed treatment (>4 weeks), open rupture/tendon laceration, inclusion of only patients with Achilles tendon re-rupture, non-English articles, non-human studies, bilateral ruptures. Studies including cohorts of both included and excluded populations (for example, a study comparing outcomes in a cohort of acute Achilles tendon rupture versus chronic Achilles tendon rupture) were included, but only data meeting inclusion for the review was included in the data analysis (acute Achilles tendon rupture in this example).

To ensure that each study met the inclusion criteria, studies were reviewed first by title. Title review primarily excluded articles not relating to Achilles tendon rupture, basic science studies not relevant to the purpose of this study, or studies pertaining to chronic rupture. Articles were then reviewed by abstract, followed by a full text review to ensure that the study included RTP outcomes either in the abstract or full text. All articles were reviewed by title and abstract by two independent reviewers to determine if the study met selection criteria. If consensus was unable to be reached, a third reviewer was consulted. For full text review, two independent reviewers each independently reviewed 25% of studies. Reviewers were consistently able to agree on inclusion of studies, and, therefore, the remaining studies were divided between the two reviewers due to the volume of studies identified and time constraints. If there were any studies that did not clearly meet selection criteria, this study was brought to the attention of the second reviewer to ensure consensus in the studies included in the review. Again if consensus was unable to be reached, a third reviewer was consulted.

5.2.3 Risk of bias

All articles included for full text review were scored for risk of bias using the scoring system described by Ardern et al.[164]. This scoring system utilizes six criteria, with studies scoring a point for the presence of each criterion. To score a full six points, the study must include selection criteria for patient inclusion/exclusion, report patient demographic data, report results of a representative population, report patients' pre-injury level, compare patients' post-intervention/post-injury sports level to their pre-injury level, and be of prospective study design. If presence of a given criteria was unclear, a score of zero was assigned. Studies were rated for risk of bias by two reviewers.

5.2.4 Data extraction and synthesis

Upon inclusion into the review, data extraction was again performed by two reviewers. The following data was extracted from each study: number of patients, patient demographics (age, sex), study design, percentage of patients returning to sport activity, measures of performance utilized, time frame to return to sport (with measure of variance), and time of evaluation of RTP. In studies which reported RTP percentages at multiple time points, data from the final study time point was used in the analysis. In retrospective studies where a mean follow-up time was reported, this value was used for time of evaluation of RTP. Studies that included measures of sport/activity performance but did not report a return to play percentage were included in the demographics analysis, but were not included in the RTP rate meta-analysis.

When there is no definition of measurement method, the risk of bias is considered very high, therefore, each study was scored based on the presence of clear, repeatable methodology used to determine return to sport. Studies were classified into one of two groups. Group 1 included studies in which the measure could be implied based on how return to activity/sport was reported or the measure of RTP was clearly described in the study's methods. For example, this group included studies that specified patients had returned to play at the same level as prior to injury or provided exact wording of interview/survey questions to patients or subscales of questionnaires specific to return to sport. Group 2 studies included those which reported a return to play percentage or timeframe in the results, but the measure to determine RTP was not described and unable to be inferred based on the phrasing of the results, making it impossible to reproduce the method of evaluation. An example would be including a statement in the results such as, “X% of patients returned to sport.” Two reviewers grouped studies into methodology classifications. The reviewers were calibrated by independently reviewing a subset of articles. Following calibration, the remaining articles were divided between reviewers and reviewed by a single reviewer. If grouping classification was unclear, the second reviewer was requested to provide a classification rating. If a consensus was not achieved, a third reviewer was consulted.

5.2.4.1 Statistical Analysis

Means and standard deviations were calculated for demographic data. Pooled proportion of RTP rate, 95% confidence intervals, and I^2 index (a measure of heterogeneity)[165] were calculated for the total group and for the two RTP measure sub-group classifications using StatsDirect Statistical Software (StatsDirect Ltd, England). A one-way analysis of variance (ANOVA) test was used to determine differences in RTP rates between the two RTP measure groups. Pearson’s correlations were conducted to identify relationships between RTP rate with the year of study and time of RTP evaluation. ANOVA and correlations were done using SPSS software (SPSS Inc. Released 2014. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). Weighted mean (weighted by number of patients) and standard deviation was calculated for time to return to play means across all studies reporting a time to RTP mean with measure of variance.

5.3 Results

5.3.1 Search Results and Description of Studies

The database searches yielded 552 articles. Three hundred twenty-two articles were excluded based on title. Of the 230 articles reviewed by abstract, 199 articles were included for full text review. Of those, a total of 108 articles met inclusion criteria and were included in data analysis (Figure 5.1, Table 5.1). Of the 108 studies included in this review, 71 reported selection criteria, 106 reported patient demographic data, 24 reported pre-injury level, 82 compared post-intervention/post-injury sports outcome compared with pre-injury level, and 57 studies were prospective in design. The Mean (SD) qualitative assessment score of all included articles was 4.1 (1.1) out of 6 possible points. Studies lacking return to sport measures scored 3.6 (1.2) points and studies including return to play measures scored 4.3 (1.0) points.

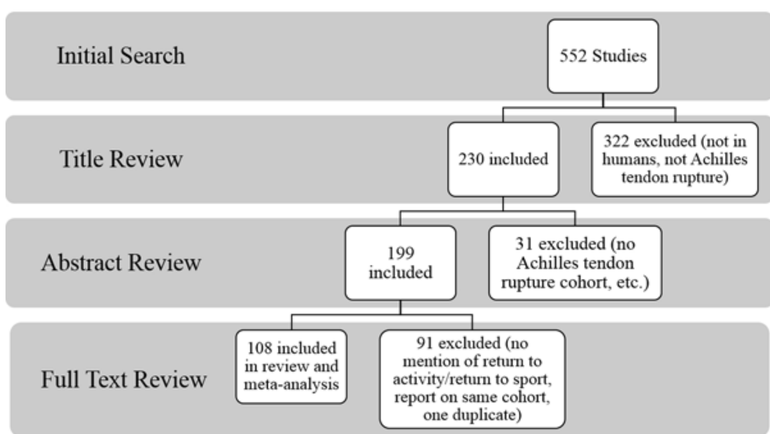

Figure 5.1: Decision tree for inclusion/exclusion of studies.

Eighty-five of the studies reported RTP measure (Group 1) and 23 were classified as lacking RTP measure (Group 2). There were 6,506 patients included in all studies – 5,535 in Group 1 and 971 in Group 2. Patients were a Mean (SD) of 41.4 (6.8) years of age, and 79.6% of patients were male. Six studies did not report patient sex[91,166–170] and five studies did not report patient age[97,168,171–173].

