Novel tools for the evaluation of Achilles tendon mechanical properties

By

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Abstract

Tendon mechanical properties have been frequently investigated in recent years in order to evaluate tendon adaptations to training and to pathology. With the development of different technologies able to measure tendon mechanical properties, highly heterogeneous values have emerged in the literature, sometimes even contradicting one another. The overall aim of this thesis was to assess the available technologies for evaluating the mechanical properties of the Achilles tendon (AT) to understand their clinimetric properties and determine their ability to assess tendons during loaded tasks.

This thesis consists of nine studies. A systematic review identified that strain elastography (SE) and shear wave elastography (SWE) have highly variable reliability results between studies with a high risk of bias within the individual studies. Furthermore, six observational studies using different technologies (SE, SWE, myotonometry and shear wave tensiometry) reported the clinimetric properties and the capability of the technologies to detect loading changes. Finally, two observational studies describe the implementation of a novel technology, shear wave tensiometry, to assess the AT in patients after Achilles tendon rupture (ATR). The results showed that shear wave tensiometry is a reliable tool and is able to detect changes between the ruptured and uninjured AT in both patients treated surgically and conservatively. Implementing shear wave tensiometry in clinical settings could be helpful to understand the behaviour of pathological tendon during load.

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List of Papers and Abstracts

During the PhD, the following papers directly related to the thesis have been published, presented in in conferences or under review at the time of the thesis submission. Therefore, different chapters of this thesis include verbatim text for published work. Sections of the thesis have been developed from published work and in this situation will resemble the published work in term of structure and content, additional changes have been made to avoid redundancies.

Published Articles

Schneebeli A., Del Grande F., Falla D., Cescon C., Clijsen R., Barbero M. 2019. A novel application of strain sonoelastography can detect changes in Achilles tendon elasticity during isometric contractions of increasing intensity. *Journal of Foot and Ankle Research*. 21;12:30. **(Appendix 1)**

Schneebeli A., Fiorina I., Bortolotto C., Barbero M., Falla D., Cescon C., Raciti MV., Tarantino F., Preda L. 2021. Shear wave and strain sonoelastography for the evaluation of the Achilles tendon during isometric contractions. *Insights Into Imaging*. 17;12(1):26 **(Appendix 2)**

Schneebeli A., Folli A., Falla D., Barbero M. 2020a. Reliability of Sonoelastography Measurements of Lower Limb Tendon Properties: A Systematic Review. *Ultrasound in Medicine & Biology*. 47(5):1131-1150. **(Appendix 4)**

Schneebeli A., Falla D., Clijsen R., Barbero M. 2020b. Myotonometry for the evaluation of Achilles tendon mechanical properties: a reliability and construct validity study. *BMJ Open Sport Exerc Med*. 12;6(1) **(Appendix 6)**

Schneebeli A., Falla D., Cescon C., Barbero M. 2022. Measurement of Achilles tendon loading using shear wave tensiometry: A reliability study. *Musculoskeletal Science and Practice*. 62:102665. **(Appendix 7)**

Schneebeli A., Barbero M., Filardo G., Testa E., Riegger M., Sangiorgio A., Cescon C., Soldini E., Falla D. 2023. Shear Wave Tensiometry Can Detect Loading Differences Between Operated and Unaffected Achilles Tendon. *Foot and Ankle International*. 44(12):1295-1304. **(Appendix 8)**

Articles Under Review

Schneebeli A., Filardo G., Testa E., Riegger M., Falla D., Sangiorgio A., Cescon C., Soldini E., Barbero M. 2024. Shear wave tensiometry in the evaluation of Achilles tendon loading: A cross-sectional study on conservatively treated tendons after rupture. (Under review)

Conference Presentations

Schneebeli A., Falla D., Del Grande F., Cescon C., Clijsen R., Barbero M. Evaluation of Achilles tendon stiffness during contraction using strain sonoelastography. Physiotherapy UK conference, Birmingham. November 2018

Schneebeli A., Falla D., Clijsen R., Barbero M. MyotonPRO; a reliable device to evaluate Achilles tendon mechanical properties. International Society of Electrophysiology and Kinesiology (ISEK) Virtual Congress. July 2020

Schneebeli A., Falla D., Cescon C., Barbero M. Intra-rater reliability of a shear wave tensiometer in the evaluation of Achilles tendon mechanical properties. International Society of Electrophysiology and Kinesiology (ISEK) Québec City. Canada. June 2022

Schneebeli A., Falla D., Cescon C., Barbero M. Mechanical versus manual impulse for the propagation of shear wave along the Achilles tendon: a congruent validity study. International Society of Electrophysiology and Kinesiology (ISEK) Québec City. Canada. June 2022

Schneebeli A., Falla D., Cescon C., Barbero M. Shear wave propagation along the Achilles tendon measured with tensiometry: mechanical versus manual impulse. World Physiotherapy Congress. Dubai. UAE. 2023

Schneebeli A., Cescon C., Filardo G., Testa E., Riegger M., Sangiorgio A., Falla D., Barbero M. Shear wave tensiometry in the evaluation of Achilles tendon loading: a cross-sectional study on conservatively treated tendon after rupture. International Society of Electrophysiology and Kinesiology (ISEK) Nagoya. Japan. June 2024

Schneebeli A., Filardo G., Falla D., Testa E., Riegger M., Sangiorgio A., Cescon C., Barbero M. Differences in shear wave speed between surgically and conservatively treated Achilles tendons following rupture. International Federation of Orthopaedic Manipulative Physical Therapists (IFOMPT) Basel. Switzerland. July 2024

Sangiorgio A., **Schneebeli A.**, Barbero M., Filardo G., Testa E., Riegger M., Cescon C., Falla D. Shear wave speed: mechanical and morphological comparison in conservatively treated and uninjured Achilles tendon. 13a Giornata della Ricerca e dell'Innovazione in Medicina Umana della Svizzera italiana, Lugano, Switzerland. September 2024.

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LIST OF ABBREVIATIONS

Acronym	Definition
AT	Achilles Tendon
ATR	Achilles Tendon Rupture
ATRS	Achilles tendon total rupture score
BMI	Body mass Index
CSA	Cross-Sectional Area
CI	Confidence interval
CV	Coefficient of Variation
GRRAS	Guidelines for Reporting Reliability and Agreement Studies
ICC	Intraclass Correlation Coefficient
IPAQ	International Physical Activity Questionnaires
KFP	Kager Fat Pad
MDC	Minimal Detectable Change
MID	Mid Tendon
MTJ	Myotendinous Junction
MVC	Maximal Voluntary Contraction
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
PT	Patellar Tendon
QAREL	Quality Appraisal tool for studies of diagnostic RELiability
QT	Quadriceps Tendon
ROI	Region Of Interest
SE	Strain Elastography

SEM	Standard Error Of Measurement
STROBE	Strengthening The Reporting of Observational Studies in Epidemiology
SWE	Shear Wave Elastography

CHAPTER 1

INTRODUCTION

1.1 Tendinopathy and tendon rupture

Tendon pathologies are a very common musculoskeletal condition, especially in the lower limb where tendinopathies have an incidence of 10.52 per 1000 person-years (Albers et al., 2016, Riel et al., 2019). Among these, the Achilles is one of the most affected tendons with a prevalence of 2.01 per 1000 persons experiencing tendinopathies (de Jonge et al., 2011) and an annual incidence of 5-50 events of tendon rupture per 100,000 persons (Huttunen et al., 2014, Sheth et al., 2017, Ganestam et al., 2016), numbers that have risen over the past decades (Jarvinen et al., 2005).

The generic term 'tendinopathy' refers to an overuse syndrome associated with a failed healing response of the tendon (Cook and Purdam, 2009). A change in tendon composition, separation and disruption of collagen fibers and proliferation of tenocytes (Maffulli et al., 2010, Maffulli et al., 2008, Maffulli et al., 2011) occurs when a tendon is repetitively put under load beyond its physiological threshold. Changes occur not only at a cellular level, but there are also changes in tendinopathic structure and an increase in vascularization and neoinnervation which lead to changes in tendon material properties and the presence of pain (Millar et al., 2021). On the other hand, when considering tendon ruptures due to an acute injury, the extrinsic factors are predominant since 90% of Achilles tendon ruptures (ATR) in sports injuries are due to an acceleration-deceleration mechanism (Sharma and Maffulli, 2006). Tendon injuries can occur when the normal protective mechanism, which usually inhibits excessive or uncoordinated muscle contraction, fails to function properly (Sharma and Maffulli, 2006). Possibly, a pre-

existing degenerative tendinopathy can lead to a reduced tensile strength of the tendon and thus predispose it to rupture. In fact, some studies show degenerative changes preceding spontaneous ATR (Kannus and Jozsa, 1991, Arner et al., 1959).

Achilles tendon (AT) tendinopathy as well as ATR are long lasting painful conditions. The recovery period can last more than a year for tendinopathies (Silbernagel et al., 2020) with a high reinjury rate which is between 27 and 44% (Silbernagel et al., 2020, Gajhede-Knudsen et al., 2013, Hagglund et al., 2007). A long rehabilitation period is also required following the repair of an ATR in order to reach normal function and in some cases, permanent functional deficits may remain (Mortensen et al., 1999, Eliasson et al., 2016).

Given the high incidence and prevalence of these conditions and the associated pain and disability that may occur, understanding the risk factors is crucial for the prevention of further AT injuries. Achilles tendinopathies and ATR share some risk factors, such as prolonged use of steroids, antibiotic use (i.e., floroquinalones) and previous lower limb tendinopathy which predisposes the AT to injury (O'Neill et al., 2016, van der Vlist et al., 2019, Xergia et al., 2022). According to a recent systematic review, limited evidence suggests that prior lower limb tendinopathy or fracture, the use of antibiotics, moderate alcohol use, decreased plantar flexor strength are among the most frequent risk factors described in the literature (van der Vlist et al., 2019). For ATR the most common risk factors are steroids or antibiotic intake, previous Achilles tendinopathies, diabetes, hyperparathyroidism, renal failure, regular participation in athletic activity and genetic factors. However, for ATR the evidence comes from low quality studies and therefore such results should be cautiously interpretated (Xergia et al., 2022). Moderate evidence from two systematic reviews suggests that decreased tendon fibril size increases the risk of ATR (Xergia et al., 2022, Claessen et al., 2014), yet the relationship between tendon mechanical properties and ATR are underexplored in literature.

Understanding if mechanical properties could increase the risk of developing tendon pathologies and if mechanical properties of the tendon are modifiable through therapeutic interventions could help prevent tendon injuries in athletes and in the general population.

1.2 Mechanical properties of tendon

Tendons are responsible for force transmission from the muscle to the bone and their role in the energy storage and release during the stretch shortening cycle is paramount (Magnusson et al., 2008, Fukunaga et al., 2001). Tendons were once believed to be an inert system, but nowadays it is clear that tendons respond to the mechanical load to which they are subjected (Bohm et al., 2015a, Magnusson et al., 2008, Wiesinger et al., 2015, Heinemeier and Kjaer, 2011). The AT is subjected to considerable changes in length for a given tensile load and plays a critical role in energy storage and release during human walking, (Lichtwark and Wilson, 2007) as well as during other daily life activities (Lichtwark et al., 2013, Obst et al., 2013, Obst et al., 2016). This constant mechanical loading and repeated strain over time may alter the mechanical properties of the tendon structure and leave it more vulnerable to overload and degeneration. (Obst et al., 2018).

Any possible change in tendon mechanical properties can have different implications: firstly a positive adaptation, a tissue that becomes more load tolerant and increases its load capacity could potentially perform better and theoretically decrease the likelihood of developing tendon pathology (Docking and Cook, 2019); secondly a negative adaptation, where repeated mechanical stimuli that exceeds a certain intensity or the absence of mechanical stimulus may lead to changes in homeostasis and consequently a maladaptive response with

damage accumulation and degeneration of the tendon tissue (Lavagnino and Arnoczky, 2005, Lavagnino et al., 2003, Wang et al., 2003) (Figure 1.1).

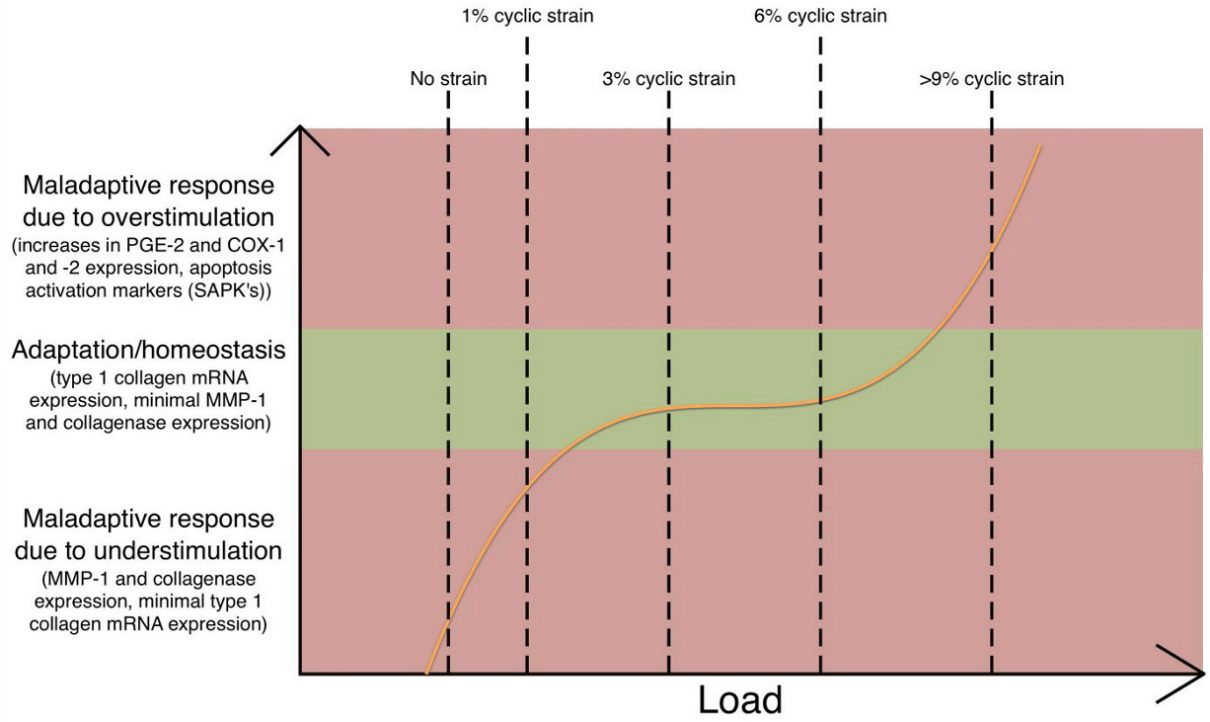


Figure 1.1: Schematic representation of how mechanical stimulus can promote adaptive or maladaptive response of the tendon. Figure from Docking and Cook (2019)

This homeostasis in the tendon is regulated by the collagen synthesis and turnover. The mechanical loading put on the tendon is one of the main drivers for the upregulation or downregulation of the collagen-inducing growth factors and therefore crucial for the tendon adaptation (Kjaer, 2004, Magnusson and Kjaer, 2018). In tendon cell culture, it has been demonstrated that an application of tensile strain at different magnitude can potentially lead to adaptation or maladaptation via an increased or reduced collagen expression (Lavagnino and Arnoczky, 2005, Lavagnino et al., 2003). Altered tendon stiffness could also impact the muscle force production in terms of efficiency and magnitude by modifying the force-length relationship of the muscle-tendon complex (Maganaris et al., 2008).

In the AT, that is considered a compliant tendon, (Lichtwark and Wilson, 2007) a lower stiffness could be a positive factor in the calibration of the length of the muscle-tendon complex in order to optimise the force production of the muscle at different stages of the stretch-shortening cycle (Lichtwark and Barclay, 2010). Conversely, from an injury perspective a tendon with lower stiffness could strain more for the same amount of stress, increasing the possibility to have tissue damage due to the frictional forces and heat production during the repeated cyclic loading (Maganaris et al., 2008, Farris et al., 2011). Thus, the balance between a compliant or a stiff tendon seems to play an important role not only from a biomechanical-performance perspective but also for a clinical perspective. For that reason, the relationship between tendon health status and mechanical properties has recently been more thoroughly investigated.

1.3 Mechanical properties of pathological tendon

From a pathology perspective, it is currently unknown whether changes in mechanical properties are linked to an increased risk of tendon pathology, or whether these changes precede the onset of the problem and therefore act as a cause, or if they are solely the consequence of the pathological condition.

Not only do tendinopathic changes alter the mechanical properties of the tissues, but acute injuries such as ATR could also lead to tissue modification and therefore changes in tendon mechanical properties. In cases of ATR, the prolonged immobilization period and the formation of scar tissue after surgery can significantly impact collagen synthesis and degradation within the tendon. This results in a higher proportion of type III collagen in the operated tendon, which weakens the tendon and reduces its tensile strength (Geremia et al.,

2015, Kannus et al., 1997). However, there are few studies reported in the literature regarding the mechanical properties of AT after rupture and the results are conflicting with some studies demonstrating a decrease in tendon stiffness, (Chen et al., 2013, Frankewycz et al., 2018, Geremia et al., 2015, McNair et al., 2013, Wang et al., 2013) while others show an increase in stiffness (Agres et al., 2015, Bravo-Sanchez et al., 2021) compared to the unaffected side when assessed up to 2-6 years after the rupture. With the limited data available, it appears that in the post-surgery healing phase (less than 1 year), where remodelling is ongoing, (Voleti et al., 2012) the tendon exhibits reduced stiffness, which gradually increase over time, reaching a value comparable to or even exceeding that of the unaffected tendon in the later stages (Agres et al., 2015).

In summary, the behaviour of the mechanical properties of the AT in the presence of pathology has not been fully examined, and results in the literature are conflicting. This is likely due to the large heterogeneity between studies including the use of different technologies to assess tendon mechanical properties.

1.4 Tendon mechanical properties and exercise

The cellular and molecular response to load of different musculoskeletal structures is a process called mechanotransduction and is at the basis of the majority of the physical interventions in physical therapy (Khan and Scott, 2009). The duration, magnitude and type of load applied to the target structure triggers a response at a cellular level (Wall and Banes, 2005). When this stimulus is applied, the loading message is distributed by the cell throughout the target tissue producing a local cellular response as well as a remote response to distant cells not directly receiving the mechanical stimulus (Wall and Banes, 2005). These signals stimulating

cells to produce and accumulate the required proteins in the appropriate structure (Arnoczky et al., 2002, Khan and Scott, 2009) by increasing protein synthesis. Increased production of growth factors occurs when fibroblasts are mechanically stimulated resulting in increased collagen expression and synthesis (Chiquet et al., 2009).

Different types of force can be applied to the tendon solely or in combination, in particular: tensile strain, shear and compression forces. Among them, tensile strain is the most studied either in vitro and in vivo showing that tendon tissue can adapt to the application of different amounts of tensile strain by inducing collagen synthesis or degradation (Lavagnino and Arnoczky, 2005, Lavagnino et al., 2003). The capability of the tendon to react to the mechanical stimuli produced by different daily activities or sport activity and the modification to the mechanical properties of the tendon are not only important from a clinical-diagnostic perspective but could have an impact on the prescription of exercises-based treatments.

Recommendations exist in clinical guidelines (Carcia et al., 2010, de Vos et al., 2021) in favour of exercise therapy to treat tendon pathology and therefore an abundance of research has attempted to understand how tendons adapt to the different activities or type of exercises. In the following sections, evidence about the impact of physical activity and exercise on tendon mechanical properties will be summarized.

1.4.1 Immediate effect of exercise on mechanical properties

Evaluating alterations in tendon structure and mechanical characteristics immediately after exercise is fundamental to the understanding of the physiological and therapeutic effect of the intervention proposed. This understanding forms the basis for delivering efficient treatment strategies applicable to both patients and athletes and for implementing preventive measures.

Baseline mechanical properties of the tendon can encounter immediate changes following activities or exercises (Obst et al., 2013) predisposing the tendon to fatigue and reduced tensile strength. It is known that the AT responds to an acute bout of exercise by reducing its stiffness especially after isometric exercises and static stretching (Obst et al., 2013) but not after exercises or activities involving the stretch-shortening cycle. This different response is thought to be due to the intrinsic function on the AT that is routinely involved in the stretch-shortening cycle and therefore more resistant to fatigue during this type of activity rather than in activities that do not involve stretch-shortening cycle.

A reduction of tendon stiffness following exercise could also provide an explanation for recent findings that maximum muscle performance is temporarily reduced after a single session of static stretching (Kay and Blazevich, 2012). When the tendon is more compliant for a given muscle-tendon unit length, it would demand muscle fibers to work at relatively shorter lengths and take comparatively more time to generate equivalent tension in the absence of other adaptations. Consequently, this would lead to a decrease in both the strength magnitude and the rate of force development during exercises that do not involve stretch-shortening cycle (Barrett and Lichtwark, 2008, Maganaris et al., 2002, Narici et al., 2008, Wang et al., 2012). The aforementioned reduction of stiffness following exercise is not only attributed to the exercise mode but also to the exercise dose. Indeed, isometric contractions at a higher maximal voluntary contraction (MVC), and static stretching for a prolonged time has been shown to lead to a greater reduction of tendon stiffness (Obst et al., 2013).

A combination of duration, magnitude and mode of exercise should be taken into consideration when prescribing exercises oriented towards modifying the immediate mechanical properties of tendons. Despite the ongoing growth of experimental and clinical studies evaluating mechanical properties of tendons, understanding the connection between

acute exercise and tendon health remains unclear due to methodological variations, as well as differences in exercise modes and doses used in studies.

1.4.2 Long-term effect of exercise on mechanical properties

The importance of understanding the effect of exercise on tendon mechanical properties becomes even more important when considering the long-term effect of rehabilitation or exercise programs. Therapeutic approaches for addressing tendon complaints often involve extended programs of exercises (>12 weeks) expected to significantly impact clinical variables also by modifying tendon mechanical properties. The relationship between these two factors however is not yet clear but a deeper understanding of how tendons adapt with exercise could help to establish optimal exercise parameters and identify more effective therapeutic interventions.

In the literature, there is more evidence on how exercises can modify the morphological and structural parameters of pathological tendons, and a tendon that heals clinically after eccentric exercises may remain "altered" structurally (Drew et al., 2014, Farnqvist et al., 2020). Conversely, the relationship between clinical improvement and changes in mechanical properties is not clear and is currently limited to only a few studies that have attempted to understand whether changes in tendon mechanical properties due to exercise are correlated with clinical improvement in populations with tendon disease. A recent study confirmed that this relationship is not yet clear (Radovanovic et al., 2022). In a cohort of participants with Achilles tendinopathy, this study examined the clinical improvement and mechanical adaptations of the AT. They showed that the induced adaptations were more marked when the tendon was subjected to high load protocols. However clinical improvements were independent of the type

of protocol proposed (high load, eccentric or passive therapy) leaving doubt about the interplay between clinical improvement and mechanical changes. The authors concluded that even if there is not a clear link between clinical improvements and mechanical adaptations, a high load protocol could potentially enhance tissue integrity by increasing tendon stiffness and reduce the risk of further strain injuries to the tendon. Further studies analysing this relationship are needed to understand if tendon mechanical properties should be used as a parameter to detect if tissue loading capacity is related to changes in clinical features.

Several studies have investigated how the mechanical properties of tendons change following exercise protocols in healthy subjects. To date, the available literature seems to agree that tendon stiffness increases after training interventions especially if high intensity or high strain is provided to the tendon (Lazarczuk et al., 2022, Ramirez-delaCruz et al., 2022, Bohm et al., 2015a, Wiesinger et al., 2015). Extensive research has demonstrated that tendons are responsive to mechanical stimuli and can adapt significantly when subjected to prolonged changes in mechanical load, by increasing stiffness (Bohm et al., 2015a, Wiesinger et al., 2015). These changes in the tendon's mechanical properties could alter its functionality, indeed a stiffer tendon undergoes less strain when subjected to a specific load and can store more energy at a given strain. Additionally, a stronger tendon can withstand higher external loads before failure occurs. Studies indicate that stiffer tendons in the lower limbs are associated to enhanced rates of force development (Bojsen-Moller et al., 2005, Kubo et al., 2007, Secomb et al., 2015), improved sprint performance (Stafilidis and Arampatzis, 2007), enhanced running efficiency (Albracht and Arampatzis, 2013, Arampatzis et al., 2006, Bohm et al., 2021), and reduced vulnerability to tendon injuries (Mersmann et al., 2021).

Some authors suggest that mechanical and morphological changes are related to the increment of collagen synthesis, to changes in the collagen fibril morphology and to the

different collagen molecular cross-linking (Heinemeier and Kjaer, 2011, Kjaer et al., 2009). More precisely, the increase of collagen synthesis could increase collagen total content and fibrils size (diameter). This change in the morphology of the tendon (increased thickness and cross-sectional area CSA) may be related to changes in the mechanical and material properties change (increased stiffness and modulus). Indeed, as stiffness is directly dependent on CSA, hypertrophy of the tendon should induce greater stiffness. However, controversial results were found in literature when analysing material properties, with some in-vivo studies showing an increase in modulus without any change in CSA (Arampatzis et al., 2010, Reeves et al., 2003) and others showing an increase of both modulus and CSA (Kongsgaard et al., 2007, Arampatzis et al., 2007a, Seynnes et al., 2009). Recent studies suggest that the primary driver to these changes seems to be a change in the material properties (i.e., increase in extracellular matrix proteins and collagen remodelling) which appear early after the application of load (Lazarczuk et al., 2022). Changes in tendon morphology (i.e., thickness and CSA) could contribute to the increase of tendon stiffness but this seems to be a long-term effect of sustained mechanical loading. Apparently, the magnitude of loading is an important component to promote adaptive changes. Indeed, exercises with high loading intensities are more likely to induce adaptive responses when compared to low intensities loads (Bohm et al., 2015a, Radovanovic et al., 2022, Wiesinger et al., 2015). These results are confirmed by other studies that suggest the importance of high muscle contraction intensities to promote AT adaptations (Arampatzis et al., 2007a, Arampatzis et al., 2010, Lazarczuk et al., 2022).

Overall, the available evidence indicates that the adaptation of tendons is not notably affected by the duration of the intervention protocol, the intensity relative to the protocol, the mode of contraction, or the volume of training. As a result, resistance training protocols with high strain are likely to be most advantageous when tendon adaptation is the intended goal

(Lazarczuk et al., 2022). These studies allow us to assert that tendons adapt to the proposed exercises and that certain types of exercises are more suitable if the goal is to modify tendon mechanical properties.

1.5 Measurement of tendon mechanical properties

It is known that tendon disorders affect the morphological characteristics of tendons (Cook and Purdam, 2009). Tendinopathies, for instance, lead to an increase in thickness, CSA, and internal composition of tendons (Cook and Purdam, 2009). Tendon ruptures, whether treated surgically or conservatively, result in an enlargement of tendon dimensions (Geremia et al., 2015). Numerous studies demonstrate that evaluating morphological parameters of tendons, such as via ultrasound, can confirm the diagnoses of tendinopathies (Matthews et al., 2018). However, these morphological parameters do not seem to be as sensitive in assessing the temporal changes of a condition. In fact, tendons that have undergone ruptures or have been subjected to overload, showing morphological alterations in the acute phase of the pathology, may not change their characteristics over time, maintaining pathological appearances even when the pathology is clinically resolved (Drew et al., 2014, Farnqvist et al., 2020). This has prompted several researchers to question the utility of tendon morphology measurements (Docking and Cook, 2019, Docking et al., 2015, Drew et al., 2014) and to adopt a different approach, assessing whether mechanical properties could provide a more comprehensive perspective on this complex phenomenon. Considering the main functions of tendons, such as transmitting forces from the muscular system to the skeletal system to facilitate movement, (Maffulli et al., 2005, Kvist, 1991, Benjamin et al., 1995) storing and releasing energy during daily activities, and contributing to postural control (Benjamin et al., 1995), it is evident that

tendons act as springs or shock absorbers. Consequently, it is relevant to consider the mechanical properties of tendons in addition to their dimensions.

In recent years, the interest in measuring mechanical properties of tendons has grown. The assumption that altered mechanical properties can be related to tendon pathology has gained ground, and as a result, numerous technologies aiming to assess these properties have been rapidly developed. The first attempts to assess the mechanical properties of tendons in vivo date back to the studies by Kubo et al. (Kubo et al., 2001) who, using a combination of ultrasonography and dynamometry evaluated muscle-tendon unit elongation during contractions and estimated the stiffness and Young's modulus of patellar tendons (PT). Later, several research groups replicated these measurements in different contexts, observing the behaviour of other tendons (Arampatzis et al., 2005, Fukashiro et al., 1995, Kubo et al., 2002, Maganaris, 2002, Maganaris and Paul, 2000, Maganaris and Paul, 2002, Magnusson, 2002). This methodology has some considerable advantages and has been used to evaluate the effect of different rehabilitation protocols (Arya and Kulig, 2010, Geremia et al., 2015) as well as examining tendons with aging and pathology (Magnusson et al., 2003, Kubo et al., 2003, Couppé et al., 2014). However, some methodological issues are related to this type of analysis. Firstly, the complexity of the experimental setup that requires the synchronization of different devices can limit the usability of this technique in clinical settings. Secondly, tendon strain is measured by tracking the displacement of the intra-muscular aponeurosis (myotendinous junction MTJ). Some authors suggest that changes in the aponeurosis could not be directly translated to the free-tendon given that this structure behaves differently when put under load (Obst et al., 2015, Magnusson et al., 2003). Thirdly, CSA is often arbitrary chosen or measured in only one site of the free tendon. Given that the CSA is not homogeneous along the tendon

(Foure, 2016, Bohm et al., 2015b), this measure may not be representative resulting in a misleading calculation of tendon stiffness.

Subsequently, with the aim to simplify and make this assessment more clinically applicable, other technologies have been developed. Among these there is sonoelastography, myotonometry, and tensiometry. All of these technologies have been implemented in tendon assessment with varying degrees of success, and each technology comes with its own advantages and disadvantages. In the following sections, the strengths and weaknesses of some of the most widely used technologies in assessing the mechanical properties of tendons will be briefly summarized.

1.5.1 Sonoelastography (strain and shear wave)

Developed about three decades ago with the aim of analysing the elastic properties of tissues, especially in gynaecological and oncological medicine (Ophir et al., 1991, Bercoff et al., 2004), ultrasound elastography (or sonoelastography) has also gained ground in the musculoskeletal field with a wide variety of clinical applications (De Zordo et al., 2009, Klauser et al., 2013, Prado-Costa et al., 2018). This technology is based on the principle that, in response to the application of a stimulus (stress force), the underlying tissues undergo internal displacement, allowing the description of the elastic properties of the material (Ophir et al., 1991). Three mayor steps are needed to obtain sonoelastography values: 1) the application of a defined force (stress); 2) the measurement of the tissue response (strain) to the applied force and 3) the estimation of the mechanical parameters.

Given its applicability and relative cost-effectiveness, the development of this technology has been very rapid, generating various techniques for assessing elasticity through

the ultrasound signal, including SWE and SE (Prado-Costa et al., 2018) (see Figure 1.2). The main difference between these two techniques is the use of different sources to generate the required stress on the tissue and allow its displacement. The first, SWE, uses an ultrasound source called focused radiation force (Bercoff et al., 2004, Sandrin et al., 2002), which travels in the tissues and generates a shear wave within the tissue. On the contrary, the source that generates stress and thus tissue displacement in SE is manual; the application occurs through brief and rapid compressions of the tissue using the ultrasound probe (Drakonaki et al., 2009) Different estimation of the elastic properties of the tissue distinguishes the two technologies with SWE providing values of shear-wave velocity, that is directly correlated to the shear modulus (G) and Young's elastic modulus (E) and SE providing a colour-coded elastogram (from blue to red) indicating hard to soft tissue.

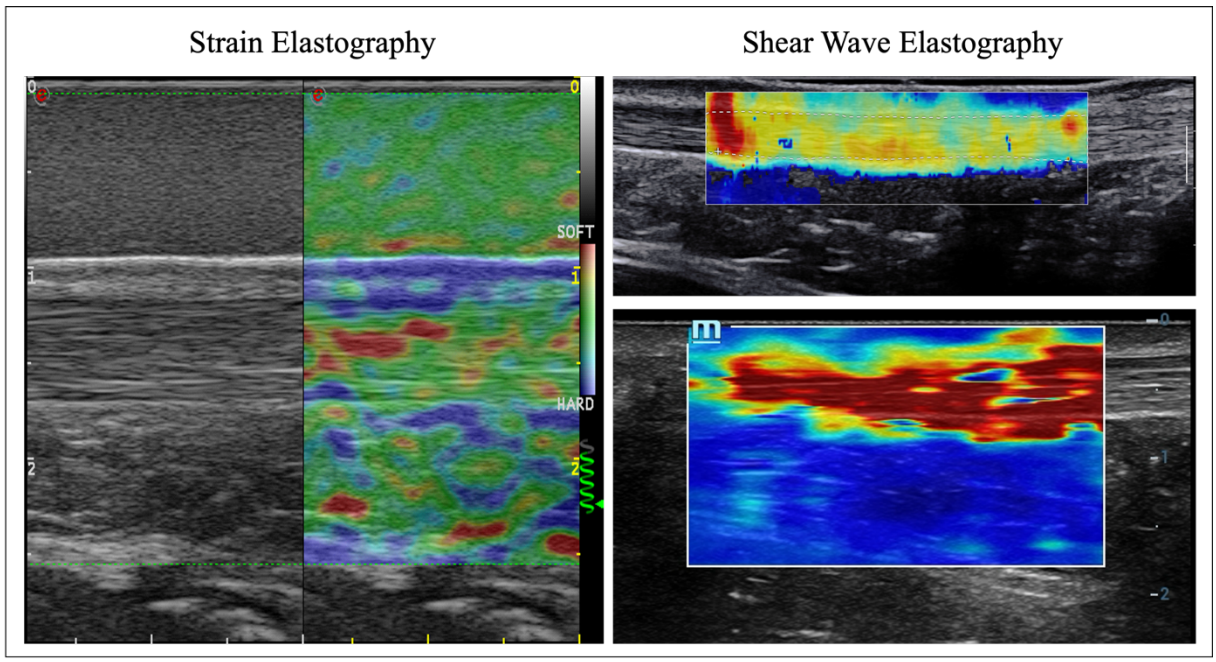


Figure 1.2: Example of the different sonoelastography technologies. Left panel represent a SE image of an Achilles tendon using an external reference material, right panel represent SWE images of Achilles tendon using two different ultrasound devices.

In the characterization of tendon mechanical properties, SWE can provide objective and quantitative values while the values obtained with SE are qualitative, due to the evaluation of colours within the elastogram. Some studies (Drakonaki et al., 2012, Schneebeli et al., 2016, Yamamoto et al., 2016) have tried to obtain objective values derived from SE by performing a semi-quantitative analysis (strain ratio) where ratio between colour in different region of interest (ROI) are computed.

Sonoelastography has been employed in various contexts, particularly to assess potential changes in tendon elasticity during pathological processes such as tendinopathies (De Zordo et al., 2009, Klauser et al., 2013) and tendon ruptures (Frankewycz et al., 2018, Zellers et al., 2019, Bravo-Sanchez et al., 2021, Chen et al., 2013, Busilacchi et al., 2016). Some authors suggest that alterations in mechanical properties, detectable through sonoelastography, might be visible even before morphological changes, as assessed by ultrasound (De Zordo et al., 2009, Hsiao et al., 2015), enabling an early diagnosis of tendinopathy. However, this cannot be asserted with certainty as only a few studies attempt to evaluate this hypothesis.

Compared to the approach proposed by Kubo et al. (Kubo et al., 2001) involving dynamometry and ultrasound, sonoelastography has the advantage of a more direct measure of the tendon. Measurements taken with sonoelastography are focused on the tendon of interest, allowing for a comprehensive evaluation not limited to the analysis of the intra-muscular aponeurosis. According to some studies (Obst et al., 2015, Kubo et al., 2006, Kubo et al., 2009, Magnusson et al., 2003), the behaviour of the free tendon (the central part of the tendon) may differ from the aponeurosis when subjected to a load. Therefore, more direct measurements on the tendon could provide a better understanding of its mechanical behaviours. Moreover, sonoelastography can be easily applicable in a clinical setting as it is user-friendly and does not

require the patient to perform high-intensity contractions using a dynamometer, which may not be possible in some painful conditions or in post-surgical patients. However, these ultrasound technologies have disadvantages and limitations. Firstly, analysis through sonoelastography requires trained operators with some competence in ultrasound imaging. Indeed, probe handling, setting adjustment and experience in the image interpretation can influence the use of this type of technology. Secondly, to date this type of technology, especially SWE, seems to be limited to an analysis of the tendon in relaxed position, high stiffness values cannot be evaluated for technical reasons. These limitations could impact on the clinimetric properties of these instruments, such as reliability, accuracy, and responsiveness, thereby hindering their clinical applicability.

1.5.2 Myotonometry

Myotonometry is a recently developed technology that uses accelerometers to measure mechanical properties of soft tissues. Developed for the evaluation of superficial muscles, this technology, and in particular the MyotonPRO device (Myoton AS, Tallinn, Estonia), has been successfully transferred to the evaluation of other musculoskeletal structures like tendons (Orner et al., 2018, Morgan et al., 2018, Liu et al., 2018, Feng et al., 2018). This device is a simple and ready to use handheld myotonometer that generates a mechanical impulse on the skin above the target structure. The oscillation of the tissues beneath the probe generates an acceleration graph representing the damped natural oscillation and allows the calculation of the tissue's viscoelastic properties (Gervasi et al., 2017, Fröhlich-Zwahlen et al., 2014, Agyapong-Badu et al., 2016). Different parameters (i.e. oscillation frequency, stiffness and mechanical stress relaxation time) can be extracted from this oscillation graph representing different

mechanical properties of the tissues. Between these parameters the most commonly used to characterise tendon mechanical properties is dynamic stiffness (N/m). Dynamic stiffness describes the resistance to deformation under oscillatory or time-varying loads and depends on frequency, evaluating both elastic and damping effects. These parameters have already been assessed both in vivo, in vitro and in phantom tissues (Sohirad et al., 2017, Bartsch et al., 2023, Shan et al., 2024). When compared to elastography measures of AT a strong association was demonstrated between Young modulus measured with SWE and stiffness measured with MyotonPRO (Feng et al., 2018).

The reliability of MyotonPRO has been largely demonstrated for skeletal muscles (Ortega-Cebrian et al., 2016, Kelly et al., 2018, Fröhlich-Zwahlen et al., 2014, Bizzini and Mannion, 2003) but less investigated in tendons. (Liu et al., 2018) Compared to sonoelastography and to ultrasound with dynamometry, MyotonPRO has the significant advantage of being a very affordable instrument, it is easy to use, and, due to its compact size and portability, it is applicable in all clinical settings. The size of the probe allows only the assessment of a small region, but due to the quick execution of the measurements, an extended area of the target tissue can be evaluated easily.

This technology does have its limitations. Firstly, it can only assess superficial structures because the impulse induced by the device is small (about 0.58 N), limiting propagation to the most superficial layers. Therefore, evaluating muscles or tendons located deeper or beneath other structures may not be possible. Secondly, the limited force of the impulse can also be a hindrance in measuring structures with high stiffness. For example, some stiffer tendon areas like the osteotendinous junction or tendons under load may reach stiffness values that cannot be accurately measured.

1.5.3 Tensiometry

Tensiometry is a technology that has been developed in recent years and allows the evaluation of the mechanical properties of tendons, particularly tendon loading, thanks to the analysis of the shear wave propagation speed within the tendon. This technique is related to SWE where the impulse to generate the shear wave is created by the ultrasound devices and the high frame rate allow an evaluation of the wave speed within the tendon and subsequently the estimation of tissue elasticity (Bercoff et al., 2004).

In shear wave tensiometry, the impulse is mechanically generated by an actuator and the wave speed propagation is detected by small accelerometers attached in series on the tendon (Martin et al., 2018). Based on a tensioned beam model the wave speed within the tendon varies in proportion to the axial stress in the tissue (Martin et al., 2018) and can be estimated based on the delay between the waveforms detected by adjacent accelerometers (Figure 1.3).

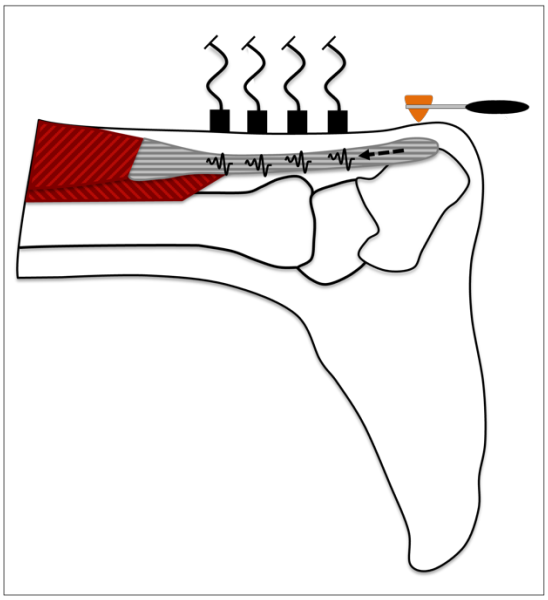


Figure 1.3: Schematic of the shear wave tensiometry device.

The development of this technology is ongoing and therefore some technical aspects need to be investigated in more detail, among these are how adjacent tissues can influence the propagation of the shear wave (Blank and Thelen, 2023) and how the tendon geometry can vary the tensiometry values. However, this technology has already been implemented in different clinical contexts to assess the relationship with ankle kinematics during walking (Ebrahimi et al., 2020, Keuler et al., 2019) and to evaluate the tendon loading in children with cerebral palsy (Ebrahimi et al., 2023). Moreover, shear wave tensiometry is a suitable technology that can measure the axial strain of the tendon at high level of loading for example with muscle MVC (Keuler et al., 2019) or during running (Reiter et al., 2024b). However, this technology is not widely available, except for a few research groups that are developing prototypes, thus its clinical applicability is not yet assured.

1.6 Measurement of tendon during loading tasks

As mentioned in the earlier sections of this Chapter, the AT acts like a shock absorber and transmits extremely high forces from the muscle to the bone. Therefore, high levels of load have to be tolerated by this structure in order to perform physical activities. For example, during running the AT is subjected to tensile forces of up to 12 times the body weight, approximately a stress of 110 MPa in each stride (Komi et al., 1992, Paavola et al., 2002). Given its function, closely linked to load absorption and release, evaluating the AT during tasks that stress the musculotendinous system could allow better characterization of the behaviour of this structure and understand both its capabilities and vulnerabilities. Therefore, the majority of the studies presented in this thesis are based on a concept that the tendon is not only measured in a relaxed position but also during different controlled isometric loads. Fixed loads were selected to ensure

a more standardized contraction in the reliability studies and avoid potential bias due to the calculation of the maximal voluntary contraction.

Isometric contraction of the ankle plantar flexors of increasing intensity gradually put load on the whole musculotendinous complex resulting in an increased tension of the AT (Maganaris, 2002, Maganaris and Paul, 1999). The use of this approach of measuring mechanical properties during loading tasks could potentially give us more information about the loading status and possibly detect adaptation or maladaptation resulting from exercises or pathology.

1.7 Thesis aims and objectives

The overall aim of this thesis is to assess the available technologies in the detection of AT mechanical properties and to characterise the tendon mechanical properties in healthy participants and participants with AT injuries during loading tasks.

In order to pursue the overall aim of the thesis, nine studies were conducted. More specifically, technologies ranging from ultrasound-based imaging to newer technologies based on the response to mechanical stimuli have been employed to understand their applicability in assessing tendons during contractions. The clinimetric properties as well as strength and weakness of each technology has been evaluated.

The specific objectives of the thesis are:

1. **Chapter Two** - To assess the capability of SE to detect AT changes in mechanical properties during contraction.
2. **Chapter Three** - To compare SWE and SE in assessing the elasticity of the AT.

3. **Chapter Four** - To assess the reliability of the available sonoelastography technology in the assessment of AT and PT.
4. **Chapter Five** - To evaluate the reliability and construct validity of myotonometry in the evaluation of AT in different position and during contraction
5. **Chapter Six and Seven** - To present a newly developed technology using shear wave speed to detect AT loading and to evaluate its reliability and clinical implementation.
6. **Chapter Eight and Nine** - To test the possibility to implement this technology in a clinical population with ATR and evaluate its capability in detect loading changes.
7. **Chapter Ten** - To evaluate strengths and weaknesses of these technologies.

A visual representation of the thesis objectives is presented in the Figure 1.4.