First Author	Number Subjects	Risk of Bias Rating	RTP Method Group	Percent RTP	RTP Definition	Other performance measures
Ahmad[147]	30	3	1	Not reported		FAAM - Sports Subscale[174]
Aktas[175]	40	5	1	87	Return to preinjury level of sport	AOFAS[176–178]
Aktas[166]	30	5	1	86.9	Return to preinjury level of sport	AOFAS
Al-Mouazzen[179]	30	4	1	Not reported	Return to preinjury level of activity	ATRS[49]
Amin[30]	18	5	1	61	Return to professional (NBA) sport	NBA Player Efficiency Rating (PER); min played per game; games played; [PER includes: points, rebounds, assists, steals, blocks, turnovers, field goals attempted and made, free throws

						attempted and made]
Amlang[180]	39	4	1	51	Return to preinjury level of sport	AOFAS
Ateschrang[148]	104	4	1	64.4	Return to preinjury level of sport	Thermann Score[181]
Barfod[93]	56	6	1	18.6	Return to preinjury level of sport	ATRS
Bassi[97]	11	2	2	100	Return to sport, level not specified	
Bevoni[150]	66	4	2	98.5	Return to preinjury level of sport	AOFAS, Leppilahti[182]
Bostick[159]	84	4	2	84	Return to sport, level not specified	
Boyden[183]	10	2	2	80	Return to preinjury activity without restriction	Boyden Scale[183]
Carmont[36]	26	5	1	61	Return to preinjury level of sport	Tegner Score[184]
Ceccarelli[185]	24	5	1	91.7	Return to preinjury level of sport	AOFAS
Chandrakant[186]	52	3	1	90	Return to desired level of	AOFAS

					activity	
Chen[98]	76	4	1	100	Return to preinjury level of activity	
Chiu[187]	19	5	1	94.7	Return to preinjury level of sport	Tegner Score, AOFAS
Coutts[188]	25	3	1	80	Return to preinjury level of sport	
Cretnik[189]	237	6	1	72.2	Return to preinjury level of activity	AOFAS
Cretnik[102]	116	4	1	96	Return to preinjury level of activity	AOFAS
Cretnik[99]	13	4	2	100	Return to preinjury activity, level unspecified	AOFAS
De Carli[190]	20	4	1	70.5	Return to preinjury level of sport	
Demirel[191]	78	6	1	77.1	Return to preinjury level of sport	
Doral[192]	32	4	1	100	Return to preinjury level of activity	FAOS[193], ATRS
Eames[194]	32	2	1	63	Return to sport, level not specified	

Feldbrin[167]	14	3	1	100	Return to preinjury level of activity	AOFAS
Fernandez-Fairen[172]	29	3	2	96.6	Return to preinjury level of sport	AOFAS
Fortis[195]	20	6	1	100	Return to preinjury level of activity	
Garabito[196]	49	4	1	89.8	Return to preinjury level of sport	AOFAS
Garrido[197]	18	3	2	72.2	Return to preinjury level of sport	AOFAS
Goren[198]	20	5	1	55	Return to preinjury level of activity	
Gorschewsky[199]	20	4	2	100	Return to original sport, level not specified	
Gorschewsky[200]	66	6	2	100	Return to original sport, level not specified	
Groetelaers[88]	55	4	1	39	Return to sport, level not specified	ARPS
Guillo[201]	23	4	1	80	Return to preinjury sport, level unspecified	ATRS, Boyden Scale

Halasi[202]	144	4	1	60.7	Return to preinjury level of sport	
Hohendorff[203]	42	3	1	88.6	Return to preinjury level of sport	Thermann Score
Hufner[173]	125	4	2	75.2	Return to preinjury level of sport	
Jaakkola[204]	55	3	2	90.9	Return to sport, level not specified	AOFAS
Jacob[168]	46	2	1	88.9	Return to preinjury sport, level unspecified for RTP percentage; return to preinjury level of activity for time to return to activity	
Jallageas[205]	31	6	1	77.5	Return to preinjury level of sport	AOFAS
Jennings[206]	30	2	1	63.6	Return to preinjury level of sport	Tegner
Josey[207]	39	3	1	66.7	Return to preinjury level of activity	AOFAS, Thermann Score
Jung[208]	30	3	2	90	Return to preinjury level of activity	
Kakiuchi[171]	22	4	1	45.5	Return to preinjury level of sport	
Karabinas[209]	34	2	2	Not	Return to	AOFAS

				reported	preinjury level of activity, non-contact sport	
Karkhanis[210]	107	3	2	77	Return to preinjury level of activity	ATRS
Keating[211]	80	5	1	66.9	Return to preinjury level of sport	
Keller[212]	100	4	1	80	Return to preinjury level of sport	
Klein[169]	34	3	2	100	Return to preinjury level of activity	VISA-A[134]
Knobe[213]	64	4	1	36.6	Return to sport, level not specified	
Kolodziej[214]	47	5	1	46	Return to preinjury level of sport	
Korkmaz[89]	47	4	1	Not reported		PAS[109]
Kraus[215]	36	5	1	53	Return to preinjury level of sport	
Labib[216]	44	4	1	65.71	Return to preinjury level of activity	
Lacoste[217]	75	5	1	63.6	Return to preinjury level of	ATRS, AOFAS

					sport	
Lansdaal[218]	163	5	1	59.5	Return to preinjury level of sport	Leppilahti Score
Lee[219]	11	4	2	Not reported	Return to preinjury level of activity	
Leppilahti[182]	101	4	1	85.7	Return to preinjury level of activity	Boyden Scale
Macquet[220]	87	4	1	68.1	Return to preinjury level of sport	
Maffulli[62]	53	3	1	92.5	Return to preinjury level of activity	Modified VISA-A
Maffulli[221]	17	4	2	94	Return to sport, level not specified	ATRS
Maffulli[222]	27	6	2	50	Return to preinjury sport, level unspecified	ATRS
Majewski[223]	84	4	1	100	Return to preinjury level of sport	Hannover Achilles Tendon Score[224]
Majewski[91]	28	5	1	65.2	Return to preinjury level of sport	Hannover Achilles Tendon Score
Mandelbaum[225]	29	4	1	100	Return to sport, level not specified	
Maniscalco[226]	7	4	1	100	Return to	Mandelbaum[225]

					sports or activity, level unspecified	& Pavanini[227] evaluation
Martinelli[228]	30	4	1	100	Return to preinjury level of sport	
McComis[41]	15	4	1	66	Return to preinjury level of activity	
Metz[229]	83	5	1	72.8	Return to preinjury level of sport	Leppilahti Score
Metz[158]	210	3	1	50	Return to preinjury sport, level unspecified	ATRS
Miller[230]	111	5	1	88	Return to sport, level not specified	
Möller[154]	112	6	1	54	Return to preinjury level of sport	Functional Index for the Lower leg and ankle (unpublished prior to use in this study)
Mortensen[51]	57	5	1	70	Return to preinjury level of sport	
Mortensen[231]	61	5	1	54.1	Return to preinjury level of sport	
Motta[232]	71	6	1	28	Return to preinjury level of	

					sport	
Mukundan[233]	21	6	1	95.2	Return to preinjury level of sport	AOFAS, Leppilahti
Nestorson[234]	25	4	1	36	Return to preinjury level of activity	
Nilsson-Helander[28]	97	6	1	Not reported		PAS, ATRS
Olsson[14]	100	6	1	Not reported		PAS, ATRS, FAOS
Orr[235]	15	3	2	100	Return to unrestricted active duty military status	AOFAS
Ozsoy[236]	13	4	1	92	Return to preinjury activity, level unspecified	AOFAS
Pajala[128]	60	6	1	100	Return to preinjury level of activity	Leppilahti Score
Parekh[237]	31	5	1	64.3	Return to professiona l (NFL) sport	Power ratings per-season & game
Park[238]	14	2	2	Not reported	Return to sport, level not specified	
Rajasekar[239]	35	3	1	50	Return to preinjury level of activity	Tendo-Achilles injury questionnaire (developed by authors)
Rebeccato[240]	59	4	1	98.4	Return to preinjury	

					level of sport or activity	
Rettig[241]	89	3	1	100	Return to preinjury level of activity	
Richardson[242]	30	3	1	77	Return to preinjury level of sport	AOFAS
Sanchez[170]	12	4	1	58	Return to preinjury sport, level unspecified	Modification of the Cincinnati Function Scales[243]
Schepull[83]	10	3	1	40	Return to preinjury level of activity	Thermann Score
Silbernagel[13]	8	4	1	Not reported		ATRS, FAOS
Soldatis[244]	30	5	1	61	Return to preinjury level of activity	
Solveborn[245]	17	4	1	94	Return to preinjury level of sport	Arner-Lindholm rating scale[246]
Sorrenti[247]	52	4	2	100	Return to preinjury activity, level unspecified	
Speck[248]	20	4	1	100	Return to sport, level not specified	
Stein[249]	27	3	1	92	Return to sport, level not specified	