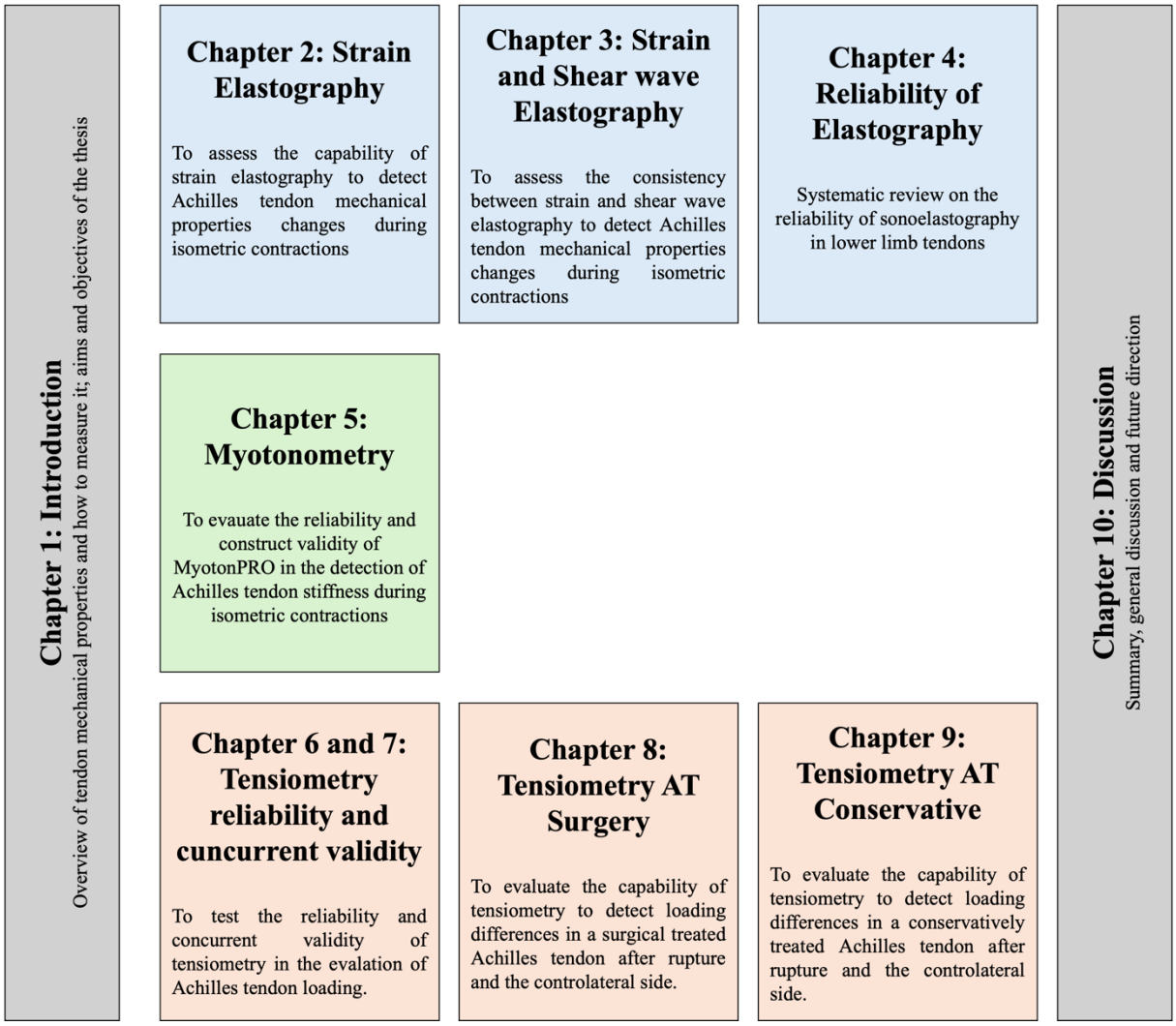


Figure 1.4. Visual representation of the thesis chapters with the objectives. Blue boxes represent the studies done with sonoelastography, the green box refers to an evaluation with myotonometry and orange boxes are studies using shear wave tensiometry.

1.8 Thesis chapters overview

In the current Chapter - Chapter one - an overview of the available technologies for measuring tendon mechanical properties has been presented and the importance of tendon mechanical properties in the clinical assessment of tendon disease has been highlighted. This chapter has established the context for the following chapters. Chapter two and three are

observational studies that evaluate the capability of different sonoelastography technologies to detect AT mechanical properties during isometric contraction and to determine the consistency between the two technologies (SE and SWE). Chapter four reports the results of a systematic review on the reliability of SE and SWE applied in the detection of mechanical properties of lower limb tendons. This systematic review was conducted based on the results of Chapter two and three since the use of SE and SWE had raised doubts about its applicability. Chapter five describes an observational study done on healthy AT with an innovative, ready to use device, called MyotonPRO. The aim was to test its reliability and construct validity in the detection of AT stiffness during load. In Chapter six and seven**,** a promising technology based on the tensiometry principle has been presented and evaluated through a reliability study (Chapter six) and a pilot laboratory study (Chapter seven) with the aim to test the possibility to implement this technology in the evaluation of a clinical population. Chapter eight reports the results of a cross-sectional study that uses tensiometry to detect differences in tendon loading between a surgically treated AT after rupture and the contralateral healthy side, whereas Chapter nine describes the use of the same technology in another population: participants with ATR treated conservatively. Finally, Chapter ten, summarizes and discuss the findings of the preceding chapters. In particular, a general discussion on the clinical utility of mechanical properties measurement is presented with a special focus on the strengths and limitations of the different technologies used. Suggestions for future research in the field is also provided.

CHAPTER 2

A NOVEL APPLICATION OF STRAIN SONOELASTOGRAPHY CAN DETECT CHANGES IN ACHILLES TENDON ELASTICITY DURING ISOMETRIC CONTRACTIONS OF INCREASING INTENSITY

This chapter reports in full the contents of a published manuscript by the thesis author (Schneebeli et al. 2019). It includes verbatim text from the published manuscript and some changes employed for the purpose of this thesis.

Publications and Presentations

1. **Schneebeli A**., Del Grande F., Falla D., Cescon C., Clijsen R., Barbero M. 2019. A novel application of strain sonoelastography can detect changes in Achilles tendon elasticity during isometric contractions of increasing intensity. Journal of Foot and Ankle Research. 21;12:30. **(Appendix 1)**
2. **Schneebeli A**., Falla D., Del Grande F., Cescon C., Clijsen R., Barbero M. Evaluation of Achilles tendon stiffness during contraction using strain sonoelastography. Physiotherapy UK conference, Birmingham. November 2018

2.1 ABSTRACT

Mechanical and morphological properties of the AT are altered in disease and in response to changes in mechanical loading. In the last few years different ultrasound-based technologies have been used to detect tendon mechanical properties changes mainly in resting condition. The aim of this chapter was to evaluate if SE can identify changes in AT elasticity during isometric contractions of increasing intensity.

This cross-sectional study enrolled 37 healthy volunteers (19 women) with mean (±SD) age of 27.1 (±7.0) years between January and June 2017. SE images of the AT were acquired during an isometric ramp force (0 kg, 0.5 kg, 1 kg, 2 kg, 5 kg and, 10 kg). An external reference material was used to provide a comparison between the examined tissue and a material of constant elasticity. Friedman test with post hoc pairwise comparison were used to determine the correlation between the difference contraction levels.

The median and interquartile range (IQR) values for the strain ratio were 1.61 (1.5–2.9) in a relaxed state and 1.30 (1.07–2.02), 1.00 (0.76–1.66), 0.81 (0.70–1.19), 0.47 (0.39–0.73) and 0.33 (0.28–0.40) for 0.5 kg, 1 kg, 2 kg, 5 kg and 10 kg, respectively revealing increased tendon hardness with increasing contraction intensities. Friedman test revealed significant differences ($p < 0.05$) in the strain ratio between all contractions except between 0.5 kg – 1 kg ($p = 0.41$); 1 kg – 2 kg ($p = 0.12$) and 5 kg – 10 kg ($p = 0.12$).

SE can detect changes in AT elasticity between different contraction intensities. The results provide an original force-elasticity curve for the AT in a healthy, asymptomatic population.

2.2 Introduction

As discussed in Chapter one**,** mechanical and morphological properties of the AT are altered in tendon pathology and in response to changes in mechanical loading, including a reduction in tendon stiffness and a softening of the tendon measured with SE in individuals with chronic tendinopathy (Arya and Kulig, 2010, Aubry et al., 2015).

A healthy AT with intact mechanical and morphological properties is expected to become stiffer and harder with increased tensile load during isometric contraction (Muraki et al., 2015, Schneebeli et al., 2016). As shown by Magnusson et al. (Magnusson et al., 2003), both deformation and strain of a healthy AT increase with an increase in tendon isometric force. Similarly, Lersch et al. (Lersch et al., 2012) demonstrated increased strain of the AT when the tendon was subjected to an increased load. Wren et al. (Wren et al., 2001) showed an increased Young's modulus in a similar in vitro investigation using a servo-hydraulic materials testing machine, and although in vivo and in vitro results are not directly comparable, the AT seems to behave similarly.

SWE is based on acoustic radiation force impulses through tissue to obtain the elastic modulus (Young modulus, kPa) and is typically employed to measure AT elasticity. However, given that the upper limit of 800 kPa of Young modulus is often reached in the AT when the ankle is near 0° of plantar flexion, this measurement technique is not suitable for the evaluation of the tendon in a functional position (near 0° plantar flexion), during usual movement or with additional load (Aubry et al., 2013). Moreover, signal saturation occurs when the AT approaches the 0° plantar flexion or a dorsiflexed position and leads to an underestimation of the shear wave speed (DeWall et al., 2014).

SE is another ultrasound-based technique that enables the elasticity of musculoskeletal structures to be evaluated (De Zordo et al., 2009, Yanagisawa et al., 2011). Tissue compression with an ultrasound probe is applied to a surface producing a displacement within the tissue. The displacement, which is less pronounced in harder than in softer materials, is calculated by comparing B-mode image pairs before and after compression (Ophir et al., 1991). A novel method using SE and calculation of a strain ratio was recently developed and provides a semi-quantitative evaluation of the tendon based on the elastography colour scale (Schneebeli et al., 2016). Combined with an external reference material, this approach can identify changes between a contracted and relaxed state (Schneebeli et al., 2016), however the accuracy of this novel method to detect small changes in tendon mechanical properties due to load, needs further investigation. The use of an external reference material with known elasticity properties allows the computation of the strain ratio between the tendon colour scale and the external material which is not affected by changes during contraction. This method has established reliability (Schneebeli et al., 2016, Yamamoto et al., 2016). The added value of this methods is the combination of a measure of elasticity, provided by the transverse compression force of the probe, and the progressive longitudinal mechanical load given by the contraction of the triceps surae muscle.

A more comprehensive analysis of the AT with evaluation of the tendon under load is warranted as this approach could provide a clearer indication about the functional impairment of tendon structure. Therefore, together with clinical history and standard imaging this technology could ultimately lead to an enhancement of the diagnosis and management of tendinopathy.

This chapter addresses the thesis objective number one as follows: the aim was to evaluate if SE using the strain ratio, can accurately detect changes in AT elasticity during isometric contractions of varying intensity in healthy volunteers.

2.3 Methods

The study was approved by the Ethics Committee of Canton Ticino (CE 2752 see Appendix 9), conducted according to the Declaration of Helsinki and written informed consent forms were signed by participants. The report of this study adheres to STROBE (Strengthening The Reporting of Observational Studies in Epidemiology) guidelines (von Elm et al., 2007).

2.3.1 Study population

Thirty-seven healthy participants (19 women) were prospectively enrolled in the study between January to June 2017. The mean (±SD) age, height and weight were 27.1 (±7.0) years, 172.2 (±9.8) cm and 67.5 (±13.2) kg, respectively. Inclusion criteria for the selection of the sample were: no history of tendon and/or foot injury or surgery; any painful episodes in the lower limb in the last year. Exclusion criteria were: history of connective tissue, endocrine or metabolic diseases; systemic inflammatory disorder; spondyloarthropathy, rheumatoid arthritis, or hypercholesterolemia. Furthermore, those usually taking oestrogen or steroid treatment were excluded.

Mean and standard deviation values of relaxed and contracted strain ratios from a previous study (Schneebeli et al., 2016) using the same experimental setup were used to calculate the minimal sample size necessary to ensure a statistical power of 90% at the 5%

significance level for a two-tailed hypothesis test. The Cohen's d effect size has been calculated using the pooled standard deviation of the previous study (Schneebeli et al., 2016). Effect size was very large (d = 1.69). The calculation, performed with STATA 14 (College Station, TX, USA), showed that the minimal sample size of n = 32 was required.

2.3.2 Ultrasound and sonoelastography

A MyLab Class C ultrasound device (Esaote, Genoa, Italy) with a linear probe (3–13MHz) and elastography software were used to perform the measurements. The AT was visualized through a custom-made external material (Zerdine® CIRS, Norfolk, VA, USA). The properties of the reference material were tested by the manufacturer, the elasticity was 102 kPa, speed of sound was 1580 m/s, and the attenuation coefficient was 0.5 dB/cm/MHz. The external reference material was utilized to guarantee a comparison between the AT and a material with known elasticity (102 kPa). Furthermore, the reference material was used as stand-off pads to create a steady contact between the transducer and the skin and to enhance the stability of the sonographer's hand (Drakonaki et al., 2012). Light and rhythmic perpendicular compression was applied by the operator with the ultrasound probe on the reference material. A quality indicator graph on a screen in front of the operator was controlled to regulate the amount of the compression across condition and participants. Compression–relaxation cycles were provided for 5 s (approximately 100 frames) for each acquisition, during this time the sonoelastogram remained as stable as possible.

2.3.3 Dynamometry

The torque of the ankle was assessed using a dynamometer connected to a force sensor that operated linearly in the range between 0 and 100N (Mod. TF2/S; CCT Transducers, Turin, Italy). The force sensor was attached to a wooden board connected to a hinge that allowed natural dorsiflexion and plantar flexion of the ankle (Figure 2.1). The board was fixed in order to permit isometric contractions only at a fixed angle of 0° dorsiflexion. The force measured by the force sensor was proportional to the torque exerted at the ankle level. Force signals were amplified using MISO-II (OT Bioelettronica, Turin, Italy; bandwidth 0– 80 Hz) and presented to the participants as real time visual feedback (60 Hz refresh rate) on a PC monitor positioned 50 cm in front of the subjects.

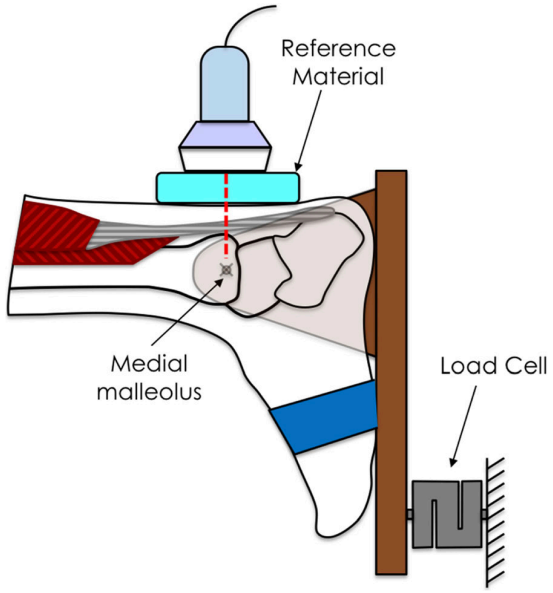


Figure 2.1 Schematic of the experimental setup. The foot was securely attached to a dynamometer with a wooden board at a fixed angle of 0° of dorsiflexion. The force measured by the load cell was proportional to the torque exerted at the ankle level. The ultrasound probe was placed in a longitudinal scan at the level of the medial malleolus.

2.3.4 Procedures

Participants were asked to lie in a prone position with the foot tightly secured within the dynamometer with the ankle in a neutral position (0° of plantarflexion). Prior to the recordings, the participants practiced the contraction with the instruction to "push on the board as if you were pushing onto the top of your toes") and a contraction of 10 kg (maximum strength required) was performed to verify that the heel remained in contact with the dynamometer and to familiarize the participant with the visual feedback. Heel movement was prevented during the contraction by firmly securing the foot in the dynamometer with two belts over foot and ankle.

Both the left and right AT of each participant were evaluated during isometric plantar flexion under increasing contraction intensities (0 kg, 0.5 kg, 1 kg, 2 kg, 5 kg and, 10 kg) performed in a randomized order. SE of the AT was performed in a longitudinal scan using the Elasto-Dual software (Figure 2.3). The external reference material was included in the image and the measurement were performed at the level of the medial malleolus applying an established and reliable method (Schneebeli et al., 2016). To guarantee the evaluation of the same tendon part under the different conditions, a reference point on the medial malleolus was drawn and the ultrasound transducer was aligned with the point each time. All the ultrasound procedures were conducted by the same, well-trained operator, with 8 years of ultrasound and elastography experience.

The colour scale of the elastograms ranged from red, showing soft tissue, to blue showing hard tissue, whereas green to yellow indicating medium tissue elasticity. The elastograms were automatically constructed maintaining the same ideal settings during the entire study, as recommended by Havre et al. (Havre et al., 2008) in a previous study.

2.3.5 Image analysis

The analysis of the 5 s ultrasound clip was leaded using a customized MATLAB® software (MathWorks, Natick, MA, USA). Two different ROI were drawn on the sonoelastographic images, including the reference material and the AT (Figure 2.3). The range between soft and hard (from red to blue) was divided into 256 levels (0–255) according to the depth of colour of the sonoelastographic image where blue corresponds to 0 and red to 255. The frames of the entire clip were averaged to extract a single image where the colour distribution was calculated. The median and interquartile range of colours was computed for each acquisition. Strain ratios were calculated between the AT median range of colours and the external reference material median range of colours, comparisons between the different contraction levels were computed for each tendon.

2.3.6 Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 22 (SPSS, Chicago, IL, USA) was used to perform statistical analysis. Descriptive statistics (mean ± SD) were used to describe the characteristics of the sample. Shapiro-Wilk test was used to evaluate if the data were normally distributed. Non-parametric, independent samples, Mann-Whitney test was then used to assess whether there were significant differences in AT elasticity between men and women and between the right and left AT.

Since the data were not normally distributed, Friedman test with post hoc pairwise comparison (Wilcoxon signed-rang test) were used to determine the correlation between elasticity measured at different contraction levels. Bonferroni correction was applied and

statistical significance was set to $\alpha = 0.05$. Data are presented as median and interquartile range (IQR).

2.4 Results

No significant difference in AT strain ratios was observed between men median (IQR) 1.31 (0.96–1.81) and women 2.00 (1.19–2.81) ($p = 0.6$) or between the left 1.48 (1.13–2.06) and right AT 1.71 (0.94–2.91) ($p = 0.5$), therefore the data were pooled and further analysed as an entire sample. The median (IQR) values for the strain ratio were 1.61 (1.5–2.9) in a relaxed state and 1.30 (1.07–2.02), 1.00 (0.76–1.66), 0.81 (0.70–1.19), 0.47 (0.39–0.73) and 0.33 (0.28–0.40) for 0.5 kg, 1 kg, 2 kg, 5 kg and 10 kg, respectively. Friedman test for related samples showed significant ($p < 0.01$) differences between all contraction levels except for 0.5 kg – 1 kg ($p = 0.41$); 1 kg – 2 kg ($p = 0.12$) and 5 kg – 10 kg ($p = 0.12$) (Figure 2.2)

Detailed pairwise comparison for all the contraction levels are presented in Table 2.1.

Contraction levels (Kg)	Pairwise comparison	Contraction levels (Kg)	Pairwise comparison	Contraction levels (Kg)	Pairwise comparison	Contraction levels (Kg)	Pairwise comparison	Contraction levels (Kg)	Pairwise comparison
0 - 0.5	**p < 0.01**	0.5 - 1	p = 0.41	1 - 2	p = 0.12	2 - 5	**p < 0.01**	5 - 10	p = 0.12
0 - 1	**p < 0.01**	0.5 - 2	**p < 0.01**	1 - 5	**p < 0.01**	2 - 10	**p < 0.01**	-	-
0 - 2	**p < 0.01**	0.5 - 5	**p < 0.01**	1 - 10	**p < 0.01**	-	-	-	-
0 - 5	**p < 0.01**	0.5 - 10	**p < 0.01**	-	-	-	-	-	-
0 - 10	**p < 0.01**	-	-	-	-	-	-	-	-

Table 2.1 Pairwise comparison for the different contraction levels. Statistically significant results ($p < 0.01$) are represented in bold

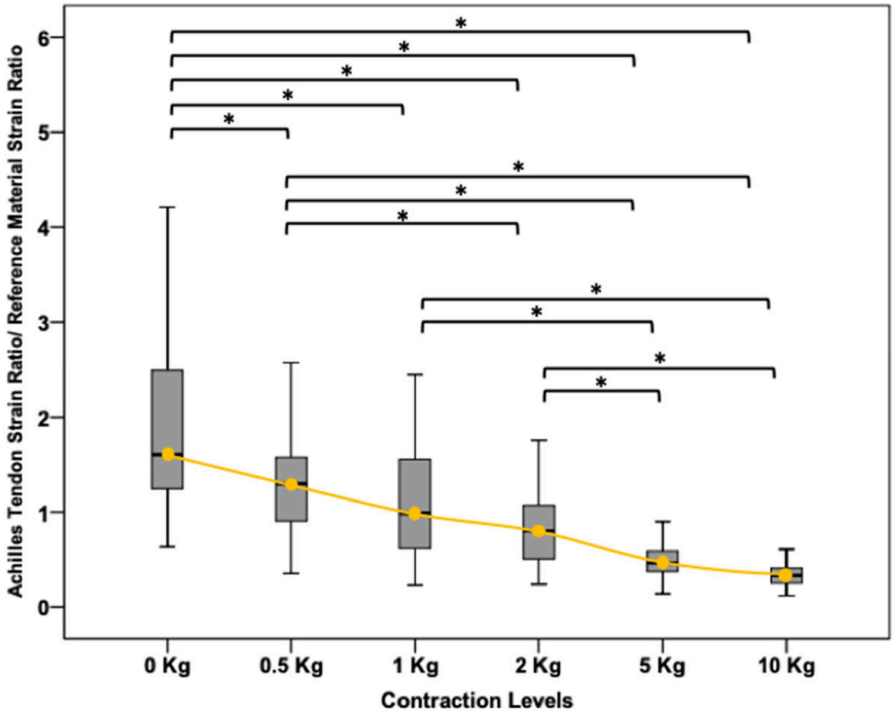


Figure 2.2. Force-elasticity curve. Box plot showing the median and interquartile range of values of the entire sample during the different contraction levels. The orange line represents the force-elasticity curve. * p < 0.01; statistically significant difference between the different contraction levels

2.5 Discussion

This is the first study to evaluate changes in AT elasticity using strain sonoelastography during progressive increases in contraction force. The results provide an original force-elasticity curve for the AT in a healthy, asymptomatic population (Figure 2.2).

This study confirms that SE can detect changes in AT elasticity between a relaxed state and all the examined contraction levels; the AT progressively become harder across the different contraction levels, and this increment was seen as a reduction of the strain ratio as previously reported in other studies (Muraki et al., 2015, Schneebeli et al., 2016). A previous study (Schneebeli et al., 2016) with a similar experimental setup showed large variability of the

AT strain ratio between healthy subjects when measured in the resting state. This variability, similarly to our study, is reduced when load is put on the tendon (Figure 2.2). The large variability seen between participants when the tendon is measured in the relaxed state is likely related to variation in physical activity levels, age and individual anatomical differences. Although tendon elasticity changed across contraction intensities, the contraction levels with similar intensity (0.5 kg – 1 kg ($p = 0.41$); 1 kg – 2 kg ($p = 0.12$) and 5 kg – 10 kg ($p = 0.12$)) revealed similar measures of elasticity thus likely the difference in load was insufficient to change tendon mechanical properties to a significant extent.

Previous studies (Busilacchi et al., 2016, Drakonaki et al., 2009, Ooi et al., 2015, Ozturk and Sayinbatur, 2018) used the Kager Fat pad (KFP) as a medium to calculate the strain ratio in the evaluation of AT elasticity. The results showed moderate to good reliability (Drakonaki et al., 2009) and the authors suggested the use of SE in the evaluation of the AT following surgery (Busilacchi et al., 2016). However, caution should be taken when measuring strain ratio with a biological tissue such as KFP since other tissues could encounter changes in elasticity due to pathology, recovery or to different measurement conditions. The mechanical properties of the KFP changes following the hardening of the AT and this change is not always linear, likely because of anatomical differences between subjects e.g. longer soleus muscle, more connective tissue, or due to the compression of the AT on the underlying tissues. In the current study, we used an external material with a constant elasticity. Figure 2.3 shows an apparent softening of the reference material as the tendon became harder. The sonoelastography algorithm implemented in the ultrasound machine display the elasticity of the tendon with an "auto-scale" colour range. The softest and the hardest structure visible in each of the ROI analysed are displayed in red and blue respectively. For this reason, we can observe a progressive colour change of the reference material (green at 0 kg, red at 10 kg) (see Figure

2.3) because the tendon progressively becomes the harder structure within the ROI. However, strain ratios (i.e. ratios between the median colours) have been used as an index of elasticity which is not affected by the “auto--scale” colour range.

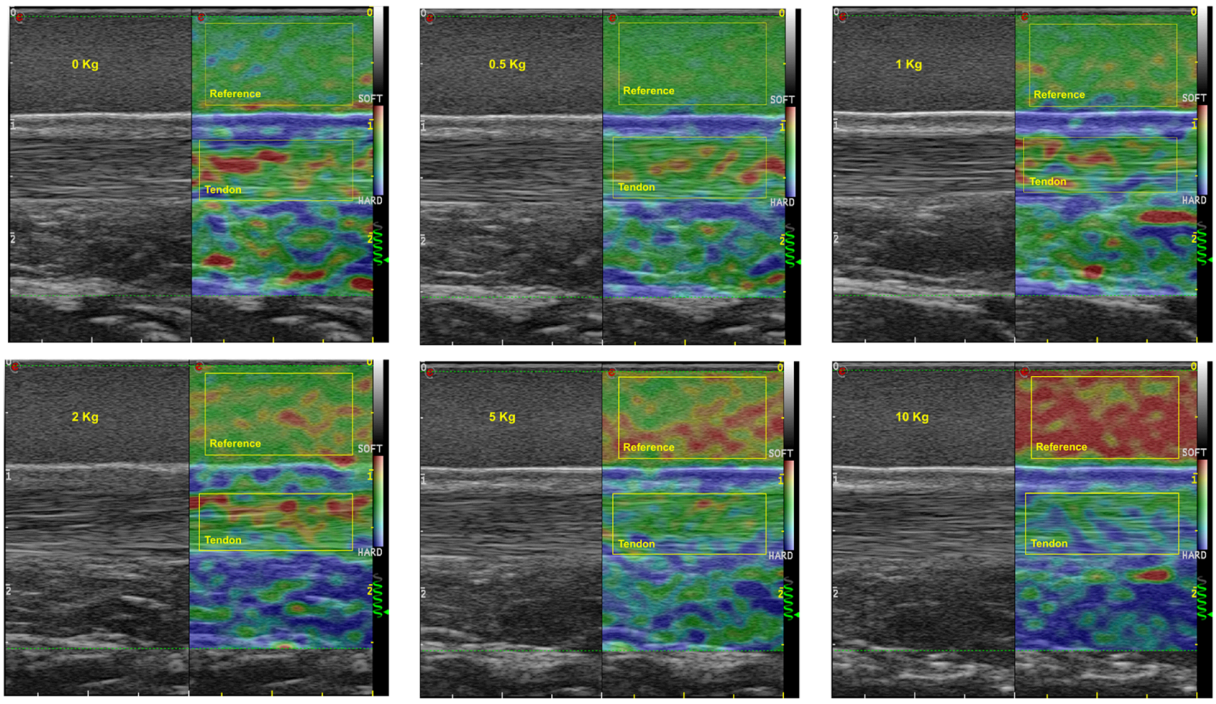


Figure 2.3. Achilles tendon sonoelastography during an isometric ramp contraction. Elasto-Dual images of the Achilles tendon during the isometric ramp contraction; the regions of interest (i.e., yellow boxes) define the two tissues examined for the calculation of the strain ratio. The six different boxes represent the different contraction levels

The findings of the present study are supported by other investigations which measured strain of the AT using a strain tracking procedure during MVC (Arampatzis et al., 2007b, Magnusson et al., 2003). However, in these studies tendon displacement and tendon strain were measured using the aponeurosis-tendon complex while in the present study we have characterised changes in tendon elasticity with a direct measure of the free tendon. Other

ultrasound-based techniques with direct measures of the tendon (i.e. SWE) have measured an increase of Young modulus (kPa) while the tendon is tensioned by changing the degree of ankle flexion (Aubry et al., 2013, DeWall et al., 2014). However, in those studies it was suggested that the use of SWE should be limited to the relaxed tendon to avoid saturation of the signal.

Another promising 2D ultrasound technology, based on a speckle tracking algorithm (Bogaerts et al., 2017) has been proposed. A non-uniform regional strain behaviour of the different layers of the AT has been observed. However given the different nature of SE measurement compared to the speckle tracking technique, the results cannot be directly compared.

Future studies which apply SE to evaluate the free tendon in different ankle positions or under different conditions (i.e. varying contraction intensity; functional tasks) are now warranted to better understand and characterise the behaviour of the AT. Moreover, the addition SE measures of the AT during loaded contractions may increase diagnostic capability in Achilles tendinopathy and future research is needed to explore this. SE requires manual compression and therefore variation in the level of pressure of the transducer on the skin may affect the results. To reduce such variability, both very high and low pressure was avoided as proposed by Itoh et al. (Itoh et al., 2006) and visual feedback of the applied pressure was provided so that it could be constantly controlled by the experienced operator.

Furthermore, strain ratio employed in this study offers a measure of elasticity provided by a transverse compression force of the ultrasound probe on the tendon structure. Further research is needed to establish the relationship between strain ratio and tendon longitudinal mechanical properties.

2.6 Conclusions

In this chapter, the use of SE to detect changes in AT elasticity during isometric contraction is presented. SE can detect changes in AT elasticity between different contraction intensities. It was observed that tendon elasticity was not modified between some contraction intensities. The reduction of the strain ratio between the tendon and the reference material indicates a constant increase of tendon elasticity during contractions of increasing intensity and provides an original force-elasticity curve. Based on the findings of this chapter, the third chapter evaluates the differences between SE and SWE in AT mechanical properties during isometric contractions.

CHAPTER 3

SHEAR WAVE AND STRAIN SONOELASTOGRAPHY FOR THE EVALUATION OF THE ACHILLES TENDON DURING ISOMETRIC CONTRACTIONS

This chapter reports in full the contents of a published manuscript by the thesis author (Schneebeli et al. 2021). It includes verbatim text from the published manuscript and some changes employed for the purpose of this thesis.

Publications and Presentations

1. **Schneebeli A.**, Fiorina I., Bortolotto C., Barbero M., Falla D., Cescon C., Raciti MV., Tarantino F., Preda L. 2021. Shear wave and strain sonoelastography for the evaluation of the Achilles tendon during isometric contractions. *Insights Into Imaging*. 17;12(1):26 **(Appendix 2)**

3.1 ABSTRACT

Changes in mechanical loading as well as pathology can modify the AT mechanical properties and therefore detection of these changes is relevant for the diagnosis and management of Achilles tendinopathy. This chapter presents a comparison between SE and SWE and evaluates their ability to detect changes in the AT mechanical properties during a series of isometric contractions.

Longitudinal sonoelastography images of the AT were acquired from 20 healthy participants using four different ultrasound devices: two implementing SE technology (SE1, SE2) and two SWE technology (SWE1, SWE2).

SE1 showed a decreasing strain ratio (tendon become harder) during the different contraction levels from 1.51 (0.92) to 0.33 (0.16) whereas SE2 showed a decreasing strain ratio from 1.08 (0.76) to 0.50 (0.32). SWE1 measured decreasing tendon stiffness during contractions of increasing intensity from 33.40 (19.61) to 16.19 (2.68) whereas SWE2 revealed increasing tendon stiffness between the first two contraction levels from 428.65 (131.5) kPa to 487.9 (121.5) kPa followed by decreasing stiffness for the higher contraction levels from 459.35 (113.48) kPa to 293.5 (91.18) kPa.

SE used with a reference material was able to detect elasticity changes between the different contraction levels whereas SWE was less able to detect changes in AT stiffness when under load. Inconsistent results between the two technologies should be further investigated.

3.2 Introduction

The findings presented in Chapter two confirmed the possibility to use SE using an external reference material in the evaluation of AT during contractions. In addition, other studies have evaluated AT stiffness and elasticity not only with SE but also using SWE (Aubry et al., 2013, Bercoff et al., 2004, De Zordo et al., 2009, DeWall et al., 2014, Ophir et al., 1991).

SE provides qualitative data of tissue elasticity on colour elastograms, exploiting the displacement determined by the operator through repeated compressions and de-compressions with the probe (Ophir et al., 1991). Given that the force applied by the operator to the tissue is unknown, in order to obtain a semi-quantitative evaluation of tissue elasticity, the ratio between two different ROI within the tissue is calculated. This "strain ratio", is often obtained by using subcutaneous fat (Drakonaki et al., 2012) or external material (Schneebeli et al., 2016, Yamamoto et al., 2016) as a reference tissue. In contrast, SWE applies an acoustic radiation force via the ultrasound beam to the tissue, in which the propagation velocity correlates with the tissue elasticity which can be quantified (in m/s or kPa) (Bercoff et al., 2004, Sandrin et al., 2002).

Ultrasound-based elastography offers both researchers and clinicians a fast, non-invasive, quantitative assessment of tendon mechanical properties. It can be applied in the evaluation of acute and chronic Achilles tendinopathy (De Zordo et al., 2009, Klauser et al., 2013) or to define the response to several different mechanical loads, (Coombes et al., 2018) and additionally has the potential to improve the diagnosis of tendon disorders (Dirrichs et al., 2016).

Although these technologies have been commonly used in research and clinical settings, the reliability of measurements from the AT is still debated (Corrigan et al., 2019, Payne et al.,

2017). Limits and constraints of both SWE and SE have been reported (Prado-Costa et al., 2018) especially when used to analyse the tendon structure, indicating the importance of a systematic and structured approach. Nevertheless, some studies have confirmed the superiority of SE and SWE in terms of specificity, sensitivity and accuracy compared to conventional ultrasound for diagnosing Achilles tendinopathy (Prado-Costa et al., 2018).

Surprisingly, there has been no attempt to compare the available sonoelastography techniques. Therefore, the aim of this chapter was to evaluate and compare in-vivo mechanical properties of the AT measured during contractions of increasing intensity when using three different SE/SWE devices to address thesis objective number 2. In addition, this chapter aims to establish if there is a correlation between the strain ratio methods and SWE in the evaluation of AT stiffness.

3.3 Methods

Twenty asymptomatic volunteers (12 males, 8 females, mean age 28.95±4.16 years) were recruited for this repeated measures study. Height (centimetres) and weight (kilograms) were recorded, and the body mass index (BMI) was calculated.

Subjects with a history of tendon injury and/or previous foot surgery or any painful episodes in the lower limbs in the last year, or systemic inflammatory disorders such as rheumatoid arthritis, spondyloarthropathies and hypercholesterolemia were excluded. All participants were informed about the content of the study and signed the informed consent form prior to the experimental procedure. The study was approved by the Ethics Committee of the Policlinico San Matteo, Pavia. (ID:0579) (Appendix 10)

Longitudinal sonoelastography images of the left and right AT was performed with three ultrasound devices, using two different systems of SE and SWE technologies. The systems with SE were: Resona 7, Mindray, Shenzhen, China (SE1) and Aplio 500, Toshiba Medical Systems Corp., Tokyo, Japan (SE2). The systems with SWE were: Resona 7, Mindray, Shenzhen, China (SWE1) and Aixplorer; SuperSonic Imagine, Aix-En-Provence, France (SWE2).

All examinations were performed bilaterally using multifrequency linear transducers (14L5 probe for Toshiba, L14-6VU for Mindray and 4-15 MHZ, SL15-4 for Aixplorer). The participants were asked to lie in a prone position, exposing both AT, with the legs extended and the feet placed over the examination couch, in contact with a dynamometer (Figure 3.1).

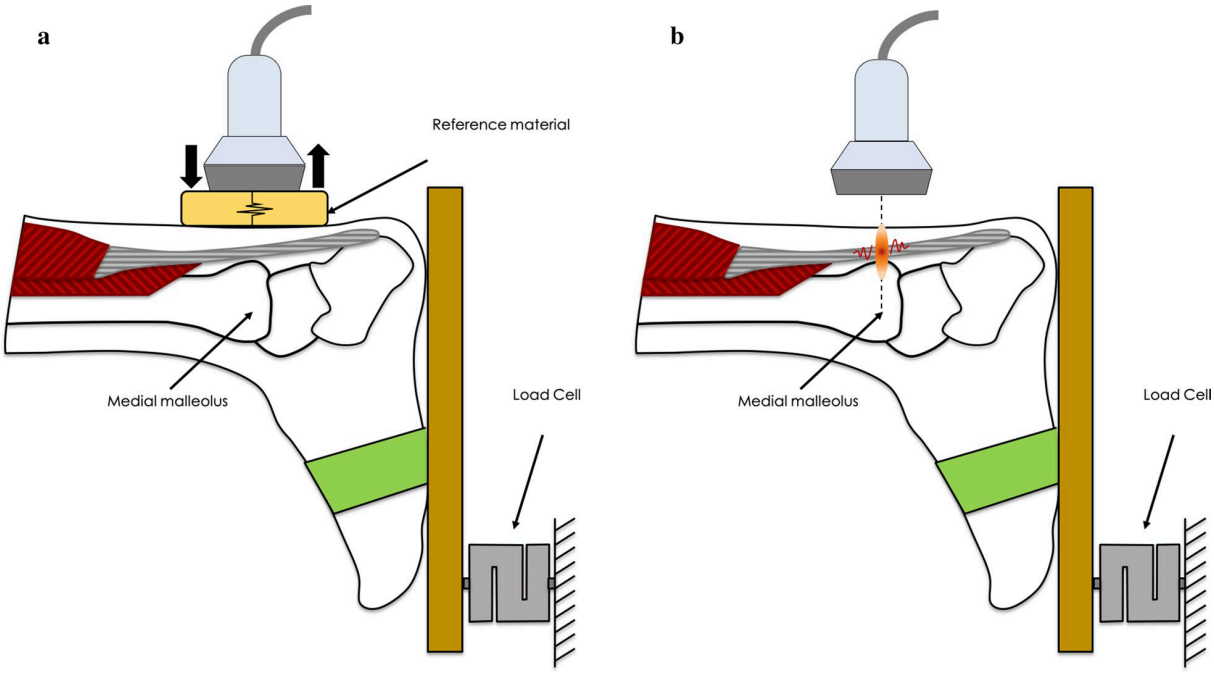


Figure 3.1 Schematic of the experimental setup. a) SE with reference material b) SWE. Ultrasound probe was placed in a longitudinal scan at the level of the medial malleolus

The examination included AT long axis evaluation using B-mode, SE and SWE. Images were acquired at the level of the medial malleolus in order to minimize "bone proximity" hardening artefacts (Bhatia et al., 2012, Bortolotto et al., 2017). The participants were instructed to perform contractions of different intensities (0 kg, 0.5 kg, 1 kg, 2 kg, 5 kg, and 10 kg) in plantar

flexion using an ankle ergometer; the examiner performed one measurement on each tendon at every load. The side of the tendon as well as the sequence of the isometric contractions were randomized. All evaluations were performed by an experienced musculoskeletal radiologist with 7 years of experience with elastography and experience with all devices used.

3.3.1 Data acquisition

Specific musculoskeletal pre-sets were used and no ultrasound setting changes were allowed during the study; only simple tuning was allowed (e.g. depth, brightness and contrast) in order to obtain the best possible image. For the SE analysis, we used an external reference material (Zerdine®, CIRS, Inc., Norfolk) with known elastic properties (elasticity - 102 kPa, speed of sound - 1,580 m/s, and attenuation coefficient - 0.5 dB/cm/MHz). The external reference material was placed on the participant's AT, included in the B-mode scans, and used to provide a comparison between the examined tendon and a material in which a constant elasticity was present.

SE images were analysed using a custom-made software; colour scale pixel count was made and colour histograms were extracted from two regions of interest (the reference material and AT). The range between soft and hard (from red to blue) was divided into 256 steps (0-255) according to the ultrasound image colour depth. Strain ratios between the tendon and the reference material were calculated and the comparison between different contraction levels were made. Higher strain ratio between the AT and the reference material indicates a softer tendon. This method has been validated, and reliability established in a previous study (Schneebeli et al., 2016, Schneebeli et al., 2019). The use of strain ratios with a reference

material with known elasticity properties becomes even more relevant when comparing different ultrasound devices.

SWE images were analysed on the ultrasound device, ROI were manually drawn in post processing and included the full extent of the examined tendon displayable in the saved image. Reliability maps were available in dual screen for both systems and were used to check the quality of the obtained images. The acquired SWE information was evaluated quantitatively; the shear elastic modulus (Young modulus) was calculated by the measuring tools of the ultrasound systems in kPa. This procedure was repeated for both AT and at different contraction levels. A higher value obtained with the SWE correspond to a harder tendon. All images and data were stored in the ultrasound workstations. The comparison between different contraction levels for each of the ultrasound devices were made. Figure 3.2 showed an example of SE and SWE images for the AT for the 0 kg load condition.

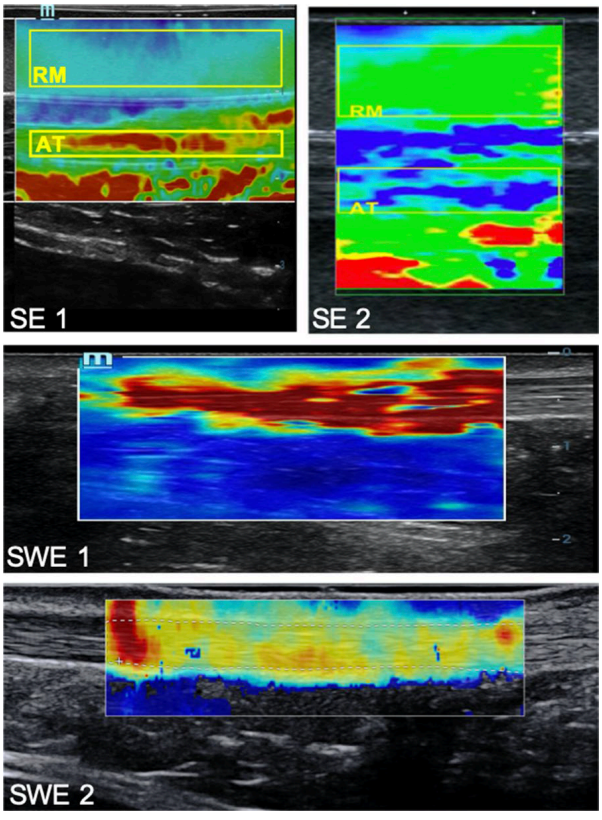


Figure 3.2. Example of the Achilles tendon mechanical properties at 0 kg measured with the different sonoelastography devices. SE1, strain elastography Resona 7, Mindray; SE2, strain elastography Aplio 500, Toshiba Medical Systems Corp.; SWE1, shear wave elastography Resona 7, Mindray; SWE2, shear wave elastography Aixplorer; SuperSonic Imagine. RM, reference material; AT, Achilles tendon

3.3.2 Statistical Analysis

The Shapiro-Wilk test was used to test the normal distribution of quantitative variables. Non-parametric, independent samples, Mann-Whitney test was used to assess differences in stiffness of the AT between the left and right side and between men and women. A non-parametric test (Friedman test with post hoc pair wise comparison) was used to compare differences of stiffness for each of the ultrasound devices. Bonferroni correction was applied and an overall p value less than .05 was considered a significant difference. Medians and interquartile ranges (IQR; 25^{th} and 75^{th} percentile) were used to report the results. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 22.0 software (SPSS, Chicago, IL, USA).

3.4 Results

There were no significant differences in elastographic parameters between genders or between the left and right AT, therefore the data were pooled and further analysed as an entire sample. The median age of the participants was 28 years (range 26-41 years), with a sex ratio (M:F) of 12:20. The mean ± SD height, weight and BMI were 173.6 (±7.4) cm, 68.2 (±10.5) kg and 22.5 (±2.35) respectively.

3.4.1 Comparison of the SE strain ratio values

The median (IQR) values for the strain ratio measured at difference contraction levels are represented in Table 3.1.

	0 kg	0.5 kg	1 kg	2 kg	5 kg	10 kg
SE 1 (TE/REF)	1.51 (0.92)	1.12 (0.49)	0.99 (0.33)	0.91 (0.37)	0.50 (0.32)	0.33 (0.16)
SE 2 (TE/REF)	1.08 (0.76)	1.02 (0.48)	1.02 (0.26)	0.97 (0.18)	0.79 (0.37)	0.50 (0.32)
SWE 1 (kPa)	33.40 (19.61)	23.75 (10.12)	19.54 (6.48)	17.33 (4.41)	16.56 (4.09)	16.19 (2.68)
SWE 2 (kPa)	428.65 (131.5)	487.9 (121.5)	459.35 (113.48)	393 (83.83)	319.7 (94.75)	293.5 (91.18)

Table 3.1. Median (IQR) of the strain ratio (tendon/reference material) and Young's modulus (kPa) at different contraction levels.