Strauss[250]	54	3	1	74	Return to preinjury level of activity	Boyden Score, AOFAS
Suchak[251]	98	6	2	65	Return to partial sport activity	
Talbot[252]	15	3	1	66.7	Return to preinjury level of sport	AOFAS
Tenenbaum[253]	29	4	1	90	Return to preinjury level of activity	AOFAS, Modified Boyden Score
Troop[254]	13	4	1	94	Return to preinjury level of sport	
Uchiyama[255]	100	5	1	100	Return to preinjury level of sport	
Valente[256]	35	4	2	100	Return to sport, level not specified	AOFAS
Wagnon[257]	57	6	1	40	Return to preinjury sport, level unspecified	
Wallace[258]	945	5	1	100	Return to preinjury level of sport	
Wallace[259]	140	5	1	37	Return to preinjury level of sport	
Young[260]	84	4	1	Not reported		Leppilahti Score, Halasi

						Score[261], Self-rated Achilles tendon score

Table 5.1: Description of included studies.

5.3.2 Rate of RTP

The pooled rate of RTP in all studies was 80% ($CI_{95\%}$: 75 - 85%, I^2=95.8%) (Figure 5.2). Three studies[209,219,238] did not report a return to play percentage but reported return to play time frames. These studies were included in the analysis for subject demographics and time frame to return to sport. In Group 1 studies, rate of return to play 0.77 ($CI_{95\%}$: 0.70-0.83) (Figure 5.2). In Group 2 studies, rate of return to play was 0.91 ($CI_{95\%}$: 0.84-0.96) (Figure 5.3). Lower return to play rates were significantly lower in Group 1 versus Group 2 studies ($p < 0.001$). There was no relationship between RTP rate and year of study (Pearson r = -0.030, p = 0.765).

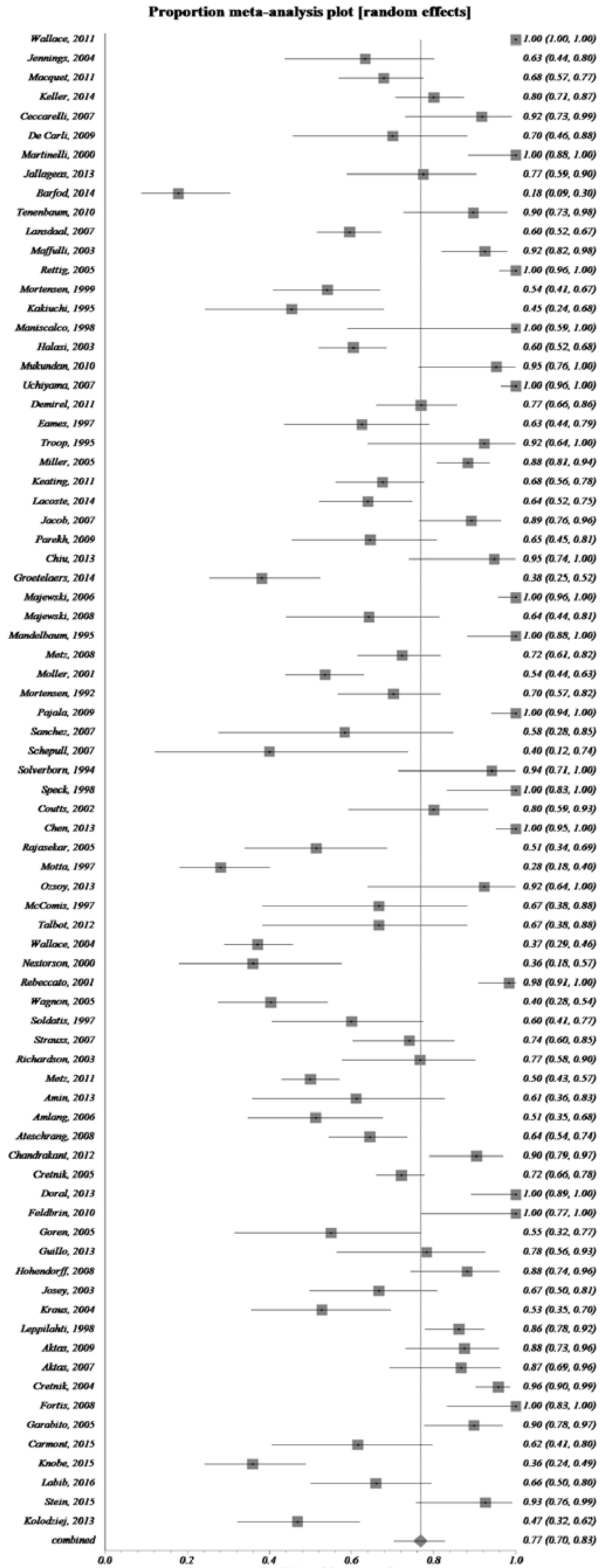
Proportion meta-analysis plot [random effects]
Wallace, 2011 1.00 (1.00, 1.00)
Jennings, 2004 0.63 (0.44, 0.80)
Macquet, 2011 0.68 (0.57, 0.77)
Keller, 2014 0.80 (0.71, 0.87)
Ceccarelli, 2007 0.92 (0.73, 0.99)
De Carli, 2009 0.70 (0.46, 0.88)
Martinelli, 2000 1.00 (0.88, 1.00)
Jallageas, 2013 0.77 (0.59, 0.90)
Barfod, 2014 0.18 (0.09, 0.30)
Tenenbaum, 2010 0.90 (0.73, 0.98)
Lansdaal, 2007 0.60 (0.52, 0.67)
Maffulli, 2003 0.92 (0.82, 0.98)
Rettig, 2005 1.00 (0.96, 1.00)
Mortensen, 1999 0.54 (0.41, 0.67)
Kakiuchi, 1995 0.45 (0.24, 0.68)
Maniscalco, 1998 1.00 (0.59, 1.00)
Halasi, 2003 0.60 (0.52, 0.68)
Mukundan, 2010 0.95 (0.76, 1.00)
Uchiyama, 2007 1.00 (0.96, 1.00)
Demirel, 2011 0.77 (0.66, 0.86)
Eames, 1997 0.63 (0.44, 0.79)
Troop, 1995 0.92 (0.64, 1.00)
Miller, 2005 0.88 (0.81, 0.94)
Keating, 2011 0.68 (0.56, 0.78)
Lacoste, 2014 0.64 (0.52, 0.75)
Jacob, 2007 0.89 (0.76, 0.96)
Parekh, 2009 0.65 (0.45, 0.81)
Chiu, 2013 0.95 (0.74, 1.00)
Groetelaers, 2014 0.38 (0.25, 0.52)
Majewski, 2006 1.00 (0.96, 1.00)
Majewski, 2008 0.64 (0.44, 0.81)
Mandelbaum, 1995 1.00 (0.88, 1.00)
Metz, 2008 0.72 (0.61, 0.82)
Moller, 2001 0.54 (0.44, 0.63)
Mortensen, 1992 0.70 (0.57, 0.82)
Pajala, 2009 1.00 (0.94, 1.00)
Sanchez, 2007 0.58 (0.28, 0.85)
Schepull, 2007 0.40 (0.12, 0.74)
Solverborn, 1994 0.94 (0.71, 1.00)
Speck, 1998 1.00 (0.83, 1.00)
Coutts, 2002 0.80 (0.59, 0.93)
Chen, 2013 1.00 (0.95, 1.00)
Rajasekar, 2005 0.51 (0.34, 0.69)
Motta, 1997 0.28 (0.18, 0.40)
Ozsoy, 2013 0.92 (0.64, 1.00)
McComis, 1997 0.67 (0.38, 0.88)
Talbot, 2012 0.67 (0.38, 0.88)
Wallace, 2004 0.37 (0.29, 0.46)
Nestorson, 2000 0.36 (0.18, 0.57)
Rebeccato, 2001 0.98 (0.91, 1.00)
Wagnon, 2005 0.40 (0.28, 0.54)
Soldatis, 1997 0.60 (0.41, 0.77)
Strauss, 2007 0.74 (0.60, 0.85)
Richardson, 2003 0.77 (0.58, 0.90)
Metz, 2011 0.50 (0.43, 0.57)
Amin, 2013 0.61 (0.36, 0.83)
Amlang, 2006 0.51 (0.35, 0.68)
Ateschrang, 2008 0.64 (0.54, 0.74)
Chandrakant, 2012 0.90 (0.79, 0.97)
Cretnik, 2005 0.72 (0.66, 0.78)
Doral, 2013 1.00 (0.89, 1.00)
Feldbrin, 2010 1.00 (0.77, 1.00)
Goren, 2005 0.55 (0.32, 0.77)
Guillo, 2013 0.78 (0.56, 0.93)
Hohendorff, 2008 0.88 (0.74, 0.96)
Josey, 2003 0.67 (0.50, 0.81)
Kraus, 2004 0.53 (0.35, 0.70)
Leppilahti, 1998 0.86 (0.78, 0.92)
Aktas, 2009 0.88 (0.73, 0.96)
Aktas, 2007 0.87 (0.69, 0.96)
Cretnik, 2004 0.96 (0.90, 0.99)
Fortis, 2008 1.00 (0.83, 1.00)
Garabito, 2005 0.90 (0.78, 0.97)
Carmont, 2015 0.62 (0.41, 0.80)
Knobe, 2015 0.36 (0.24, 0.49)
Labib, 2016 0.66 (0.50, 0.80)
Stein, 2015 0.93 (0.76, 0.99)
Kolodziej, 2013 0.47 (0.32, 0.62)
combined 0.77 (0.70, 0.83)
0.0
0.2
0.4
0.6
0.8
1.0
proportion (95% confidence interval)