Evaluation with SE1 revealed a strain ratio of 1.51 (0.92) for the AT in the relaxed position and a progressive decrease of tendon strain ratio (the tendon became progressively harder) during increasing contraction levels, with median (IQR) values of 1.12 (0.49) at 0.5 kg, 0.99 (0.33) at 1 kg, 0.91 (0.37) at 2 kg, 0.50 (0.32) at 5 kg, and 0.33 (0.16) at 10 kg. Friedman test for related samples, revealed a significant difference ($p<0.01$) between all contraction levels except for the adjacent levels (Table 3.2 and Figure 3.3a). Evaluation with SE2 revealed a strain ratio of 1.08 (0.76) for of the AT in the relaxed position, and a progressive decrease of the tendon strain ratio during contractions of increasing intensity, with median values of 1.02 (0.48) at 0.5 kg, 1.02 (0.26) at 1 kg, 0.97 (0.18) at 2 kg, 0.79 (0.37) at 5 kg, and 0.50 (0.32) at 10 kg. Friedman test for related samples, revealed a significant difference ($p<0.01$) between the highest contraction levels (10 kg and 5 kg) and the other contractions but no difference ($p>0.05$) between the adjacent and the lowest contraction levels (Table 3.2 and Figure 3.3b).

3.4.2 Comparison of the SWE Young modulus (kPa)

Evaluation with SWE1 revealed a median (IQR) elastic modulus of 33.40 (19.61) kPa for the AT in the relaxed position and a progressive decrease of Young modulus (indicating reduced stiffness) during the progressive contraction levels, with median values of 23.75 (10.12) kPa at 0.5 kg, 19.54 (6.48) kPa at 1 kg, 17.33 (4.41) kPa at 2 kg, 16.56 (4.09) kPa at 5 kg, and 16.19 (2.68) kPa at 10 kg. Friedman test for related samples, revealed a significant difference ($p<0.01$) between the lowest contraction levels (0 kg and 0.5 kg) and the other contractions but no difference ($p>0.05$) between the adjacent and the highest contraction levels (Figure 3.4a).

SE 1 / SE 2	0 kg	0.5kg	1 kg	2 kg	5 kg	10 kg
0 kg	-	1.000	0.405	**0.000**	**0.000**	**0.000**
0.5 kg	1.000	-	1.000	**0.002**	**0.000**	**0.000**
1 kg	1.000	1.000	-	0.632	**0.000**	**0.000**
2 kg	1.000	1.000	1.000	-	0.062	**0.000**
5 kg	**0.004**	**0.001**	**0.000**	**0.015**	-	0.062
10 kg	**0.000**	**0.000**	**0.000**	**0.000**	0.128	-

SWE 1 / SWE 2	0 kg	0.5kg	1 kg	2 kg	5 kg	10 kg
0 kg	-	0.073	**0.000**	**0.000**	**0.000**	**0.000**
0.5 kg	0.625	-	0.475	**0.011**	**0.000**	**0.000**
1 kg	1.000	1.000	-	1.000	0.127	0.106
2 kg	1.000	0.053	0.735	-	1.000	1.000
5 kg	**0.000**	**0.000**	**0.000**	**0.008**	-	1.000
10 kg	**0.000**	**0.000**	**0.000**	**0.001**	1.000	-

Table 3.2. Friedman test p values between the different contraction levels for the different technologies. Bold values indicate statistically significant difference between the different contraction levels $p < 0.05$

Evaluation with SWE2 showed median (IQR) elastic modulus of 428.65 (131.5) kPa for the AT in the relaxed position and an increase of Young modulus (higher stiffness) to 487.9 (121.5) kPa at 0.5 kg followed by a progressive decrease of tendon modulus (reduced stiffness) during higher contraction levels, with median values of 459.35 (113.48) kPa at 1 Kg, 393

(83.83) kPa at 2 Kg, 319.7 (94.75) kPa at 5 Kg, and 293.5 (91.18) kPa at 10 Kg. Friedman test for related samples revealed a significant difference ($p<0.01$) between the highest contraction levels (10 kg and 5 kg) and the other contractions but no difference ($p>0.05$) between the adjacent and the lowest contraction levels (Figure 3.4b).

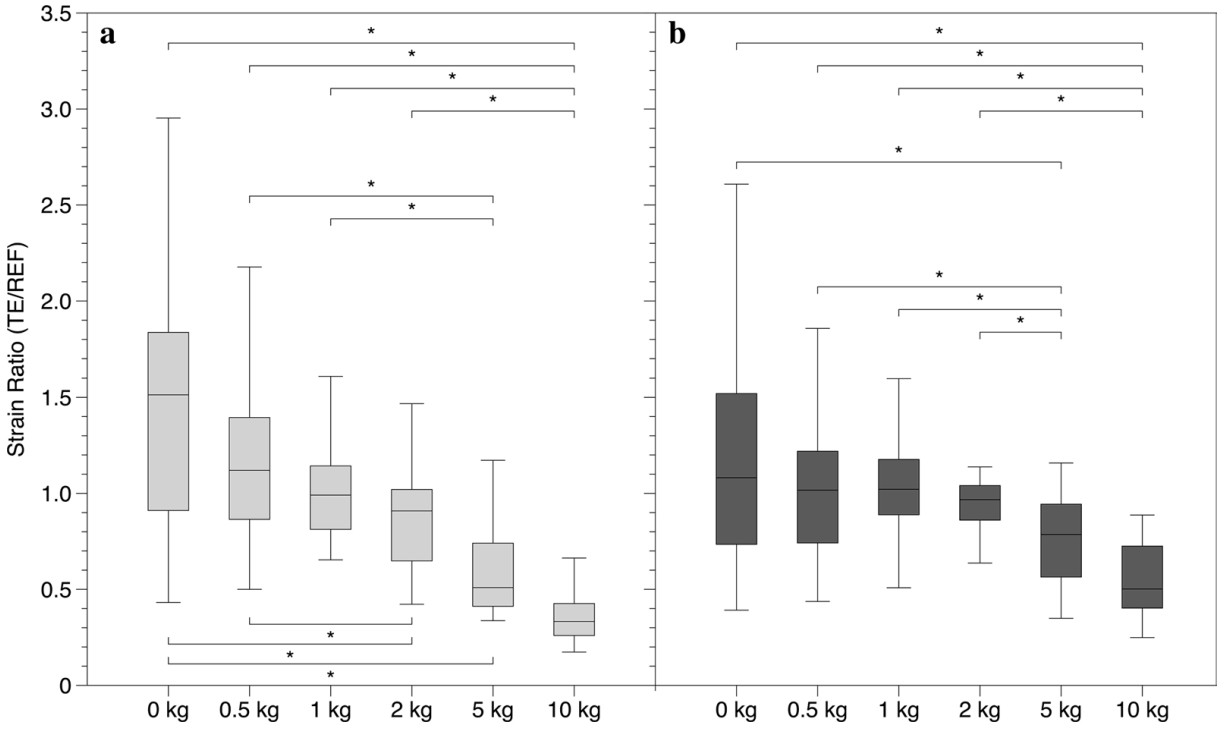


Figure 3.3. Strain sonoelastography. Box plot showing the median and IQR strain ratio (TE/REF) values of the entire sample for the different contraction levels a) SE1 and b) SE2. *p < 0.05; statistically significant difference between the different contraction levels

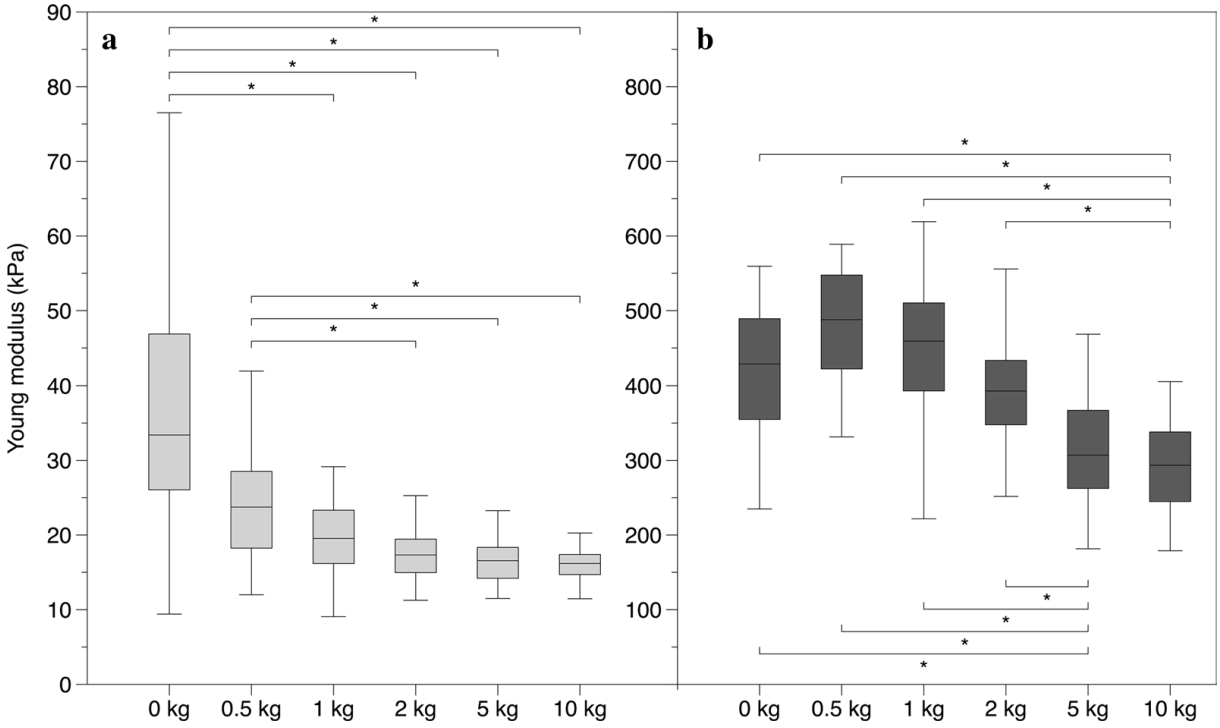


Figure 3.4. Shear wave sonoelastography. Box plot showing the median Young's modulus and IQR values of the entire sample for the different contraction levels a) SWE1 and b) SWE2. *p < 0.05; statistically significant difference between the different contraction levels.

3.5 Discussion

This chapter assessed the consistency of SE and SWE in the evaluation of the AT at different contraction levels, compared elasticity results using commercially available scanners and explored the performances using different ultrasound imaging. Different behaviour was observed for the two sonoelastography techniques as well as for the different devices indicating limitations of both techniques. The observed differences can be explained by the inconsistent methodological and computational approaches used to estimate tissue stiffness/elasticity. This

has important consequences for both researchers and clinicians. Secondary research such as systematic reviews or meta-analysis are also hindered due to the limitations when pooling datasets from different studies. The lack of a reference standard constitutes a barrier for a diffuse application of SE/SWE the clinical practice.

The behaviour of both SE1 and SE2 are similar to previous published studies showing a decrease of the strain ratio values when the tendon becomes harder due to an increase in plantarflexion strength (Schneebeli et al., 2019) or with supraspinatus contraction (Muraki et al., 2015) and similar results were obtained using a semiquantitative method with SE (Minafra et al., 2020). Moreover, these results are in line with a myotonometry evaluation of the AT (Schneebeli et al., 2020) which showed increased stiffness when the tendon is under load.

As showed by Schneebeli et al. (Schneebeli et al., 2019), higher variability of strain ratio values between the participants was present in the relaxed position and at low levels of contraction. This variability is reduced when the tendon is put under load. This behaviour is clearly visible in both SE techniques (Figure 3.3) and could be explained by inter-individual difference in age, level of activity and anatomical differences (gastrocnemius and soleus length). A lack of accuracy of these techniques in the relaxed position, leading to a large variability in the strain ratio results, cannot be excluded. However, this method has high intra-rater reliability when used in both a relaxed and contracted state (Schneebeli et al., 2016).

Strain ratio values between SE1 and SE2 appear to be different with SE1, showing a relaxed value of 1.51 (0.92) and a rapid decrease in strain ratio when the tendon is put under load (Figure 3.3), while SE2 showed a starting value of 1.08 (0.76) and similar values at the low contraction levels. Values of SE1 are highly comparable with another study (Schneebeli et al., 2019) reporting a strain ratio of 1.61 (1.5-2.9) in the relaxed state, 1.30 (1.07–2.02) at 0.5 kg, 1.00 (0.76–1.66) at 1 kg, 0.81 (0.70–1.19) at 2 kg, 0.47 (0.39–0.73) at 5 kg and 0.33 (0.28–

0.40) at 10 kg. Pairwise comparison between different contraction levels showed that SE1 could not detect changes between contraction levels of similar intensity and at the beginning of the isometric contraction (0 kg-0.5 kg (p=1.000), 0 kg-1 kg(p=0.405)). Similarly, SE2 could not distinguish the adjacent contraction levels but additionally, differences between low level contraction levels were not detected by this device. Differences were only observed at the higher contraction levels (5kg, 10kg). This low sensitivity in the initial phase of the contraction could be attributed to a different colour scale implemented in the device that considers mid-range values (green levels) more so than the higher or lower values.

Conversely, SWE using two different devices showed a different result compared to SE and to the expected biomechanical behaviour. Previous studies evaluating AT at different ankle angles indicate an increase of the shear modulus and shear wave velocity with an increase of ankle dorsiflexion (Aubry et al., 2013, DeWall et al., 2014, Corrigan et al., 2019).

In this study SWE 1 showed the opposite behaviour with a decrease of shear modulus with an increase in the contraction level and thus tension on the AT. It could be that the upper limit of the device (66.7 kPa) was surpassed. The implemented algorithm in SWE 1 does not present saturated values as a loss of signal (as for SWE 2) (Appendix 3). Moreover, the values obtained with SWE 1 at 0° of ankle plantar flexion (33.40 (19.61)) are extremely low compared to values reported in other studies, (Aubry et al., 2013, Chino and Takahashi, 2015, Siu et al., 2016) questioning the possibility of using Mindray shear wave sonoelastography to analyse tendon mechanical properties.

Values reported in Table 3.2 and Figure 3.4 which indicate a significant difference between different contraction levels, should be interpreted cautiously given the unusual shear modulus values indicating an opposite behaviour of this technology compared to SE and

biomechanical studies. Further studies using SWE 1 are needed to evaluate the feasibility of this technology to measure mechanical properties of tendinous structures.

SWE 2 measured an increase of tendon stiffness during isometric plantar flexion from 0 Kg to 0,5 Kg load with shear modulus median values ranging from 428.65 (131.5) to 487.9 (121.5). This increment is followed by a progressive decrease of the Young modulus for isometric plantar flexion at 1, 2, 5 and 10 Kg (Table 3.1). This behaviour does not reflect tendon biomechanics, and it appears that the upper limit of the device (800 KPa) was reached. SWE 2 images of isometric contraction higher than 0.5 kg, revealed signal saturation with a signal loss within the elastogram. This signal loss is probably due to the alignment or the displacement of the fibrillary structure within the AT that could increase the speed of the shear waves or could generate an abnormal propagation of the shear wave that cannot be registered by the device. The absence of signal within some portion of the AT could have led to a miscalculation of the shear modulus resulting in a reduction of the kPa which was not attributed to the actual behaviour of the tendon. (Appendix 3). Given the upper limit of the shear modulus in these technologies, some authors suggested (Aubry et al., 2013, Chino and Takahashi, 2015) to limit the evaluation of AT to a relaxed or plantar flexed position and to not put tendon under load by means of a dorsiflexed position or any additional weight.

SWE has been largely used to evaluate the AT, a in natural relaxed position. In 1165 healthy Chinese adults, a Young modulus of 374.24 ± 106.12 kPa was reported (Cao et al., 2019). However, inconsistency between studies exists when tendon is analysed at 0° of plantar flexion as in the present study. Shear modulus varied from 723.1 (kPa) (Aubry et al., 2013) to 174.1 (kPa) (Corrigan et al., 2019) with one study reporting 322 (kPa) for the dominant leg and 320 (kPa) for the non-dominant (Siu et al., 2016). Chino et al. (Chino and Takahashi, 2015) reported values to those measured with SWE2 in the present study with 430 (±96) kPa at

measured at 10% of the lower limb length and 470 (±151) kPa at 15% of the lower limb length. The present study reported a median (IQR) value of 428.65 (131.5). Even though, these studies evaluated AT in the free tendon part, differences between results could be attributed to the transducer position along the free tendon or to challenges using this technology to evaluate the tendon under tension as in the 0° ankle position.

Using SWE 1, we measured median (IQR) values of 33.40 (19.61) at 0° of plantar flexion. Since this device, to our knowledge, has never been used to analyse tendinous structures, there are no data to compare to. However, considering the values obtained with other devices, these results appear to be far below the expected kPa values questioning the possibility to compare results between different ultrasound devices. The lack of relationship between these two methods may be related to the inherent differences in the parameters measured. SE evaluates tissue elasticity before and after manual compression, while SWE estimates Young modulus on the basis of the ultrasound propagation shear wave velocity. In addition, SWE is more susceptible to measurement interference due to the anisotropic nature of the tendon.

Considering the fundamental role of load in the development of tendon pathology as well as in the management of tendon rehabilitation, by means of loaded-based exercises, a device which is able to detect changes in the mechanical properties of tendon during tasks that directly challenge the tendinous structure (i.e., contraction) could provide a better understanding of tendon injury and rehabilitation effects. Strain evaluation appears to be the best technique to assess the elastic changes of the AT during isometric plantar flexion, nevertheless SE provides only semi-quantitative values (strain ratios) and this data, unlike Young's modulus, does not represent the tissue intrinsic properties (Prado-Costa et al., 2018). Moreover, the use of manual compression and reference material required higher technical skills leading to a more operator-dependent procedure.

There are some limitations to the current study. Firstly, the selection of the devices and technology used was limited to those available. Secondly, the application of SE and SWE was limited to the evaluation of the AT. Generalizability of these findings to other devices and other tendons may not be possible. Further studies, which also evaluate the mechanical properties of pathological tendons, are necessary.

3.6 Conclusion

SE with the use of reference material is able to detect changes in AT elasticity when measured in ankle plantar flexion during different contraction levels and the results are in line with the expected physiological and mechanical behaviour. Nevertheless, SE can only provide semi-quantitative (i.e. strain ratio) values and requires higher technical skills for operation. Conversely, SWE measured changes in tendon stiffness which were contradictory to the mechanical characteristics of the AT, probably due to the propagation shear wave velocity and the fibrillary structure in the AT. SE appears more suitable for the evaluation of the AT when under load. Caution should be taken when comparing results of different devices on the AT. The inconsistency of the results between the different devices presented in this chapter may hinder the clinical applicability of SE and SWE.

CHAPTER 4

RELIABILITY OF SONOELASTOGRAPHY MEASUREMENTS OF LOWER LIMB TENDON PROPERTIES: A SYSTEMATIC REVIEW

This chapter reports in full the contents of a published manuscript by the thesis author (Schneebeli et al. 2020). It includes verbatim text from the published manuscript and some changes employed for the purpose of this thesis.

Publications and Presentations

1. **Schneebeli A.,** Folli A., Falla D., Barbero M. 2020. Reliability of Sonoelastography Measurements of Lower Limb Tendon Properties: A Systematic Review. *Ultrasound in Medicine & Biology*. 47(5):1131-1150. **(Appendix 5)**

4.1 ABSTRACT

This chapter investigated the reliability of sonoelastography techniques in quantifying lower limb tendon elasticity. A literature search was conducted using PubMed, Web of Science and CINAHL. The quality of the selected papers was evaluated using the Guidelines for Reporting Reliability and Agreement Studies (GRRAS) and the Quality Appraisal Tool for Studies of Diagnostic Reliability checklist. Reliability (QAREL) values were extracted and synthesized.

Twenty-four studies were included and were divided by the two main technologies used: SE and SWE. The overall methodological quality was questionable; all studies were at risk of bias. Highly variable results ranging from poor to excellent reliability were found for both technologies and for all tendons considered. Intra-rater reliability of SE on the AT and SWE on the patellar and quadriceps tendon (QT) was adequate. Inter-rater, inter-session and inter-machine reliability was insufficient.

Caution should be used when interpreting results from sonoelastography studies measuring lower limb tendon elasticity.

4.2 Introduction

As extensively described in Chapter one, the relationship between tendon mechanical changes and pathology or performance is still debated, however the importance of measuring these parameters is well established (Docking and Cook, 2019). Clinicians would benefit from technologies that measure mechanical changes during or after their treatments, and this would lead to (case-by-case optimisation) tailoring of the interventions according to objective measurements.

Currently, many different measurement techniques are used to measure tendon mechanical properties, with sonoelastography being the most common technique because it can be used to directly assess free tendons (Coombes et al., 2018, Prado-Costa et al., 2018). A 2018 review by Prado-Costa et al. (Prado-Costa et al., 2018) analysing the feasibility and applicability of SWE and SE to assess tendon pathology and injury showed potential application in the evaluation of tendinopathies. However, the authors suggest that a more structured and systematic approach is needed to overcome the limitations of both technologies. Even if these technologies have been largely used to describe elasticity in different tendons and in different conditions, methodological studies aiming to evaluate the reliability of these techniques are scarcely present in the literature, and results are often conflicting.

Reliability, as well as other measurement properties, must be determined before any measurement device or assessment tool can be applied in a clinical or research setting (Koo and Li, 2016). When no accepted reference standard is available, as for in vivo tendon elasticity measures, and validity or accuracy measures are not possible, reliability studies of high methodological quality become crucial to guarantee the applicability of these measures. Criteria for conducting and reporting robust reliability studies are present within the literature (Kottner

et al., 2011, Lucas et al., 2010, Mokkink et al., 2010a), and guidelines for the interpretation of results are also available (Koo and Li, 2016, Shrout and Fleiss, 1979). Nevertheless, to date no attempt to synthesize current knowledge on reliability of sonoelastography measurement has been done. Therefore, to address thesis objective number 3, the aim of this chapter was to determine the reliability of sonoelastography techniques for measuring lower limb tendon elasticity and to investigate the quality of these studies.

4.3 Methods

4.3.1 Registration

The present systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (Moher et al., 2009) (Appendix 5) and was registered in the International Prospective Register of Systematic Reviews (PROSPERO nr. CRD42020148572) on February 3, 2020.

4.3.2 Eligibility criteria

The population, intervention, comparator, outcome and study design (PICOS) framework was used and adapted for this type of study (Akers, 2009). Articles were included if the full text article was published in a peer-reviewed journal, if one of the aims of the study was to investigate the reliability of sonoelastography on lower limb tendons, and if the population included healthy individuals or patients with tendon disease (i.e., patients with lower limb tendinopathies or tendon rupture). Studies using animal models were excluded. We also

excluded studies using ex vivo or human models because this review is focused on the clinical application of the technology. We included observational studies, such as cross-sectional studies and repeated measurement studies. Studies were included if an ethics committee or institutional review board approved the protocol. Observational studies were excluded when reliability was not the primary aim but was investigated in a preliminary or pilot study and was not described in the methods. Randomized controlled trials were excluded. A PRISMA flowchart illustrating the study screening and selection process is presented in Figure 4.1.

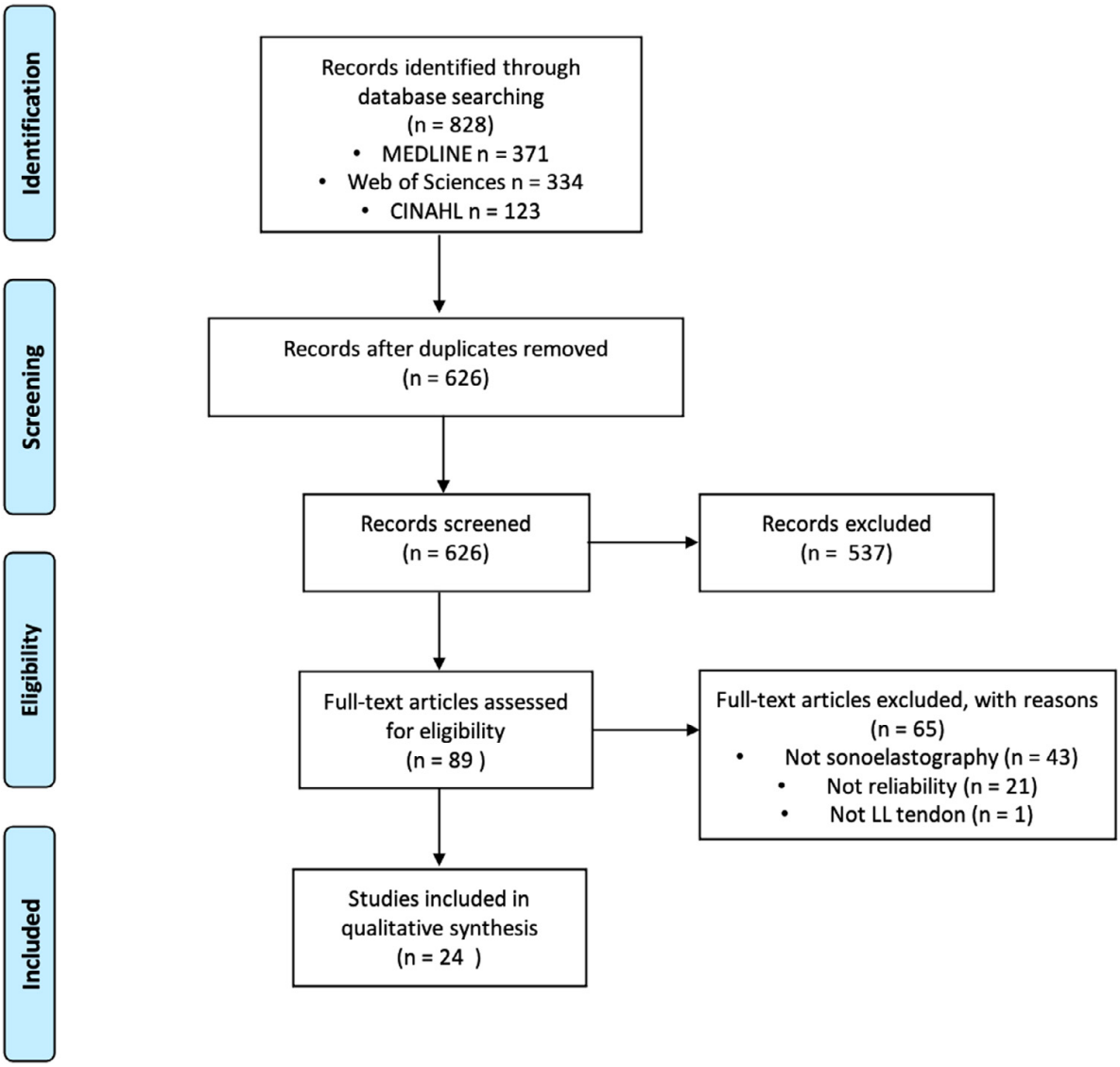


Figure 4.1. Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flowchart of study identification, screening and eligibility. LL, lower limbs.

4.3.3 Search strategy

A comprehensive search of the databases MEDLINE (PubMed), Web of Science and CINHAL was conducted by the first reviewer (A.S.) the February 26, 2020. The full electronic search strategy used for PubMed is presented as an example: ("Achilles tendon" OR ("Achilles" AND "tendon") OR ("calcaneal" AND "tendon") OR ("triceps surae" AND "tendon") OR ("gastrocnemius" AND "tendon") OR ("soleus" AND "tendon") OR ("plantarflexor" AND "tendon") OR ("calf" AND "tendon") OR ("patellar" AND "tendon") OR ("patellar" AND "ligament") OR ("hamstring" AND "tendon") OR ("lower extremities" AND "tendon") OR ("lower limb" AND "tendon") OR "tendons") AND ("Elastic modulus" OR "Elasticity" OR "Elastic" OR "viscoelastic" OR ("visco" AND "elastic") OR ("young" AND "modulus" OR "moduli") OR "compliance" OR "lengthening" OR "stiffness" OR "properties" OR "strain" OR "mechanical") AND ("reliability" OR "reliabilities" OR "reproducibility" OR "test-retest"). Additionally, the search strategy was adapted for Web of Science and CINAHL databases. To avoid the exclusion of relevant papers, search filters (i.e., animal studies, type of study, in vitro) were not included (Doust et al., 2005). No publication date or language restrictions were applied. Moreover, reference lists of included studies were checked. Studies obtained using the search strategies were exported to EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA) by the first reviewer (A.S.), and duplicates were removed.

4.3.4 Study selection

Two reviewers (A.S. and A.F.) independently screened titles and abstracts to determine which studies met the inclusion and exclusion criteria. Studies whose eligibility could not be

established from the screening of title or abstract were searched for full-text review. Any disagreement between reviewers were resolved by consulting a third reviewer (M.B.).

4.3.5 Quality assessment

The included studies were assessed using two different quality assessment tools for reliability studies. To assess the quality of the reporting of the included studies, the GRRAS (Kottner et al., 2011) checklist was used. To guarantee the correct interpretation and synthesis of the results of other studies, adequate and clear reporting was mandatory.

The items covered by GRRAS evaluate if the information about the sample selection, study design, rater characteristics and statistical analysis are properly reported. This 15-item checklist was used, and a quality score was given depending on the number of items reported in the correct section of the article. GRRAS items are the following. Title/abstract; item 1: Identify in title or abstract that inter-rater/intra-rater reliability or agreement was investigated. Introduction; item 2: Name and describe the diagnostic or measurement device of interest explicitly. Item 3: Specify the subject population of interest. Item 4: Specify the rater population of interest (if applicable). Item 5: Describe what is already known about reliability and agreement and provide a rationale for the study (if applicable). Methods; item 6: Explain how the sample size was chosen. State the determined number of raters, patients/objects, and replicate observations. Item 7: Describe the sampling method. Item 8: Describe the measurement/rating process (e.g., time interval between repeated measurements, availability of clinical information, blinding). Item 9: State whether measurements/ratings were conducted independently. Item 10: Describe the statistical analysis. Results; item 11: State the actual number of raters and patients/objects that were included and the number of replicate

observations that were conducted. Item 12: Describe the sample characteristics of raters and patients (e.g., training, experience). Item 13: Report estimates of reliability and agreement including measures of statistical uncertainty. Discussion; item 14: Discuss the practical relevance of results. Auxiliary material; item 15: Provide detailed results if possible (e.g., online) (Figures 4.2 and 4.3).

The quality in the design and conduct (internal quality) of the studies was assessed using the quality appraisal tool for studies of diagnostic reliability (QAREL). This checklist was developed by Lucas et al. (Lucas et al., 2010) with the aim to critically appraise reliability studies. Previous checklists investigating diagnostic accuracy (i.e., the Quality Assessment of Diagnostic Accuracy Studies [QUADAS]) (Whiting et al., 2006) have been developed, nevertheless, when there is no accepted reference standard to relate to, as in the case of elasticity measures, reliability studies become crucial.

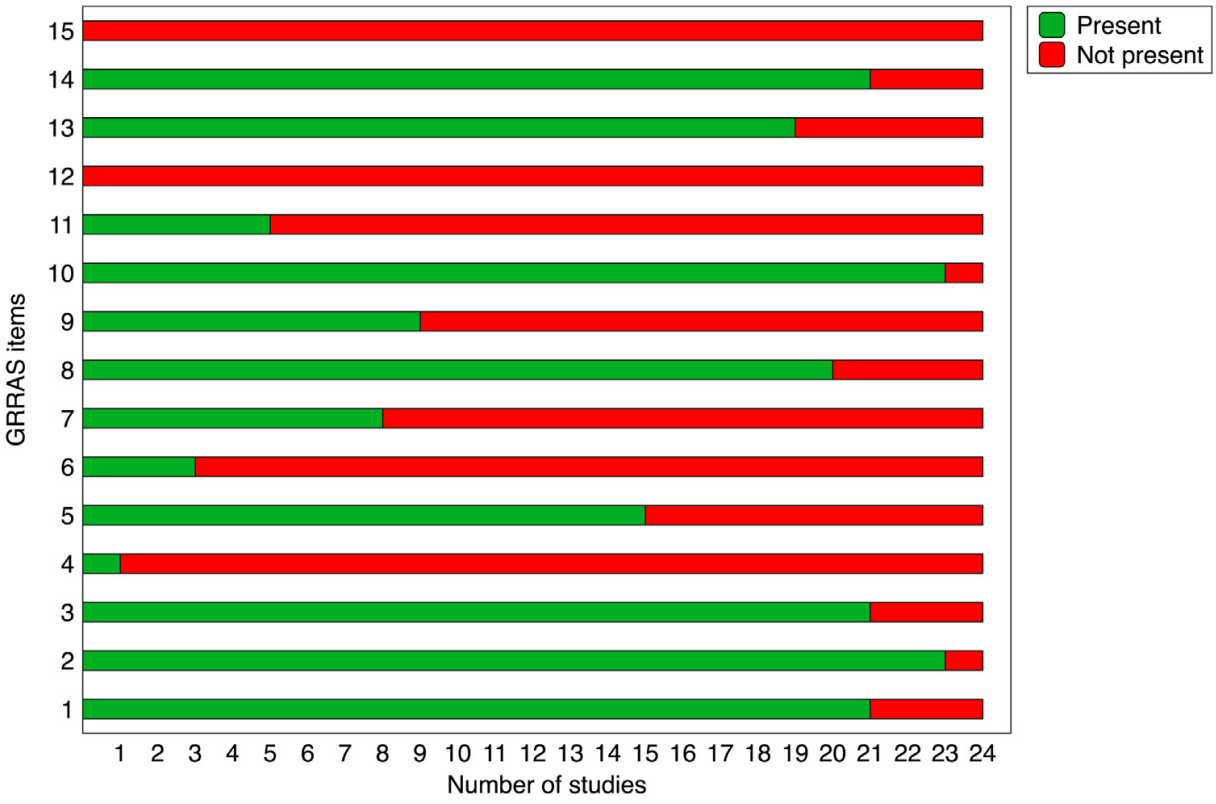


Figure 4.2. Bar chart showing the presence of the different Guidelines for Reporting Reliability and Agreement Studies (GRRAS) items in the selected studies (n = 24).

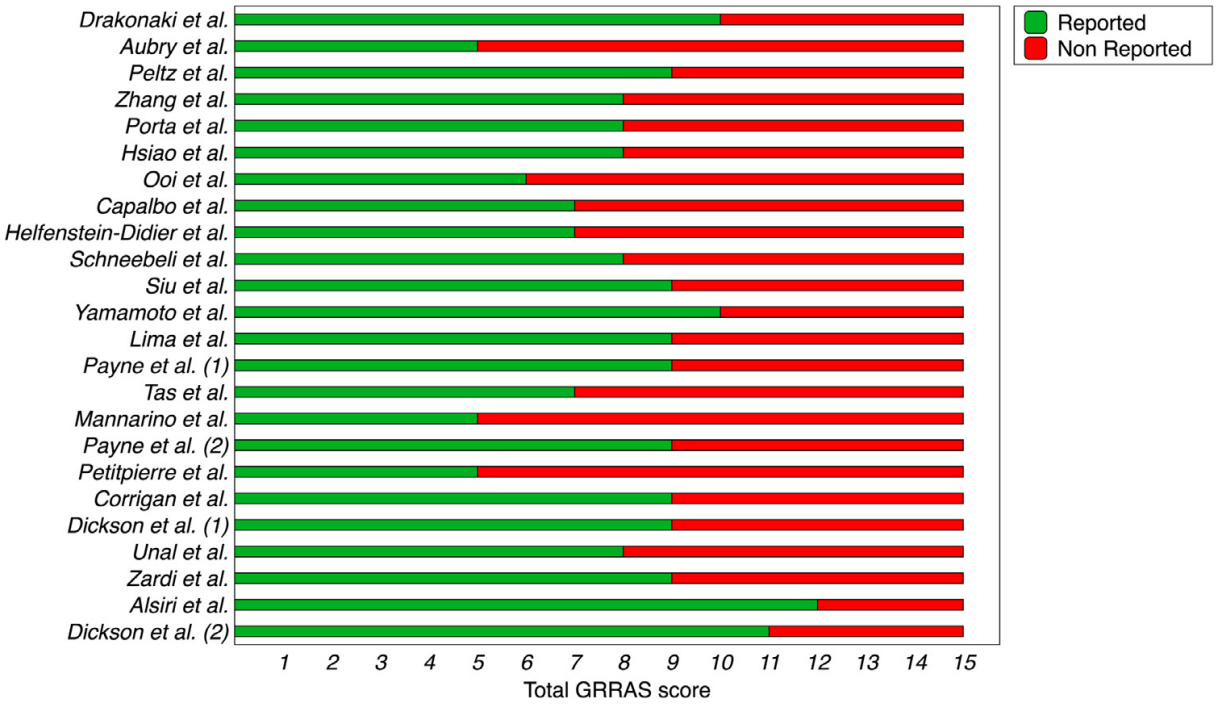


Figure 4.3. Bar chart showing the total Guidelines for Reporting Reliability and Agreement Studies (GRRAS) score of the different selected studies.

The QAREL is an 11-item checklist covering the spectrum of patients, examiners, appropriate test application and statistical analysis specific for reliability studies. QAREL items can be answered as “no,” “unclear” and “yes”; additionally, the option “not applicable” can be used in some items. The more “yes” responses, the higher the quality of the study; conversely, a single “no” answer may invalidate the study findings. Five out of 11 items can be scored as “not applicable,” therefore the final score of the article will take into account the real total value (11 items, not applicable [N/A]). QAREL items are the following. Item 1: Was the test evaluated in a sample of patients who were representative of those to whom the authors intended the results to be applied? Item 2: Was the test performed by raters who were representative of

those to whom the authors intended the results to be applied? Item 3: Were raters blinded to the findings of other raters during the study? Item 4: Were raters blinded to their own prior findings of the test under evaluation? Item 5: Were raters blinded to the results of the reference standard for the target disorder (or variable) being evaluated? Item 6: Were raters blinded to clinical information that was not intended to be provided as part of the testing procedure or study design? Item 7: Were raters blinded to additional cues that were not part of the test? Item 8: Was the order of the examination varied? Item 9: Was the time interval between repeated measurements compatible with the stability (or theoretical stability) of the variable being measured? Item 10: Was the test applied correctly and interpreted appropriately? Item 11: Were appropriate statistical measures of agreement used? (Figure 4.4). Disagreements in the ratings of the QAREL and the GRRAS checklists among the two reviewers (A.S. and A.F.) were discussed and resolved after consulting with the third reviewer (M.B.).

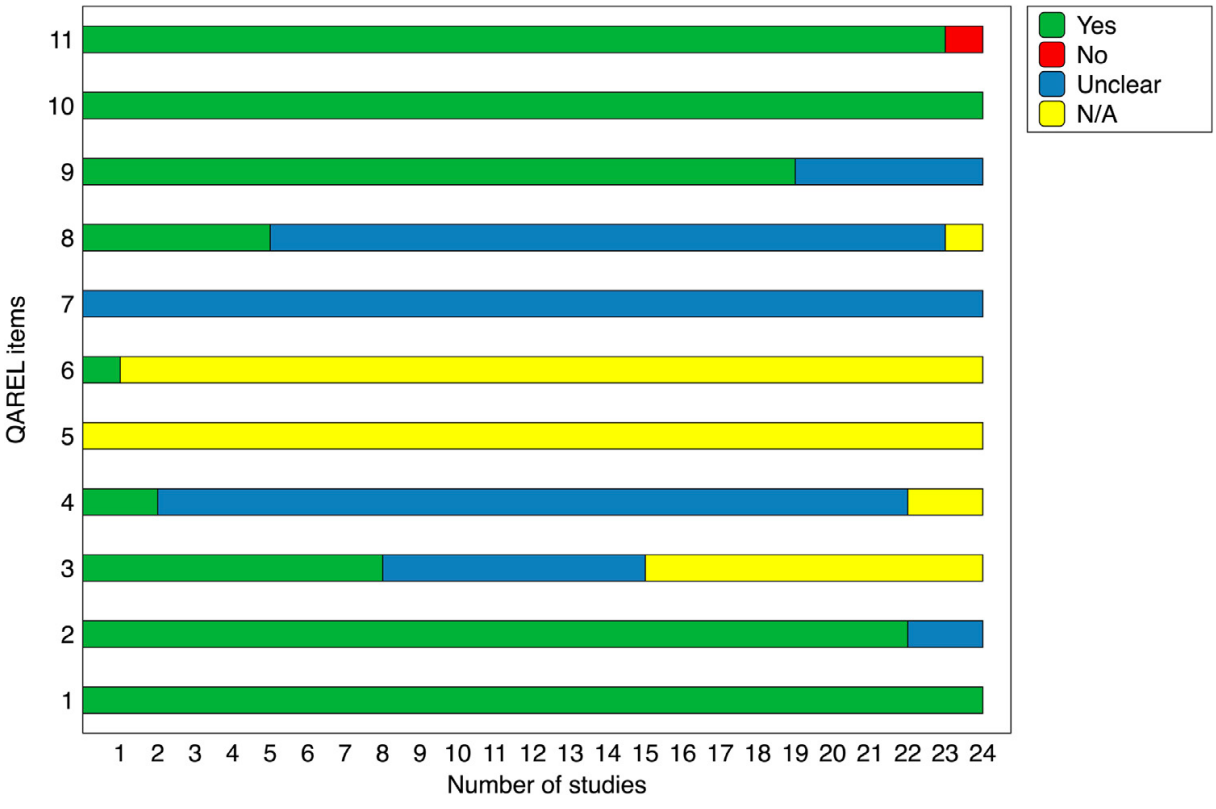


Figure 4.4. Bar chart showing the presence of the different QAREL items in the selected studies (n = 24). N/A, not applicable.

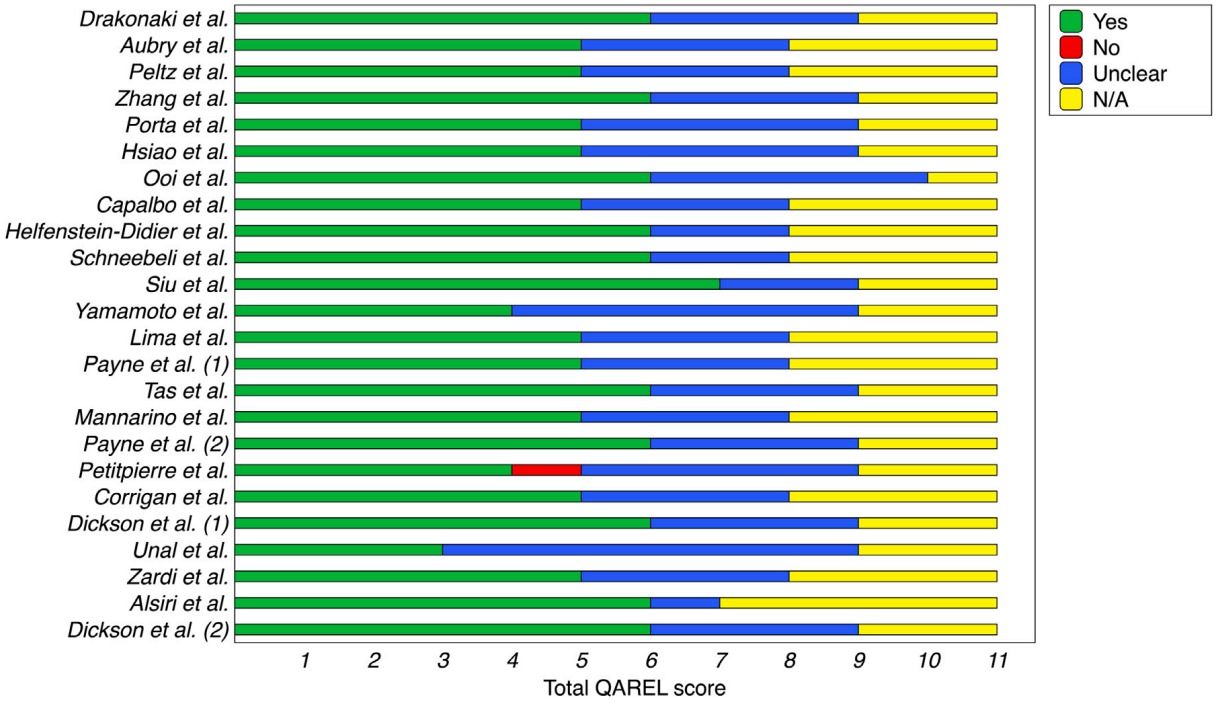


Figure 4.5. Bar chart showing the total QAREL score of the different selected studies.

4.3.6 Data extraction

Information was independently extracted by a reviewer (A.S.) and was controlled by a second reviewer (A.F.). Study characteristics, including number of participants, tendons analysed, ultrasound device and technique used, reliability type, operators experience and measurement protocol were extracted and collected in a descriptive table (Table 4.1). Study results are reported in separate tables divided by the type of sonoelastography technique. These tables summarize the condition evaluated and the relative and absolute reliability results.

Relative reliability calculated with intraclass correlation coefficient (ICC) was interpreted as follows:

- ICC values less of than 0.5 indicate poor reliability, values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.9 show good reliability and values greater than 0.9 indicate excellent reliability (Portney and Watkins, 2015).
- As suggested by Koo and Li (Koo and Li, 2016), where 95% confidence interval (CI) of ICC were reported, the rating considers not only the point estimation but the lower and upper limit of the 95% CI.
- A cut-off point of ICC of >0.6 was used to consider the clinical relevance of the measurements (Chinn, 1990, Munro, 2005).