Figure 5.2: Rate of Return to Play (RTP) in Group 1 studies reporting percent RTP. Error bars indicate 95% confidence intervals, square markers indicate proportion of patients able to return to play reported in each study. The diamond marker and vertical line indicate the proportion of patients able to return to play in all Group 1 studies combined.

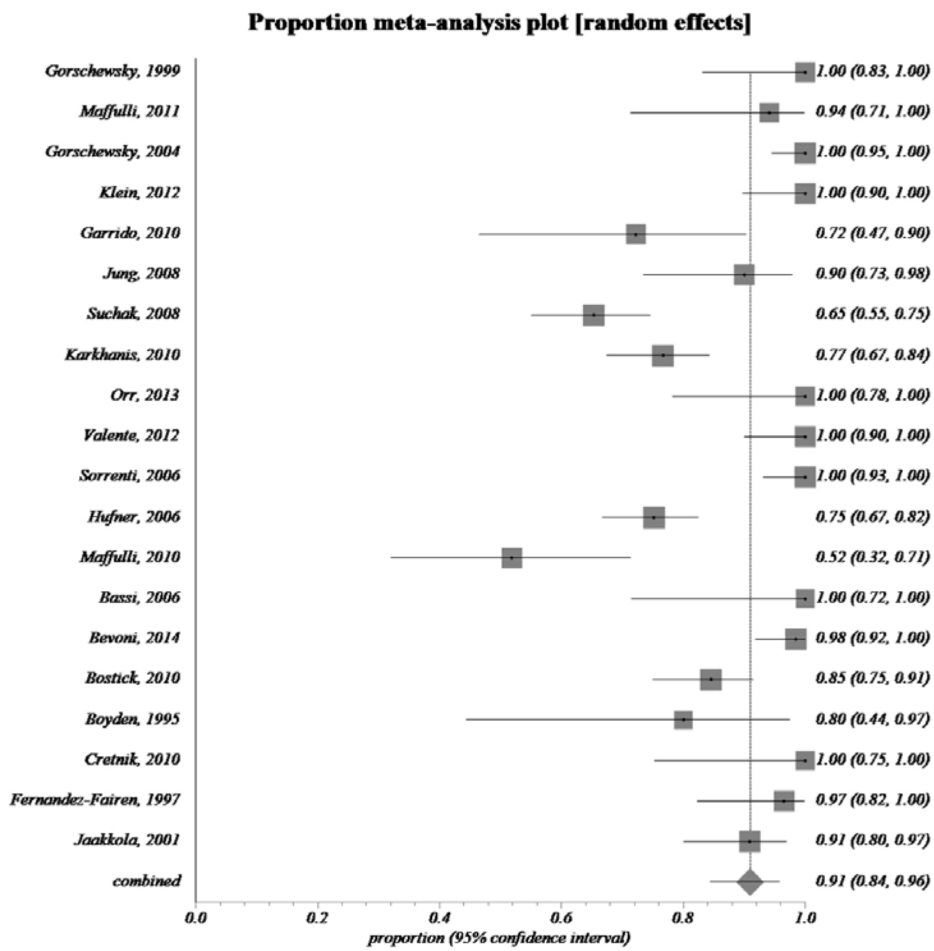

Figure 5.3: Rate of Return to Play (RTP) in Group 2 studies reporting percent RTP. Error bars indicate 95% confidence intervals, square markers indicate proportion of patients able to return to play reported in each study. The diamond marker and vertical line indicate the proportion of patients able to return to play in all Group 2 studies combined.

5.3.3 Relationship Between RTP and Time of Evaluation

The time of evaluation varied between 5 and 145.2 months (mean = 23.8 months SD = 22.9 months). There was no observed relationship between time of evaluation and RTP rate (Pearson's r = -0.026, p = 0.803).

5.3.4 Time to RTP

Thirty-seven studies reported time to return to play with a measure of variance, with a Mean (SD) of means across all studies of 6.0 (1.8) months. Of those studies, six reported variance with a standard deviation, six reported variance without specification of type of variance, and 25 reported variance as a range (Figure 5.4).

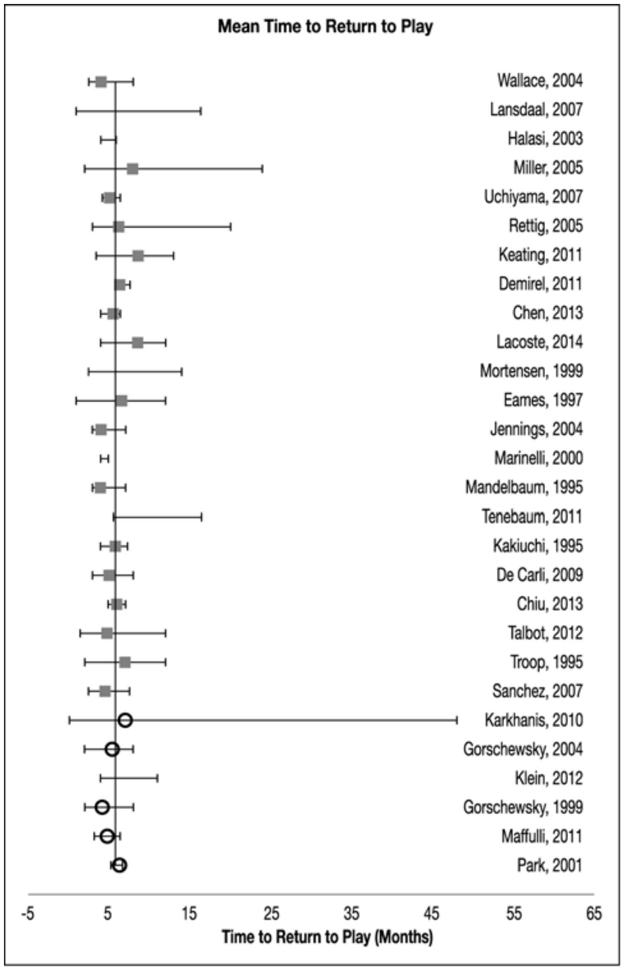

Figure 5.4: Time to Return to Play (RTP). Forest plot of time to return to play in months. Error bars indicate range as that was the most commonly reported measure of variance. Six studies reported a range without a mean and appear with only bars indicating reported range. The vertical line indicates the group mean for all studies reporting mean with measure of variance for time to return to play. Group 1 studies are indicated with squares for means, Group 2 studies are indicated with circles for means. Studies are ordered by RTP methodology group, then by number of patients with studies larger number of patients higher on the y-axis.

5.3.5 Measures of Performance/Functional Outcomes

In addition to reporting RTP rates, several studies utilized established questionnaires to gauge functional performance. These included the American Orthopaedic Foot and Ankle Society Ankle-Hindfoot Score (AOFAS)[176–178] in 27 studies, the Achilles Tendon Total Rupture Score (ATRS)[49] in 12 studies, the Leppilahti score[182] in six studies, the Boyden Scale[183] in five studies, the Tegner Scale[184] in four studies, the Thermann Score[181] in four studies, the Foot and Ankle Outcome Score (FAOS)[193] in three studies, the Physical Activity Scale (PAS)[109] in three studies, the Hannover Achilles Tendon Score[224] in two studies, the Foot and Ankle Ability Measure (FAAM) – sports subscale [262] in one study, and other questionnaires not specific to the foot and ankle in nine studies. Sport-specific performance metrics were utilized in two studies in professional athletes.

5.4 Discussion

The results of this systematic review indicate that rate of RTP is dependent on the measure used to determine RTP. In the process of identifying how different studies evaluated RTP, we found that numerous studies report a rate of RTP without including how this rate was measured. While the rate of RTP for studies describing RTP measures fell 3% below the rate for all included studies, the rate of RTP for studies without described RTP measures (and higher risk of bias) was 11% higher than the rate for all included studies. In general, while there is good consensus that RTP is a goal in this population, the literature regarding the resumption of sports activity to pre-injury levels following Achilles tendon rupture is limited. Return to play is reported as an outcome in a minority (19.7%) of studies on recovery of function following Achilles tendon rupture and a smaller number, 15.4% out of 552 articles, report RTP with indication of what measure was used to gauge RTP. For the individual patient, RTP is often a primary goal and is an important component of success of treatment following Achilles tendon rupture. This points to the need for better, standardized measures for gauging RTP that encompass the multiple aspects that comprise an individual's ability to RTP.

This is the first review to evaluate RTP rates and assess the quality of measures studies used for determining RTP after Achilles tendon rupture. Measures to assess RTP range from patient interview to the use of sports participation scores to objective sports performance indicators[30,237]. The measures used to assess return to play performance address multiple aspects of play, including volume/frequency of play, type of sport/sport demands, level of play, and play performance. Considering these aspects will be important in developing comprehensive measures that seek to capture RTP as a multi-faceted concern.

5.4.1 Rate of RTP

There were large variations on return to play rates and timeframes among the included studies. While the results indicate that 80% of subjects were able to return to play, studies reported as few as 18.6% and as large as 100% return to play rates. Prior studies done in the ACL population have reported similar trends in which increasing stringency of RTP definition results in lower percentages of athletes able to RTP[164,263]. Therefore, the more conservative estimate of 77% provided by the Group 1 studies is likely the more accurate, though likely still optimistic, estimate of true RTP rates.

There was no relationship observed between time of evaluation of RTP and RTP rate. This suggests that, while there was variability in time of evaluation, the majority of studies were of long enough duration to capture RTP outcomes.

5.4.2 Time to RTP

On average, time frame to return to sport was 6.0 months, but this also varied with study means/medians as low as 2.95 months and as high as 10.4 months. This estimate seems to coincide with timing of functional capacity recovery post-rupture, which has been reported to recover rapidly 3 and 12 months[11,14,40,88,211], followed by slowed rates of change between 1 and 2 years post-rupture[8]. Prior studies evaluating the return of functional capacity following Achilles tendon rupture have reported large variations between individuals[10,61]. Some of the variation seen in this analysis may be due to those individual variations. Additionally, differences in study design and definition of RTP may contribute to the variance in reported time of RTP. Moving forward, consistency and standardization of measurement of RTP will assist in establishing RTP time frames that allow for improved comparison of multiple cohorts across studies.

5.4.3 Measures of Performance/Functional Outcomes

There are a variety of validated, reliable questionnaires that assess different aspects of RTP that have been applied for use in this population. For instance, the Physical Activity Scale[109] includes measures of activity intensity and duration. The Halasi score[261], an adaptation of the Tegner score[184], captures factors such as type and level of sport activity. The Foot and Ankle Outcome Score[193] and Foot and Ankle Ability Measure[174] both have a sport-specific scale, which captures perceived difficulty with sport-related maneuvers. While these scores capture certain components of the whole RTP picture, the challenge with using these scores is that they were not developed specifically for use in this unique population and many have not been validated in the Achilles tendon rupture population. Despite the lack of RTP-specific measures in this population, there is an Achilles tendon rupture specific patient reported outcome score, the Achilles tendon Total Rupture Score[49], which has been shown to be valid, reliable, reproducible and responsive in individuals following Achilles tendon rupture. While this questionnaire has clinical utility, particularly in the earlier stages of recovery, this questionnaire is not specific enough for the RTP question.

Ultimately, while there are numerous questionnaires, which measure various aspects of RTP, there is none that comprehensively addresses the needs of this specific population. Given the importance of RTP for these individuals and the need to standardize measures to evaluate RTP, it would be beneficial for a measure to be developed that emphasizes volume as well as type of sport with consideration of Achilles tendon loading, and touches on sport performance.