Where present, agreement or correlation were interpreted as follows:

- Cohen's kappa value for categorical data were interpreted according to the Landis and Koch scale (Landis and Koch, 1977), where <0 indicates poor agreement, 0.00-0.20 indicate slight agreement, 0.21-0.40 indicate fair agreement, 0.41-0.60 indicate moderate agreement, 0.61-0.80 indicate substantial agreement and 0.81-1.00 indicate almost perfect agreement.
- Correlation between measures using Spearman's rank was considered weak when rs <0.3, moderate when rs = 0.31-0.70 and strong when rs >0.71 (Dancey and Reidy, 2002).

Absolute reliability by mean of standard error of measurement (SEM), coefficient of variation (CV) and Bland and Altman plots were reported in the Tables 4.2-4.5 when presented in the studies.

4.4 Results

4.4.1 Literature search and selection of studies.

The initial electronic search through MEDLINE, Web of Science and CINHAL identified 828 potentially eligible articles. After the removal of duplicates, 626 articles were screened by title and abstracts with an agreement between the two reviewers of K = 0.73. Eighty-nine full text articles were assessed for eligibility. Twenty-four studies met all the inclusion criteria and were included in the final qualitative synthesis (Figure 4.1). The agreement on the full-text screening between the two reviewers was K = 0.97. The majority of the studies were excluded after full-text screening for the following reasons: not using sonoelastography, not assessing reliability and not examining a tendon of the lower limb.

4.4.2 Characteristics of included studies

Characteristics of included studies are presented in Table 4.1. The number of participants included in the included studies ranged from a minimum of 5 to a maximum of 50. In the majority of the studies, participants were healthy (n = 23). Only one study evaluated reliability in patients with Achilles tendinopathy (Ooi et al., 2015). In the included studies, the following tendons were evaluated: AT (n = 15); PT (n = 5); PT and QT (n = 3); and AT, PT and QT (n = 1).

Two major sonoelastography techniques were evaluated: SE (n = 11) and SWE (n = 13). Nine out of 11 studies using SE analysed the values by mean of the strain ratio. Strain ratio is defined as the elasticity ratio between the tendon and another material (i.e., fat tissue [n = 5],

subcutaneous tissue [n = 2] and an external reference material [n = 2]). Of those, three studies added the evaluation of the colour scale by mean of the colour grading.

One study used only colour grading (Capalbo et al., 2016), and another study used the percentage of displacement between the compressions (Payne et al., 2017).

Nine out of 13 studies using SWE calculated the elasticity values by the mean of shear modulus measured in kPa or mPa, whereas 2 studies used velocity of the shear-wave propagation (m.s-1). Two studies (Aubry et al., 2013, Hsiao et al., 2015) used both parameters; shear modulus and shear-wave speed.

Authors (y)	Subj.	Tendon	SE/SWE	Device	Reliability type	Protocol (measure distance)	Operators (experience)
Drakonaki et al. (2009)	50	AT	SE	Hitachi	Intra-Inter rater	1 session 2 measurements (2 h)	2 musculoskeletal radiologists (NR)
Aubry et al. (2013)	30	AT	SWE	Aixplorer	Inter-rater	1 session 3 measurements (NR)	3 medical doctors (>6 yr)
Peltz et al. (2013)	12	AT PT QT	SWE	Aixplorer	Intra-rater	2 sessions D1: 2 measurements (4 h) D2: 2 measurements (4 h) 2 days between D1 and D2	1 trained operator (NR)
Zhang and Fu (2013)	11	PT	SWE	Aixplorer	Intra-Inter rater	1 session 2 measurements (1 h)	1 operator (5 yr) and 1 physical therapist (2 yr)
Porta et al. (2014)	11	PT	SE	Esaote	Intra-Inter rater	1 session 3 measurements (NR)	2 medical doctors (>8 yr)
Hsiao et al. (2015)	5	PT	SWE	Aixplorer	Intra-Inter rater	2 sessions D1: 1 measurement D2: 1 measurement 1 week between D1 and D2	2 operators (>1 yr)
Ooi et al. (2015)	10	AT	SE	Philips	Intra-Inter rater	2 sessions D1: 1 measurement D2: 1 measurement 1 week between D1 and D2	2 sonographers (>10 and >20 yr)
Capalbo et al. (2016)	40	AT	SE	Hitachi	Inter-rater	NR	2 radiologists (10 and 4 yr)
Helfenstein-Didier et al. (2016)	7	AT	SWE	Aixplorer	Intra-rater	1 session 5 measurements (immediate)	1 operator (NR)
Schneebeli et al. (2015)	24	AT	SE	Esaote	Intra-rater	1 session 2 measurements (1 min)	1 Physical therapist (NR)
Siu et al.(2016)	36	AT	SWE	Aixplorer	Intra-Inter rater	1 session 3 measurements (NR)	3 sonographers (>1 yr)

Yamamoto et al. (2017)	25	AT	SE	Hitachi	Intra-Inter rater	1 session 3 measurements (NR)	2 medical doctors (7 and 8 yr)
Lima et al. (2017)	24	AT	SWE	Aixplorer	Intra-rater Inter-session	2 sessions D1: 1 measurement D2: 1 measurement 1 week between D1 and D2	1 operator (NR)
Payne et al. (2017)	8	AT	SE	Siemens	Intra-rater Inter-session	6 sessions D1: 5 measurements (1 h) D2-D6: 1 measurement	1 operator (NR)
Tas et al. (2017)	12	PT	SWE	Siemens	Intra-rater Inter-rater Inter-session	2 sessions D1: 2 measurements (20 min) D2: 1 measurement 1 week between D1 and D2	1 radiologist and 1 physical therapist with different experience (5-1 yr)
Mannarino et al. (2018)	23	PT	SWE	Aixplorer	Intra-rater Inter-session	2 sessions D1: 2 measurements D2: 2 measurements 1 week between D1 and D2	1 operator (NR)
Payne et al. (2018)	14	AT	SWE	Siemens	Intra-rater Inter-session	6 sessions D1: 5 measurements (1 h) D2-D6: 1 measurement	1 sport scientist (3 yr)
Petitpierre et al. (2018)	15	AT	SWE	Aixplorer	Inter-rater	1 session 2 measurements (NR)	2 radiologists (6 and 3 yr)
Corrigan et al. (2019)	20	AT	SWE	Ultrasonix	Intra-rater	2 sessions D1: 4 measurements (30 min; 2 / 4 h) D2: 1 measurement 2 weeks between D1 and D2	1 operator (NR)
Dickson et al. (2019)	20	PT QT	SE	GE	Intra-Inter rater	1 session 6 measurements (NR)	3 operators (12, 7 and 0 yr)
Unal et al. (2019)	42	AT	SE	Toshiba and Hitachi	Intra-Inter rater Inter-machine	2 sessions D1: 2 measurements with 2 devices D2: 2 measurements with 2	2 operators (NR)

						devices 10 days between D1 and D2	
Zardi et al. (2019)	18	PT QT	SWE	Esaote	Intra-rater	1 session 2 measurements (15 min)	1 sonographer (>10 yr)
Alsiri et al. (2020)	18	AT	SE	GE	Intra-rater	1 session 2 measurements (1 h)	1 Physical therapist (4 yr)
Dickson et al. (2020)	20	PT QT	SE	GE and Esaote	Intra-Inter rater Inter-machine	1 session 8 measurements (15 min)	2 operators (12 and 0 yr)

Table 4.1. Study characteristics of included articles. AT, Achilles tendon; PT, patellar tendon; QT, quadriceps tendon; SE, strain elastography; SWE, shear wave elastography; NR, not reported; D, day.

4.4.3 Type of reliability and raters

In 19 of 24 studies, the primary study aim was to test the reliability, whereas in five of 24 studies, reliability was a secondary aim. In these latter studies, the primary aim was quantification of tendon elasticity (n = 4) and the effect of exercise on tendon elasticity (n = 1). Intra-rater reliability was assessed in 21 studies, inter-rater reliability was assessed in 14 studies, intra-rater inter-session reliability was assessed in five studies and inter-machine reliability was assessed in two studies. In the majority of the studies (n = 22), ICC was used to analyse the relative reliability, while in two studies (Capalbo et al., 2016, Petitpierre et al., 2018) reliability was assessed using Cohen k or p values. Of the 22 studies using ICC, only 12 studies reported the 95% CI despite the recommendation to do so in reporting guidelines (Koo and Li, 2016). Other studies used p values (n = 4), only the point value of ICC (n = 6) or the ICC range (n = 1). After formal request of additional data, authors of five studies (Dickson et al., 2020, Dickson et al., 2019, Helfenstein-Didier et al., 2016, Payne et al., 2018, Payne et al., 2017) provided 95% CI for ICC values.

Absolute reliability was assessed in 13 of 24 studies, with SEM (n = 4), CV (n = 9), mean difference (MD) with upper and lower limit of agreement (n = 2) and smallest detectable changes (n = 1).

In the majority of studies, the rater was described as a general operator, and their profession was not reported (n = 11), whereas seven studies declared the raters to be a radiologist or sonographer, four studies involved medical doctors as raters, two studies involved a physical therapist, and one study involved a sport scientist. The years of ultrasound experience of the raters ranged from 0 y (novice) to more than 20 y (senior). Ten of 24 studies did not report the raters' years of experience.

4.4.4 Methodological and reporting quality

Reporting quality (GRRAS). The mean score for all the selected studies was 7.9 out of 15 items, with a lowest score of 5/15 (Aubry et al., 2013, Mannarino et al., 2018, Petitpierre et al., 2018) and a highest score of 12/15 (Alsiri et al., 2020). None of the included studies provided auxiliary material to detail the results of the study; therefore item 15 was not reported in any article.

Item 12, regarding the description in the results section of the rater and subject characteristics, was not reported in any of the included studies. However, in 15 of the selected studies, this information was reported in the methods section.

There were a high number of studies missing on one or more of the following items: item 4: only one study (Dickson et al., 2020) specified the rater population of interest in the introduction; item 6: only three studies (Alsiri et al., 2020, ÜNal et al., 2019, Yamamoto et al., 2016) explained in the methods how sample size was chosen; item 7: eight of 24 studies described the sampling methods; item 11: five of 24 studies stated, in the results section, the actual number of raters and patients included.

Detailed scores for each item are reported in Figure 4.2. Conversely, a large amount of the studies included (>21) reported the items regarding the description of the study design (item 1) and of the technology included (item 2), specified the subject population of interest (item 3), described the statistical analysis (item 10) and discussed the practical relevance of the results (item 14). All the items of the GRRAS scale divided for each study are reported in the Figure 4.3. The mean agreement between the two reviewers scoring on the GRRAS scale was 95.8%. Disagreement on one item of three different studies were resolved by the third reviewer.

4.4.5 Methodological quality (QAREL).

The QAREL checklist was used to appraise the methodological quality of the included studies. Item 5 regarding the blinding of the disease status was rated N/A in all studies whereas item 7 regarding the blinding of additional cues was rated as unclear in all studies. Once the N/A score was removed, the maximum score possible ranged from 7-10. The maximum of "yes" answers were obtained by Siu et al. (Siu et al., 2016) with a score of 7 of 9. A minimum of one and a maximum of six "unclear" answers were reported in all 24 studies selected, indicating uncertainty in the methodological quality, exposing all the studies to a possible risk of bias. Detailed scores for each item are reported in Figure 4.4.

The study that presented with the highest "yes" answers net of the total score is the study of Alsiri et al. (Alsiri et al., 2020), with only one "unclear" answer. One study (Petitpierre et al., 2018) obtained a "no" answer for the item 11 regarding the appropriate statistical analysis. As defined by Lucas et al. (Lucas et al., 2010), the items rated as "no" can invalidate the study and compromise the findings. Therefore, the aforementioned study was not included in the qualitative syntheses of the present review.

QAREL items divided for each study are reported in Figure 4.5. The mean agreement was 96.2% between the two reviewers scoring on the QAREL checklist. Disagreement on one item of two different studies were resolved by the third reviewer.

4.4.6 Reliability

The heterogeneity of the analysed studies precluded a quantitative analysis; therefore, a qualitative analysis was performed, dividing the studies by the type of technology used (SE or

SWE) and the tendon analysed (AT, PT and QT). Relative and absolute reliability for the different tendons and technologies are reported in Tables 4.2-4.5. A visual representation of relative reliability with ICC values is presented in Figures 4.6-4.9.

The qualitative synthesis of the studies was performed considering the following criteria:

- The ICC punctual value has to be ≥ 0.6.
- The lower limit of the 95% CI has to exceed 0.5.

If one of these criteria was not fulfilled, this study was considered to have inconclusive reliability. Moreover, where 95% CI were not reported, the study was cautiously evaluated.

Authors (y)	Parameters	Conditions	Intra-rater reliability		Inter-session reliability		Inter-rater reliability	
			Relative	Absolute	Relative	Absolute	Relative	Absolute
Drakonaki et al. (2009)	Strain ratio (Tendon/fat)	Axial Longitudinal	ICC 0.43 ● OP1 0.45 ● OP2 0.78 ● OP1 0.66 ● OP2	CV % 39% 37% 30.5% 30.1%			ICC 0.41 ● 0.51 ●	CV % 30% 29.6%
Ooi et al. (2015)	Strain ratio (Tendon/fat) Colour grading	Longitudinal Strain ratio Colour grading	ICC 0.87 ● Cohen K 0.70				ICC 0.79 ● Cohen K 0.70	
Capalbo et al. (2016)	Colour grading	Longitudinal Left Right					Cohen K 0.89 0.91	
Schneebeli et al. (2016)	Strain ratio (Tendon/ reference material)	Longitudinal Relaxed Contracted	ICC (95%CI) 0.87 (0.75-0.93) ● ● 0.94 (0.90-0.97) ● ●	MD (LoA) 0.13 (0.73/-0.47) 0.00 (0.16/-0.17)				
Yamamoto et al. (2016)	Strain ratio (Tendon/ reference material)	Longitudinal	ICC (95%CI) 0.93 (0.89-0.96) ● ● OP1 0.87 (0.80-0.92) ● ● OP2	SEM 0.06 0.07			Spearman rank 0.61	
Payne et al. (2017)	% of displacement	Longitudinal Fixed Relaxed Axial Fixed Relaxed	ICC 0.11 (-0.07-0.54) ● ● 0.06 (-0.12-0.49) ● ● 0.00 (-0.16-0.38) ● ● 0.00 (-0.19-0.31) ● ●	CV% 111.5% 105.7% 112.4% 53.6%	ICC 0.01 (-0.14-0.40) ● ● 0.10 (-0.08-0.53) ● ● 0.02 (-0.14-0.43) ● ● 0.11 (-0.10-0.55) ● ●	CV% 92.8% 80.8% 80.4% 60.9%		

Unal et al. (2019)	Strain ratio (tendon/fat)	Longitudinal Hitachi Toshiba Hitachi-Toshiba	ICC (95%CI) 0.98 (0.95-0.99) ● ● OP1 0.98 (0.96-0.99) ● ● OP2 0.97 (0.92-0.99) ● ● OP1 0.96 (0.93-0.98) ● ● OP2		ICC(95%CI) 0.85 (0.26-0.95) ● ●		ICC (95%CI) 0.84 (0.74-0.89) ● ● M1 0.81 (0.70-0.88) ● ● M2 0.73 (0.57-0.83) ● ● M1 0.75 (0.61-0.84) ● ● M2	
Alsiri et al. (2020)	Strain ratio (tendon/subc. fat) Strain index Colour Pixel %	Longitudinal Strain ratio Lower SI Higher SI Red pixel % Green pixel % Blue pixel %	ICC (95%CI) 0.82 (0.53-0.93) ● ● 0.91 (0.76-0.97) ● ● 0.91 (0.78-0.97) ● ● 0.99 (0.97-1.00) ● ● 0.91 (0.77-0.97) ● ● 0.94 (0.85-0.98) ● ●	MD (LoA) -0.33(2.70/-3.24) 0.00(0.03/-0.02) 0.02(0.15/-1.12) -0.33(3.51/-4.17) -2.07(20.07/-24.21) 2.41(25.36/-20.54)				

Table 4.2. Strain sonoelastography reliability results on Achilles tendon. Colour dots in the table describes the ICC value. ● poor reliability, ● moderate reliability, ● good reliability, ● excellent reliability. When 2 dots are present they indicate the lower and upper limit of the 95%CI. ICC, Intraclass correlation coefficient; CI, confidence interval; CV, coefficient of variation; OP, operator; MD, mean difference; LoA, limit of agreement; SEM, standard error of measurement; SI, strain index; M, measurement.

Authors (y)	Parameters	Conditions	Intra-rater reliability		Inter-session reliability		Inter-rater reliability	
			Relative	Absolute	Relative	Absolute	Relative	Absolute
Porta et al. (2014)	Strain ratio (tendon/subcutaneous tissue)	Longitudinal Proximal Middle Distal	ICC (95%CI) 0.79 (0.63-0.90) 🟡🟢 OP1 0.75 (0.56-0.88) 🟡🟢 OP2 0.65 (0.43-0.83) 🔴🟢 OP1 0.74 (0.55-0.87) 🟡🟢 OP2 0.71 (0.50-0.85) 🟡🟢 OP1 0.67 (0.44-0.83) 🔴🟢 OP2				ICC (95%CI) 0.64 (0.31-0.84) 🔴🟢 0.59 (0.24-0.81) 🔴🟢 0.53 (0.15-0.77) 🔴🟢	
Dickson et al. (2019)	Strain ratio (tendon/fat)	Longitudinal Strain ratio PQT DQT PPT MPT DPT PQT DQT PPT MPT DPT PQT DQT PPT MPT DPT	 ICC 0.49 (0.07-0.76) 🔴🟢 OP1 0.43 (0.00-0.73) 🔴🟢 OP1 0.85 (0.66-0.94) 🟡🟢 OP1 0.13 (-0.33-0.53) 🔴🟡 OP1 0.91 (0.78-0.96) 🟢🟢 OP1 0.30 (-0.16-0.65) 🔴🟡 OP2 -0.20 (-0.58-0.26) 🔴🔴 OP2 0.49 (0.07-0.76) 🔴🟢 OP2 0.44 (0.01-0.74) 🔴🟡OP2 0.41 (0.08-0.76) 🔴🟢 OP2 0.17 (-0.29-0.56) 🔴🟡 OP3 0.01 (-0.43-0.44) 🔴🔴 OP3 0.40 (-0.01-0.72) 🔴🟡 OP3 0.21 (-0.24-0.59) 🔴🟡 OP3 0.22 (-0.24-0.60) 🔴🟡 OP3				 ICC 0.10 (-0.05-0.34) 🔴🔴 M1 0.25 (-0.60-0.39) 🔴🔴 M1 0.15 (-0.07-0.45) 🔴🔴 M1 0.08 (-0.10-0.35) 🔴🔴 M1 0.10 (-0.05-0.33) 🔴🔴 M1 0.14 (-0.14-0.50) 🔴🟡 M2 0.38 (-0.08-0.45) 🔴🔴 M2 0.11 (-0.10-0.40) 🔴🔴 M2 0.18 (-0.02-0.45) 🔴🔴 M2 0.22 (0.00-0.50) 🔴🟡 M2	
	Colour grading	Colour grading PQT DQT PPT MPT DPT	Mean % agreement 72% 77% 83% 82% 93%				Mean % agreement 60% M1 / 57% M2 50% M1 / 48% M2 83% M1 / 83% M2 68% M1 / 80% M2 87% M1 / 93% M2	

Dickson et al. (2020)	Strain ratio (tendon/fat)	Longitudinal Strain ratio	ICC		Pearson and Spearman (p values)&		t-Test # (p values)	
		PQT	0.49 (0.07-0.76) ● ● OP1 G *		0.575 OP1 M1		**<0.001** G M1	
		DQT	0.43 (0.00-0.73) ● ● OP1 G *		0.794 OP1 M1		**<0.001** G M1	
		PPT	0.85 (0.66-0.94) ● ● OP1 G *		0.267 OP1 M1		0.896 G M1	
		MPT	0.13 (-0.33-0.53) ● ● OP1 G *		0.711 OP1 M1		**0.03** G M1	
		DPT	0.91 (0.78-0.96) ● ● OP1 G *		0.138 OP1 M1		0.36 G M1	
		PQT	0.17 (-0.30-0.56) ● ●OP2 G *		0.574 OP2 M1		0.086 G M2	
		DQT	0.01 (-0.43-0.44) ● ● OP2 G *		0.846 OP2 M1		**<0.001** G M2	
		PPT	0.40 (-0.01-0.72) ● ● OP2 G *		0.122 OP2 M1		0.765 G M2	
		MPT	0.21 (-0.24-0.59) ● ● OP2 G *		0.901 OP2 M1		**0.048** G M2	
		DPT	0.22 (-0.24-0.60) ● ● OP2 G *		0.493 OP2 M1		0.09 G M2	
		PQT	0.27 (-0.19-0.63) ● ● OP1 E		0.963 OP1 M2		0.575 E M1	
		DQT	0.51 (0.10-0.77) ● ● OP1 E		0.324 OP1 M2		0.213 E M1	
		PPT	0.48 (0.05-0.75) ● ● OP1 E		0.224 OP1 M2		0.455 E M1	
		MPT	0.67 (0.32-0.85) ● ● OP1 E		0.369 OP1 M2		**0.035** E M1	
		DPT	0.15 (-0.31-0.60) ● ● OP1 E		0.619 OP1 M2		0.25 E M1	
		PQT	0.35 (-0.10-0.68) ● ● OP2 E		0.983 OP2 M2		0.533 E M2	
		DQT	0.20 (-0.26-0.58) ● ● OP2 E		0.964 OP2 M2		0.092 E M2	
		PPT	0.46 (0.04-0.75) ● ● OP2 E		0.092 OP2 M2		0.615 E M2	
		MPT	0.41 (-0.03-0.71) ● ● OP2 E		0.756 OP2 M2		**0.044** E M2	
		DPT	0.57 (0.18-0.80) ● ● OP2 E		0.441 OP2 M2		0.145 E M2	
	Colour grading	Colour grading	Mean % agreement		Mean % agreement		Mean % agreement	
		PQT	81% G / 63% E		58%		68% G / 63% E	
		DQT	85% G / 75% E		64%		53% G / 53% E	
		PPT	80% G / 80% E		86%		80% G / 93% E	
		MPT	83% G / 88 % E		81%		73% G / 95 % E	
		DPT	95% G / 80 % E		64%		95% G / 70 % E	

Table 4.3. Strain sonoelastography reliability results on patellar and quadriceps tendon.

Colour dots in the table describes the ICC value. ● poor reliability, ● moderate reliability, ● good reliability, ● excellent reliability. When 2 dots are present they indicate the lower and upper limit of the 95%CI. & significant values indicated inter-machine association # significant values (bolt) indicated no inter-rater reliability. * Same dataset as Dickson et al. 2019 OP1 and OP3

ICC, Intraclass correlation coefficient; CI, confidence interval; OP, operator; M, measurement; PQT, proximal quadriceps tendon; DQT, distal quadriceps tendon; PPT, proximal patellar tendon; MPT, mid patellar tendon; DPT, distal patellar tendon; G, GE ultrasound; E, Esaote ultrasound.

Authors (y)	Parameters	Conditions	Intra-rater reliability		Inter-session reliability		Inter-rater reliability	
			Relative	Absolute	Relative	Absolute	Relative	Absolute
Aubry et al. (2013)	Velocity (m.s-1)	Axial P1 max PF P2 45° PF P3 0° PF P4 45° DF					ICC 0.15 ● 0.06 ● 0.29 ● 0.19 ●	
		Longitudinal P1 max PF P2 45° PF P3 0° PF P4 45° DF					ICC 0.46 ● 0.22 ● -0.01 ● 0.03 ●	
	Elasticity (kPa)	Axial P1 max PF P2 45° PF P3 0° PF P4 45° DF					ICC 0.16 ● 0.02 ● 0.31 ● 0.17 ●	
		Longitudinal P1 max PF P2 45° PF P3 0° PF P4 45° DF					ICC 0.43 ● 0.01 ● -0.02 ● 0.04 ●	
	Anisotropy Coefficient (A)	Longitudinal P1 max PF P2 45° PF P3 0° PF P4 45° DF					ICC 0.21 ● 0.10 ● 0.23 ● 0.20 ●	
Peltz et al. (2013)	Elasticity (kPa)	Longitudinal Achilles Left	ICC 0.54 ● D1 T1 0.31 ● D1 T2 0.66 ● D2 T1 0.82 ● D2 T2					

		Achilles Right	0.19 ● D1 T2 0.00 ● D1 T2 0.11 ● D2 T1 0.37 ● D2 T2					
Helfenstein-Didier et al. (2016)	Compression modulus (MPa) Shear modulus (kPa)	Longitudinal Compression modulus 45° 35° 25° Shear modulus 45° 35° 25°	ICC 0.42 (0.05-0.83) ● ● 0.73 (0.40-0.94) ● ● 0.85 (0.60-0.97) ● ● 1.00 (1.00-1.00) ● ● 1.00 (1.00-1.00) ● ● 1.00 (1.00-1.00) ● ●	CV% and SEM 0.81% and 2.14 0.60% and 2.04 0.48% and 1.37 0.07% and 10.69 0.05% and 6.45 0.05% and 3.5				
Siu et al.(2016)	Elasticity (kPa)	Longitudinal	ICC 0.85 ● OP1 0.84 ● OP2 0.80 ● OP3	CV % 0.09% 0.1% 0.11%			ICC 0.59 ●	CV % 0.13%
Lima et al. (2017)	Elasticity (kPa)	Longitudinal Left Right	ICC 0.93 ● 0.82 ●	CV % 23% 25%	ICC 0.42 ● 0.60 ●			
Payne et al. (2018)	Velocity (m.s-1)	Longitudinal Fixed Relaxed Axial Fixed Relaxed	ICC 0.71 (0.50-0.83) ● ● 0.54 (0.21-0.73) ● ● 0.62 (0.29-0.78) ● ● 0.71 (0.50-0.82) ● ●	CV%; SEM and MDC 4.9%; 0.23 and 0.65 2.9%; 0.19 and 0.51 3.9%; 0.19 and 0.53 6.0%; 0.26 and 0.71	ICC 0.67 (0.44-0.81) ● ● 0.55 (0.24-0.73) ● ● 0.78 (0.62-0.87) ● ● 0.85 (0.74-0.91) ● ●	CV%; SEM and MDC 5.2%; 0.27 and 0.76 3.1%; 0.20 and 0.55 4.4%; 0.17 and 0.46 6.3%; 0.19 and 0.53		
Petitpierre et al.(2018)	Elasticity (kPa)	Longitudinal PF MTJ Pre insertional Enthesis Longitudinal DF					p values 0.163 0.153 0.075	

		Body Pre insertional Enthesis Axial PF MTJ Body Enthesis Axial DF MTJ Body Enthesis					0.236 0.070 0.096 0.305 0.304 0.273 0.134 0.096 0.169	
Corrigan et al. (2019)	Elasticity (kPa) static and dynamic shear modulus. Viscosity (Pa*s)	Longitudinal Static modulus Dynamic modulus Viscosity	ICC (95%CI) 0.70 (0.39-0.87) ● ● 0.86 (0.72-0.94) ● ● 0.86 (0.72-0.94) ● ●					

Table 4.4. Shear wave sonoelastography reliability results on Achilles tendon. Colour dots in the table describes the ICC value. ● poor reliability, ● moderate reliability, ● good reliability, ● excellent reliability. When 2 dots are present they indicate the lower and upper limit of the 95%CI.

ICC, Intraclass correlation coefficient; CI, confidence interval; CV, coefficient of variation; SEM, standard error of measurement; MDC, minimal detectable change; OP, operator; PF, plantar flexion; DF, dorsi flexion; MTJ, musculotendinous junction.

Authors (y)	Parameters	Conditions	Intra-rater reliability		Inter-session reliability		Inter-rater reliability	
			Relative	Absolute	Relative	Absolute	Relative	Absolute
Peltz et al. (2013)	Elasticity (kPa)	Longitudinal Patellar Left Patellar Right Quadriceps Left Quadriceps Right	ICC 0.90 ● D1 T1 0.49 ● D1 T2 0.40 ● D2 T1 0.67 ● D2 T2 0.45 ● D1 T1 0.74 ● D1 T2 0.24 ● D2 T1 0.23 ● D2 T2 0.67 ● D1 T1 0.80 ● D1 T2 0.79 ● D2 T1 0.81 ● D2 T2 0.67 ● D1 T1 0.61 ● D1 T2 0.87 ● D2 T1 0.67 ● D2 T2					
Zhang and Fu (2013)	Elasticity (kPa)	Longitudinal Proximal	ICC (95%CI) 0.98 (0.93-0.99) ● ●	SEM / MDC (kPa) 1.54 / 4.27			ICC (95%CI) 0.97 (0.93-0.98) ● ●	SEM / MDC (kPa) 1.64 / 4.54
Hsiao et al. (2015)	Elasticity (kPa)	Longitudinal Proximal Middle Distal	ICC (95%CI) 0.87 (0.58–0.97) ● ● OP1 0.83 (0.32–0.96) ● ● OP2 0.97 (0.87–0.99) ● ● OP1 0.99 (0.96–1.00) ● ● OP2 0.84 (0.47–0.96) ● ● OP1 0.88 (0.51–0.97) ● ● OP2				ICC (95%CI) 0.74 (0.04–0.94) ● ● 0.82 (0.28–0.96) ● ● 0.78 (0.13–0.95) ● ●	
Tas et al. (2017)	Velocity (m.s-1)	Longitudinal	ICC (95%CI) 0.92 (0.82-0.97) ● ● OP1 0.91 (0.80-0.96) ● ● OP2	CV% / SEM 6.5% / 0.48 5.9% / 0.44	ICC (95%CI) 0.83 (0.57-0.95) ● ● OP1 0.81 (0.57-0.93) ● ● OP2	CV% / SEM 7.5% / 0.56 7.1% / 0.51	ICC (95%CI) 0.71 (0.32-0.88) ● ●	CV% / SEM 9.3% / 0.70
Mannarino et al. (2018)	Elasticity (kPa)	Longitudinal Dominant Non-dominant	ICC (95%CI) 0.89 (0.55-0.92) ● ● D1 0.93 (0.80-0.97) ● ● D2	CV% 40.19% 62.79%	ICC (95%CI) 0.65 (0.09-0.87) ● ● 0.63 (0.07-0.85) ● ●	CV% 41.26% 48.19%		

			0.89 (0.61-0.97) ● ● D1 0.90 (0.65-0.97) ● ● D2	62.98% 48.37%				
Zardi et al. (2019)	Elasticity (kPa)	Longitudinal Quadriceps Patellar	ICC (95%CI) 1.00 (0.99-1.00) ● ● 0.99 (0.98-1.00) ● ●	CV (M1/M2) 0.527 / 0.528 0.623 / 0.629				

Table 4.5. Shear wave sonoelastography reliability results on patellar and quadriceps tendon. Colour dots in the table describes the ICC value. ● poor reliability, ● moderate reliability, ● good reliability, ● excellent reliability. When 2 dots are present they indicate the lower and upper limit of the 95%CI.

ICC, Intraclass correlation coefficient; CI, confidence interval; CV, coefficient of variation; SEM, standard error of measurement; MDC, minimal detectable change; OP, operator.

SE: Achilles tendon.

Eight studies evaluated the reliability of AT elasticity measures using SE. Moderate to excellent intra-rater reliability was found for the longitudinal measurement of strain ratio; results ranged from an ICC of 0.66-0.99. Inter-rater reliability was moderate to good (ICC = 0.51-0.84), with some studies showing values below the 0.6 threshold.

A moderate inter-rater correlation was also found in one study (rs 0.61) (Yamamoto et al., 2016). Another study (ÜNal et al., 2019) analysing the inter-machine reliability showed an ICC of 0.85 (0.26-0.95), indicating good reliability but with very large 95% CI. Agreement on the colour grading of SE images was considered substantial (k = 0.70) for intra-rater evaluation and was considered substantial to almost perfect (k = 0.70-0.91) for inter-rater evaluation.

Poor reliability was found for intra-rater (ICC = 0.06-0.11) and for inter-session (ICC = 0.01-0.10) when using the percent of displacement values (Payne et al., 2017). Axial scan using SE was evaluated in two studies (Drakonaki et al., 2009, Payne et al., 2017) showing poor intra- and inter-rater reliability (ICC < 0.45).

Overall, intra- and inter-rater reliability for AT elasticity measured with SE strain ratios in a longitudinal scan was adequate. Inter-machine reliability tested in one study reported inconclusive results. Colour grading intra- and inter-rater agreement was substantial.

SE: patellar and quadriceps tendons.

Two studies (Dickson et al., 2020, Dickson et al., 2019) shared part of the data set; therefore, intra-rater reliability values obtained with the GE ultrasound device were reported

only for the study by Dickson et al. (Dickson et al., 2019), eliminating the other study (Dickson et al., 2020).

PT strain ratio was evaluated in three studies, showing intra-rater reliability values ranging from poor to good (ICC = 0.40-0.85) for the proximal, (ICC = 0.13-0.67), middle (ICC = 0.15-0.91) and distal part of the tendon. Inter-rater reliability ranged from poor to moderate (ICC = 0.11-0.64) for the proximal (ICC = 0.08-0.60), middle (ICC = 0.22-0.96) and distal part of the tendon. Inter-rater agreement of strain ratio using a t-test (*p* values) (Dickson et al., 2020) revealed mixed results with good values only documented for the proximal and distal part of the PT (Table 4.3). Inter-machine association using strain ratios was evaluated in one study (Dickson et al., 2020) showing significant results, indicating no association between the two ultrasound devices for the PT. Mean percent of agreement on the colour grading for PT was >80% for intra-rater, between 68% and 95% for inter-rater and between 64% and 86% for inter-machine (Dickson et al., 2020, Dickson et al., 2019).

QT strain ratio was evaluated in two studies revealing poor intra-rater (ICC<0.5) and inter-rater (ICC<0.5) reliability and no inter-machine association ($p > 0.05$). Mean percent of agreement on the colour grading for QT was between 63% and 85% for intra-rater, between 48% and 68% for inter-rater and between 58% and 64% for inter-machine (Dickson et al., 2020, Dickson et al., 2019).

Overall, reliability of SE measures using strain ratios on the PT was adequate only for intra-rater reliability when measured in the proximal part of the PT and if analysed by expert operators. QT measures were not reliable. Intra-rater agreement in the colour grading was good for the PT and QT. Inter-rater agreement was adequate in the PT and lower on the QT.

SWE: Achilles tendon.

Eight studies evaluated the reliability of using SWE to measure AT elasticity in a longitudinal scan. Results indicated poor to excellent intra-rater reliability (ICC = 0.17-1.00) for the elasticity or shear modulus (kPa), moderate intra-rater reliability (ICC = 0.54-0.71) for velocity ($m.s^{-1}$) and poor to good intra-rater reliability (ICC = 0.42-0.85) for compression modulus (MPa). In two studies (Aubry et al., 2013, Helfenstein-Didier et al., 2016), reliability results were also divided according to angle of the ankle when the measurements were performed (Table 4.4). Inter-rater reliability was poor to moderate (ICC = -0.02 to 0.59) for shear modulus (kPa) and poor (ICC < 0.5) for velocity ($m.s^{-1}$). Inter-session reliability was poor to moderate (ICC = 0.42-0.60) for shear modulus (kPa) and moderate (ICC = 0.55-0.67) for velocity ($m.s^{-1}$).

One study (Payne et al., 2018) showed moderate to good intra-rater and inter-session reliability for velocity axial values (ICC = 0.62-0.85), whereas another study (Aubry et al., 2013) showed poor inter-rater axial values (ICC <0.5) for shear modulus and for velocity.

Overall, inter-rater and inter-session reliability of SWE measures for AT was inconclusive. Intra-rater reliability was conflicting, with some studies indicating good reliability and others poor reliability.

SWE: patellar and quadriceps tendon.

Six studies evaluated intra-rater reliability of PT measurements with poor to excellent results (ICC = 0.45-1.00) for shear modulus (kPa) and excellent intra-rater reliability (ICC = 0.91-0.92) for velocity ($m.s^{-1}$). Inter-session reliability was moderate (ICC = 0.63-0.65) for

shear modulus (kPa) and good (ICC = 0.81-0.83) for velocity ($m.s^{-1}$). Inter-rater reliability ranged from moderate to excellent (ICC = 0.71-0.97) for both shear modulus and velocity.

Two studies evaluated the QT intra-rater reliability, one with moderate results (ICC = 0.72-0.77) (Peltz et al., 2013) and the other with excellent results (ICC = 0.99-1.00) (Zardi et al., 2019). Overall, intra-rater reliability of SWE was satisfactory for the PT and QT. Inter-rater and inter-session reliability results were conflicting.

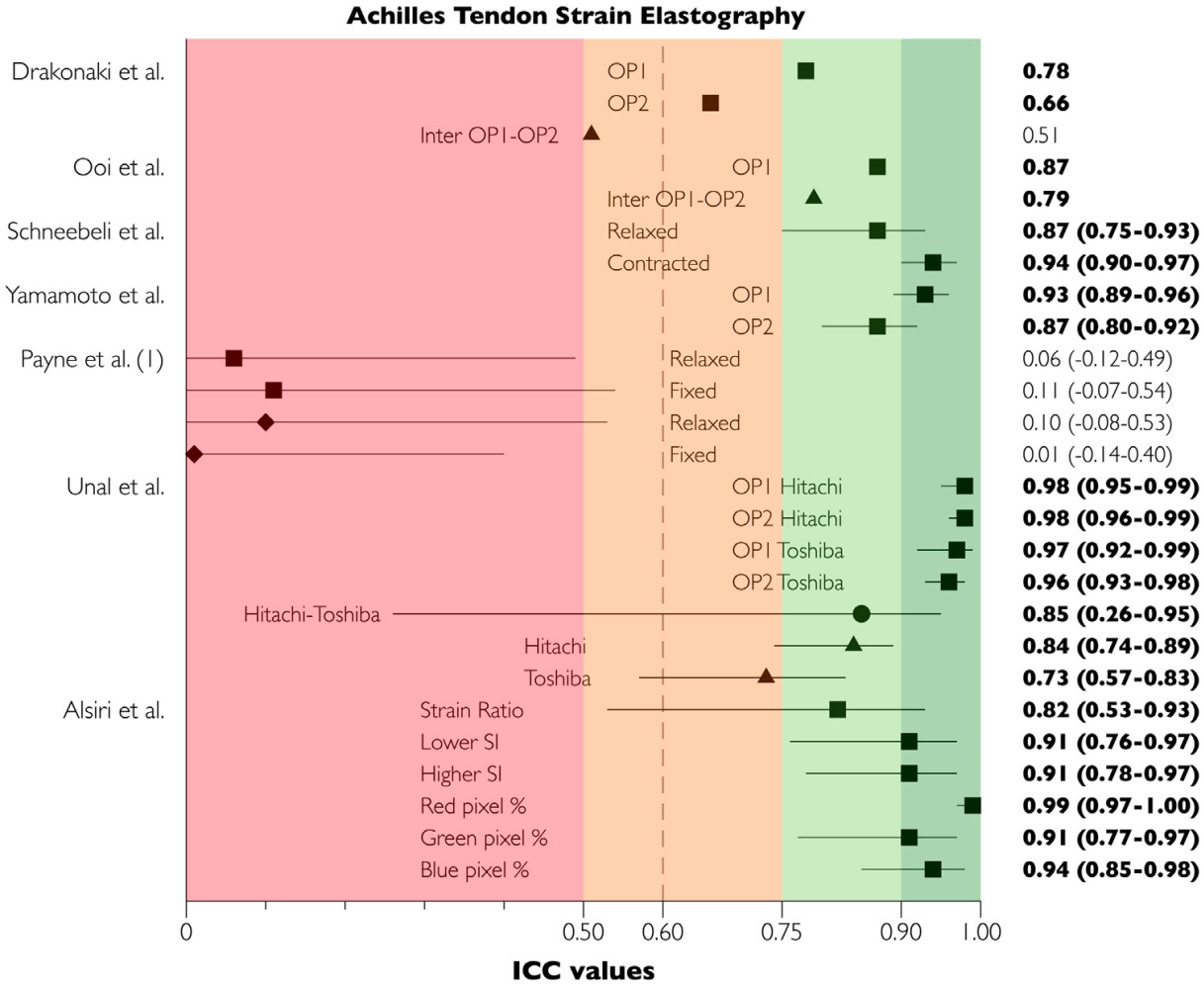


Figure 4.6. Forest plot representing the intraclass correlation coefficient (ICC) values of the study analysing strain elastography (SE) reliability in the Achilles tendon in the longitudinal scan. Dotted line, ICC = 0.6 clinical relevance threshold. Red, orange, light green and dark green areas represent poor, moderate, good and excellent reliability values, respectively. ■; Intra-rater reliability ▲; Inter-rater reliability ◆; Inter-session reliability ●; Inter-machine reliability. OP, operator; SI, strain index.

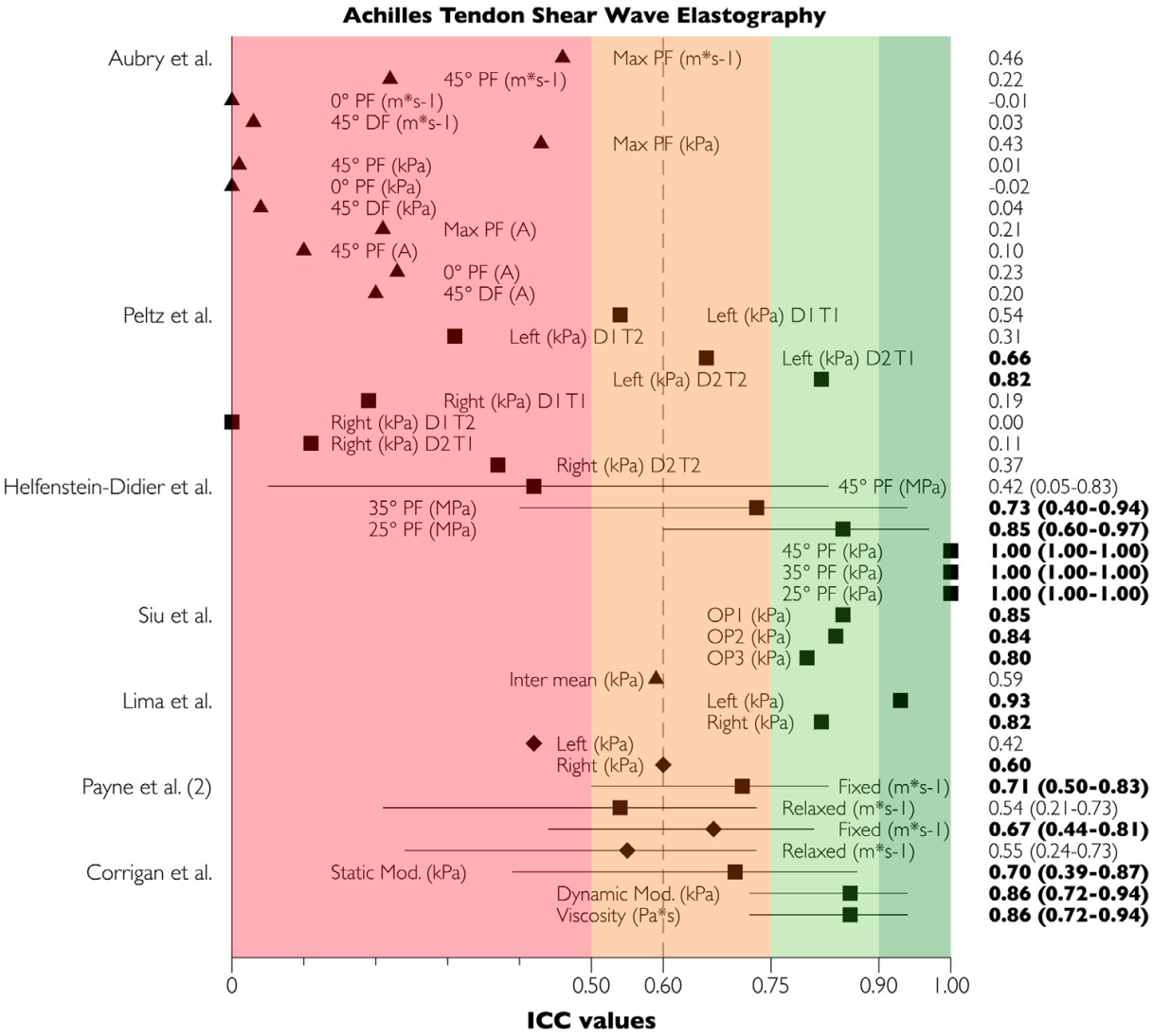


Figure 4.7. Forest plot representing the intraclass correlation coefficient (ICC) values of the study analysing shear-wave elastography (SWE) reliability in the Achilles tendon in the longitudinal scan. Dotted line, ICC = 0.6 clinical relevance threshold. Red, orange, light green and dark green areas represent poor, moderate, good and excellent values, respectively. ■; Intra-rater reliability ▲; Inter-rater reliability ◆; Inter-session reliability. A, anisotropy coefficient; D, day; DF, dorsi flexion; Mod., modulus; OP, operator; PF, plantar flexion; T, trial.