5.4.4 Suggestions for Clinical Practice and Research

From a study design and reporting standpoint, there are ways to improve measure of RTP using the tools currently available. While a majority of studies compare post-injury to pre-injury rates, this was done via patient interview or unvalidated questionnaire in the majority of studies and only 22.2% of studies report a measure for pre-injury performance. Pre-injury rates are often obtained at time of follow-up and rely on accurate patient recollection of activity participation status. Prospective data regarding sport performance is ideal, but not always available. It may be beneficial to have patients rate sport performance early post-injury as opposed to a follow-up several weeks to months post injury. Another thing to consider is improving the frequency of reporting sport-specific subscales of already validated questionnaires. The AOFAS[176], FAOS[193,264,265] and Thermann[181] scores include sports and activity sub-scales but these subscales are infrequently reported. Finally, though all terms implying sports participation of activity were included in this systematic review, it was noted that a number of different terms were used in the literature. Activity, level, standard, performance, and intensity were all used, however, these may mean different things to patients and responses may vary accordingly. Variations in terminology further complicate search strategy when attempting to find relevant literature. Based on a recent consensus statement, the use of return to play is recommended to improve consistency in phrasing[266].

5.4.5 Study Strengths and Limitations

This systematic review assessed studies based on two separate set of criteria. The criteria developed by Ardern et al.[164] was utilized to evaluate study risk of bias. This tool was able to be applied to the present study, and provided the flexibility to allow for evaluation of studies with varying study designs. A second set of criteria was developed by the study authors to evaluate study methodology with regard to measuring RTP based on reproducibility. The combination of both methods of assessing study risk of bias and methodology did provide the ability to distinguish between quality in reporting between groups of studies, which was useful.

There are some limitations to this study. Included studies covered a range of research questions with a variety of set time points for follow-up and various types of treatments. Studies incorporated data from varied populations (ex. recreational as well as professional athletes), which could impact return to play rate and timeframe. Broad study inclusion is beneficial for understanding RTP in the larger, varied population of individuals with Achilles tendon rupture. Similarly, while many terms were included in this literature search to capture the large number of different terms currently used to describe return to play, this allows for improved generalizability to this population of individuals. Exclusion criteria did eliminate studies of portions of the population of patients with Achilles tendon rupture (ex. AT laceration, delayed treatment), so the findings of this study may not be generalizable to these populations. Unpublished and non-English language studies were not included in this study, which introduces the possibility of publication and language bias.

5.4.6 Conclusion

Achilles tendon rupture tends to be related to sport activity, however, return to play rates and time frames are under-reported and dependent on the quality of measure used to assess RTP. Studies with well-defined RTP measures demonstrate lower RTP rates. Approximately 80% of patients will be able to RTP, however, it is anticipated that this may be an over-estimate. It is important that future studies clearly define the measure used to determine RTP and report some measure of pre-injury status. Furthermore, development of a standardized, comprehensive measure specific to this patient population would be beneficial to evaluate patient outcomes for improved treatment and rehabilitative guidance.

Chapter 6

CONCLUSION

Achilles tendon rupture is a traumatic injury that has an annual incidence of 31.2-37.3 100,000 people[1–4]. While rerupture rates are reported to be less than 10%[2,17,230,258,267,268], long-term calf deficits[23,24] point to the importance of optimizing recovery in this patient population. The overall goal of this work was to investigate patient outcomes across the spectrum of the International Classification of Functioning, Disability, and Health (ICF) model[31]. Patient outcomes after Achilles tendon rupture are variable, likely due to differences between individuals as well as systematic differences in study methodology. The first three aims investigated impairment and activity domains of the ICF model, studying the relationships between tendon structure and patient function. The intention of these aims is to provide the foundation for identifying structural characteristics of the Achilles tendon which may serve as biomarkers of tendon recovery following rupture. The final aim investigated the participation domain to describe the rate of return to play in individuals following Achilles tendon rupture.

6.1 Aim 1: Side-to-side Differences in Achilles Tendon Geometry and Mechanical Properties Following Achilles Tendon Rupture

The purpose of this aim was to examine side-to-side differences in Achilles tendon structure (shear modulus, viscosity, tendon length, tendon thickness) and their relationship to clinical outcomes (Achilles tendon resting angle, self-reported function, and heel-rise test) within one year post-rupture. Prior studies have reported tendon elongation[9,13] and decreased elastic modulus[61] to relate to performance on the heel-rise test. These studies did not incorporate other measures of tendon structure, such as tendon thickness, and are limited by the invasive technique utilized to measure elastic modulus. Therefore, the present study broadens the knowledge base regarding tendon geometry and applies a new technique, cSWE, for assessment of tendon mechanical properties.

6.1.1 Hypothesis 1.1: Differences will be observed between ruptured and non-ruptured sides in tendon structural outcomes.

6.1.1.1 Hypothesis 1.1a: Within the first year, tendon mechanical properties will be lower on ruptured compared to non-ruptured sides.

This hypothesis was partially supported. Tendon shear modulus was not found to be different between ruptured and non-ruptured sides, but tendon viscosity was found to be lower on the ruptured side.

6.1.1.2 Hypothesis 1.1b: Within the first year, tendon length and thickness will be greater on ruptured compared to non-ruptured sides.

This hypothesis was supported as tendon length and thickness were both found to be greater on the ruptured side when compared to the non-ruptured side.

6.1.2 Hypothesis 1.2: Improved tendon structure on the ruptured side will positively relate to improved clinical outcomes.

6.1.2.1 Hypothesis 1.2a: Higher tendon viscoelastic properties and lower tendon length/thickness on the ruptured side will positively relate to improved clinical outcomes.

This hypothesis was partially supported. Lesser amounts of tendon elongation were found to relate to improved heel-rise test performance. There was a relationship between tendon thickness and clinical outcomes, however, it was in the opposite direction than hypothesized (thicker tendons related to better outcomes). There was no relationship between raw values of tendon shear modulus or viscosity and clinical outcomes.

6.1.2.2 Hypothesis 1.2b: More symmetrical values of tendon structure will positively relate to improved clinical outcomes.

This hypothesis was not supported. Decreased symmetry of tendon shear modulus (indicated using LSI values) and tendon thickness (indicated using relative differences between sides) related to improved clinical outcomes. There was no relationship between tendon viscosity and clinical outcomes.

6.2 Aim 2: Changes in Tendon Structure During 6 Months Following Achilles Tendon Rupture

The purpose of this aim was to establish the relationship between weight bearing and recovery of tendon structure and functional performance (heel-rise and jump tests) within 6-months post-injury. Prior studies in animal models have suggested that weight bearing promotes healing in ruptured tendons, with formation of a tendon callus[54] and improved mechanical properties[84]. In humans, early weight bearing has been found to be safe and deliver comparable outcomes to conservative weight bearing protocols[32,57,87–90,269]. The present study builds on growing evidence[32,51,55,82] regarding the recovery of tendon structure over time.

The first portion of this aim investigated changes in tendon structure over the course of the first 6 months of recovery.

6.2.1.1 Hypothesis 2.1: Tendon structure (mechanical properties, length, cross-sectional area) will increase between 4-weeks and 6-months post injury/surgery.

This hypothesis was partially supported. The instantaneous shear modulus at 400 Hz and tendon cross-sectional area were found to increase over time. Tendon length was not found to significantly increase over time.

The second portion of this aim investigated the role of weight bearing on patient outcomes including both functional and tendon structural outcomes.

6.2.1.2 Hypothesis 2.2: Individuals able to perform a unilateral heel-rise at 12-weeks post injury/surgery will have a higher number of weight bearing days during the first 12-weeks compared to patients who are unable to perform a unilateral heel-rise.

This hypothesis was not supported. There were no significant differences in weight bearing days during the first 12-weeks between patients who were able versus unable to perform a unilateral heel-rise.

6.2.1.3 Hypothesis 2.3: A higher number of weight bearing days during the first 12-weeks will positively relate to improved recovery of functional performance (heel-rise and jumping tests) at 6-months.

This hypothesis was not supported. There was no relationship between weight bearing days during the first 12-weeks and recovery of functional performance at 6-months.

6.2.1.4 Hypothesis 2.4: A higher number of weight bearing days during the first 12-weeks will positively relate to greater tendon cross-sectional area and mechanical properties values, and lower tendon elongation at 12-weeks post injury/surgery.

This hypothesis was partially supported. Individuals with higher numbers of weight bearing days during the first 12-weeks did have greater tendon cross-sectional area. There was no relationship observed between weight bearing days during the first 12-weeks and tendon instantaneous shear modulus at 400 Hz or tendon elongation.

6.2.1.5 Hypothesis 2.5: Patients who are weight bearing by 6-weeks post injury/surgery will have a smaller difference in tendon structure between the healthy and injured side at the 6-month follow-up.

This hypothesis was not supported. There were no differences in tendon structure at 24 weeks between typical and delayed weight bearing groups.

6.3 Aim 3: Timing of Muscle Activation Onset Differs by Muscle and Task in Individuals with Achilles Tendon Repair

The purpose of this aim was to identify adaptations at the muscle-level which accommodate for tendon dysfunction (tendon elongation or decreased viscoelastic properties) between one and two years post-injury. Specifically, we were interested whether or not tendon dysfunction relates to differences in the temporal component of muscle activation of the triceps surae. When considering compensatory mechanisms during higher level jumping and running tasks, there is evidence suggesting that one strategy individuals with Achilles tendon rupture may use is to shift power generation away from the ankle plantar flexors and toward the knee[19]. In addition to shifting power generation proximally, it has been suggested in two prior studies[26,48] that the triceps surae may change its activation pattern to compensate of the triceps surae for tendon dysfunction. The current work adds to these studies by incorporating tendon mechanical properties that are independent of volitional contraction, observing muscle level adaptations in a variety of tasks, and looking at each of the muscles of the triceps surae. This aim was comprised of two hypotheses.

6.3.1 Hypothesis 3.1: Muscle activation will occur earlier on the ruptured side compared to the uninjured side during heel-rise and jumping tasks.

This hypothesis was partially supported. Muscle activation did occur earlier on the ruptured compared to the uninjured side in the medial gastrocnemius during the hopping task. There were larger differences in muscle activation timing when comparing the ruptured side to a healthy cohort.

6.3.2 Hypothesis 3.2: Earlier muscle activation onset with clinical testing will positively relate to greater tendon elongation and lower tendon mechanical properties.

This hypothesis was partially supported. Tendon elongation was related to earlier activation (greater electromechanical delay) of the lateral gastrocnemius during the hopping task, and instantaneous shear modulus at 400 Hz was related to earlier activation of the soleus during the heel-rise task.

6.4 Aim 4: Return to Play Post Achilles Tendon Rupture – A Systematic Review and Meta-analysis of Rate and Measures of Return to Play

The purpose of this aim was to determine the rate of, and time to return to play following Achilles tendon rupture. Achilles tendon rupture occurs most often in recreationally active populations, making return to play of importance[3,153,154]. Despite its importance, there seemed to be large variation in return to play rates. Therefore, a secondary purpose of this aim was to examine methodological contributors to return to play. This was accomplished in three hypotheses.

6.4.1 Hypothesis 4.1: Determine the rate of return to play following Achilles tendon rupture.

The rate of return to play following Achilles tendon rupture is, on average, 80%.

6.4.2 Hypothesis 4.2: Rate of return to play will be lower in studies with a reported method for return to play measurement than in studies with undescribed methods.

This hypothesis was supported. Studies reporting a method for return to play measurement reported significantly lower return to play rates compared to those with undescribed methods.

6.4.3 Hypothesis 4.3: Determine the typical time to return to play following Achilles tendon rupture.

On average, return to play occurred at 6 months (range: 2.95-10.4 months) following injury.

6.5 Limitations

The majority of limitations to this work stem from the exploratory nature of the methods utilized and the study population. For aims 1 and 2, treatment varied (surgical versus non-surgical, rehabilitation strategy, etc.) and sample sizes limited the ability to perform subgroup analyses or group comparisons. This heterogeneity may weaken the relationships seen. For aim 3, while all participants were surgically managed, the post-operative rehabilitation varied. This heterogeneity, while potentially limiting study findings, improves generalizability of these findings to other individuals after Achilles tendon rupture. Small sample sizes also precluded our ability to control for confounding variables such as participant age, sex, and body mass index.

6.6 Conclusions and Clinical Significance

After injury, patients often want to know what to expect. “When will I be able to walk normally?” “When can I start running again?” In the context of rehabilitating these patients answering these questions are a challenge, particularly when there is a lack of objective data driving the decision-making.

Historically, time-based criteria have guided these decisions. Using rehabilitation following anterior cruciate ligament reconstruction (ACLR) as an example, we see a shift from time-based to criteria-based rehabilitation progression[270,271]. This phase-shift appreciates that multiple other factors – patient age, sex, comorbid conditions, psychosocial factors – play a role in the way an individual heals[272–274]. In the ACLR body of literature, objective guidelines have been developed to help guide these decisions[271]. Patients should demonstrate certain criteria – no effusion, a quadriceps strength limb symmetry index of at least 80%, et cetera – in order to progress to the next phase of rehabilitation[271,275].

In the context of Achilles tendon rupture, however, these criteria are in their infancy. Prior work in both animals and humans has suggested that healing tendon responds to and recovers with mechanical loading[54,82,84], which supports the use of a criteria-based rehabilitation progression to guide clinical decision-making. Furthermore, it seems that patients' long term prognosis relates to how well an individual recovers within the first year[8,9]. In particular, recovery of a single leg heel-rise seems to relate to patient recovery within and after the first year[9–11]. The heel-rise has limited use within the first 12 weeks of recovery due to the need for the patient to weight bear without immobilization and due to the concern that only 50% of individuals are able to perform the single-leg heel-rise at 12 weeks[10]. This points to the need for objective criteria that are sensitive to changes in the early healing trajectory of the patient that can be used to guide treatment and predict outcomes. Tools to assess patient status and guide dosage of mechanical load are continuing to be developed and further work on their use in making clinical decisions is needed. This dissertation work supports the use of ultrasound imaging to assess the structural response of the healing tendon to treatment as one component of a comprehensive patient examination. This work suggests that ultrasound-based measures of tendon geometry and viscoelasticity are safe to assess early following Achilles tendon rupture, are different relative to the uninjured side in the presence of tendon rupture, are reliable, are sensitive to change over time, and are related to triceps surae and patient function. At this time, tendon geometry has a larger body of literature to support its use in clinical decision making at an individual level, however, tendon mechanical properties measured using cSWE may provide interesting information at the group level in a research context.

6.7 Future directions

This work supports the use of tendon structural characteristics as part of a comprehensive assessment of outcomes in individuals with Achilles tendon rupture. Future work investigating the use of changes in tendon structure as part of a criteria-based progression would be potentially informative for objectively determining patient progression of activity.