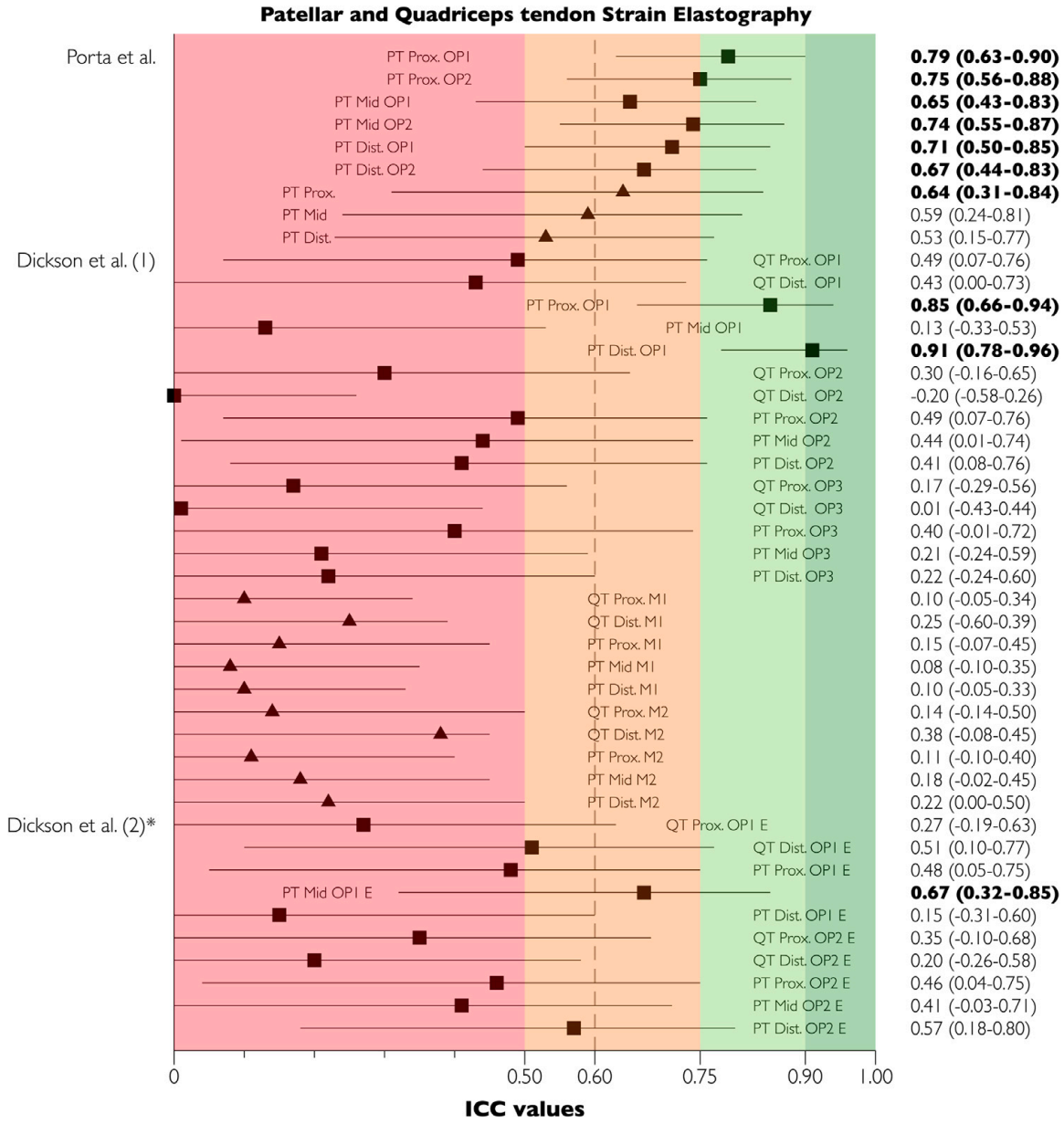


Figure 4.8. Forest plot representing the intraclass correlation coefficient (ICC) values of the study analysing strain elastography (SE) reliability in the patellar and quadriceps tendons in the longitudinal scan. Dotted line, ICC = 0.6 clinical relevance threshold. Red, orange, light green and dark green areas represent poor, moderate, good and excellent reliability values, respectively. ■; Intra-rater reliability ▲; Inter-rater reliability.

D, day; Dist., distal; Dom., dominant; E, Esaote ultrasound, N-Dom, non-dominant; OP, operator; Prox., proximal; PT, patellar tendon; QT, quadriceps tendon. * For GE ultrasound values of this study, see Dickson et al. (I) OP1 and OP3.

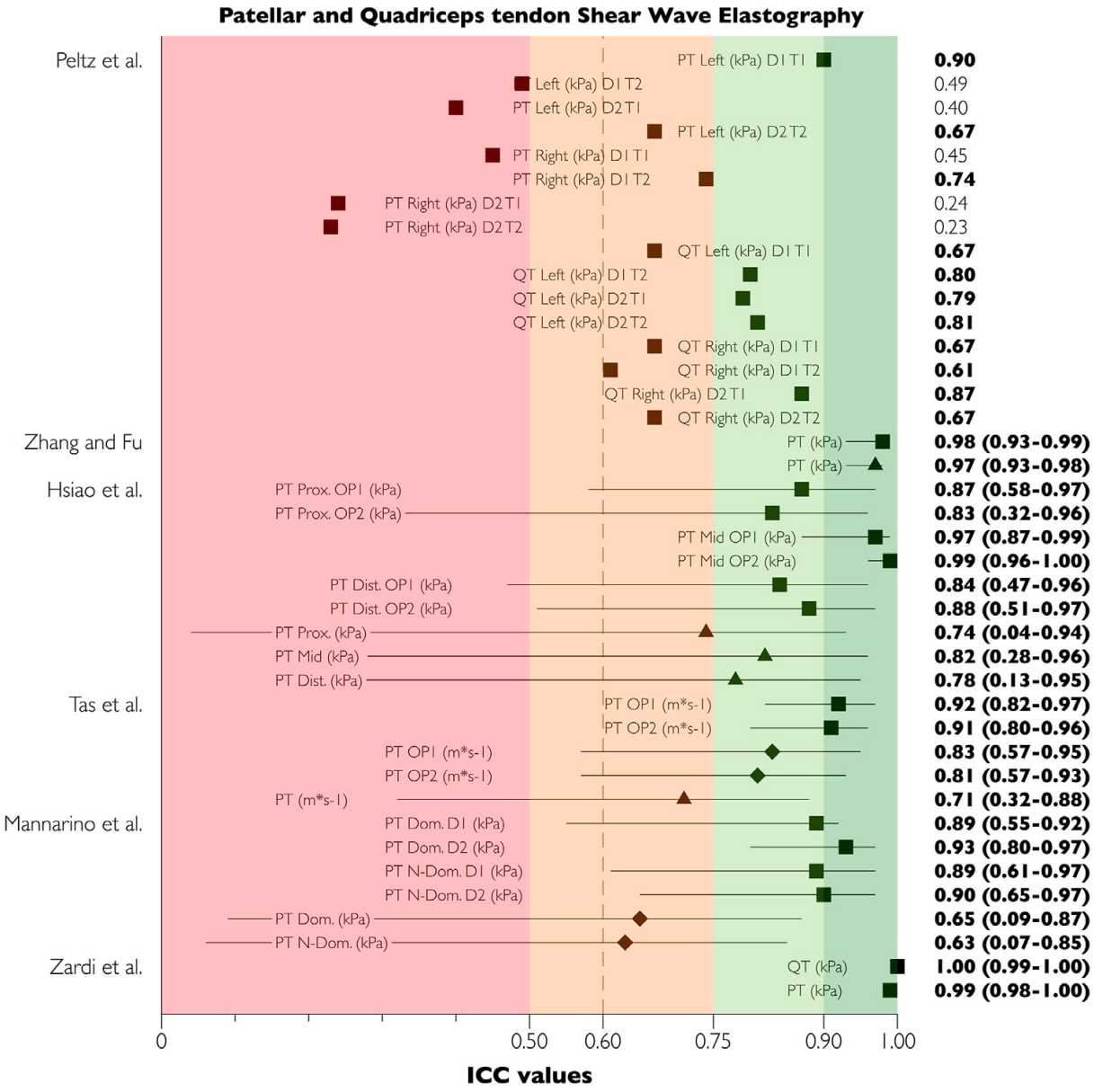


Figure 4.9. Forest plot representing the intraclass correlation coefficient (ICC) values of the study analysing shear-wave elastography (SWE) reliability in the patellar and quadriceps tendons in the longitudinal scan. Dotted line, ICC = 0.6 clinical relevance threshold. Red, orange, light green and dark green areas represent poor, moderate, good and excellent reliability values, respectively. ■; Intra-rater reliability ▲; Inter-rater reliability ◆; Inter-session reliability.

D, day; Dist., distal; Dom., dominant; N-Dom, non-dominant; OP, operator; Prox., proximal; PT, patellar tendon; QT, quadriceps tendon; T, trial.

4.5 Discussion

The present chapter aimed to synthesize the evidence regarding the reliability of sonoelastography for the assessment of lower limb tendon mechanical properties. Reliability and validity are prerequisites to the clinical applicability of a measure. These measurement properties should be confirmed before this technology is used in clinical settings. The results of this systematic review suggest that reliability is highly variable across the studies, and therefore the use of this technology in a clinical setting should be further evaluated in high-quality reliability studies. Furthermore, other clinimetric properties (i.e., validity and responsiveness) should be further investigated.

Twenty-four articles were included and reviewed in subgroups of studies divided by technology used and tendons analysed. High heterogeneity was found between studies even when using the same technology on the same tendon. Different joint angles and position, different probe orientation (longitudinal or axial scan), different parameters used to calculate elasticity and different ultrasound devices used challenged the possibility of comparing results between studies. Nevertheless, a qualitative synthesis was conducted, and overall, there was a large variability of the results regardless of the technology used or the tendon analysed with variable reliability findings; these conflicting results could be attributed to the low methodological quality of the included studies.

As expected, intra-rater reliability results were superior to inter-rater or inter-session values, confirming that this type of ultrasound-based technology, whether with qualitative or quantitative elastogram analysis, is particularly dependent on the operator's manual skills and experience (Prado-Costa et al., 2018). However, we cannot exclude that the lower reliability found for inter-rater and inter-session is related to the paucity of studies analysing this type of reliability. Different results were found between the lower limb tendons, suggesting that the

reliability of sonoelastography could be influenced by the structural and morphologic characteristics of the tissues evaluated. Very wide 95% CI of the ICC values were found across the majority of the studies, questioning the sample size used. The use of inadequate sample size is confirmed by the low score on the GRRAS scale (item 6).

The quality of the reporting in the selected papers was poor, with only two studies with more than 10 out of 15 points on the GRRAS scale (Alsiri et al., 2020, Dickson et al., 2020). The majority of the studies lacked a description of the raters and patients of interest in the definition of the sampling methods and the calculation of the sample size.

Although the reviewed papers were designed specifically to evaluate reliability, many were not reported adequately. Moreover, the comparison between studies and the replication of an individual study is compromised by the lack of detailed reporting of the procedures. Furthermore, even the methodological quality of the studies included, screened with the QAREL checklist, showed a possible risk of bias owing to shortcomings in the study design. Considering the real total score without "N/A" answers, the majority of the included studies (17 out of 24) scored at maximum 2 or 3 points less than the possible highest value. Nevertheless, in almost all of the included studies, one or more items were scored as "unclear," indicating possible methodological bias (Figure. 4.5). The lack of clarity in the experimental design mainly concerned the blinding of the raters to the finding of other raters (item 3), the blinding to their own prior findings (item 4), the blinding to additional cues that were not part of the test (item 7) and the varied order of examination (item 8). The "unclear" score did not invalidate the study but made it vulnerable to possible bias. These limitations may be attributed to insufficient reporting rather than real methodological bias. Given the low quality in reporting and the possible methodological bias present in all studies, caution should be used in the interpretation of the results.

Future studies evaluating reliability should adhere to validated quality assessment tools to improve methodological quality and reporting of the results.

SE: Achilles tendon

The majority of the included studies showed that SE has acceptable (ICC >0.6) intra-rater reliability except for one study (Payne et al., 2017) that showed very low reliability values. High intra-rater reliability values were found when the AT was analysed using semi-quantitative analysis using strain ratio with an external reference material (Schneebeli et al., 2016, Yamamoto et al., 2016). Variable results (moderate to excellent) were obtained when using strain ratio for the KFP (Drakonaki et al., 2009, Ooi et al., 2015, ÜNal et al., 2019) or subcutaneous fat (Alsiri et al., 2020) and low results when using the percent of displacement calculation (Payne et al., 2017).

Inter-rater results were variable (moderate to high) between studies, with one study presenting results lower than the threshold of 0.6 (Drakonaki et al., 2009) and two studies with moderate to good reliability (Ooi et al., 2015, ÜNal et al., 2019). Overall, both intra- and inter-rater SE measurements of the AT appear reliable when using semi-quantitative strain ratio analysis. Conversely, calculating the percent of displacement in SE seems unreliable (Payne et al., 2017). When analysing the tendon qualitatively with colour grading, the agreement is substantial to almost perfect.

In addition to strain ratio measurements, Alsiri et al. (Alsiri et al., 2020) presented another method to quantify SE images using the colour pixel analysis. This method is based on the quantification of the percentages of each colour in the SE image. Intra-rater reliability of this method on the AT appeared higher than the strain ratio measure. However, caution should

be used in the analysis of elastograms without an external reference material not affected by changes in elasticity owing to pathology, recovery or different measurement conditions. A simple count of the colour pixel within the same structure disregards the algorithm implemented in SE ultrasound devices that uses an "auto scale" colour range (Schneebeli et al., 2019). Ünal et al. (ÜNal et al., 2019) evaluated the inter-machine reliability, showing variable results ranging from ICC of 0.26-0.95. Given this result, the author suggests evaluating the tendon separately for each device. The latter study emphasizes one of the major limitations of SE. The semi-quantitative analysis obtained by a colour scale may differ depending on the algorithm implemented by different companies and from the amount of compression with the probe permitted by different devices.

The differences between devices in the generation of the colour scale may hinder the clinical applicability of SE. Caution should be taken when comparing results obtained from different devices on the same structure.

SE: patellar and quadriceps tendon

In contrast to the AT, SE using strain ratios on the PT and QT have questionable intra- and inter-rater reliability results. 95% CI of the reliability measurement often fell below the 0.6 threshold, indicating poor to moderate reliability and weak clinical relevance.

Porta et al. (Porta et al., 2014) showed moderate to good intra-rater reliability with almost all the CI values below 0.6 and poor inter-rater reliability. Two studies (Dickson et al., 2020, Dickson et al., 2019) reported mixed results with measurements on some part of the PT appearing to be reliable when measured by an expert rater. Overall, the results of those studies indicate poor reliability except for the proximal PT when analysed by expert operators. When

using colour grading, agreement between operators appears to be better compared with using semi-quantitative analysis (Dickson et al., 2020, Dickson et al., 2019). Operator experience seems to play an important role to be able to measure the PT and QT in a reliable way. The different reliability values obtained with SE on the AT, QT and PT could be attributed to differences in anatomy between tendons, where the first two are tendons with one bone insertion and muscle while the latter is attached to a bony structure on both sides. Compression with the ultrasound probe on a "free" tendon rather than on a more solid structure with the proximity of prominent bone projection, as for PT, could affect reliability results. Furthermore, the different structures used for the strain ratio, subcutaneous tissue (Porta et al., 2014) and Hoffa fat pad (Dickson et al., 2020, Dickson et al., 2019) could have led to a difference in reliability compared with AT measurements using an external reference material (Schneebeli et al., 2016, Yamamoto et al., 2016) or KFP (Alsiri et al., 2020, Drakonaki et al., 2009, Ooi et al., 2015, ÜNal et al., 2019).

To date, only three studies with a small sample size are present in the literature. Given the high variability of these results, further studies with high methodological quality are needed to establish the reliability of SE when measuring these tendons.

SWE: Achilles tendon

SWE measurements of the AT showed conflicting results with two studies (Aubry et al., 2013, Peltz et al., 2013) showing poor to moderate intra- and inter-rater reliability for longitudinal and axial scans. One of these studies (Peltz et al., 2013) indicated a reliability slightly over the 0.6 threshold but only for the left tendon. Two other studies (Corrigan et al., 2019, Helfenstein-Didier et al., 2016) revealed moderate to excellent intra-rater reliability for

compression and shear modulus (Helfenstein-Didier et al., 2016) except for the compression modulus at 45° and 35° plantarflexion and moderate to excellent intra-rater reliability for dynamic modulus and viscosity (Corrigan et al., 2019) with inconclusive results for the static modulus.

Furthermore, two studies (Lima et al., 2017, Siu et al., 2016) showed good to excellent intra-rater reliability but poor or moderate inter-rater (Siu et al., 2016) and inter-session reliability (Lima et al., 2017). Finally, Payne et al. (Payne et al., 2018) showed acceptable intra-rater reliability in the longitudinal scan when the ankle was fixed at 0° plantarflexion, but doubtful reliability for the relaxed position. Surprisingly, this study showed higher values (moderate to high) when the tendon was analysed in the axial scan.

Indeed, waves propagate along the fibers, as for longitudinal scan, more easily than across the fiber, as for axial scan. Moreover, during an axial scan, inhomogeneous compression with the edges of the probe could occur, which may affect the reliability. Considering these results, further studies are needed to better understand the value of axial scans in the analysis of tendon elasticity.

Although the majority of the SWE studies used the Aixplorer ultrasound equipment, two studies (Corrigan et al., 2019, Payne et al., 2018) analysed AT with a different SWE device but obtained similar results to the other studies. Overall, the results indicated relatively good intra-rater reliability but poor inter-rater and intersession reliability. The main reasons for the lack of inter-rater reliability are, according to the authors, because of the difficulties in the stabilization of the ankle joint position (Aubry et al., 2013, Peltz et al., 2013) and measurement bias related to positioning, the direction of the transducer or to the positioning of the ROI (Aubry et al., 2013). Moreover, anisotropic changes of the tendon owing to a slightly different position of the ankle can occur. Furthermore, some authors (Aubry et al., 2013, Chino and

Takahashi, 2015, DeWall et al., 2014) suggested that the higher shear modulus achievable with this technology (600-800 kPa) was not sufficient to calculate tendon elasticity in a position near to 0° plantarflexion or in dorsiflexion because of saturation of the signal.

SWE: patellar and quadriceps tendon

The six studies evaluating the PT and QT with SWE showed high intra- and inter-rater reliability with all the point values of ICC of more than 0.6, except for the PT in the study of Peltz et al. (Peltz et al., 2013). Inter-session reliability was also considered moderate to high in two studies (Mannarino et al., 2018, Tas et al., 2017). Two studies (Zardi et al., 2019, Zhang and Fu, 2013) reported excellent intra- and inter-rater reliability values for PT and QT. Nevertheless, considering the 95% CI of all the ICC results (Figure 4.9*),* the majority of the included studies, especially for inter-rater and inter-session reliability, presented CI values substantially lower than 0.5 and therefore should be considered as poor reliability. These values are often neglected by authors and readers but are critical when analysing and interpreting ICC values. Indeed, the CI gives the range within which the true ICC value is supposed to be, and this could be at any point between the lower and the higher limits. Therefore, the true ICC value could largely be lower than the estimate value (Koo and Li, 2016, Shrout and Fleiss, 1979). Considering this large CI, Hsiao et al. (Hsiao et al., 2015) concluded that the only suitable part of the PT to make SWE evaluation is the (MID) and that inter-rater reliability should be cautiously interpreted. Overall, intra-rater reliability was adequate for PT and QT but dubious for inter-rater and inter-session. According to the authors, the reason for this variability between studies could be attributed to the difference in the ROI placement and size. Furthermore, some authors (Chen et al., 2013, Drakonaki et al., 2012, Hsiao et al., 2015) suggested that another

possible cause of heterogeneity in the results are the saturation of the signal with high shear modulus (kPa) values and the excessive noise signal when measuring soft tissue near bone. Finally, the small sample size present in some of these studies may have led to an increased 95% CI.

Limitations

To improve the quality of the included articles, the search was restricted to full peer-reviewed published papers; relevant grey literature may have been excluded. The high heterogeneity of the included studies, which used varying joint angles, tendon portion, conditions, ultrasound scan, extracted parameters and statistical methods, made generalization of the results difficult. Graphical synthesis of the results was done in a sub-portion of the data of the included studies. Given the high heterogeneity of the data reported, especially regarding the parameter used to calculate elasticity, a quantitative synthesis with meta-analysis was not possible. This systematic review included only reliability measures on lower limb tendons and therefore the results may not be generalized to other tendons. Other measurement properties apart from reliability (i.e., validity, diagnostic accuracy, sensitivity, specificity) were not evaluated in this systematic review; different sonoelastography measurement properties need to be reviewed in the future. Moreover, the majority of the studies assessed tendon in healthy participants, and therefore it is not possible to generalize these results to a clinical context in the assessment of pathologic tendons.

4.6 Conclusions

In this chapter reliability values of SE and SWE in assessing lower limb tendons are presented. Overall, the reliability of these measures remains highly variable across studies. SE on AT is reliable when using strain ratio, and good agreement was found in the colour grading analysis, but this was not the case for the PT.

The reliability of SWE measurements was highly variable between studies; nevertheless, it seems to be more reliable on PT than on AT, especially if different operators are compared. However, weakness in the reporting and possible methodological bias were present in all studies, making it difficult to recommend one technology over another. The interpretation of reliability results was often over-estimated given the lack of consideration of the CI. The lack of inter-rater, inter-session and inter-machine reliability found in this systematic review raises important doubts about the clinical applicability of these technologies. Caution should be used when interpreting results from sonoelastography measures.

Further reliability studies of high methodological quality are needed to better understand the value of these technologies in the assessment of lower limb tendon mechanical properties to transfer the use of these measures in clinical settings to provide meaningful information about tendon status.

CHAPTER 5

MYOTONOMETRY FOR THE EVALUATION OF ACHILLES TENDON MECHANICAL PROPERTIES: A RELIABILITY AND CONSTRUCT VALIDITY STUDY

This chapter reports in full the contents of a published manuscript by the thesis author (Schneebeli et al. 2020b). It includes verbatim text from the published manuscript and some changes employed for the purpose of this thesis.

Publications and Presentations

1. **Schneebeli A**., Falla D., Clijsen R., Barbero M. 2020b. Myotonometry for the evaluation of Achilles tendon mechanical properties: a reliability and construct validity study. *BMJ Open Sport Exerc Med*. 12;6(1) **(Appendix 6)**
2. **Schneebeli A**., Falla D., Clijsen R., Barbero M. MyotonPRO; a reliable device to evaluate Achilles tendon mechanical properties. International Society of Electrophysiology and Kinesiology (ISEK) Virtual Congress. July 2020

5.1 ABSTRACT

In this chapter, the intra-rater and inter-rater reliability of the MyotonPRO and its construct validity for the assessment of AT stiffness is presented.

Forty healthy participants were assessed using the MyotonPRO by two raters on two different occasions. Tendon was evaluated in three different positions (relaxed, 0° plantarflexion and standing) and during different isometric contractions (range 0–3 kg). Reliability was calculated using ICC, 95% CI, SEM and minimal detectable change (MDC). Construct validity was evaluated between the different positions and the different contraction intensities using Friedman test.

Intra-rater reliability was very high ICC2,k 0.87–0.98. The reliability of the 0.5 kg contraction was moderate with an ICC2,k of 0.59. Inter-rater reliability ranged from high to very high with an ICC2,k of 0.76–0.86. The reliability of the 0.5 kg, 1 kg contraction and the standing position was moderate with an ICC2,k of 0.55, 0.54 and 0.56 respectively. Inter-session reliability ranged from high to very high with an ICC2,k of 0.70–0.89. The reliability of the 0.5 kg contraction was moderate with an ICC2,k of 0.54. Construct validity was demonstrated between different contraction levels and different positions.

MyotonPRO is a reliable tool for the evaluation of AT stiffness during different contraction levels and in different positions. Construct validity was supported by changes of tendon stiffness during the explored conditions. MyotonPRO can be implemented, as a ready to use device, in the evaluation of tendon tissue mechanical properties.

5.2 Introduction

Given the clinical and research interest in evaluating tendon stiffness as a parameter to describe tendon behaviour and tendon health, different measurement techniques have been developed. In the previous chapters (Chapters two, three and four) AT mechanical properties have been evaluated with different sonoelastography techniques. In this chapter a recent, non-invasive, ready to use technology, the MyotonPRO (Muomeetria, Tallinn, Estonia) is presented. This device is a handheld myotonometer producing a mechanical impulse to the skin overlying the target structure. The oscillation of the tissues underneath the probe permits calculation of the viscoelastic properties of the tissue (Gervasi et al., 2017, Fröhlich-Zwahlen et al., 2014, Agyapong-Badu et al., 2016). One parameter that can be extracted with this device is dynamic stiffness (N/m), which has been used in different studies to characterise the behaviour of different musculoskeletal tissues. This device has recently been used to evaluate tendon stiffness (Orner et al., 2018, Morgan et al., 2018, Liu et al., 2018, Feng et al., 2018) with a recent work showing decreased stiffness over the tendinopathic region of the tendon in people with Achilles tendinopathy and a significant difference in tendon stiffness between weight-bearing and non-weight-bearing positions.

The reliability of the MyotonPRO has been demonstrated for the evaluation of muscle stiffness, (Ortega-Cebrian et al., 2016, Kelly et al., 2018, Fröhlich-Zwahlen et al., 2014, Bizzini and Mannion, 2003) however, the reliability of MyotonPRO for measuring AT stiffness requires further investigation, (Sohirad et al., 2017, Liu et al., 2018, Finnamore et al., 2019, Feng et al., 2018) especially regarding the capability of this device to measure the tendon in different conditions. In contrast to muscle, values of AT stiffness are extremely high and even higher when tested under load (Morgan et al., 2018). Being able to quantify AT mechanical

properties with a ready to use and affordable device which provides a reliable and valid evaluation of the tendon under different conditions, would provide new opportunities to characterise the mechanical behaviour of the AT, for example, in people with Achilles tendinopathy or following an intervention.

This chapter address the thesis objective number 4 and aims to evaluates the intra-rater and inter-rater reliability of using the MyotonPRO to measure stiffness of asymptomatic AT in different position and during increasing load and to determine the construct validity of this device for measuring tendon stiffness.

5.3 Methods

The study was conducted between January and July 2019 at the University of Applied Sciences and Arts of Southern Switzerland. The study reporting adheres to the GRRAS (Kottner et al., 2011). The study was approved by the Ethics Committee of Canton Ticino (ID:2018–01483/CE3391) (Appendix 11) and written informed consent was provided by the participants.

A convenience sample of 40 healthy participants (18 women, 22 men, aged 33.8±14.2 years) were prospectively recruited trough public announcement at the University. Their mean (±SD) height and weight were 172.2 (±8.2) cm and 71.7 (±12) kg. Health-related physical activity was monitored using the International Physical Activity Questionnaires Short form (IPAQ) (Craig et al., 2003); 23 participants were categorised as high, 15 as moderate and 2 as having low physical activity levels. Participants were excluded if they had a history of tendon or foot injury or surgery, connective tissue, metabolic or endocrine disease. Furthermore, participants with systemic inflammatory disorders, rheumatoid arthritis, spondyloarthropathy or hypercholesterolaemia were excluded.

Sample size was estimated according to Walter et al. (Walter et al., 1998) using the following parameters: two replicates, p0=0.6, p1=0.80, α=0.05 and β=0.2. The optimal sample size was 39.1, and we rounded up to 40 participants.

5.3.1 Procedures

The AT mechanical properties were randomly analysed by two independent operators who were both physiotherapists with a minimum of 4 hours of training with the MyotonPRO prior to the study. Two measurement sessions were planned within 7 days. During the first session, the two operators consecutively performed the measures in order to evaluate the intra-rater and inter-rater reliability. The second session was used to evaluate inter-session reliability. Testing location and room temperature (21°C–23°C) was kept constant across sessions. Participants were asked to maintain the same activity level between the two testing days.
The resistance of the soft tissues to the deformation induced by the MyotonPRO is calculated from an acceleration graph representing the damped natural oscillation of the tissues. Dynamic stiffness, calculated in N/m, is computed by multiplying the maximum acceleration of the oscillation graph to the mass of the probe divided by the maximum displacement of the tissue; higher values represent a stiffer tissue.

Both the left and right AT were evaluated at the most central point of the tendon following a trajectory from the most central component of the medial malleolus as this point has been suggested as the most prevalent region for tendinopathy (Mahieu et al., 2006). Furthermore, a previous study using MyotonPRO to evaluate stiffness of the AT in people with Achilles tendinopathy and asymptomatic controls showed that changes in mechanical

parameters are more likely to be detected from 8 to 12 cm from the plantar aspect of the heel, corresponding to the free tendon part (Morgan et al., 2018).

MyotonPRO was setup with a multiscan sequence of 5 impulses (1 s apart), a short duration (15 ms) impulse involving minimal mechanical force with a precompression of 0.18 N and an impulse of 0.40 (total=0.58 N) was exerted on the tendon.

Measurements were taken in three different positions: standing, a relaxed position and during isometric contractions of the plantar flexors of increasing intensities, in order to evaluate construct validity (Figure 5.1). As the triceps surae contracts to increase plantarflexor force, the passive tension within the tendon increases as shown in previous studies (Kjaer, 2004). Since tendon stiffness and tendon displacement are directly related to plantarflexor strength (Magnusson et al., 2003) and ankle angle, (Arampatzis et al., 2007a) myotonometry values are expected to increase with increasing muscle contraction and with increased plantarflexion. To illustrate this construct, stiffness of the AT was compared across the five different contraction levels and between the three different positions. Testing in the three different positions as well as the sequence of the isometric contractions were randomized using a random number table.

5.3.2 Isometric contractions

The participants were positioned in prone with the foot secured within a dynamometer with the ankle in 0° of dorsiflexion/plantarflexion. Different intensities of isometric contractions of the plantar flexors were performed (0, 0.5, 1, 2 and 3 kg). The torque at the ankle joint was evaluated using a dynamometer connected to a force sensor operating in a 0–100 n range (CCT Transducers, Turin, Italy). The force sensor was attached to a wooden board connected to a hinge that enabled natural movement of the ankle joint in dorsiflexion and

plantarflexion (Figure 5.1A). The board was then fixed in order to permit isometric contractions only at a defined angle of 0° dorsiflexion. The force detected by the sensor was proportional to the torque exerted at the ankle level. Force signals were amplified using MISO-II (OT Bioelettronica, Turin, Italy) and visual feedback was provided to the participants. A practice phase prior to the recording was conducted by asking the patient to familiarise with the visual feedback and perform contractions with the instruction to 'push on the board as if you want to reach a tip-toe position'. During this practice phase, the lift of the heel was controlled. In order to prevent the detachment of the heel from the board, the foot and ankle were tightly secured in the dynamometer with two belts.

5.3.3 Standing

For the analysis in the standing position, participants were asked to stand on a Wii-Balance board (Nintendo, Kyoto, Japan) with the centre of mass on the middle of the board with the feet equally spaced (Figure 5.1B). Visual feedback was provided by the BrainBLOX Software (University of Colorado, Boulder, Colorado, USA) to the participant in order to ensure that the centre of mass remained in the same position. Participants were asked to rest their hands on a fixed box which ensured the stability of the standing position and avoided oscillation of the centre of mass during the measurement that could affect the tension of the triceps surae muscle-tendon complex.

5.3.4 Relaxed position

The measurements in the relaxed position were performed with the participants in prone on an examination bed and the feet hanging freely over the edge (Figure 5.1C). The participants were instructed not to move their feet during the measurement.

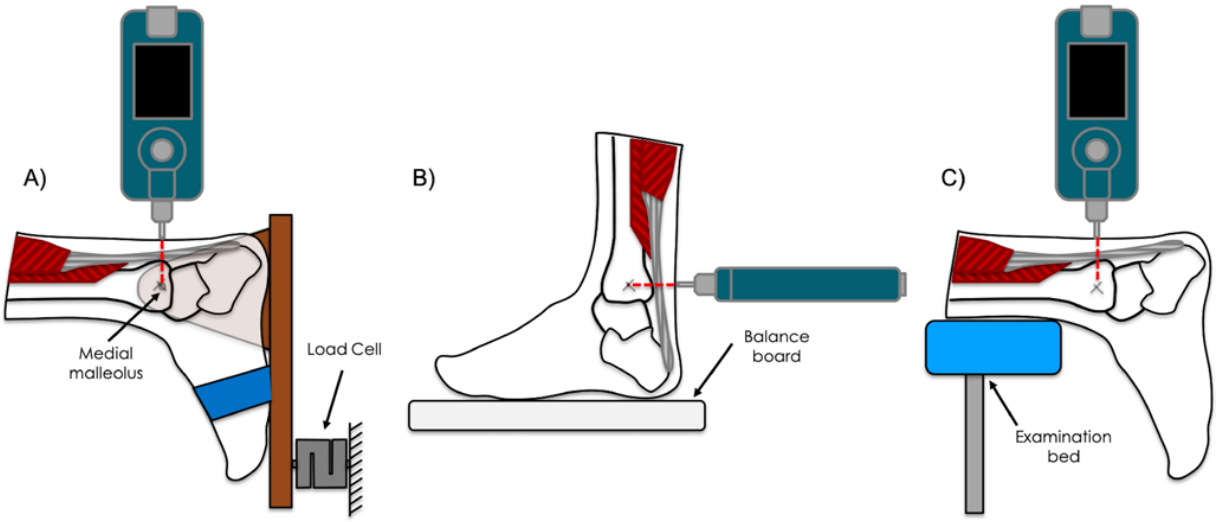


Figure 5.1 Schematic of the experimental setup. (A) Isometric contractions: the foot was securely attached to a dynamometer with a wooden board at a fixed angle of 0° of dorsiflexion. The force measured by the load cell was proportional to the torque exerted at the ankle level. (B) Standing position: participants were asked to stand on a Wii balance board (Nintendo, Kyoto, Japan) with the centre of mass centred on the centre of board with the feet equally spaced. (C) Relaxed position: the feet were hanging freely over the edge of the examination bed. MyotonPRO was applied to the most central point of the tendon at the level of the medial malleolus.

5.3.5 Statistical analysis

Statistical Package for the Social Sciences (SPSS V.24) was used to perform statistical analysis. Descriptive statistics (mean±SD) were used to describe the demographic

characteristics of the sample. The distribution of the values was assessed using the Shapiro-Wilk test. Given the non-normal distribution of the data, non-parametric, independent samples, Mann-Whitney test was used to assess whether there were significant differences in AT mechanical properties between men and women, between participants with different physical activity levels based on their IPAQ score.

Intra-rater and inter-rater reliability was assessed using ICC2,k and the absolute reliability was calculated using SEM and MDC (Atkinson and Nevill, 1998). Furthermore, a cut-off point of ICC >0.6 was used to consider the clinical relevance of the measurements (Chinn, 1990, Munro, 2005).

Construct validity was tested analysing the correlations between the five different contraction levels and the three different positions using Friedman test with post hoc pairwise comparison Bonferroni correction was applied and statistical significance was set to $\alpha=0.05$. Data are presented as median and IQR.

5.4 Results

No significant difference in AT stiffness was observed between men and women ($p=0.6$) or between participants with different physical activity levels based on their IPAQ score ($p=0.9$), therefore, the data were pooled and further analysed across the sample. Table 5.1 reports the descriptive statistics for the sample in the different conditions.

A total of eighty AT of 40 healthy participants were assessed by the two physical therapists. Intra-rater reliability was very high with an ICC2,k of 0.95 for 0 kg, 0.87 for 1 kg, 0.95 for 2 kg, 0.94 for 3 kg, and 0.98 and 0.87 for the relaxed and standing positions

respectively. The intra-rater reliability of measuring AT stiffness during the 0.5 kg contraction was moderate with an ICC2,k of 0.59.

		Sample (Mean±SD)			Stiffness N/m (Median IQR)						
	N.	Age (y)	Height (cm)	Weight (kg)	0 kg	0.5 kg	1 kg	2 kg	3 kg	Relax	Standing
Total	40	33.8	172.2	71.7	1043.0	1096.5	1110.5	1180.5	1381.5	771.0	1596.0
		±14.2	±8.2	±12.0	132.3	62.0	121.3	255.5	214.3	105.3	339.3
Men	22	35.6	177.7	77.4	1057.5	1089.5	1086.5	1117.5	1333.0	792.0	1577.5
		±13.8	±5.6	±10.6	144.0	65.0	132.3	143.3	198.3	124.0	337.3
Women	18	32.4	167.6	67.0	1041.0	1099.5	1129.5	1284.0	1435.5	753.0	1616.5
		±15.1	±6.9	±11.0	139.0	89.5	129.8	279.8	201.3	83.3	363.5

Table 5.1 Descriptive statistics. Sample characteristics and stiffness values.

Inter-rater reliability between the two raters ranged from high to very high with an ICC2,k of 0.76 for 0 kg, 0.79 for 2 kg, 0.81 for 3 kg and 0.86 for the relaxed position. The inter-rater reliability of measuring AT stiffness during the 0.5 kg, 1 kg contraction and the standing position was moderate with an ICC2,k of 0.55, 0.54 and 0.56, respectively.

Inter-session reliability ranged from high to very high with an ICC2,k of 0.88 for 0 kg, 0.70 for 1 kg 0.86 for 2 kg, 0.78 for 3 kg, 0.89 and 0.75 for the relaxed and standing positions, respectively. The inter-session reliability of measuring AT stiffness during the 0.5 kg contraction was moderate with an ICC2,k of 0.54. Table 5.2 reports the relative reliability with ICC and 95% CI and absolute reliability with SEM and MDC.

	Intra-rater			Inter-rater			Inter-session		
	ICC (95% CI)	SEM	MDC	ICC (95% CI)	SEM	MDC	ICC (95% CI)	SEM	MDC
0 kg	0.95 (0.92-0.97)	19.3	53.5	0.76 (0.62-0.84)	43.2	119.6	0.88 (0.82-0.93)	30.5	84.6
0.5 kg	0.59 (0.36-0.74)	40	111	0.55 (0.30-0.72)	50.2	139.1	0.54 (0.29-0.71)	49.8	137.9
1 kg	0.87 (0.80-0.92)	36	99.8	0.54 (0.28-0.71)	66.2	183.5	0.70 (0.54-0.81)	56.1	155.6
2 kg	0.95 (0.91-0.97)	39.3	109	0.79 (0.67-0.87)	83.3	231	0.86 (0.78-0.91)	65.8	182.5
3 kg	0.94 (0.91-0.96)	47.7	132.1	0.81 (0.69-0.88)	85.9	238.2	0.78 (0.66-0.86)	92.7	256.9
Relax	0.98 (0.97-0.99)	10.8	30	0.86 (0.78-0.91)	30.5	84.6	0.89 (0.83-0.93)	24.7	68.4
Standing	0.87 (0.89-0.92)	70.7	196.1	0.56 (0.29-0.73)	130.1	360.5	0.75 (0.60-0.84)	101.5	281.3

Table 5.2 Absolute and relative reliability for the different conditions.

ICC: intraclass correlation coefficient; SEM: standard error of measurement; MDC: minimal clinical difference; CI: confidence interval

Changes in AT stiffness between the different conditions were calculated using Friedman test for related samples. Significant differences ($p<0.01$) were found between all contraction levels except for 0–0.5 kg ($p=0.9$); 0.5–1 kg ($p=0.9$); 1–2 kg ($p=0.7$) and between the different positions (Figure 5.2).

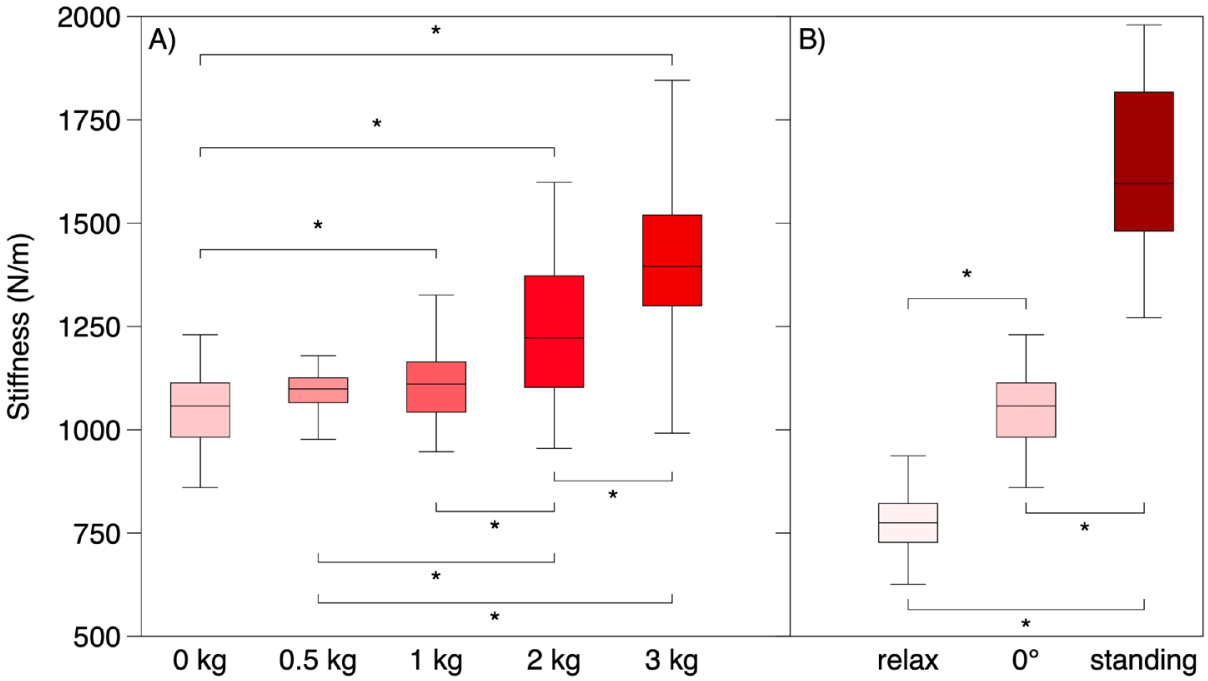


Figure 5.2. Construct validity. Box plot showing the stiffness median and IQR values of the entire sample for the different contraction levels (A) and for the different positions (B). *p<0.01; statistically significant difference between the different conditions.

5.5 Discussion

This chapter evaluated the absolute and relative reliability of the myotonometry to measure the stiffness of AT in different conditions. Even though the MyotonPRO was developed to evaluate the stiffness and tone of skeletal muscle, the present study shows the transferability of this technology and that measuring stiffness of tendon tissue is feasible and reliable. Intra-rater and inter-rater reliability ranged from high to very high in most of the tested conditions. Moreover, stiffness changes between the different contraction intensities and the different positions were detected, demonstrating the construct validity of this device.

One of the conditions in the current study was assessing AT stiffness with the person in a relaxed position with the feet hanging freely over the edge of the examination bed. A previous

study (Finnamore et al., 2019) also showed high intra-rater reliability when the AT was evaluated in a relaxed position (ICC: 0.80 in healthy participants). A further study evaluating the effect of dorsiflexion of the ankle joint on tendon stiffness (Liu et al., 2018) showed high to very high intra-reliability and inter-reliability when measured in a relaxed position (ICC >0.88). Our results strengthen these previous observations by confirming high to very high intra and inter-rater reliability (ICC >0.86), now demonstrated in a larger sample. The stiffness values vary slightly between studies with an average of 873 N/m reported by Finnamore et al, (Finnamore et al., 2019) 776.11±71.70 reported by Liu et al, (Liu et al., 2018) and 771±105.3 N/m observed in the present study. Nevertheless, collectively the current and previous findings confirm that MyotonPRO is a reliable device to evaluate AT stiffness in a relaxed position on the same day, between different days and between different operators.

Stiffness values increased from 1043±132.3 N/m when tendon was assessed in a 0° ankle dorsiflexion position with 0 kg of contraction to 1381±214 N/m for the isometric contraction at 3 kg. The ICC values showed high to very high intra-rater and inter-rater reliability for the majority of the isometric contraction levels (Table 5.2). Moderate intra-rater and inter-rater reliability was found for the 0.5 kg contraction level and the level of reliability did not exceed the cut-off point of ICC =0.6 considered as the threshold for clinical relevance (Chinn, 1990). The low reliability for the contraction at 0.5 kg is likely due to the difficulty in maintaining the force feedback stable during such a low contraction of the plantar flexors. A previous study18 evaluating AT stiffness at different ankle angles showed similar results to the present study with an average stiffness of 1143 N/m at 0° of dorsiflexion compared with 1043±132 N/m found in the current study. Liu et al. (Liu et al., 2018) did not examine reliability at different ankle angles, however, the data reported in this article demonstrated a statistically significant increase in tendon stiffness due to the change in ankle dorsiflexion angle from 1143

N/m at 0° to 1329 N/m at 30°. These results are in line with the present study, which showed a significant increase in tendon stiffness with contractions of increasing intensity. Thus, the MyotonPRO can reliably detect changes in AT stiffness whether the tendon is stretched from contraction of the triceps surae muscle or stretched as a result of a change in the angle of the ankle.

Another study (Orner et al., 2018) analysing the tissue properties of the AT and plantar fascia in healthy volunteers found slightly different stiffness values when the tendon was measured at 0° of dorsiflexion. The article reports a mean (±SD) of 848 (±95.73) N/m and 847.3 (±101.5) N/m for the left and right AT, respectively, whereas we observed higher values with an average stiffness of 1043±132 N/m.

Tendon structural and mechanical adaptations are strongly related to the load magnitude exerted to the musculotendinous complex (Obst et al., 2018, Magnusson and Kjaer, 2018, Bohm et al., 2015a) and the majority of interventions targeting pathological tendon tissue are loading-based exercise regimens (Silbernagel et al., 2001, Silbernagel et al., 2007, Mafi et al., 2001, Kongsgaard et al., 2009, Alfredson and Lorentzon, 2000). The current results support the evaluation of the tendon tissue behaviour during load with a reliable and easy to use device could be helpful to detect possible mechanical adaptation following different rehabilitation protocol.

Stiffness of the AT was also evaluated in standing position in this study to verify the feasibility of MyotonPRO to analyse the tendon in a weight-bearing position. Intra-rater reliability was very high and inter-session reliability was high. Conversely inter-rater reliability in the standing position was moderate. It is important to note, however, that in the standing position the average stiffness values were 1596 (±339) N/m which is approaching the upper limit that the device is able to detect. The lower reliability could be a consequence of the

measurement threshold of the device such that when it is close to the higher limit, there were difficulties in providing a mechanical impulse strong enough to give a proper oscillation wave. Morgan et al. (Morgan et al., 2018) found similar results in a population of healthy participants in a weight-bearing position. Despite the possible technical limitation of analysing tendon stiffness in a weight-bearing position, the results demonstrate good intra-rater reliability but only moderate inter-rater reliability.

This is the first study to evaluate changes in AT stiffness between different contraction levels using the MyotonPRO. The results confirm a significant difference in tendon stiffness between the different contraction levels. Although stiffness changes can be detected across different contractions, the levels with similar intensity (0–0.5 kg (p=0.9); 0.5–1 kg (p=0.9); 1–2 kg (p=0.7)) showed similar stiffness values likely as the difference between consecutive contraction levels was not sufficient to change the mechanical properties of the tendon. These results are consistent with those reported in a previous sonoelastography evaluation (Schneebeli et al., 2019) showing an increase of tendon elastography colour scale index when the AT was gradually put under tension by isometric contractions of increasing intensity. In further support of the construct validity, pairwise comparisons showed a difference in AT stiffness between the different positions (relaxed, 0° ankle angle and standing). Similarly, a previous study using shear wave sonoelastography (Aubry et al., 2015) showed an increase in wave velocity, indicating a hardening of the AT, when the ankle angle changed from a plantarflexed position to 0° of dorsiflexion.

There are some limitations of this study which should be noted. Healthy participants were recruited, and stiffness was evaluated in only one point of the tendon and it is therefore unknown whether variation may exist in different regions of the tendon. Another potential limitation was the selection of the contraction intensities. The upper limit of this ramp was

chosen because after a certain amount of load (approximately 5 kg) the device cannot detect stiffness values. The small changes between the different contraction levels could be not sufficient to fully describe the behaviour of the tendon during load.

5.6 Conclusions

In this chapter, reliability and construct validity of myotonometry in the evaluation of AT is reported. MyotonPRO is a reliable tool to measure AT stiffness in different conditions including when the tendon is in a relaxed position and under load. Reliability is confirmed for the same rater, between different days and between two raters. Construct validity was supported by changes of tendon stiffness during the explored contractions and ankle positions. MyotonPRO can be implemented, as a ready to use device, in the evaluation of tendon tissue mechanical properties.

CHAPTER 6

MEASUREMENT OF ACHILLES TENDON MECHANICAL PROPERTIES USING SHEAR WAVE TENSIOMETRY: A RELIABILITY STUDY

This chapter reports in full the contents of a published manuscript by the thesis author (Schneebeli et al. 2022). It includes verbatim text from the published manuscript and some changes employed for the purpose of this thesis.

Publications and Presentations

1. **Schneebeli A**., Falla D., Cescon C., Barbero M. 2022. Measurement of Achilles tendon loading using shear wave tensiometry: A reliability study. *Musculoskeletal Science and Practice*. 62:102665. **(Appendix 7)**
2. **Schneebeli A**., Falla D., Cescon C., Barbero M. Intra-rater reliability of a shear wave tensiometer in the evaluation of Achilles tendon mechanical properties. International Society of Electrophysiology and Kinesiology (ISEK) Québec City. Canada. June 2022

6.1 ABSTRACT

This chapter presents a recently developed technology called shear wave tensiometry able to measure tendon mechanical properties and particularly tendon loading. Given the paucity of studies conducted using tensiometry, knowing the clinimetric features (e.g., reliability) is important for use in clinical and research settings. Therefore, the aim of this chapter was to evaluate the inter-session reliability of a novel shear wave tensiometer for the assessment of AT loading. A further aim was to test the construct validity of this device by evaluating its precision in detecting AT loading changes induced by a plantar flexor isometric contraction of increasing intensity.

Ten healthy participants were recruited. Five measurements were performed at different time points to evaluate inter-session reliability. Shear wave speed along the AT was evaluated during different isometric contractions using a shear wave tensiometer composed of an array of four accelerometers fixed on the tendon, ranging from 4 to 8.5 cm from the calcaneal insertion of the tendon. Test-retest, intra- and inter-session reliability were determined using ICC3.1. Absolute reliability was calculated using the SEM and MDC.

Test-retest reliability was good to excellent (ICC3.1 0.87–0.99) for each of the contraction levels examined. Intra-session reliability was good to excellent (ICC3.1 0.85–0.96) and inter-session reliability was also good to excellent (ICC3.1 0.75–0.93) for each of the contraction levels.

This chapter confirms the reliability of this novel device. Future studies analysing participants with Achilles tendinopathy are needed to evaluate the capability of shear wave tensiometry to detect transient changes in loading due to pathology.

6.2 Introduction

The previous chapters evaluated commercially available technologies for assessing the mechanical properties of tendons. As highlighted in the study limitations, each technology has its weaknesses. Among these, the low reliability and the difficulty of these technologies in measuring the AT under high loads are notable. Given the importance of evaluation during loading, especially for the AT, whose main function is energy storage and release during activities such as walking and running, having technologies that reliably measure this parameter is important.

Recently, a promising technology known as shear wave tensiometry, has been developed and validated (Martin et al., 2018). This technology uses accelerometers to measure wave propagation along the tendon generated by a tapping device in order to measure muscle-tendon loading. The principle behind this technology is based on the concept that squared tendon wave speed varies in proportion to the axial stress in the tissue (Martin et al., 2018). Recent studies have demonstrated a relationship between AT wave speed and ankle kinetics during locomotion (Martin et al., 2018, Keuler et al., 2019) and different tendon loading between older and younger adults during walking (Ebrahimi et al., 2020). Evaluation of the inter-session reliability of this device is important to apply this measure with confidence in a clinical setting and in longitudinal studies.

Therefore, to address objective number 5 of the thesis, the aim of this chapter was to evaluate the inter-session reliability of a novel shear wave tensiometer for the assessment of AT loading. An additional aim was to test the construct validity of this device by evaluating its precision in detecting transient changes in tendon loading induced by a plantar flexor isometric contraction of increasing intensity.

6.3 Methods

The study was conducted between May and July 2021 at the University of Applied Sciences and Arts of Southern Switzerland. The study was approved by the Ethics Committee of Canton Ticino (ID:2021–00611/CE3844) (Appendix 12) and written informed consent was provided by the participants. Reporting of this study adheres to the GRRAS (Kottner et al., 2011).

6.3.1 Participants

Ten (5 male and 5 female) healthy, asymptomatic participants were prospectively recruited. Participants were excluded if they had a history of foot or tendon injury or surgery, metabolic, connective tissue or endocrine disease. Participants with systemic inflammatory disorders, spondyloarthropathy, rheumatoid arthritis, or hypercholesterolemia were excluded. The size of the sample was estimated according to Walter et al., (Walter et al., 1998) using the following parameters: five replicates, $\rho 0 = 0.6$, $p1 = 0.9$, $\alpha = 0.05$, and $\beta = 0.2$. The ideal sample size was 6.4. Given the choice of healthy participants and the non-invasive procedures, 10 were recruited. p0 was selected according to the clinical relevance threshold for the reliability measurement in clinics (0.6) (Munro, 2005) whereas p1 of 0.9 was chosen after a structured pilot study involving four healthy participants.

6.3.2 Procedures

A test-retest without repositioning of the participant and the device (test-retest) followed by a third measure where the participants were asked to stand up and come back to the examination bed (intra-session) was performed on the first day. Two between day measures were performed following 1 week and 2 weeks (inter-session). Participants were asked to maintain the same activity level throughout the entire study. Wave speed along the AT (m/s) was measured using four accelerometers placed longitudinally on the AT during a ramp of isometric contractions with a randomized level of intensity corresponding to 0-1.75-3.5-7-17.5-35 Nm of the ankle joint torque.

The participants were positioned in prone with the foot secured within a dynamometer with the ankle in 0◦ of dorsiflexion/plantarflexion (Figure 6.1). Prior to the first session, the participants attended a practice session to learn how to perform the isometric contraction and familiarize themselves with the visual feedback. The instruction ‘push on the board as if you want to reach a tip-toe position’ was given. Detachment of the heel from the dynamometer was monitored by the investigator and a tight fixation of the foot and ankle was ensured by two belts. The detection software acquired a set of 10 repeated measures for each of the contraction levels for both the left and right AT for each participant. The mean of these 10 measurements were used to determine the reliability values. The same test location and times were maintained throughout the study.



Figure 6.1. Image of the experimental setup. The participant was positioned in prone with the foot secured within a dynamometer with the ankle in 0° of dorsiflexion/plantarflexion. Force feedback was presented to the participants in real time. The bottom right box shows a detailed image of the tapping device and accelerometers.

6.3.3 Equipment

The shear wave tensiometer was composed of an array of four accelerometers (Analog Devices, ADXL202JE) which were fixed with double adhesive tape on the tendon, equally spaced at a distance of 15 mm (Figure 6.1) The most distal accelerometer was positioned 4 cm to the calcaneal insertion of the tendon (previously identified with ultrasound imaging). Ultrasound imaging was also used to check whether all the accelerometers were placed on the tendon and not on the MTJ. The signals were acquired using a Sessantaquattro (OTBioelettronica, Torino, Italy) with a sampling frequency of 10 kHz. The signals were analysed in order to identify the propagation velocity of the mechanical waves on the tendon, based on the delay between the waves. Since the four accelerometers were equally spaced and

given the hypothesis that the wave propagates at a constant speed, the delay between the waveforms detected by adjacent accelerometers was expected to be constant. The technique for propagation velocity estimation is based on the estimation of this delay using the cross-correlation function between pairs of signals. Once the average delay from each possible pair of signals was determined, the propagation velocity was calculated as the ratio between the inter-accelerometer distance and the average delay (Farina et al., 2001). The algorithm is the same used in the field of surface electromyography for the computation of muscle fiber conduction velocity (Farina et al., 2004, Farina et al., 2001). The outcome variable was one propagation speed value (m/s) for each tap provided to the tendon (Figure 6.2).

The mechanical impulse was generated by a custom developed tapper based on an electromagnetic transductor. A current impulse was used to activate an electromagnet, which attracts the iron arm connected to a wooden stick. In its rest position the wooden stick was held a few millimetres away from the tendon. The tapping frequency was set to 4 Hz. The opening and closing of the switch was controlled by a microcontroller (Arduino UNO, Italy) programmed to provide intermittent pulses with constant time intervals (250 ms). The tapper was positioned 2 cm proximally from the end of the calcaneal bone. This location was checked by means of ultrasound imaging.

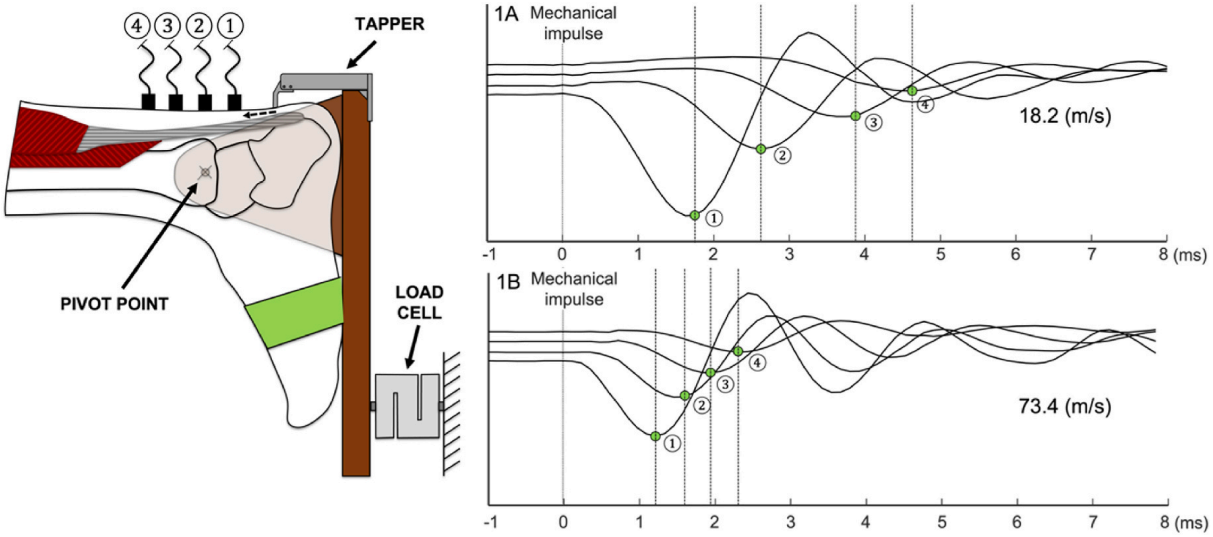


Figure 6.2. Schematic of the shear wave tensiometer. The tapper device was mounted on the dynamometer and placed on the Achilles tendon at 2 cm from the calcaneus insertion. The four accelerometers (1–4) were attached to the skin in series with a 15 mm inter-accelerometer distance. Shear wave speed signals of the Achilles tendon at 0 Nm (1A) and at 35 Nm of isometric ankle torque (1B). The propagation velocity of the wave was calculated based on the delay between the waves passing from the accelerometers.

Participants performed different intensities of isometric contractions of the plantar flexors (0-1.75-3.5-7-17.5-35 Nm). The torque of the ankle was assessed using a dynamometer connected to a force sensor that operated linearly in the range between 0 and 100N (Mod. TF2/S; CCT Transducers, Turin, Italy). The force sensor was attached to a wooden board connected to a hinge that allowed natural dorsiflexion and plantar flexion of the ankle. The board was fixed in order to permit isometric contractions only at a fixed angle of 0° dorsiflexion. The force measured by the force sensor was proportional to the torque exerted at the ankle level. Force signals were amplified using MISO-II (OT Bioelettronica, Turin, Italy; bandwidth 0–80 Hz) and presented to the participants as real time visual feedback. A practice phase prior to the recording was conducted in order to familiarize the participant with the visual feedback and practice the contractions.

6.3.4 Statistical analysis

Descriptive statistics, mean ± SD, were determined to characterise the demographics of the sample. Statistical Package for Social Sciences (SPSS v. 26) was used for statistical analysis. Test-retest, intra-session and inter-session reliability was calculated using ICC3.1 based on a single-rater (k = 1), absolute agreement, 2-way mixed effect model. Absolute reliability was calculated using the SEM and MDC (Atkinson and Nevill, 1998). An ICC >0.6 was used to consider the clinical relevance of the measurements (Munro, 2005). Inter-measurement variability was calculated using the CV of the 10 measurements for each participant and contraction level. The distribution of the data was determined using Shapiro-Wilk test and non-parametric independent samples, Mann-Whitney test was performed to assess significant differences in AT wave speed between men and women and between the dominant and non-dominant leg. A linear regression model was used for each participant to test the linear relationship between squared wave speed and ankle joint torque to determine construct validity. The goodness of fit of the subject specific model was assessed using the coefficient of determination (R2). Wave speed values are presented as median and IQR.

6.4 Results

Data from 10 healthy participants (5 female) were analysed. Their mean (±SD) age, height and weight were 31 (6.9) years, 173 (8.2) cm and 65 (9.3) kg respectively. Data were pooled and analysed across the entire sample given that no significant difference in AT wave speed was observed between men and women ($p = 1.000$) or between the left and right side ($p = 0.853$). Wave speed values at the different contraction levels and inter-measurement

variability are reported in Table 6.1. Test-retest reliability was good to excellent with a minimum value of ICC3.1 0.87 and a maximum of ICC3.1 0.99 considering all contraction levels. Intra-session reliability was good to excellent with a minimum value of ICC3.1 0.85 and a maximum of ICC3.1 0.96 considering all contraction levels. Inter-session reliability was also good to excellent with a minimum value of ICC3.1 0.75 and a maximum of ICC3.1 0.93 considering all contraction levels. The measure at 17.5 Nm showed good reliability but the lower limits of 95% CI were below the cut-off point of >0.6 considered to be the clinically relevant threshold. Reliability data with 95% CI and absolute reliability calculated with SEM and MDC are reported in detail in Table 6.1.

Ankle torque	**Shear wave speed values (m/s)**	**Variability**	**Test-retest reliability**			**Intra-session reliability**			**Inter-session reliability**		
Nm	Median (IQR)	Cov (%)	ICC	SEM	MDC	ICC	SEM	MDC	ICC	SEM	MDC
0	21.53 (4.4)	2.3%	0.99 (0.98-0.99)	0.3	0.8	0.96 (0.91-0.99)	0.6	1.8	0.93 (0.86-0.97)	0.9	2.5
1.75	27.24 (6.3)	2.8%	0.95 (0.87-0.98)	0.8	2.3	0.92 (0.79-0.97)	1.2	3.4	0.83 (0.65-0.93)	1.9	5.1
3.5	31.3 (5.8)	2.6%	0.94 (0.84-0.98)	1.0	2.7	0.95 (0.86-0.98)	0.9	2.6	0.84 (0.65-0.93)	1.9	5.3
7	36.08 (6.8)	2.4%	0.96 (0.89-0.98)	1.0	2.7	0.85 (0.62-0.94)	2.0	5.4	0.81 (0.60-0.92)	2.3	6.4
17.5	54.6 (9.2)	2.5%	0.93 (0.83-0.97)	1.7	4.6	0.90 (0.75-0.96)	2.0	5.7	0.75 (0.48-0.89)	3.4	9.5
35	76.33 (22.6)	2.1%	0.87 (0.67-0.95)	4.7	13.1	0.90 (0.75-0.96)	3.7	10.3	0.84 (0.66-0.93)	4.7	12.9

Table 6.1. Shear wave speed values of the sample, inter-measurement variability, absolute and relative reliability values for the different contraction levels.

Linear regression models showed that squared wave speed was quite accurately predicted by ankle joint torque for each of the participants (R2 =0.991 ± 0.01 and 0.992 ± 0.01, mean ±SD, for the left and right tendon respectively) (Figure 6.3) For every Nm of torque

increase, the squared wave speed increased by 139 (m^2s^{-2}) on average among the participants. The ankle joint torque-wave speed relationship was however variable across participants, ranging from a minimum value of 84.9 to a maximum of 211.7 (m^2s^{-2}).

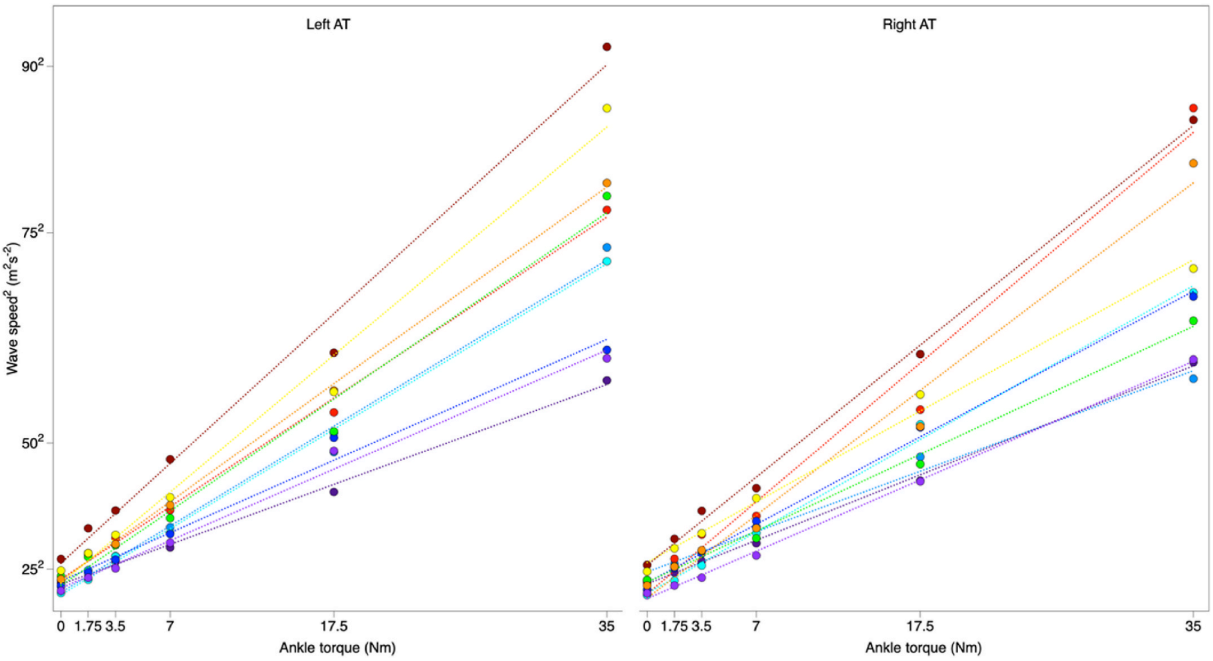


Figure 6.3. Scatter plot showing the squared shear wave speed values of each of the participants tendons (n = 20) for the different levels of ankle torque. The two panels show the values of the left and right Achilles tendon. Each dot is the average of three sessions and each colour represents a participant. Lines represent the linear regression for each tendon (R2).

6.5 Discussion

The purpose of this chapter was to evaluate the reliability of a shear wave tensiometer for the evaluation of AT loading at different contraction levels. The results showed that this device is highly reliable (ICC>0.75) not only when a test-retest without repositioning of the

accelerometers was performed but also with the repositioning (intra-session) and between different sessions (inter-session).

Every contraction level assessed in the study (from 0 to 35 Nm) resulted in high reliability values showing that this instrument is precise even when the tendon is under load and is subject to a transient loading change. Moreover, absolute reliability calculated with the SEM and MDC showed a very small error when compared to the shear wave speed values obtained in the different contraction levels. As the plantar flexor force increase, AT should increase its strain and its stiffness (Kjaer, 2004, Magnusson et al., 2003), and therefore an increment in the shear wave speed should be found when the tendon is gradually put under load by isometric contractions to confirm this construct. Construct validity of the measurement was confirmed, and indeed for each participant the coefficient of determination (R2) was very high (R2 =0.991 ± 0.01 and 0.992 ± 0.01, mean ± SD, for the left and right tendon respectively) indicating that the increase in the squared wave speed was strongly correlated with the increase of the ankle joint torque. Despite this strong relationship, highly variable results were found between participants showing possible individual behaviour of the tendon during load. Further studies are needed to better understand these changes.

This novel technology has been previously validated and used to assess AT loading during gait (Martin et al., 2018). Only a few studies (Martin et al., 2018, Keuler et al., 2019) tested this device during isometric contractions and the results are comparable with the present study with a wave speed that varies from 15 to 20 (m/s) when the muscles were relaxed, to 60 to 80 (m/s) when maximal contractions were performed. In the present study, values ranged from 21.53 m/s (IQR 4.4) with no contraction to 76.33 m/s (IQR 22.6) with a 35 Nm contraction. The device used in the current study consisted of 4 accelerometers in series with an inter-accelerometer distance of 1.5 cm which allows a larger (4.5 cm) portion of the Achilles

free tendon to be assessed compared to previous studies which analysed 1 cm of the tendon (Keuler et al., 2019, Ebrahimi et al., 2020, Acuna et al., 2019). Considering that it was not possible to assume a constant wave speed between accelerometers pairs, due to possible variation of the tendon CSA or wave dispersion, a larger spatial sampling with multiple detection points allowed us to average the wave speed.

There are some limitations of this study that need to be acknowledged. Firstly, the study evaluated a novel shear wave tensiometer under controlled conditions, and therefore the results cannot be generalized to other types of shear wave tensiometers. Sample size was estimated for the calculation of the reliability values, therefore values of the correlation between contraction levels with this sample size could be underpowered. Moreover, the results cannot be generalized to other tendons or to different conditions.

6.6 Conclusions

This chapter confirms the reliability and construct validity of shear wave tensiometry. Future studies analysing participants with AT pathology (i.e., tendinopathies or tendon rupture) are needed to evaluate the capability of shear wave tensiometry for use in clinical practice.

CHAPTER 7

MECHANICAL VERSUS MANUAL IMPULSE FOR THE PROPAGATION OF SHEAR WAVE ALONG THE ACHILLES TENDON: A PILOT CONVERGENT VALIDITY STUDY

This chapter reports the contents of two conference presentation (ISEK Conference 2022, Canada; WP Congress 2023, United Arab Emirates) presented by the thesis author. It includes verbatim text from the poster presentation and some changes employed for the purpose of this thesis.

Publications and Presentations

1. **Schneebeli A**., Falla D., Cescon C., Barbero M. Mechanical versus manual impulse for the propagation of shear wave along the Achilles tendon: a congruent validity study. International Society of Electrophysiology and Kinesiology (ISEK) Québec City. Canada. June 2022

2. **Schneebeli A**., Falla D., Cescon C., Barbero M. Shear wave propagation along the Achilles tendon measured with tensiometry: mechanical versus manual impulse. World Physiotherapy Congress. Dubai. UAE. 2023

7.1 ABSTRACT

Shear wave tensiometry is a promising technology able to detect tendon loading; in Chapter six the reliability and construct validity was tested and confirmed in healthy participants. In the previous chapter, the impulse used to elicit the shear wave within the AT was performed using a custom developed mechanical tapper based on an electromagnetic transductor. To make this technology easier to use and therefore more clinically applicable, a simplification of the experimental setup was necessary. Therefore, the aim of this chapter was to test in a pilot laboratory study the convergent validity of two different methods to generate mechanical impulses (i.e., tapping device versus reflex hammer) given to calculate mechanical shear wave along the AT.

Ten healthy participants (5 males and 5 females) were enrolled prospectively. Shear waves in the AT were induced in two ways: a mechanical impulse generated by an electromagnetic actuator, and a manual impulse delivered by a trained operator using a reflex hammer. Measurements were taken in a relaxed state and during isometric contractions.
The convergent validity between the two types of impulses was assessed using the ICC. The Bland-Altman analysis was used to evaluate the agreement between the two methods.

Convergent validity between the two impulse types was very high (almost perfect) with ICC values ranging from 0.961 to 0.981. The Bland Altman plot confirmed the validity of this measure; the mean of the difference between the measures was 0.66 and the upper and lower limit of agreement ranged between 4.08 and -2.76 m/s.

Convergent validity between a manual and a mechanical impulse for the calculation of tendon shear wave speed was confirmed.

7.2 Introduction

Shear wave tensiometry is an innovative technology for measuring the speed of propagation of mechanical waves along the tendon. Its capacity to characterise the AT mechanical properties has been confirmed both in vitro and in vivo (Martin et al., 2018).

Clinimetrics properties of this technology were tested in Chapter six through a reliability and construct validity study (Schneebeli et al., 2022). The technology uses accelerometers to measure wave propagation along the tendon generated by a tapping device that provides a mechanical impulse on the tendon. The impulse can be generated also manually using a common reflex hammer, which has potentially positive implications in terms of costs and clinical applicability. To address the thesis objective number five, the aim of this chapter was to test the convergent validity of two different methods to generate mechanical impulses (i.e. tapping device versus reflex hammer) given to calculate mechanical shear wave along the AT.

7.3 Methods

The study was conducted between March and May 2022 at the University of Applied Sciences and Arts of Southern Switzerland. The study was approved by the Ethics Committee of Canton Ticino (ID:2021–00611/CE3844) (Appendix 12) and written informed consent was provided by the participants.

7.3.1 Participants

Ten healthy asymptomatic participants (five male and five female) were consecutively recruited through a public announcement within our department. Participants with a history of foot or tendon injuries or surgeries, or with metabolic, connective tissue, or endocrine diseases, were not included. Additionally, those with systemic inflammatory disorders, spondyloarthropathy, rheumatoid arthritis, or high cholesterol were excluded.

7.3.2 Procedures

Participants were asked to lie on an examination bed with the foot in 0° of plantar flexion and perform two isometric contractions (3.5 Nm and 35 Nm of ankle torque). A measure was also performed in the relaxed state (0 Nm). Measurements were repeated in the same day in a randomized order for both the manual and mechanical impulse. The detection software acquired a set of 10 repeated measures for each of the contraction levels for both the left and right AT for each participant. The mean of these 10 measurements were used to determine the convergent validity.

7.3.3 Equipment

Wave propagation along the tendon was calculated using four accelerometers (Analog Devices, ADXL202JE) aligned along the direction of the tendon and equally spaced at 1.5 cm distance. Impulse on the AT to generate shear wave was provided in two different ways, one mechanical impulse provided by an actuator based on electromagnetic transductor and one

manual impulse performed by a trained operator with a reflex hammer (Figure 7.1). Signals were analysed in order to identify the propagation velocity of the mechanical waves on the tendon, based on the delay between the waves (Figure 7.2). A similar experimental setup to that of the previous chapter was used; a more detailed description of the equipment utilized can be found in Chapter six.

7.3.4 Statistical analysis

Convergent validity between the two types of impulse was calculated using the ICC. The Bland Altman analysis was performed to quantify the agreement between the two methods. Bland and Altman plots and 95 % CI (+1.96SD; -1.96SD) were used to provide a visual representation of size and range differences between the two measurements.

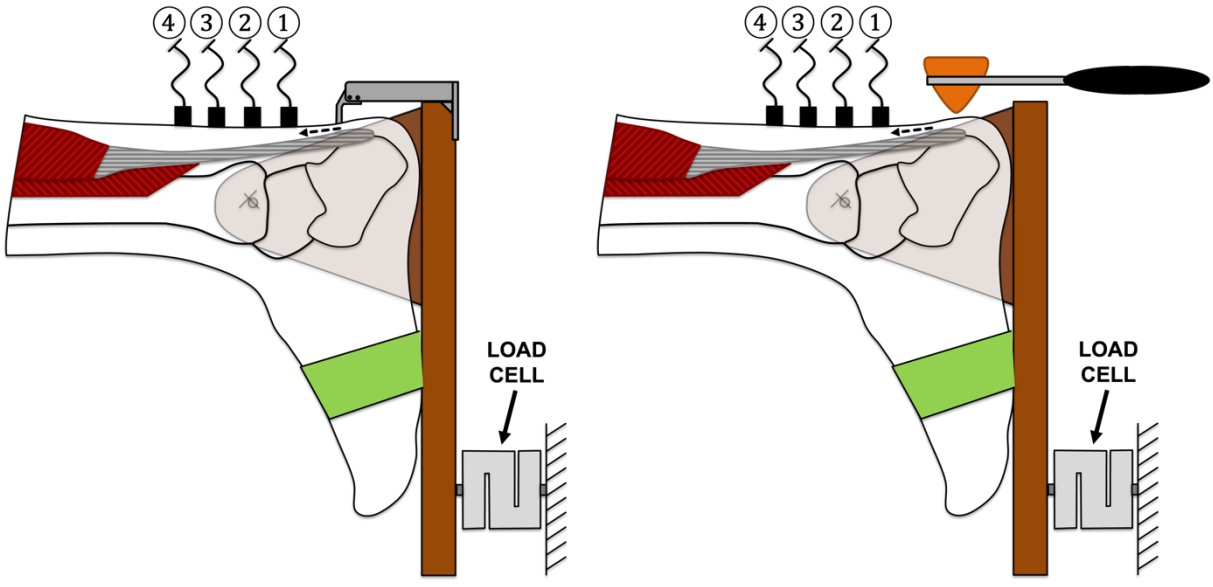


Figure 7.1. Schematic of the shear wave tensiometer. Mechanical impulse (left panel) and manual impulse (right panel).

7.4 Results

Descriptive statistics of shear wave speed for the relaxed state and for the different contraction intensities are presented in Table 7.1. Convergent validity between the two types of impulse is very high (almost perfect) with ICC values ranging from 0.961 to 0.981. The Bland Altman plot confirm the validity of this measure; the mean of the difference between the measures was 0.66 and the upper and lower limit of agreement ranged between 4.08 and -2.76 m/s (Figure 7.3).

	Wave speed manual		**Wave speed mechanical**		**ICC**	**Bland & Altmann**		
	Mean (m/s)	SD	Mean (m/s)	SD	ICC (95%CI)	Mean of the diff. (m/s)	+1.96 SD	-1.96 SD
All	-	-	-	-	**0.998 (0.997-0.999)**	**0.66**	4.08	-2.76
0 Nm	**20.8**	3.0	**21.1**	3.3	**0.961 (0.902-0.984)**	**0.35**	2.69	-1.98
3.5 Nm	**30.4**	5.4	**31.6**	6.0	**0.981 (0.837-0.995)**	**1.13**	3.40	-1.14
35 Nm	**68.9**	9.2	**69.4**	9.0	**0.981 (0.952-0.992)**	**0.50**	5.44	-4.43

Table 7.1 Shear wave speed values of the sample and convergent validity values for the different contraction levels.

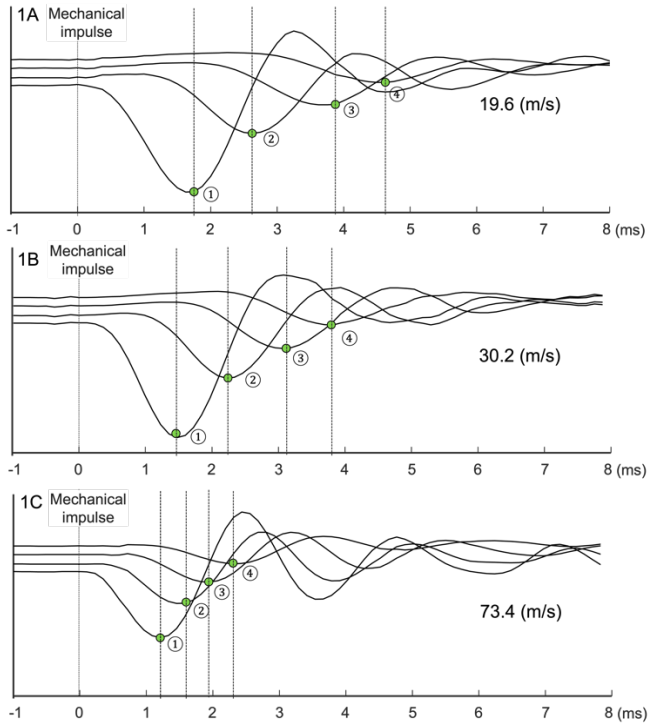


Figure 7.2. Shear wave speed signals of the Achilles tendon at 0 Nm (1A), 3.5 Nm (1B) and at 35 Nm of isometric contraction (1C). The propagation velocity of the wave was calculated based on the delay between the waves passing from the accelerometers (1-4).

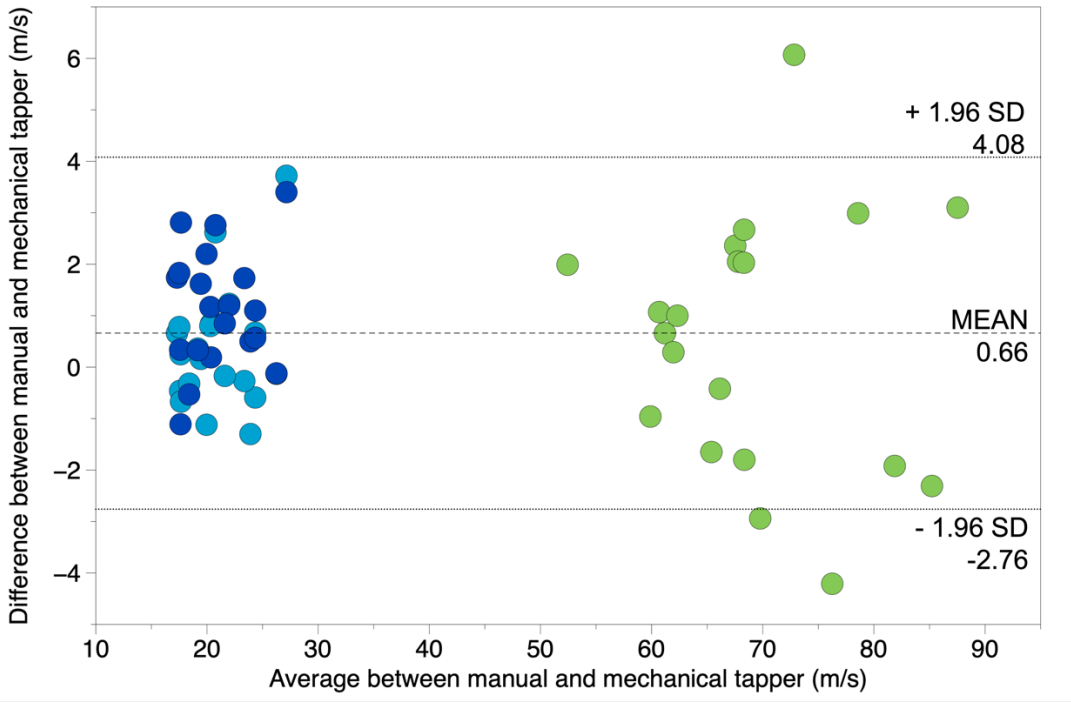


Figure 7.3. Bland & Altman plot showing the difference between manual and mechanical impulse in the different contraction levels (0 Nm light blue; 3.5 Nm dark blue; 35 Nm green).

7.5 Discussion

This chapter aimed to assess whether a manually generated impulse using a reflex hammer could be comparable to an automatically generated impulse using an electromagnetic actuator, with the objective of simplify the experimental setup for the further studies and making this technology more clinically applicable.

The results suggest high convergent validity both when the tendon is in a relaxed state (ICC = 0.961) and during low (ICC = 0.981) and high intensity isometric contractions (ICC = 0.981). Additionally, the values reported by the Bland-Altman plots confirm the agreement between the measurements, as the mean differences are consistently close to zero (range 0.35 to 1.13), and the CI are narrow compared to the absolute value of the measurement.

This technology has previously undergone validation and application in evaluating AT loading during walking (Martin et al., 2018). A limited number of studies (Martin et al., 2018, Keuler et al., 2019, Schneebeli et al., 2022) have examined this device in isometric contractions, showing results comparable to the current study, where wave speeds ranged from 15 to 20 m/s during muscle relaxation, to 60 to 80 m/s during maximal contractions. Particularly, these results are comparable to those of the previous chapter were the same device and experimental setup were used (Schneebeli et al., 2022).

This study presents some limitation that need to be acknowledged. The sample consist in ten healthy young participants, it is not possible to state with certainty that these results can also be obtained in a different population. The manual impulse provided with the reflex hammer

was performed by a trained operator, we cannot assume that different results may arise from different operators. A simple training phase that considers the speed and location of the impulse might be sufficient to obtain stable and comparable shear wave speed values.

7.6 Conclusions

Convergent validity between the manual and the mechanical impulse for the calculation of tendon shear wave speed is confirmed. The manual impulse could increase the clinical applicability of this device in the measurement of tendon properties or to evaluate the effect of exercise on the AT mechanical properties.

CHAPTER 8

SHEAR WAVE TENSIOMETRY CAN DETECT LOADING DIFFERENCES BETWEEN OPERATED AND UNAFFECTED ACHILLES TENDON

This chapter reports in full the contents of a published manuscript by the thesis author (Schneebeli et al. 2023). It includes verbatim text from the published manuscript and some changes employed for the purpose of this thesis.

Publications and Presentations

1. **Schneebeli A.**, Barbero M., Filardo G., Testa E., Riegger M., Sangiorgio A., Cescon C., Soldini E., Falla D. 2023. Shear Wave Tensiometry Can Detect Loading Differences Between Operated and Unaffected Achilles Tendon. *Foot and Ankle International*. 44(12):1295-1304. **(Appendix 8)**

8.1 ABSTRACT

This chapter represents the first step toward the implementation of the shear wave tensiometry in a clinical setting. The purpose of this cross-sectional study was to test if shear wave tensiometry is able to detect AT loading changes between a surgically managed AT rupture versus the unaffected contralateral tendon. Our secondary aims were to evaluate differences in mechanical properties when measured with myotonometry and morphological properties of the tendons measured with ultrasonographic imaging.

Twenty-one patients with surgically treated AT ruptures were investigated 12-37 months after surgery. Tendon load was measured using a shear wave tensiometer composed of an array of 4 accelerometers fixed on the tendon. Shear wave speed along the AT was evaluated at different levels of ankle torque for both the operated and the unaffected side. Mechanical properties of the tendons were evaluated using MyotonPRO and morphological properties using ultrasonographic imaging. Friedman test was used to assess differences in AT wave speed, stiffness, thickness, and CSA between the operated and the unaffected tendon.

We found a significant shear wave speed difference between sides at every ankle joint torque ($P < .05$) with a large effect size for the lowest ankle torque and small to medium effect sizes for higher ankle torque. Stiffness, thickness, and CSA of the operated tendon remained significantly higher compared to the unaffected side.

In this cohort, we found that shear wave tensiometry can detect differences between operated and unaffected AT during a standardized loading procedure. The shear wave speed along the operated tendon, as well as the mechanical and morphologic properties, remains higher for 1-3 years after a rupture.

8.2 Introduction

As thoroughly discussed in Chapter one, pathological processes affecting the AT can alter the mechanical and morphological properties of the tendon structure, resulting in a modification of the stiffness, Young modulus, tendon CSA, and diameter (Magnusson and Kjaer, 2018, Obst et al., 2018, Geremia et al., 2015, Kannus et al., 1997).

The healing process of a ruptured AT can last more than a year, (Voleti et al., 2012, Galloway et al., 2013) and several studies have shown that during this period the tendon structure and mechanical properties are altered (Geremia et al., 2015, Frankewycz et al., 2018, Zellers et al., 2019). However, despite the growing interest in assessing the mechanical properties of tendons during the healing process, still limited and conflicting data are available. To date, no gold standard device exists to evaluate the mechanical properties of tendons, and all technologies have their advantages and disadvantages.

As presented in the previous chapters shear wave tensiometry has been recently proposed as a technology able to describe tendon mechanical properties in different population (Martin et al., 2018, Keuler et al., 2019, Ebrahimi et al., 2020).

Given that investigating the tendon's mechanical changes during the clinical course of a rupture can help to better understand the tissue healing process of tendons, in this chapter, to address the thesis objective number 6, we aimed to test if shear wave tensiometry is able to detect AT loading changes between a surgically managed AT after rupture and the unaffected contralateral tendon. Our secondary aims were to evaluate differences in mechanical properties when measured with myotonometry and morphological properties of the tendons measured with ultrasonographic imaging.

8.3 Methods

This cross-sectional study was conducted at the orthopaedic department of the Ente Ospedaliero Cantonale. The study was approved by the Ethics Committee of Canton Ticino (ID:2022- 01707/CE4192) (Appendix 13) and written informed consent was provided by the participants. Because no previous study investigating AT after surgery based on measurements taken with this technology was available, the sample size calculated based on a pilot to ensure a statistical power of 80% at the 5% significance level for a 2-tailed hypothesis test was n = 20. The study reporting adheres to the STROBE guidelines for observational studies (von Elm et al., 2007).

8.3.1 Participants

The database of the Ente Ospedaliero Cantonale was retrospectively screened to search for participants who underwent unilateral surgery of the AT following ATR between 2018 and 2021.

Inclusion criteria:

- Unilateral open repair AT tenorrhaphy following complete AT rupture
- Surgery >1 year and <4 years
- Age ≥18 years
- Time from rupture to surgery < 3 weeks

Exclusion criteria:

- Arthrodesis of one of the upper foot/ankle joints

- History of problems with the contralateral AT (i.e., Achilles tendinopathy, previous AT rupture, pain in the AT for more than 1 month)
- Other surgical interventions involving scar tissue on the posterior part of the leg or AT
- History of connective tissue, metabolic, and endocrine diseases
- Systemic inflammatory disorders, rheumatoid arthritis, spondyloarthropathy, or diabetes
- Currently using systemic antibiotics (fluoroquinolones, i.e., ciproxin) and steroids.