Additionally, the Achilles tendon serves as a convenient model to study tendon injury. Therefore, moving forward it would be of interest to apply measures of tendon structure and their relationship to patient outcomes in other tendon injuries to determine the extent to which findings in the Achilles tendon carry over to other tendons. Ultimately, the goal of this work and the anticipated forward trajectory is to provide standardized recommendations with which to appropriately gauge patient response to treatment and individualize rehabilitation.

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Appendix A

RELIABILITY INFORMATION

Reliability information has been previously reported for tendon length measurement using B-mode ultrasound imaging[106] as well as calf circumference[37]. Reliability of the cSWE technique, tendon cross sectional area, tendon thickness, and Achilles tendon resting angle was performed within our laboratory on 20 individuals with health Achilles tendons. Test-retest reliability was performed via two assessments using cSWE taken several minutes apart. Procedural reliability for cSWE was performed via two assessments separated by 2 weeks. The assessments separated by 2 weeks sought to establish reliability for identification of cSWE location as well as to begin to investigate the stability of tendon mechanical properties over time.

	SEM	***ICC***	***$MDC_{95\%}$ individual***	***$MDC_{95\%}$ group***
Shear Modulus (kPa)	9.4	0.67	26.1	6.0
Viscosity (Pa*s)	6.0	0.80	16.7	3.8
Dynamic Shear Modulus (kPa)	23.1	0.767	63.9	14.3
Thickness (mm)	0.19	0.871	0.53	0.12
Cross Sectional Area (cm^2)	0.016	0.985	0.043	0.010
Tendon Length (cm)[106]	0.67	0.944	1.83	0.43
Achilles Tendon Resting Angle (degrees)	1.29	0.917	3.57	0.82
Calf circumference (cm)[37]	0.6	0.97	1.66	0.42

Table A.1 Test-retest reliability for ultrasound and clinical measures

	SEM	***ICC***	***MDC95% individual***	***MDC95% group***
Shear Modulus (kPa)	11.2	0.44	30.9	6.9
Viscosity (Pa*s)	6.9	0.69	19.1	4.3
Dynamic Shear Modulus (kPa)	24.3	0.70	67.3	15.0

Table A.2 Procedural reliability for continuous shear wave elastography (cSWE). Assessments separated by 2 weeks.

Reliability has been previously reported for the heel-rise test[276] and jump tests[14,15].

	SEM	***ICC***	***MDC95% individual***	***MDC95% group***
Heel-rise Test[276]				
Repetitions	6.7	0.77	18.6	3.0
Maximum Height (cm)	0.80	0.85	2.22	0.36
Total Work (J)	419	0.84	1161	188
Counter Movement Jump Height (cm) [14,15]	1.2	0.91	3.3	0.5
Hopping Plyometric Quotient[14,15]	0.10	0.83	0.28	0.04
Drop Counter Movement Jump Height (cm) [14,15]	1.7	0.88	4.7	0.7

Table A.3 Reliability for functional performance outcomes

Appendix B

ABBREVIATIONS LIST

ACLR	Anterior cruciate ligament reconstruction
ANOVA	Analysis of variance
AOFAS	Academy of Foot and Ankle Surgeons – hindfoot scale score
ATRS	Achilles tendon Total Rupture Score
BMI	Body mass index
CI	Confidence interval
cm	centimeter
CMJ	Counter movement jump
cSWE	Continuous shear wave elasography
EMD	Electromechanical delay
EMG	Electromyography
FAAM	Foot and ankle outcome measure
FAOS	Foot and ankle outcome score
FHL	Flexor hallucis longus
Hz	Hertz
ICC	Intraclass correlation coefficient
ICF	International Classification of Functioning, Disability, and Health
IQR	Interquartile range
J	Joules
LG	Lateral gastrocnemius
LSI	Limb symmetry index
MDC	Minimal detectable change
MG	Medial gastrocnemius
MRI	Magnetic resonance imaging
NBA	National Basketball Association
Pa	Pascal
PAS	Physical activity scale
PER	Player efficiency rating
PQ	Plyometric quotient
RSA	Roentgen stereophotogrammetric analysis
RTP	Return to play
s	Second
SD	Standard deviation

SEM	Standard error of measurement
Shear modulus$_{400}$ (μ_{400})	Dynamic shear modulus
SSI	supersonic shear-wave imaging
VISA-A	Victorian Institute of Sport Assessment – Achilles Questionnaire

Appendix C

INSTITUTIONAL REVIEW BOARD APPROVAL DOCUMENTS FOR INCLUDED STUDIES

Aim 1

RESEARCH OFFICE

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

DATE:	June 24, 2014
TO:	Daniel Cortes, PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[608145-1] continuous shear wave elastography as a marker for tendinopathy
SUBMISSION TYPE:	New Project
ACTION:	APPROVED
APPROVAL DATE:	June 24, 2014
EXPIRATION DATE:	May 20, 2015
REVIEW TYPE:	Full Committee Review

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 Full Committee 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.

Please note that any revision to previously approved materials must be approved by this office prior to initiation. Please use the appropriate revision forms for this procedure.

All SERIOUS and UNEXPECTED adverse events must be reported to this office. Please use the appropriate adverse event forms for this procedure. All sponsor reporting requirements should also be followed.

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:	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.

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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:	September 11, 2015
TO:	Karin Silbernagel, PT, ATC, PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[784188-1] Evaluation of tendon recovery following an Achilles Tendon Rupture.
SUBMISSION TYPE:	New Project
ACTION:	APPROVED
APPROVAL DATE:	September 11, 2015
EXPIRATION DATE:	August 18, 2016
REVIEW TYPE:	Full Committee Review

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 Full Committee 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
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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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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:	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)*

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.

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:	September 11, 2015
TO:	Karin Silbernagel, PT, ATC, PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[784188-1] Evaluation of tendon recovery following an Achilles Tendon Rupture.
SUBMISSION TYPE:	New Project
ACTION:	APPROVED
APPROVAL DATE:	September 11, 2015
EXPIRATION DATE:	August 18, 2016
REVIEW TYPE:	Full Committee Review

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 Full Committee 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.

UNIVERSITY OF DELAWARE

RESEARCH OFFICE

210 Hullihen Hall
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Newark, Delaware 19716-1551
Ph: 302/831-2136
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DATE:	August 25, 2016
TO:	Karin Silbernagel, PT, ATC, PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[784188-5] Evaluation of tendon recovery following an Achilles Tendon Rupture.
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED
APPROVAL DATE:	August 25, 2016
EXPIRATION DATE:	August 18, 2017
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review category # *(9)*

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 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
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DATE:	July 21, 2017
TO:	Karin Silbernagel, PT, ATC, PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[784188-8] Evaluation of tendon recovery following an Achilles Tendon Rupture.
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED
APPROVAL DATE:	July 21, 2017
EXPIRATION DATE:	August 18, 2018
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review category # *(9)*

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.

Aim 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:	May 3, 2017
TO:	Jennifer Zellers, DPT
FROM:	University of Delaware IRB
STUDY TITLE:	[899284-3] Relationship between muscle function and tendon health in individuals with Achilles tendon pathology
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED
APPROVAL DATE:	May 3, 2017
EXPIRATION DATE:	May 17, 2018
REVIEW TYPE:	Expedited Review
REVIEW CATEGORY:	Expedited review category # 9

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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