8.3.2 Clinical Outcomes

Participants were asked to complete a validated questionnaire designed to evaluate clinical features of AT conditions, the Achilles tendon total rupture score (ATRS) (Vascellari et al., 2018) (Appendix 15). The Tegner activity level scale was used to evaluate differences in the level of physical activity before and after surgery (Tegner and Lysholm, 1985) (Appendix 16). Ankle dorsiflexion range of motion was measured bilaterally using a simplified version of the weightbearing ankle lunge test (Cejudo et al., 2014). Range of motion was quantified using a smartphone application (GetmyROM, Interactive Medical Production, LCC) with the smartphone placed 2 cm below the tibial tuberosity. The maximal calf circumference was measured with the subject seated with the knee at 90 degrees.

8.3.3 Shear wave tensiometry

Tendon loading was measured with a shear wave tensiometer consisting of 4 accelerometers (Analog Devices, ADXL202JE) in series fixed on the skin posterior to the tendon with adhesive tape and equally spaced at a distance of 10 mm. The accelerometers were

positioned on the skin posterior to the AT following ultrasonographic imaging to ensure the correct position on the free part of the AT (3-6 cm to the calcaneal insertion) and not on the MTJ. The small impulse needed to elicit the wave propagation along the tendon was performed manually with a reflex hammer. This technique has been previously tested in a pilot study with 10 participants and the convergent validity with an automatic impulse confirmed (see Chapter seven). A set of 5 repeated measures (1 per second) for each of the contraction levels for both left and right AT of each subject was acquired, and the mean of these 5 measurements was used to perform the calculation of the tendon wave speed. Within- and between-session reliability of this technology has been evaluated in a previous study, which found good to excellent reliability (ICC 0.75-0.96) (Schneebeli et al., 2020, Schneebeli et al., 2022).

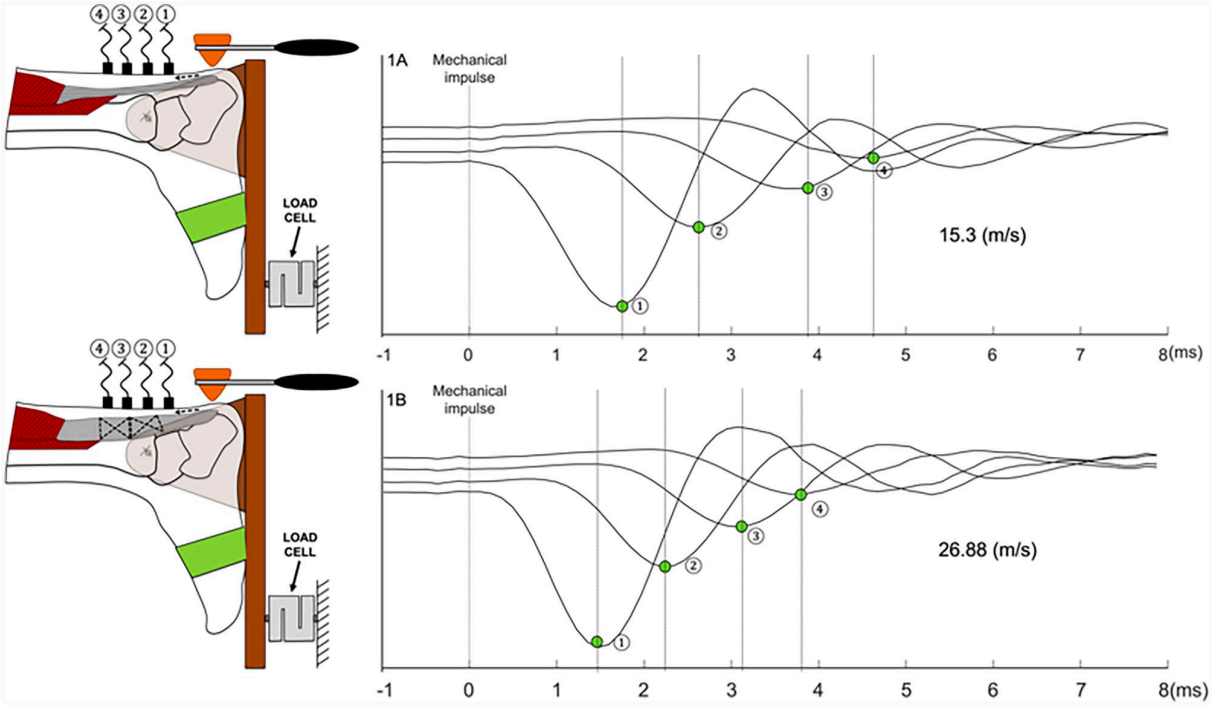


Figure 8.1. Schematic of the shear wave tensiometer. The impulse was provided at 2 cm from the calcaneal insertion. The 4 accelerometers (1-4) were attached to the skin in series with a 10-mm interaccelerometer distance. Shear wave speed signals of the (A)

unaffected Achilles tendon and of the (B) operated Achilles tendon at 0 Nm. The propagation velocity of the wave was calculated based on the delay between the waves passing from the accelerometers.

A Sessantaquattro (OTBioelettronica, Torino, Italy) with a sampling frequency of 10 kHz was used to acquire the signals. The signals were analysed based on the time delay between the different waves provided by the accelerometers and the propagation of the mechanical wave on the tendon. The technique for estimating propagation velocity used the cross-correlation function between signal pairs (Farina et al., 2001, Farina et al., 2004). Each impulse corresponded to a propagation speed value (m/s) (Figure 8.1). The participants were in a prone position with the foot firmly fixed in a dynamometer at 0 degrees of plantarflexion (Figure 8.2). Ten different isometric contractions of increasing intensity (0-35 Nm) were performed. Ankle torque was assessed with a dynamometer connected to a force sensor (Mod.TF2/S; CCT Transducers, Turin, Italy) operating in a 0- to 100-N range. A MISO-II (OT Bioelettronica, Turin, Italy) was used to present the force signal to the participants as real-time visual feedback. Participants were instructed to push on the dynamometer as if they want to stand on their tiptoes.

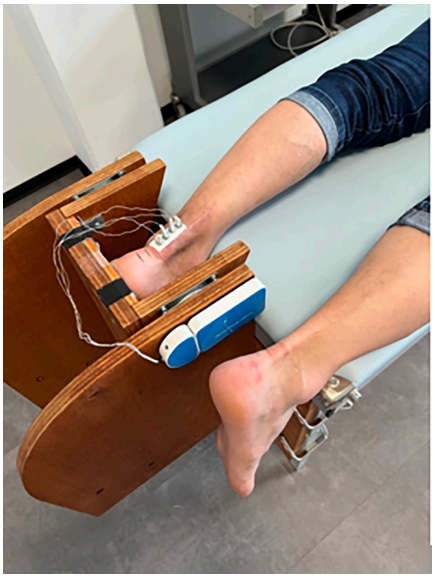


Figure 8.2. Image of the experimental setup. The participant was placed in a prone position, with the foot securely held within a dynamometer, maintaining the ankle at 0 degrees of dorsiflexion/ plantarflexion. The accelerometers were attached to the skin with a 10-mm inter-accelerometer distance.

8.3.4 Myotonometry

Tendon mechanical properties were measured with a MyotonPRO (Muomeetria, Tallinn, Estonia) following a predefined protocol (Schneebeli et al., 2020). The affected and unaffected AT were measured in 2 different regions of the free tendon (distal part: at 3 cm; proximal part: at 6 cm from the calcaneal insertion) with the participants' feet hanging freely over the edge of the examination bed.

8.3.5 Ultrasound imaging

Thickness and CSA were measured at 0 degrees plantarflexion using an ultrasound (MyLab25 gold, Esaote, Genoa, Italy) with a 13- to 4-MHz linear array (LA523). Thickness images were acquired using a longitudinal scan from 2 to 7 cm from the calcaneal insertion whereas CSA images were acquired using a transverse scan at 3 and 6 cm from the calcaneal insertion.

8.3.6 Statistical analysis

The distribution of the data was assessed using the Shapiro-Wilk test, and because of non-normality, the nonparametric related sample Friedman test was used for AT wave speed between tendons (SPSS, version 28). Post hoc pairwise comparison Bonferroni correction was applied, and statistical significance was set to $P < .05$. Effect size was calculated using the Kendall W, results were evaluated using the Cohen interpretation guidelines, with 0.2, 0.5, and 0.8 representing small, medium, and large effect, respectively (Cohen, 1988). For each tendon, a linear regression model was used to test the relation between squared wave speed and ankle joint torque. The model's goodness of fit was assessed using the coefficient of determination (R2). Wave speed values were presented as median and interquartile range (IQR). Friedman test was also used to assess differences between the operated and unaffected tendons for the additional outcomes. Correlations between shear wave speed values and clinical outcomes (ATRS, Tegner scale, and time after surgery) were performed using Spearman correlation (ρ).

8.4 Results

Twenty-three participants were screened for eligibility, 1 participant was excluded because of a recent injury of the contralateral tendon and 1 participant was excluded because of technical difficulties during the placement of the accelerometers on the AT (patient suffered from foot hyperhidrosis). Thus, 21 male participants were analysed. Participants had a mean age of 47.3 ± 14.2 years, and the mean time from surgery was 20.3 ± 8.1 months (range 12-37). All the sutures were performed with Krackow or Kyrchmeyer- Kessler technique, using PDS 0 suture and PDS 4-0 to close the paratenon.

8.4.1 Clinical Outcomes

The Tegner activity level scale showed that 57% of the participants returned to an equal level of sport activity compared with before the operation. The ATRS showed a mean score of 88/100 ± 14.7, with the lowest value of 40 and the highest value of 100. ATRS ($\rho = 0.19$), Tegner activity level scale ($\rho = 0.15$), and time after surgery ($\rho = 0.11$) were not correlated with shear wave speed values.

Mean ankle dorsiflexion range of motion was significantly higher for the unaffected AT compared to the operated AT ($P = .039$), with 41.6 ± 4.4 degrees vs 39.4 ± 4.5 degrees range of motion, respectively. Mean calf circumference was also significantly higher for the leg on the unaffected side compared to the leg of the operated side ($P < .01$), with 39.7 ± 3.3 cm vs 36.6 ± 2.4 cm respectively.

8.4.2 Shear wave tensiometry

Shear wave speed values between the operated and the unaffected AT at different ankle joint torques are reported in Table 8.1 and Figure 8.3. Friedman test showed a significant difference between sides at every ankle joint torque ($P < .05$) with a large effect size for the lowest ankle torque (0-21 Nm) and small to medium effect sizes for higher ankle torque (24.5-35 Nm).

The linear regression model calculated for every AT during the different ankle torque conditions showed a mean coefficient of determination (R2) of 0.97 ± 0.02 for the unaffected side and 0.93 ± 0.05 for the operated side, indicating a linear fit between wave speed and ankle

torque for both the operated and the unaffected side, with no difference between the 2 tendons (P = .127). The slope of the regression lines was similar between sides (mean of 0.79 ± 0.28 for the unaffected and 0.74 ± 0.14 for the operated side; P = .513), indicating a similar behaviour of the shear wave speed during contraction for both AT (Figure 8.4).

SWS	0 Nm		3.5 Nm		7 Nm		10.5 Nm		14 Nm		17.5 Nm		21 Nm		24.5 Nm		28 Nm		31.5 Nm		35 Nm	
	H	OP	H	OP	H	OP	H	OP	H	OP	H	OP	H	OP	H	OP	H	OP	H	OP	H	OP
Median (m/s)	13.30	18.21	18.92	25.43	21.91	28.97	24.58	31.88	26.92	35.31	28.85	38.06	31.23	39.66	33.69	43.03	36.19	44.16	38.66	46.02	41.30	47.48
IQR	3.28	4.91	3.92	2.79	4.03	3.46	5.14	4.05	5.81	5.46	7.86	5.19	7.75	4.61	8.49	7.26	9.01	7.45	9.49	10.97	9.14	10.10
p	**<0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**0.001**		**0.001**		**0.016**		**0.016**	
Effect size	0.80		0.80		0.80		0.80		0.80		0.70		0.80		0.50		0.50		0.30		0.30	

Table 8.1. Shear Wave Speed Values of the Entire Sample at Different Ankle Torques. Boldface indicates significance (P < .05). Ab

H, Healthy tendon; OP, Operated tendon; SWS, shear wave speed.

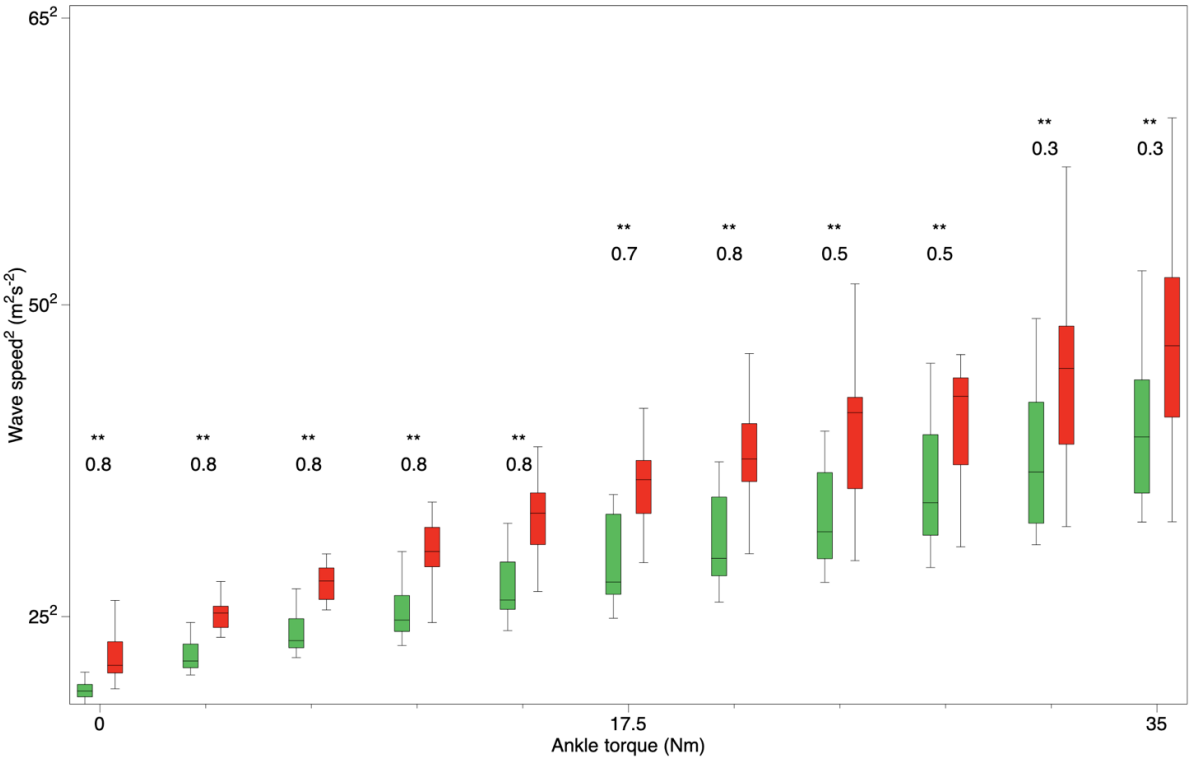


Figure 8.3. Box plot showing the median (interquartile range) squared shear wave speed of the entire sample at different ankle torques. Green boxes and red boxes represent the unaffected and the operated side, respectively. **P < .05; numbers below represent the effect size.

8.4.3 Myotonometry

Stiffness of the AT measured in the distal part with MyotonPRO showed a median (IQR) of 813 N/m (124) for the unaffected side and 919 N/m (61.5) for the operated AT, indicating an increased stiffness of the operated AT (P < .01). The stiffness in the proximal part was higher in the operated AT with 844 N/m (73.3) compared to the unaffected AT with 838 N/m (119) (P = .03).

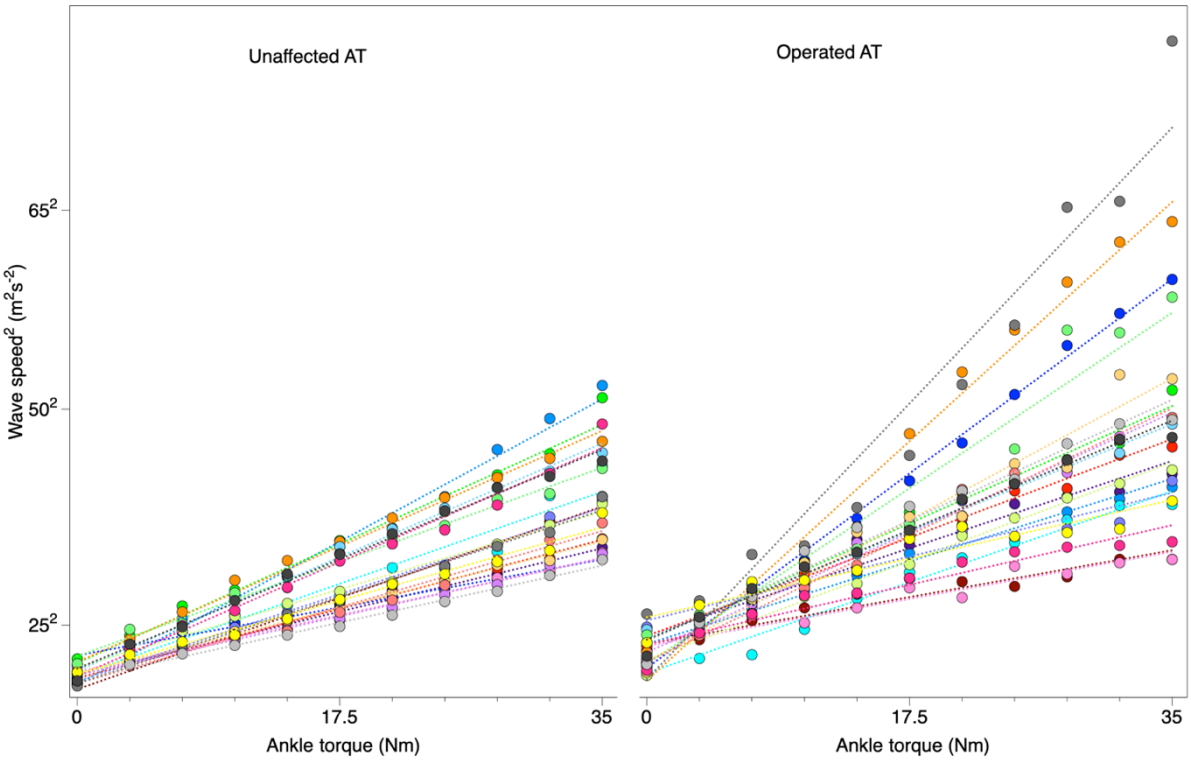


Figure 8.4. Scatter plot showing the relationship between wave shear wave speed and ankle torque. Left panel shows the unaffected AT while right panel shows the operated AT. Lines represent the linear regression for each tendon.

8.4.4 Ultrasound imaging

The median (IQR) thickness was 5.15 mm (1.5) and 13.2 mm (2.2) for the unaffected and the operated AT, respectively (P < .01) (Figure 8.5). The CSA median (IQR) values for the unaffected AT were 62.4 mm2 (7.3) and 56.1 mm2 (9.1) in the distal and proximal part, respectively, whereas for the operated AT they were 176 mm2 (40) and 196 mm2 (43) (P < .01).

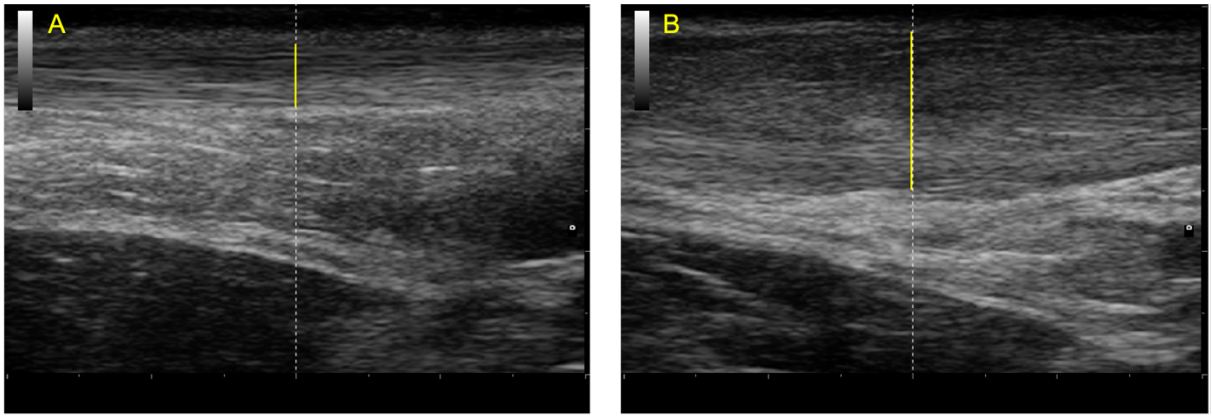


Figure 8.5. Longitudinal ultrasound images of the unaffected (A) and operated (B) Achilles tendon.

8.5 Discussion

The present chapter represents the first investigation assessing tendon loading using shear wave tensiometry in a cohort of individuals who underwent AT surgery. The sample evaluated consisted of 21 male participants with a mean time from surgery of approximately 20 months, and generally low levels of disability except for 2 participants with an ATRS score <60. The results are comparable with other studies that showed that people generally report low levels of disability 1 year (Busilacchi et al., 2016) or several years after surgery (Rosso et al., 2015). A recent large randomized trial (Myhrvold et al., 2022) involving 526 patients with AT rupture showed a preinjury ATRS score of 93.9 ± 15 suggesting that our current sample had a score comparable to that of a healthy population. Nevertheless, the Tegner activity level scale showed that only 57% of the participants had returned to an equal level of sport activity compared with before the operation. Thus, although our sample showed that the level of disability in their daily life (measured with the ATRS) had almost returned to the normal values, when asked about high demand performance in sport, half of the participants had not returned

to their preinjury level. The lack of complete recovery could be explained by persistent abnormalities detected in the operated tendon or by changes in behaviour toward higher-demand activities.

Calf circumferences of the operated leg was significantly smaller that the unaffected leg; thus, muscle trophism asymmetry appears to persist over time. Indeed Rosso et al. (Rosso et al., 2015) showed similar results 7.5 years after AT rupture (37.9 cm for the affected and 39.2 for the unaffected AT). In addition, a different range of motion between the 2 ankles was found, albeit of small magnitude.

Differences in shear wave speed between tendons have been found across all the torque levels evaluated, with a higher effect size (0.8) at lower torque and small effect size (0.3-0.5) at higher torque levels. The operated tendons showed a higher shear wave speed compared to the contralateral unaffected tendons at every ankle torque evaluated (Table 8.1). These results build on previous studies (Keuler et al., 2019, Martin et al., 2018) using shear wave speed during isometric contractions in healthy participants. Values ranged from 15 to 20 m/s with the muscles relaxed and from 60 to 80 m/s during a maximal contraction and provide important new information on the debate about mechanical changes of the tendon after AT rupture repair. Previous studies found decreased stiffness (Chen et al., 2013, Frankewycz et al., 2018, Geremia et al., 2015, McNair et al., 2013, Wang et al., 2013) whereas other studies reported increased tendon stiffness (Agres et al., 2015, Bravo-Sanchez et al., 2021) compared to the unaffected side 2-6 years after rupture. This variation could partially be explained by the time point of evaluation. It appears that in the healing phase after surgery (<1 year) the tendon has less stiffness, which progressively increases toward normal value or even exceeds the values of the unaffected tendon in the later phases, as identified in the current work. Indeed, shear wave speed values remain higher even in participants examined long time after surgery (in this study up to

37 months). However, no significant correlations were found between shear wave speed and time elapsed since surgery, ATRS and Tegner activity level scale.

One possible explanation is that mechanical properties and clinical features are not closely interrelated; alternatively, it is likely that the sample size was not large enough to achieve sufficient statistical power, and the findings of this study must be considered to be preliminary. The behaviour of the tendon shear wave speed and its relationship with the distance from the surgery, clinical features (ATRS and Tegner activity level scale), or level of injury is currently unclear and should be further investigated.

Several parameters have been used to describe the mechanical properties of tendons and therefore not all results are directly comparable given the different technology used. In the current study, we use tendon tension/loading as an index to measure the axial stress as the shear wave speed is proportional to the axial stress in the tissue. During isometric contraction of increased intensity, force/torque, AT axial strain, and stiffness should all increase (Kjaer, 2004, Magnusson et al., 2003). In this study and previous studies (Martin et al., 2018, Schneebeli et al., 2022), shear wave speed increases when tension is put on the AT by an isometric contraction. However, because of the possible relationship between stiffness and tension measured with shear wave tensiometry, the previously ruptured and surgically repaired AT appears stiffer than the healthy contralateral tendon. This finding is also supported by the myotonometry results, which found increased stiffness (N/m) in the operated AT compared to the unaffected side both in the most distal and proximal region of the tendon. Similarly, Bravo-Sanchez et al. (Bravo-Sanchez et al., 2021) found increased stiffness in the operated tendon.

Several potential explanations exist for the distinct loading values observed. Changes in collagen type have been shown in tendon following surgery, with a greater proportion of type III collagen in repaired tendon when compared to unaffected tendons that contain mainly type

I collagen (Maffulli et al., 2000). Type I collagen has more tensile strength than type III; therefore, the composition of the tendon can influence its capacity to tolerate load (Liu et al., 1995) and the tendon's mechanical properties (Kannus et al., 1997, Leadbetter, 1992). Thus, the higher proportion of type III collagen relative to type I might stiffen the tendon (Bravo-Sanchez et al., 2021, Tan et al., 2012).

Differences between the operated and the unaffected tendon were also present in the morphological properties measured with ultrasonographic imaging. Tendon thickness and CSA remain higher in the operated tendon even after more than 1 year post surgery. These results are in line with other studies showing increased tendon thickness and CSA in the longer term after the surgery (Bravo-Sanchez et al., 2021, Frankewycz et al., 2018, Geremia et al., 2015, Khair et al., 2022, Tan et al., 2012). Indeed, operated tendons are characterised by a round irregular area of increased size (Tan et al., 2012) with disorganised collagen fiber due to scar maturation and remodelling. Morphological parameters can influence the mechanical parameters as the tendon shear wave speed is directly correlated to the tendon CSA (Martin et al., 2018).

The linear relationship between squared shear wave speed and ankle torque has been evaluated to test the consistency of the tensioned beam model (Martin et al., 2018). As previously shown in healthy participants (Schneebeli et al., 2022), squared AT wave speed increases linearly with the increment of ankle torque. In the present study the coefficient of determination R2 of both the operated and unaffected tendon was close to 1 (0.93 and 0.97, respectively), showing a close linear relationship between shear wave speed and ankle torque (Figure 8.4). Moreover, tendon loading is highly variable between participants, especially with higher ankle torque; IQR values increased as torque increases, showing different tendon behaviour between participants as previously shown in healthy participants (Schneebeli et al.,

2022). This variability is particularly noticeable for the operated tendon (Figure 8.4) where the values are more evenly spread, especially at higher ankle torque. This is probably due to different muscular activation patterns between plantarflexor muscles in different individuals. As previously shown in other studies (Finni et al., 2006, Heikkinen et al., 2017, Khair et al., 2022), the contribution of flexor hallucis longus muscles and of the soleus can change after AT ruptures. Furthermore, calf muscle trophism in the operated limb as well as muscle MVC remain significantly lower long term after the injury (Keuler et al., 2019, Rosso et al., 2015); collectively, these factors can contribute to different muscle activity patterns. The different contribution of the plantarflexor muscles cannot be distinguished by the tensiometer that measures AT wave speed.

This study presents some limitations. First, the exact surgical procedure as well as the rehabilitation protocol has not been systematically recorded; all participants underwent open repair surgery; however, it remains unclear if the outcomes measured were affected by slight variations in operational treatments or rehabilitation protocols. Also, and critically important to consider, is that this study was of 21 male patients—both a small sample size and one that is hard to generalize. Another aspect is the acquisition of the tensiometry values from 0 to 35 Nm of ankle torque at 0 degrees of plantarflexion; we cannot exclude that the results may be different at different ankle torque levels or at different ankle angles. Lastly, different loading between the 2 tendons could be related to the different resting length of the tendon after the suture. Two factors can influence the residual length of the operated AT, the position in which the tendon is sutured and the lengthening that possibly occurs during the rehabilitation phase. When this type of surgery is performed, the foot is positioned in the equinus to facilitate the approaching of the 2 tendon stumps.

Previous studies showed greater tendon resting length (Agres et al., 2015, Khair et al., 2022, Zellers et al., 2019) in the operated tendon compared to the unaffected side. However, the tendon resting length was not assessed in this study, and therefore we cannot establish whether tendon length influences shear wave speed. Future studies to evaluate the relationship between shear wave speed and tendon resting length could be relevant.

Further studies are also needed to better understand the clinical relevance of shear wave tensiometry in measuring tendon loading and guiding the treatment of AT rupture. Having an instrument able to precisely detect changes in tendon loading responses over time not only holds the potential to enhance our understanding of tendon behaviour during the healing phase but also can support clinicians in developing patient-specific rehabilitation protocols.

8.6 Conclusion

This chapter shows that shear wave tensiometry can precisely detect differences between operated and unaffected AT during a standardized loading procedure. The shear wave speed along the operated tendon remains higher in the long-term after a rupture. This study represents the first step toward the implementation of this technology in clinical settings in order to monitor the evolution of the mechanical properties of the AT over time for patients affected by AT rupture and other tendon pathologies.

CHAPTER 9

SHEAR WAVE TENSIOMETRY IN THE EVALUATION OF ACHILLES TENDON LOADING: A CROSS-SECTIONAL STUDY ON CONSERVATIVELY TREATED TENDONS AFTER RUPTURE

This chapter reports in full the contents of a manuscript that has been submitted for publication. It combines verbatim text from the original manuscript with changes employed for the purpose of this thesis.

Publications and Presentations

1. **Schneebeli A.**, Cescon C., Filardo G., Testa E., Riegger M., Sangiorgio A., Falla D., Barbero M. Shear wave tensiometry in the evaluation of Achilles tendon loading: a cross-sectional study on conservatively treated tendon after rupture. International Society of Electrophysiology and Kinesiology (ISEK) Nagoya. Japan. June 2024

2. **Schneebeli A.**, Filardo G., Falla D., Testa E., Riegger M., Sangiorgio A., Cescon C., Barbero M. Differences in shear wave speed between surgically and conservatively treated Achilles tendons following rupture. International Federation of Orthopaedic Manipulative Physical Therapists (IFOMPT) Basel. Switzerland. July 2024

3. Sangiorgio A., **Schneebeli A.**, Barbero M., Filardo G., Testa E., Riegger M., Cescon C., Falla D. Shear wave speed: mechanical and morphological comparison in

conservatively treated and uninjured Achilles tendon. 13a Giornata della Ricerca e dell'Innovazione in Medicina Umana della Svizzera italiana, Lugano, Switzerland. September 2024. **Awarded as best poster in clinical or epidemiological research**.

9.1 ABSTRACT

This chapter presents a further investigation into the mechanical properties of the AT measured with tensiometry, but in a different clinical population from the previous one: people with ATR treated conservatively. The aim of this study was to quantify differences in the shear wave speed between a conservatively treated AT after rupture and the unaffected contralateral tendon.

Twenty-nine participants who received conservative treatment following ATR were enrolled. Tendon load was assessed using a shear wave tensiometer comprising a set of four accelerometers attached to the tendon. Stiffness, thickness, and CSA were also assessed using MyotonPRO and ultrasound imaging.

No significant differences in shear wave speed were found between the affected AT and the unaffected side ($p>0.05$). A significant difference between sides was found only at 3.5 Nm and 7 Nm ($p=0.001$ and $p=0.020$) for participants that experienced a lesion of the MID, and higher plantar flexor strength was found for the unaffected side (320 ± 99.5 Nm) compared to the affected side (261 ± 80 Nm; $p=0.001$). Stiffness values were significantly lower (825 N/m) for the affected tendon compared to the unaffected side (913 N/m; $p=0.006$). Thickness and CSA in the proximal and distal part of the tendon were significantly higher in the affected tendon compared to the unaffected side ($p<0.001$).

There is no difference in shear wave speed values between the affected and the unaffected AT in the longer-term after the rupture. However, some differences were detected in shear wave speed between participants that experienced a lesion of the MID and in the MTJ at low level contractions, with side-to side differences in participants who had experienced a MID lesion. Moreover, tendon thickness and CSA as well as plantar flexor strength remain different between the affected and the unaffected AT.

9.2 Introduction

As mentioned in Chapter one, the number of ATR in the general population are rising in the next years. To date, the most suitable treatment for ATR is still not defined and remains controversially discussed in the literature. A mounting body of evidence indicates comparable long-term patient-reported outcomes for both surgical and conservative treatment (Nilsson-Helander et al., 2010, Olsson et al., 2013, Myhrvold et al., 2022). These findings were confirmed by Ochen et al. (Ochen et al., 2019) in their comprehensive systematic review, which demonstrated comparable patient-reported outcome measures for both treatments. However, their analysis revealed a higher risk of re-rupture associated with conservative treatment and a greater incidence of postoperative complications in surgically treated AT.

A recent large clinical trial involving a cohort of over 500 patients diagnosed with ATR aimed at discerning differences among open repair surgery, minimally invasive surgery, and conservative treatment concerning patient-reported outcomes and the incidence of tendon re-rupture (Myhrvold et al., 2022). The findings revealed that 12 months post-ATR, all three approaches exhibited similar results in the assessed outcomes. The conservative treatment group experienced a lower occurrence of nerve injuries. However, the conservative treatment group exhibited a slightly higher re-rupture rate (6.2%) than the surgical groups (0.6%).

As emphasized in Chapter eight mechanical properties of the AT post-surgery have been assessed using various technologies at different stages of the healing process (Chen et al., 2013, Frankewycz et al., 2018, Geremia et al., 2015, McNair et al., 2013, Wang et al., 2013, Agres et al., 2015, Bravo-Sanchez et al., 2021, Schneebeli et al., 2023). However, the mechanical properties of AT after conservative treatment have not been well documented in the literature.

The few studies that have explored differences between the affected tendon and the unaffected side have observed no differences in mechanical properties of the tendons after one year (Khair et al., 2022) or even a higher tendon stiffness in the affected compared to the contralateral tendon (Yoshida et al., 2023).

To address the thesis objective number six, the aim of this study was to evaluate differences in shear wave speed between conservatively treated ATs after rupture and the unaffected contralateral tendons. Additionally, morphological properties, thickness and CSA of the tendons were measured using ultrasound, and tendon stiffness was measured using myotonometry.

9.3 Methods

The study was carried out at the Orthopaedic Department of the Ente Ospedaliero Cantonale (Lugano and Bellinzona, Switzerland) between November and December 2022. Approval for the study was obtained from the Ethics Committee of Canton Ticino, Switzerland (ID: 2022-01707/CE4192), (Appendix 14) and participants provided written informed consent. Reporting of the study followed the STROBE guidelines for observational studies (von Elm et al., 2007).

Sample size was calculated based on the mean and standard deviation of the paired differences between the affected and unaffected AT found in a previous study (Schneebeli et al., 2023). A minimum sample size of 30 participants was required to achieve a statistical power of 90% at a significance level of 5% for a two-tailed hypothesis test.

9.3.1 Participants

Participants who underwent conservative treatment following ATR between 1 and 7 years prior to selection were identified through the hospitals' database We included all patients aged 18 or more without surgical treatment for ATR. Exclusions criteria were:

- arthrodesis of one of the upper ankle joints
- history of contralateral AT disease
- connective tissue or metabolic diseases
- systemic inflammatory disorders
- rheumatoid arthritis
- spondyloarthropathy
- diabetes
- current use of systemic antibiotics or steroids

All recruited participants underwent measurements of mechanical and morphological properties of the AT, as well as a clinical assessment.

9.3.2 Clinical Outcomes

Participants completed health-related physical activity questionnaires and the ATRS (Vascellari et al., 2018) (Appendix 15). The Tegner activity level scale was used to evaluate the level of physical activity before and after tendon rupture (Tegner and Lysholm, 1985) (Appendix 16). Ankle dorsiflexion range of motion, calf circumference, and MVC were also measured. Information about the location of the rupture were recorded. The injury location was then confirmed by ultrasound examination.

9.3.3 Shear wave tensiometry

Tendon loading was evaluated using a shear wave tensiometer, which comprised four accelerometers (Analog Devices, ADXL202JE) arranged sequentially and affixed to the skin behind the tendon using adhesive tape. These accelerometers were evenly spaced at 10 mm intervals. To ensure correct placement on the free section of the AT (3-6 cm from the calcaneal insertion) and not on the MTJ, ultrasound imaging was employed for guidance. The minimal impulse required to initiate wave propagation along the tendon was manually administered with a reflex hammer. A series of five repeated measurements (one per second) was obtained for each contraction level, for both the left and right AT of each participant. The mean of these five measurements was then used to calculate the tendon wave speed. The reliability of this technology was assessed in a prior study, revealing good to excellent reliability (ICC 0.75-0.96) (Schneebeli et al., 2022).

The signals were acquired using a Sessantaquattro device (OTBioelettronica, Turin, Italy) with a sampling frequency of 10 kHz. The analysis of signals relied on the time delay between waves generated by the accelerometers and the propagation of the mechanical wave along the tendon (Figure 9.1). The technique for estimating the propagation velocity employed cross-correlation functions between pairs of signals (Farina et al., 2001, Farina et al., 2004). Each impulse corresponded to a propagation speed value in meters per second (m/s).

During these measurements, participants assumed a prone position with their feet securely fastened in a dynamometer at a 0-degree angle of plantar flexion. Ten different isometric contractions, ranging from 0 to 35 Nm in intensity, were performed. Ankle torque was assessed using a dynamometer linked to a force sensor (Mod.TF2/S; CCT Transducers, Turin, Italy), which functioned within a 0- to 100-N range. A MISO-II device (OT

Bioelettronica, Turin, Italy) was employed to provide real-time visual feedback of the force signal to the participants. The participants were instructed to exert force on the board as if they were trying to achieve a tiptoe position. The investigator monitored their performance to ensure that the heel remained in contact with the dynamometer, and two belts were used to secure a firm fixation of the foot and ankle.

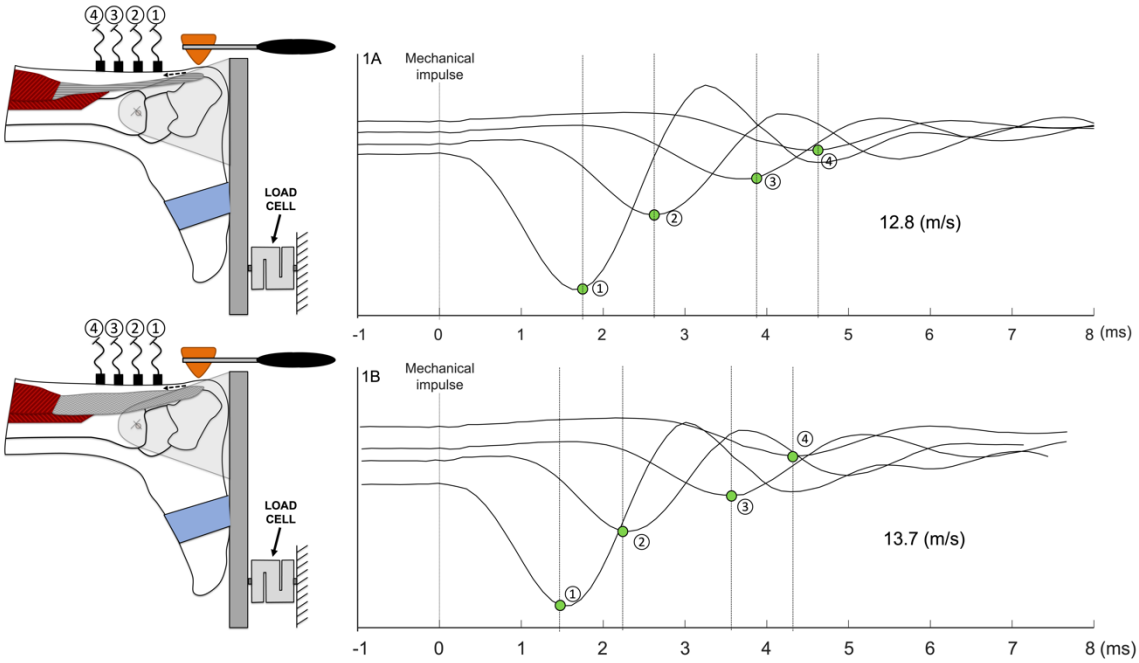


Figure 9.1. Schematic of the shear wave tensiometer. The impulse was provided at 2 cm from the calcaneal insertion. The 4 accelerometers (1-4) were attached to the skin in series with a 10-mm inter-accelerometer distance. Shear wave speed signals at 0 Nm. The propagation velocity of the wave was calculated based on the delay between the waves passing from the accelerometers. 1A) Represent a shear wave speed signals at 0 Nm for the unaffected tendon while 1B) represent a shear wave speed signals at 0 Nm for the affected tendon.

9.3.4 Myotonometry

Tendon mechanical properties were also measured using a commercially available device called MyotonPRO *(*Muomeetria, Tallinn, Estonia*)*. This device detects viscoelastic properties of different tissues and was applied following a standardized protocol (Schneebeli et al., 2020). Both the affected and unaffected AT were measured at two distinct locations along the free tendon. Specifically, the distal region, positioned 3 cm from the calcaneal insertion, and the proximal region, situated 6 cm from the calcaneal insertion. Participants' feet were hanging freely over the edge of the examination bed during the measurements.

9.3.5 Ultrasound imaging

Ultrasound images were acquired to measure the thickness and CSA of both the affected and unaffected AT. The images were obtained using an ultrasound machine (MyLab25 gold, Esaote, Genoa, Italy) with a 13- to 4-MHz linear array (LA523*)*. Thickness images were obtained through a longitudinal scan, covering the range from 2 to 7 cm from the calcaneal insertion (Figure 9.2). In contrast, CSA images were captured through a transverse scan conducted at the 3 cm and 6 cm positions from the calcaneal insertion.

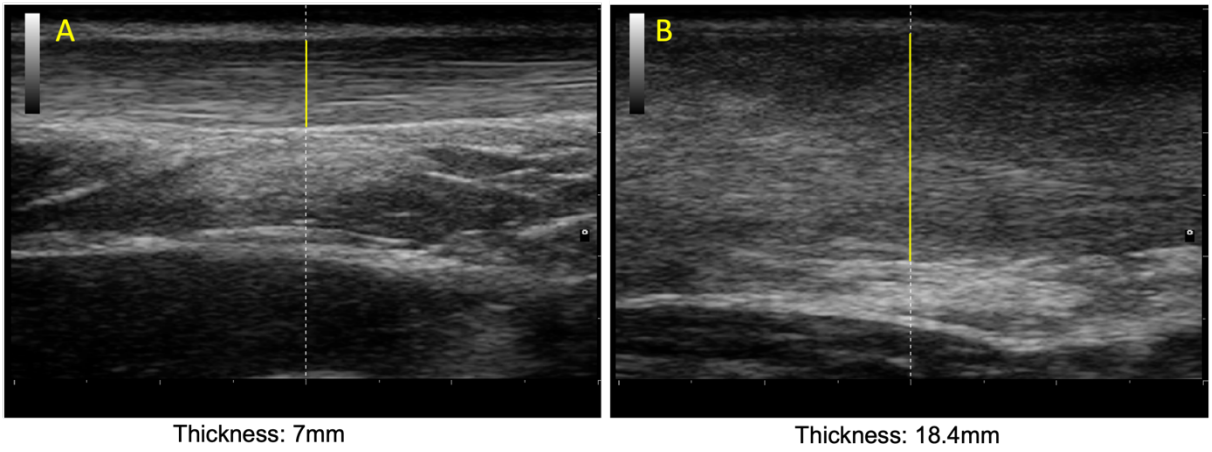


Figure 9.2. Ultrasound images representing the thickness of the Achilles tendon in a longitudinal scan. A) Unaffected side and B) affected side.

9.3.6 Statistical analysis

Nonparametric, independent samples, Mann–Whitney test was used to assess differences in shear wave speed between participants with a different injury location (MID or myotendinous junction). The non-parametric Friedman test was used to assess differences in AT wave speed and other outcomes between the affected and the unaffected side. Post hoc pairwise comparisons with Bonferroni correction were performed, and significance was set at α=0.05. Linear regression models were used to test the association between wave speed and ankle joint torque. Wave speed values were presented as median and interquartile range (IQR). The statistical analysis was conducted using SPSS (version 28).

9.4 Results

Thirty-two participants were approached and screened resulting in 3 participants being excluded (2 bilateral ruptures, 1 pain during the isometric contraction). Thus, 29 participants (3 women) were recruited for the study. Their mean (±SD) age was 54.8 (±9.0) years and the mean time from rupture was 36.0 (±24.2) months (range 10-90 months). Fifteen participants experienced a lesion of the mid tendon (MID) while 14 of the myotendinous junction (MTJ). Differences in shear wave speed were found between participants who had experienced a MID lesion or an MTJ lesion at low level contractions (0 Nm, 3.5 Nm, and 7 Nm; p=0.041, 0.006, and 0.023 respectively).

9.4.1 Clinical Outcomes

The Tegner activity level scale indicated that 72% of participants were able to resume a similar level of sports activity as before the operation. The ATRS at follow-up was 86/100 ± 16.1 ranging from 35 to 100. The average ankle dorsiflexion range of motion was not different between the affected and unaffected side (p=0.127). The mean calf circumference was significantly higher for the leg on the unaffected side compared to the affected side (p = 0.001) measuring 38 ± 3 cm versus 37 ± 3.3 cm, respectively. MVC was different between the affected and the unaffected side, with a higher torque generated on the unaffected side, 320 ± 99.5 Nm, compared to the affected side, 261 ± 80 Nm (p=0.001).

9.4.2 Shear wave tensiometry

Table 9.1 and Figure 9.3 present the shear wave speed values of the affected and unaffected AT measured at various contraction intensities. The Friedman test revealed no significant difference between sides for each of the contraction levels analysed ($p>0.059$) when the entire sample was evaluated.

A significant difference between sides was found only at 3.5 Nm and 7 Nm ($p=0.001$ and $p=0.020$) for the participants who had experienced a MID lesion. In the linear regression analysis conducted for each AT under different contraction intensities, the average coefficient of determination (R2) was 0.97 ± 0.02 for the unaffected side and 0.95 ± 0.04 for the affected side. This suggests a linear relationship between wave speed and ankle torque for both tendons.

SWS	0 Nm		3.5 Nm		7 Nm		10.5 Nm		14 Nm		17.5 Nm		21 Nm		24.5 Nm		28 Nm		31.5 Nm		35 Nm	
	H	RUP	H	RUP	H	RUP	H	RUP	H	RUP	H	RUP	H	RUP	H	RUP	H	RUP	H	RUP	H	RUP
MTJ (m/s)	13.39	12.28	19.13	17.94	22.82	21.86	25.81	25.44	29.25	27.96	31.09	29.80	32.98	30.93	36.55	33.64	38.28	34.27	41.25	36.74	42.67	39.18
IQR	2.21	3.37	1.56	5.72	1.95	6.23	2.08	6.23	3.55	7.00	4.93	8.37	5.04	9.39	6.67	9.98	5.96	12.09	7.73	13.19	5.55	15.14
p	0.782		0.405		0.782		0.782		0.782		0.782		0.405		0.052		0.166		0.405		0.405	
MID (m/s)	12.18	15.87	16.58	22.20	19.67	25.46	23.68	26.94	25.76	30.34	29.01	33.50	31.03	34.68	33.72	37.72	36.47	38.40	38.06	40.71	40.73	42.70
IQR	2.21	6.99	3.59	5.23	3.39	6.94	3.92	8.93	4.07	10.37	4.91	7.46	4.43	8.28	5.42	9.14	4.51	8.15	8.62	11.59	6.34	16.54
p	0.071		**0.001**		**0.020**		0.197		0.197		0.197		0.197		0.197		0.197		0.439		0.109	

Table 9.1. Shear wave speed values for the two groups at different ankle torques. H, healthy tendon; RUP, affected tendon; SWS, shear wave speed.

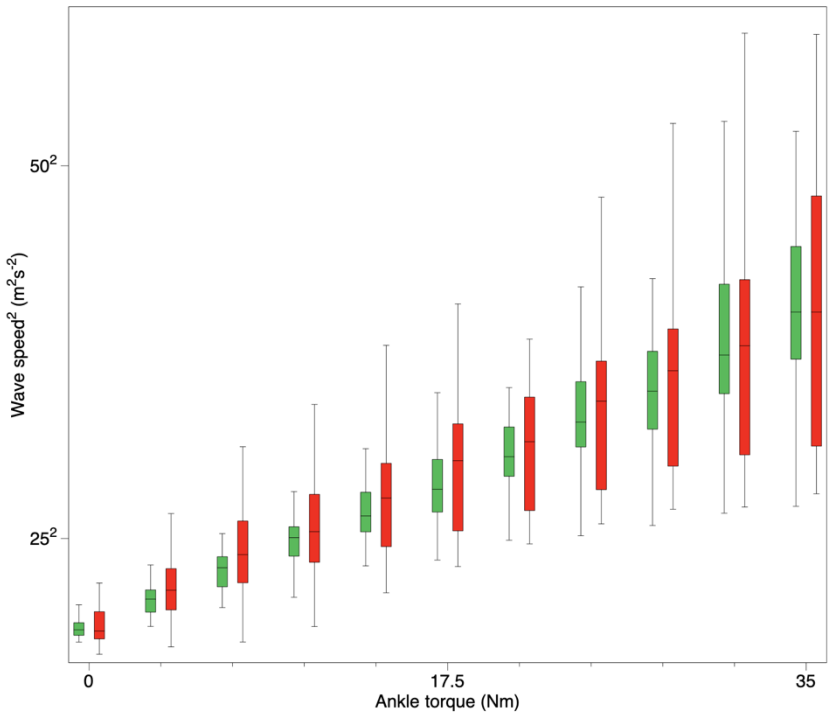


Figure 9.3. Box plot showing the median (interquartile range) squared shear wave speed of the entire sample group at different ankle torques. Green boxes and red boxes represent the unaffected and the affected side, respectively.

9.4.3 Myotonometry

Stiffness analysis using myotonometry revealed a difference between the affected and the unaffected AT but only in the proximal part of the AT with a median (IQR) of 913 N/m (122) for the unaffected side and 825 N/m (115) for the affected side, showing decreased stiffness of the affected AT (p=0.006).

9.4.4 Ultrasound imaging

Ultrasound imaging revealed a significant difference in the thickness between the affected and the unaffected AT ($p<0.001$) with a median (IQR) of 5.9 mm (1.6) for the unaffected and 10.1 mm (3.3) for the affected side.

CSA was different between sides in the distal and proximal part of the AT with a median (IQR) of 69.1 mm^2 (17.9) and 115.0 mm^2 (51.3) for the unaffected and affected side respectively in the distal part ($p<0.001$) and 67.3 mm^2 (26.3) and 135.0 mm^2 (91.0) for the proximal part ($p<0.001$).

9.5 Discussion

The main finding of this chapter evaluating AT loading using shear wave tensiometry in participants after ATR who had been treated conservatively, is that there is no overall difference in shear wave speed values between the unaffected and the affected side. At a long-term follow-up, the affected tendon restored loading capacity (measured with shear wave tensiometry) at a level that was comparable with that of the contralateral side. However, at low contraction levels there was a difference in shear wave speed between tendons in the MID group.

Different behaviour of the AT at low contraction levels could depend on the tendon length. When subjected to a change in ankle angle and to isometric contraction, the AT starts to increase its tension, and this onset of the rise in tension has been shown to be higher at lower strain values (Magnusson et al., 2003). Affected tendons in the MID group could have a slightly different tendon length that leads to an increase in tension, visible particularly when

contractions are of low intensity. High variability in tendon loading (large IQR values) has been shown in affected tendons compared to the unaffected side (Figure 9.1). This variability was shown in previous studies in healthy participants (Schneebeli et al., 2022) and in people with surgically treated ATR (Schneebeli et al., 2023). This could be related to the differences in muscle activation patterns between participants. Different plantar flexor muscles could contribute with different activation magnitude to the net ankle torque, which is particularly true in patients after ATR where the flexor hallucis longus and the soleus have different contributions to plantar flexion torque (Finni et al., 2006, Heikkinen et al., 2017, Khair et al., 2022). A different contribution of other plantar flexor muscles is probably emphasized more during low load contractions, although this different contribution cannot be measured with tensiometry located on the AT.

The variable behaviour of tendons between participants during contractions was also evaluated using a linear regression between squared shear wave speed and ankle torque. In both tendons, the coefficient of determination R2 was close to 1 (0.97 and 0.95) showing a close relationship between shear wave speed and ankle torque. These results confirmed the consistency of the tensioned beam model principle (Martin et al., 2018) of the shear wave speed during contraction.

The present study showed similar shear wave tensiometry values overall between the affected and the unaffected sides, and these results are in line with other studies. Khair et al. (Khair et al., 2022) found no difference in AT stiffness between the affected and the contralateral side 1 year after ATR which was treated conservatively. Likewise, Bressel and McNair (Bressel and McNair, 2001) found no difference in stiffness between the affected and contralateral sides when examined 1 to 5 years after ATR. Yoshida et al (Yoshida et al., 2023) investigated ATR using SWE and showed that affected tendons (treated conservatively)

reached values comparable to the unaffected side within the first 3 months after injury. However, this study showed that the elasticity values of the affected tendon exceeded that of the unaffected side one year after rupture. These differences could be explained by the different follow-up periods between the studies and by the different technologies used in the detection of tendon mechanical properties.

Other studies evaluating patients with ATR which have been treated operatively showed different long-term mechanical properties of the tendon. In the initial stages of the post-surgery healing phase (less than one year), the tendon appears to exhibit reduced stiffness (Geremia et al., 2015, Frankewycz et al., 2018, McNair et al., 2013, Wang et al., 2013, Chen et al., 2013) gradually progressing towards normal values or even surpassing those of the unaffected tendon in the later stages (Agres et al., 2015, Bravo-Sanchez et al., 2021, Schneebeli et al., 2023). A previous study evaluating AT shear wave speed after ATR which was treated surgically, showed a difference in tensiometry between the operated and unaffected AT at every level of contraction tested. Thus, it appears that tendons which are treated conservatively return to comparable shear wave speed values as the unaffected side whereas tendons which are treated surgically remain with higher shear wave speed values for a long time after surgery (Schneebeli et al., 2023).

A possible explanation is that the suture performed during the surgery reacts differently to the loading compared to the natural scar formation following conservative treatment. As demonstrated in animal models, non-surgical interventions result in a more advanced organization of collagen fibers, yielding a tendon with a healthier appearance compared to a higher proportion of scar tissue in those that received surgery (Krapf et al., 2012). To date we cannot determine whether this phenomenon is also present in humans.

Finally, the different time point of analysis after rupture between the present study and the study analysing surgically treated AT has to be taken into consideration (Schneebeli et al., 2023). In the study conducted in people following AT surgery (Schneebeli et al., 2023), participants were evaluated 20.3 ± 8.1 months post-surgery on average, which is earlier than those who underwent conservative treatment in the current study. We cannot exclude that the longer time elapsed may have led the affected tendon to return to values more similar to the contralateral side, although the correlation between shear wave speed and time after rupture were not significant in both the MID group (rho 0.155 p=0.582) and MTJ group (rho 0.231 p=0.427). Nonetheless, despite the different tensiometry values found in the two studies, in both conservatively and surgically treated AT, patient reported outcomes are similar demonstrating a low level of disability when measured 1 year after treatment.

Myotonometry evaluation of the AT revealed a significant difference of stiffness between the affected and the unaffected AT but only in the proximal part of the AT with the results showing lower stiffness in the affected tendon (p=0.006). These results appear to be in contradiction with shear wave tensiometry, which did not reveal any difference in tension between the tendons. Considering that these two technologies assess mechanical properties with different assumptions, a direct relationship between these two parameters might not be possible. To the best of our knowledge, this is the first study using myotonometry to assess people with ATR which has been treated conservatively. Other evaluations of patients with ATR which has been treated operatively reported increased stiffness (Schneebeli et al., 2023, Bravo-Sanchez et al., 2021) of the operated tendon compared to the unaffected side. The different collagen composition of scar tissue and the possible difference in tendon length after surgery can be factors that influenced the myotonometry results, leading to different values between tendons treated conservatively and those treated surgically.

Morphological properties of the tendon assessed via ultrasound imaging also revealed differences between the affected and unaffected tendons. Thickness and CSA were consistently higher in the affected tendon even beyond 1 year after ATR. These findings align with previous studies indicating a sustained increase in tendon thickness and CSA in the later stages after surgery (Khair et al., 2022, Schneebeli et al., 2023, Geremia et al., 2015, Frankewycz et al., 2018, Bravo-Sanchez et al., 2021) and even after conservative treatment (Khair et al., 2022, Yoshida et al., 2023).

Ruptured tendons exhibit an irregular, rounded region of enlarged size, characterised by disorganised collagen fibers resulting from scar maturation and remodelling (Tan et al., 2012). Ultrasound images were acquired at 2-7 cm from the calcaneal insertion and this is the region where the ATR mostly occurs (Maffulli and Wong, 2003), therefore this is where a large collagen accumulation and scar tissue formation is expected, leading to an increase tendon size. Despite the morphological changes observed in this study (increased thickness and CSA) that can last many years after ATR, the mechanical properties seem to remain similar to the unaffected side.

Clinical outcomes were in line with previous literature (Busilacchi et al., 2016, Rosso et al., 2015) showing a low level of disability post ATR. The mean score on the ATRS was 86/100 with 72 % of participants returning to a level of activity similar to the level before the rupture. Comparing across studies, the current cohort of patients who had ATR treated conservatively showed similar clinical outcomes to those treated surgically one year after the rupture (Schneebeli et al., 2023). These results are also supported by a recent clinical trial that showed similar outcomes between the two types of treatment (Myhrvold et al., 2022). However, despite good clinical outcomes, this study revealed persistent differences in strength and muscle trophism of the triceps surae. The calf on the affected side remains weaker (lower MVC,

$p<0.001$) and with a smaller circumference ($p<0.001$) in the longer-term after ATR. These results are comparable with a previous study (Rosso et al., 2015) that showed reduced torque of the plantar flexor muscles long after ATR.

There are some limitations of this study that need to be acknowledged. First, the post rupture rehabilitation protocol was not recorded; therefore, it was not possible to establish whether the measured outcomes were influenced by differences in rehabilitation protocols. Second, a different load distribution between the two tendons might by associated with the different resting length of the tendon following rupture. The length of an affected AT could have been modified by different factors and was not measured in this study. The position of the foot in the cast and the potential lengthening during the rehabilitation phase were elements that could have contributed to a different tendon length. We could therefore not establish if tendon resting length influences shear wave speed values. Additional research is required to gain a more comprehensive understanding of the clinical significance of shear wave tensiometry in assessing tendon loading and informing the management of ATR.

9.6 Conclusion

This chapter showed that shear wave tensiometry can quantify tendon loading after ATR treated conservatively. Overall, there is no difference in shear wave speed values between the affected and the unaffected AT when measured in the longer-term follow-up after ATR. However, some differences were detected in shear wave speed between MID and MTJ lesions at low contraction intensities, with side-to-side differences in participants who had experienced a MID lesion. Moreover, tendon thickness and CSA as well as plantar flexor strength remain different between the affected and the unaffected AT.

CHAPTER 10

GENERAL DISCUSSION

10.1 Summary of Findings

The main aim of this thesis was to assess technologies used to evaluate AT mechanical properties and to understand their capability in detecting changes due to increased load on the musculotendinous complex. Moreover, the implementation of shear wave tensiometry in clinical populations has been explored.

In Chapter one the rationale of the proposed technologies as well as their application in measuring mechanical properties provide the background for the thesis. Furthermore, Chapter one provides an overview of how tendons adapt to mechanical stimuli both as a result of exercise and during pathological conditions.

Chapters two and three reported the results of two observational studies that evaluate the capability of different sonoelastography technologies to detect AT mechanical properties during isometric contraction and to determine the consistency between the two technologies (SE and SWE). The results suggests that SE provided more consistent results when tendon is analysed under load if compared with SWE. SE can detect changes in AT mechanical properties during contraction but the precision of the device seems questionable, indeed small changes of load on the tendon cannot be detected. Conversely, SWE seems to have some technical limitation in measuring AT even at low levels of contraction, probably due to the alignment or the displacement of the fibrillary structure within the AT which could increase the speed of the shear waves and can generate an abnormal propagation of the shear wave that cannot be registered by the device (Schneebeli et al., 2021).

Considering the inconsistency between the two technologies that may hinder the clinical applicability a more in-depth evaluation of the clinimetric properties was necessary. Therefore, a systematic review evaluating the reliability of sonoelastography applied in the detection of mechanical properties of lower limb tendons was performed in Chapter four.

The results of the systematic review confirm that SE and SWE have highly variable results in term of reliability across studies. SE on AT seems to be reliable but poor reliability was found for PT. SWE seems to be more reliable on the PT than on the AT. The lack of inter-rater, inter-session and inter-machine reliability found in this chapter raises important doubts about the clinical applicability of these technologies.

In light of the results of this systematic review, different technologies other than sonoelastography were evaluated in the subsequent chapters. Chapter five reported results of a reliability study using myotonometry to evaluate AT mechanical properties whereas Chapter six described another reliability study using shear wave tensiometry.

The results confirmed that myotonometry (MyotonPRO) is a reliable tool for the evaluation of AT mechanical properties during different contraction levels and in different positions. Construct validity was supported by changes of tendon properties during the explored conditions. However, some technical limitation was noted at higher levels of isometric contraction; the impulse generated by the device was probably not strong enough to provide a precise evaluation of AT after a certain amount of load.

Similarly, shear wave tensiometry showed very high reliability and construct validity at every ankle torque analysed. Moreover, tensiometry seemed to be more suitable for the detection of higher load levels and therefore more applicable in the detection of AT mechanical properties.

Chapter seven reported results of a pilot study designed to simplify the experimental setup of tensiometry. The aim was to test the convergent validity of two types of impulse (manual vs mechanical) provided to generate the shear wave speed within the AT. Results showed very high convergent validity between the two types of impulse provided, therefore the use of the manual impulse was implemented in the subsequent chapters.

Chapter eight and nine reported the results of two cross-sectional studies evaluating AT mechanical properties in participants with ATR. Chapter eight analysed a cohort of participants with ATR treated surgically and showed that the mechanical properties of the operated AT remain different from the contralateral healthy tendon in the long term after the operation. Conversely, Chapter nine showed that the mechanical properties of the ruptured tendon in participants with ATR treated conservatively are similar to that of the healthy contralateral tendon. These two last chapters demonstrate the feasibility to implement shear wave tensiometry in the detection of changes in AT mechanical properties in clinical populations.

In this final chapter (Chapter ten), the aim is to summarize the main outcomes of this thesis, formulate conclusions, highlight the research's strengths and weaknesses, and explore the clinical implications along with recommendations for future studies.

10.2 Mechanical properties changes following ATR

Chapter one describes the mechanical properties changes that AT can encounter when subjected to rupture. In this thesis different technologies were used with the aim to define the most suitable to evaluate AT mechanical property changes during loading tasks. Given the promising results obtained with shear wave tensiometry, an evaluation of people with ATR was performed using this technology.

When analysing people with ATR treated surgically, it appears that mechanical properties between the healthy and the operated AT remain different even in the long term after surgery. Chapter eight showed that the operated AT has higher shear wave speed values compared to the healthy contralateral AT. These changes remain even in long term after surgery and indeed no correlation was found between shear wave speed and time elapsed since surgery. To date different results in terms of mechanical properties have been found in the literature when analysing ATR treated surgically (Figure 10.1). In the healing phase after surgery (< 1 years), the majority of the studies found a decreased or unchanged stiffness, while in long term it appears that AT increases its stiffness compared to the contralateral side. During the healing phase after surgery the AT appears to have reduced stiffness, which progressively increases toward normal values or even exceeds the values of the unaffected tendon in the later phases.

Although a considerable amount of research exists on the topic, it is not possible to draw definitive conclusions because the differences in study methodologies, technologies used, and heterogeneity among the evaluated patients make it difficult to generalize the results. There are several possible reasons for the distinct loading values observed. After surgery, tendons show changes in collagen types, with repaired tendons having a higher proportion of type III collagen compared to unaffected tendons, which primarily contain type I collagen (Maffulli et al., 2000). Type I collagen is stronger than type III in terms of tensile strength, meaning that the tendon's ability to withstand load and its mechanical properties can be influenced by its collagen composition (Kannus et al., 1997, Leadbetter, 1992, Liu et al., 1995). Consequently, an increased amount of type III collagen compared to type I may make the tendon stiffer (Bravo-Sanchez et al., 2021, Tan et al., 2012).

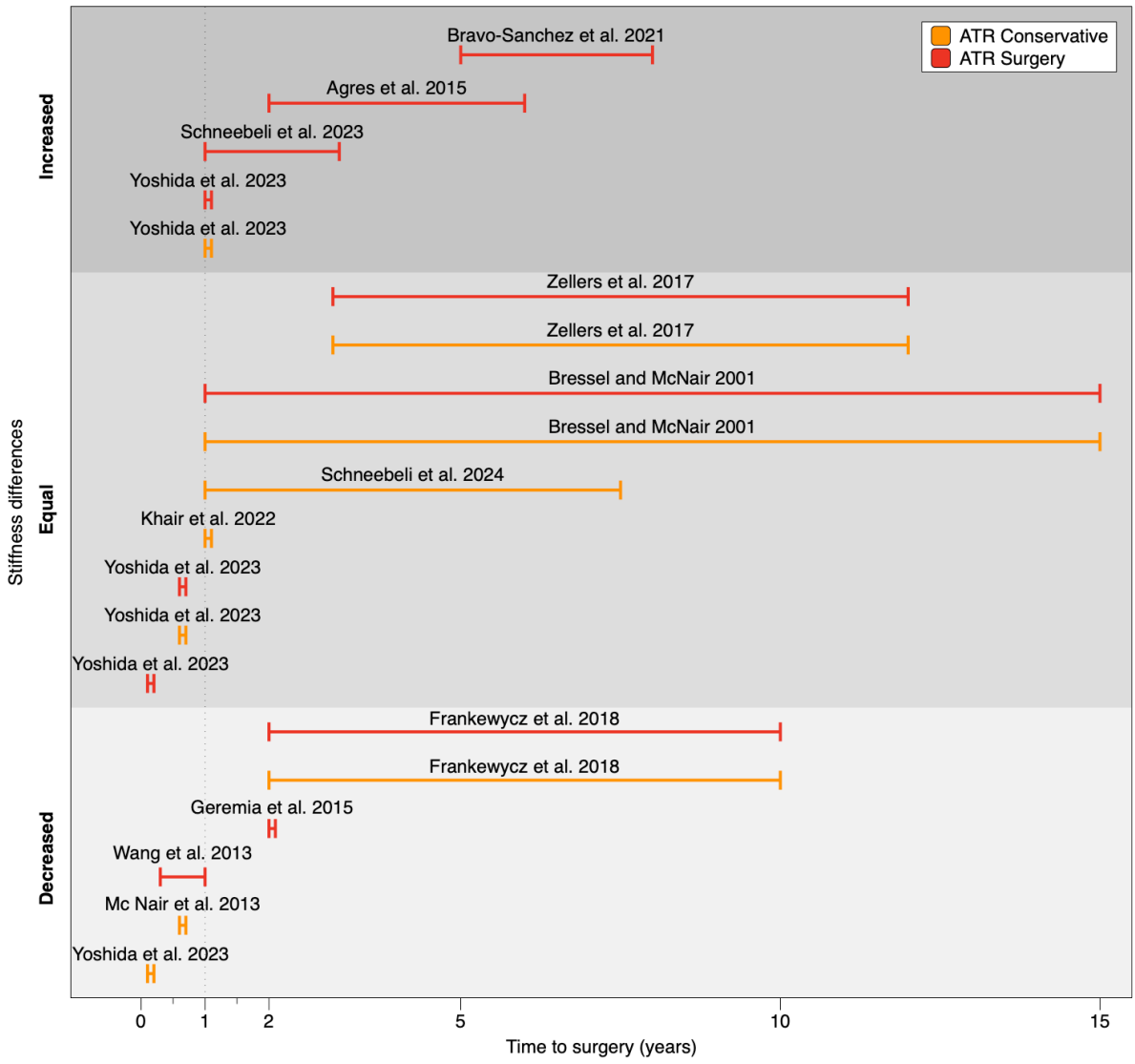


Figure 10.1. Graph describing the mechanical properties differences between the healthy and the ruptured AT at different time points across different studies.

The behaviour of the tendon mechanical properties and its relationship with the distance from the surgery and other clinical features is currently unclear and should be further investigated.

Mechanical properties of the AT following rupture and conservative treatment has been less investigated (Figure 10.1). Chapter nine showed no difference between the ruptured and

the healthy contralateral AT measured with shear wave tensiometry in the long term after ATR. Other studies are in line with these results, confirming that in the long term, there are no differences in stiffness between the tendons (Bressel and McNair, 2001, Khair et al., 2022, Zellers et al., 2017).

As for the AT treated surgically, it appears that even in the conservative treatment the initial healing phase exhibits reduced stiffness that gradually progressing towards normal values. But unlike the operated tendon, which shows increased stiffness over time, tendons treated conservatively do not seem to reach higher values compared to the healthy contralateral tendon. In light of the limited data available in the literature, the small sample sizes of the analysed studies, and the different technologies used, definitive conclusions cannot be drawn. Further studies are needed to confirm these observations.

There are a paucity of studies evaluating both surgically than conservatively treated ATR (Bressel and McNair, 2001, Frankewycz et al., 2018, Yoshida et al., 2023, Zellers et al., 2017, Schneebeli et al., 2023). The majority of the studies showed no difference in the mechanical properties among the participants who underwent the surgical or the non-surgical treatment except for the study of Yoshida and colleagues (Yoshida et al., 2023) that found a slight difference in AT stiffness in the first 4 weeks after the intervention/rupture.

Chapter eight and nine, showed that in two separate cohort of participants who underwent surgery or conservative treatment, the shear wave tensiometry values are different with the surgery group showing an increased stiffness in the operated tendon compared to the contralateral AT whereas the conservative group showed the same values between the two tendons. Differences in shear wave speed between the groups could be explained by the different time point of evaluation in the two studies, even if no correlation between time after rupture and shear wave speed has been found in both studies (rho 0.155 and rho 0.231 for

conservative treatment Chapter nine; and rho = 0.11 for surgical treatment Chapter eight) it cannot be excluded that the longer follow up period of participants in Chapter nine could have led to further mechanical properties changes. The remodelling phase in the heling process of ATR could be a long-lasting process (Galloway et al., 2013, Voleti et al., 2012) and therefore possible changes in the mechanical properties even after the restoration of symptoms cannot be excluded. Another reason for this difference could be attributed to the different scar tissue formation between the two interventions. Studies in animals suggested that the natural scar formation following conservative treatment results in a more advanced organization of collagen fibers when compared with the scar tissue following surgery (Krapf et al., 2012). This response has not yet been confirmed in humans.

A secondary analysis comparing the mechanical and morphological parameters between the two cohort of participants (Chapter eight and nine) has been performed and presented as an appendix (Appendix 17). Results suggested a between group difference in shear wave speed at low to moderate levels of contraction ($p<0.017$) with the conservative group having lower tensiometry values than the surgery group. Moreover, morphological parameters measured with ultrasound showed a between group difference for both thickness and CSA with the surgery group having a thicker and larger AT. These results seem to support the previously described hypothesis, where scar tissue formation in the conservative group is lower and more organised compared to that of the surgical group. The small sample size used in this secondary analysis cannot allow definitive conclusions to be drawn about these differences and therefore further studies can be helpful to better understand the behaviour of the AT during the healing process.

The relationship between mechanical property changes after ATR and clinical outcomes is not defined. As described in Chapter one, a stiffer AT seems to have advantages from an injury perspective. A tendon with lower stiffness could strain more for the same amount of

stress, increasing the possibility to have tissue damage due to the frictional forces and heat production during the repeated cyclic loading (Maganaris et al., 2008, Farris et al., 2011). However, changes in mechanical properties have not been identified as a risk factor to develop tendon injuries. Only two studies (Li et al., 2018, Ivanac et al., 2021) with a limited sample size reported that the contralateral tendon in patients who have suffered an ATR has reduced stiffness compared to a healthy control group. The authors suggested that the contralateral tendon with lower stiffness may be at a higher risk of future ruptures. They speculate that reduced stiffness could be due to hypoxic degenerative tendinopathy, mucoid degeneration, and tendolipomatosis (Kannus and Jozsa, 1991), which may weaken the tendon, making it less stiff and more prone to rupture. However, these studies do not longitudinally assess the occurrence of ruptures in the contralateral tendon, so a direct cause-and-effect relationship is not yet supported by the literature. As of now, we cannot assert that reduced tendon stiffness is a risk factor for rupture, but if this will be confirmed by further longitudinal studies, having accurate technology that assesses mechanical properties could become even more important in identifying tendons at risk of rupture and in applying preventive strategies.

As reported in literature, some studies suggested that people who underwent surgical treatment have a lower risk of re-rupture (Myhrvold et al., 2022, Ochen et al., 2019) if compared with those who had conservative treatment (risk rate of 0.6-2.3% in the surgical group and 3.9-6.2% in the conservative group) especially if conservative treatment involved immobilising cast treatment and do not consider early mobilization (Ochen et al., 2019, Soroceanu et al., 2012) or functional rehabilitation (Maempel et al., 2022, Nilsson-Helander et al., 2010, Willits et al., 2010, Olsson et al., 2013). The higher stiffness reported in the surgery group in Chapter eight and in other studies (Agres et al., 2015, Bravo-Sanchez et al., 2021, Olsson et al., 2013, Yoshida et al., 2023) could therefore be a protective factor to prevent re-rupture.

The identified risk factors of re-rupture are male sex, younger age, immobilising cast treatment and previous history of tendinopathy (Choi et al., 2024, Maempel et al., 2022). Given the paucity of studies analysing tendon mechanical properties after rupture and the still limited longitudinal observations of these cohorts of patients make it impossible at present to determine whether reduced stiffness could be a risk factor for a re-rupture. Further studies examining these properties could help to understand the correlation between mechanical properties and the risk of re-rupture.

If increased stiffness can be confirmed as a protective factor against ruptures and re-ruptures, rehabilitation protocols aimed at modifying the mechanical properties of tendons could help reduce the risk of re-rupture in the conservative treatment after ATR and serve as a preventive treatment for primary ruptures.

10.3 Overview of the different technologies

The large amount of research produced in recent years on the evaluation of tendon mechanical properties has led to a better understanding of this structure's behaviour both during its physiological function and in pathology. To achieve greater precision in measuring these properties, various technologies have been developed, modified, and improved. This has allowed the phenomenon of changes in tendon mechanical properties to be demonstrated from different perspectives, but at the same time, it has created challenges in interpreting results, as it is difficult to compare results from one technology to another. The aim of this thesis was to evaluate various available technologies for measuring tendon properties under load and to understand their differences.

A special focus was placed on studying the clinimetric properties of the instruments used in the thesis, especially reliability and construct validity. Clinimetrics define the quality of a clinical measurement, not only the quality of the instrument itself but also the quality of the performance of the measurements (Feinstein, 1983). It is essential that a measurement instrument has been tested to define its clinimetric properties before being used in research and clinical practice. In particular, the properties that define the performance of a measurement are the following: validity, reliability, and responsiveness.

Validity refers to the "degree to which an instrument really measures the construct it purports to measure" (Mokkink et al., 2010b). When a gold standard to measure a specific construct is present, criterion validity can be evaluated, but in absence of a gold standard, as in the case of tendon mechanical properties the best option is to evaluate construct validity (Vet, 2011). Construct validity of different measurement instrument has been calculated, the construct under evaluation was that mechanical properties (i.e., stiffness, elasticity, or shear wave speed) must increase when loading was put on the musculotendinous complex by muscle contractions. Since tendon stiffness and tendon displacement are directly related to plantarflexor strength (Magnusson et al., 2003) and ankle angle, (Arampatzis et al., 2007a) mechanical properties values are expected to increase with increasing muscle contraction and with increased plantarflexion.

Together with validity, reliability is another essential requirement for an instrument to become clinically useful. Reliability is the "degree to which the measurement is free from measurement errors" (Mokkink et al., 2010b). Since in health sciences repeating measurements is essential to track a person's health status or to understand their response to a specific treatment, the reliability and measurement error of the instruments gain even greater importance and have been thoroughly evaluated throughout the various chapters.

For an instrument to be implemented in clinical practice, it is important that the measurement can be repeated not only within the same session (test-retest or intra-rater reliability) but also on different days (inter-session reliability) and by different operators (inter-rater reliability). These aspects have been considered throughout the various chapters to allow for a more comprehensive characterization of the different technologies.

As with any measurement instrument, reliability between different operators and across different days requires a significant effort to standardize the experimental setup and ensure precision in replicating the test in the same way. It is not difficult to understand that the more complex the instrument is and the higher the standardization required, the lower its reliability will be between different operators and in sessions spaced over time, where it becomes more challenging to exactly replicate the measure. Factors such as the operator's manual skills and experience must be taken into account when using more complex technologies. All these aspects have been analysed in the subsequent chapters for each technology used.

Another important clinimetric property is responsiveness, defined as 'the ability of an instrument to detect change over time in the construct to be measured' (Mokkink et al., 2010b). To date, there are no longitudinal studies in the literature that allow us to evaluate the responsiveness of these instruments in detecting changes in tendon mechanical properties over time following interventions. If responsiveness will be confirmed in future studies these technologies could be relevant not only in understanding tendon behaviour but also in the longitudinal clinical evaluation of patients following pathologies and rehabilitation interventions.

Chapter One introduced information about the different technologies with some strength and weaknesses derived from the literature available. The other chapters contribute to providing information on various aspects of the available technologies. In this chapter, clinimetrics

properties of the evaluated technologies together with other aspects which facilitate their implementation in the clinical practice have been evaluated, and an overview of the strengths and weaknesses is described in the following sections and summarized in the table (Table 10.1).

Technology	Analysis during load	Clinimetric properties	Availability	Versatility	Clinical applicability	Conclusion
Dynamometry & ultrasonography	+	+/-	-	+/-	-	Able to detect loading changes but with limited clinical applicability.
Strain elastography	+/-	+/-	+/-	+/-	+/-	Moderate capability to detect loading changes and moderate clinical applicability
Shear wave elastography	-	+/-	+	+	+	Not able to detect loading changes but good clinical applicability
Myotonometry	-	+	+	-	+/-	Not able to detect loading changes and moderate clinical applicability
Shear wave tensiometry	+	?*	-*	-	-*	Able to detect loading changes but with limited clinical applicability. (*newly developed technology)

Table 10.1. Overview of strength and weaknesses of technologies for the evaluation of AT mechanical properties. Analysis during load refers to the capability of the technology to evaluate the tendon during load or a functional task. Clinimetric properties refer to what is reported in literature about the reliability and validity of the instrument. Availability refers to the likelihood of finding this technology on the market and to the complexity of the experimental setup. Versatility refers to the possibility to use the technology for the analysis of different tendons. Clinical applicability refers to the possibility to implement this technology in a clinical setting based on the following items: clinimetric properties, availability and versatility without considering the analysis under load.

10.3.1 Ultrasonography and dynamometry

As mentioned in Chapter one, the first technology developed to evaluate the mechanical properties of tendons is based on a combination of dynamometry and ultrasound. This technology has proven to be very precise in quantifying changes in stiffness and allows for the evaluation of high intensity levels of contraction (Seynnes et al., 2015, Theis et al., 2012). Indeed, several physiological studies have been conducted using this technology, providing important data on tendon behaviour under load (Maganaris and Paul, 1999, Maganaris and Paul, 2000, Maganaris and Paul, 2002).

This technology is considered the most suitable to evaluate tendon under load (Khair et al., 2024, Henriksen et al., 2022) and recently an investigation that compares this technology with SWE has been performed to evaluate the correlation between the two technologies (Khair et al., 2024). The results confirm that the ultrasonography and dynamometry was the best technology to detect tendon stiffness but define SWE as an easy-to-use surrogate to evaluate tendon properties but limited to low levels of load. Another evaluation that compared ultrasonography and dynamometry to SE has been performed on the PT and showed no concurrent validity between the two technologies (Henriksen et al., 2022). To date an evaluation that compares results of ultrasonography and dynamometry with other technologies (i.e., myotonometry or shear wave tensiometry) has not been performed.

Even if this technology to date is considered the best available to detect tendon under high load, its clinical applicability is very limited, as it requires complex technology and post-processing of data that is difficult to perform in a clinical setting. Furthermore, the results reported in various studies seem to differ considerably. Values of AT mechanical properties vary from 7 and 37% between the different studies (Seynnes et al., 2015) and differences were

also found in studies observing tendon mechanical properties changes in response to exercises (Seynnes et al., 2015). This inconsistency is mainly attributed to the large number of methodological approaches used by different research groups. Moreover, some authors argue that this is an indirect measure of tendon stiffness since it analyses the entire myotendinous complex rather than evaluating the behaviour of the free tendon (Docking and Cook, 2019).

Despite the multitude of examinations using this technology, reliability has been tested only in a few studies showing very high intra-rater reliability (Henriksen et al., 2022, Arya and Kulig, 2010, Hansen et al., 2006, Schulze et al., 2012). Inter-session and inter-rater reliability have not been tested. A more standardized procedure, considering different biomechanical aspects, as well as inter-rater reliability studies are therefore recommended to increase the external validity of these technology.

In summary, this technology is able to detect tendon loading changes, but its clinical applicability remains very limited due to the complexity of the experimental setup and the unknown inter-rater reliability.

10.3.2 Sonoelastography (strain and shear wave)

The second technology examined was sonoelastography, with its two types: SE and SWE. As highlighted in Chapters two, three, and four, this technology is not as precise in evaluating load changes, especially when tendon is put under load by isometric contraction. Chapter three in particular showed that two different types of SWE were not able to detect loading changes, even at low levels of isometric contraction and in addition, results between the two different ultrasound devices were contradictory. These findings were confirmed by two recent analyses that compared SWE and ultrasonography and dynamometry (Khair et al., 2024,

Mifsud et al., 2023a) and showed that SWE can detect mechanical property changes only at rest and at strains below 1%-10% of the tendon strain. The authors suggest that SWE does not provide additional insights into the mechanical properties of tendons under load-bearing conditions. Even though some ultrasound devices provide SWE values during loading, particular caution should be taken when interpreting these values, as signal saturation may occur. Some devices still compute the values even if they exceed the maximum threshold of the measurement scale (see Appendix 3), ultimately compromising the validity of the measurement.

On the contrary SE using an external reference material (Chapter two) is able to detect changes in AT elasticity during contraction but it's precision to detect small differences is limited. A recent evaluation conducted on the PT suggests that SE does not measure the same mechanical properties as ultrasonography and dynamometry. In fact, there was no evidence of concurrent validity between the two technologies (Henriksen et al., 2022). This is reasonable since SE measures the tendon's response to axial compression from the ultrasound probe by quantifying an elasticity index, whereas ultrasonography and dynamometry evaluate tendon force and deformation, providing stiffness values. Therefore, caution should be taken when comparing results from different technologies.

The clinimetric properties of SWE and SE, especially reliability, has been deeply investigated in Chapter four. Results of the systematic review indicate that SE and SWE show significant variability in reliability across different studies. SE appears to be reliable for the AT but demonstrates poor reliability for the PT. In contrast, SWE seems to be more reliable for the PT than for the AT. The observed lack of inter-rater, inter-session, and inter-machine reliability highlighted in this chapter raises serious concerns regarding the clinical usefulness of these technologies. The less inter-rater, inter-session and especially inter-machine reliability is not

surprising, indeed other studies confirm the difficulty to standardize the procedures given the number of variables involved, such as the pressure applied on the probe, the frequency of the probe used, the placement of the ROI within the tendon, and the ankle positioning during the evaluation (Prado-Costa et al., 2018, Pelea et al., 2024). As mentioned in Chapter four, the majority of the studies evaluating the reliability of SWE and SE lack an appropriate reporting of the methods used, guidelines and checklists for the methodological quality and clearness in the reporting (i.e. QAREL and GRRAS) are rarely used and can limit the interpretation of the results. Another recent systematic review (Mifsud et al., 2023b) aimed to assess clinimetric properties of sonoelastography and confirm the results reported in Chapter four underlining the inconsistency of the results between the different studies and reported the non-superiority of one of the different types of sonoelastography. Further high methodological quality studies are needed to provide meaningful information about the reliability of SWE and SE.

Validity as well as responsiveness has been less investigated. Only one study had a longitudinal design able to evaluate the responsiveness (Gatz et al., 2021) and suggests that an established measurement instrument has yet to be identified as a tool for monitoring treatment. Despite the limited literature currently available on the validity of sonoelastography in populations with tendon pathologies, some authors argue that this technology has the potential to be used in the identification of tendinopathies (Mifsud et al., 2023b) and other musculoskeletal disorders (Chowdhary et al., 2024). Moreover, several evaluations using sonoelastography, particularly SWE, for the quantification of mechanical properties following pathologies (Crawford et al., 2023, Bravo-Sanchez et al., 2021) or interventions (Dirrichs et al., 2016) are present in the literature. In light of these results, it is recommended to use SWE as a tool for the detection of differences between tendon regions and differences between groups of people in cross-sectional studies. The use of SWE for longitudinal interventional studies should

be limited to the detection of small strains (<10%) (Mifsud et al., 2023a) and should be further investigated.

Despite the previously described limitations, a major strength of this technology is its availability; these are ready-to-use instruments that are present on the market and therefore usable in clinical settings. Moreover, the capability of these technologies to evaluate deeper tendon is warranted, especially with SWE, therefore its use is not limited to superficial and more accessible tendons. Given the interest in tendon analysis with sonoelastography, the technological developments have been significant. We cannot exclude the possibility that in the future these technologies, particularly SWE, may be optimised and become even more useful for this type of assessment.

Given the limitations and advantages, it can be concluded that sonoelastography, particularly SWE is a useful technology especially in the detection of tendon mechanical property differences between populations when tested at low level of tendon strain, its availability on the market makes it useful in clinical settings, and future technological implementations could make it even more sensitive in detecting changes in tendons subjected to load. In contrast SE could better detect mechanical properties changes if used with an external reference material but is able to provide only semi-quantitative values by mean of strain ratios of the elastographic colour scale. Its availability is high, but its clinical applicability is moderate given the more complex setup.

10.3.3 Myotonometry

The third technology examined is myotonometry, specifically the commercially available device called MyotonPRO. The transfer of this technology, originally developed for

analysing the mechanical properties of muscles, to tendons seems to be successful, as the existing studies and the results of Chapter five demonstrate good reliability and comparable stiffness values across different studies. The majority of the studies tested the AT in a resting position or in different ankle angles. Few attempts have been made to calculate stiffness during loading conditions. Chapter five showed that MyotonPRO is capable of detecting stiffness at low level isometric contraction, up to a maximum of 5 kg. With higher loads and during a weight bearing positions, myotonometry values were very close to the upper measurement threshold and the calculation of the stiffness could have been influenced by the difficulties in providing a mechanical impulse strong enough to give a proper oscillation wave. These results were supported by another evaluation (Wegener et al., 2024) that showed limitation in detecting stiffness at high load levels. This is not surprising given that MyotonPRO has been developed for the evaluation of muscular structures, the impulse provided by the device is about 0.58 N that could not be sufficient to generate an oscillation wave in harder structure like tendons. Only one study (Pruyn et al., 2016) demonstrated the ability of MyotonPro to detect stiffness at 70% MVC during a sitting calf raise test. This is probably due to the 90° knee angle position during the test that partially reduce the tension on the gastrocnemius and on the AT, indeed stiffness results reported in this study (approx. 465 N/m) are significantly lower that results reported in other studies (> 750 N/m) that evaluate AT in a resting position with a 0° knee flexion (Liu et al., 2018, Finnamore et al., 2019, Tas and Salkin, 2019). However, this study (Pruyn et al., 2016) showed a very low tendon stiffness even in a lying position (approx. 390 N/m) questioning the validity of the results.

Clinimetric properties, especially reliability, has been evaluated in different studies (Sohirad et al., 2017, Liu et al., 2018, Finnamore et al., 2019, Feng et al., 2018, Pruyn et al., 2016, Tas and Salkin, 2019, Muckelt et al., 2022) with very good results, ICC ranging from

0.72 to 0.98, both for intra-rater and inter-rater reliability. Construct validity of myotonometry has been described in Chapter five; stiffness changes between the different contraction intensities and the different positions were detected, demonstrating the construct validity of this device. Positive correlations have been described between myotonometry values and the increase in tendon tension due to changes in ankle angle (Tas and Salkin, 2019), changes in position (weight bearing, non-weight bearing) (Pruyn et al., 2016), and isometric contractions of increasing intensity, supporting the construct validity of this instrument.

Another study (Feng et al., 2018) that evaluated the correlation between myotonometry and SWE found that stiffness values measured with MyotonPRO were related to the Young's modulus measured with SWE. The strong association between the two technologies indicates that there is convergent validity between the measurements, even though they assess different mechanical properties (stiffness vs. Young's modulus) and the impulse is generated with different characteristics; one mechanical, produced by the MyotonPRO device, and one acoustic, generated by the propagation of the shear wave in SWE. If these results are confirmed by further studies, it would be possible to generalize the findings from both technologies. A direct comparison between dynamic stiffness measured with MyotonPRO and stiffness measured with ultrasonography and dynamometry has never been conducted. Understanding whether these parameters are correlated could represent a further step in the validation of this device.

As for SWE, MyotonPRO has the advantage to be ready to use and available on the market and therefore usable in the clinical practice. Moreover, it is relatively inexpensive and portable, allowing for use in various settings, not only within clinics but also in field applications. It has a great versatility, making it possible to assess different portions of the same tendon or different tendons in a very short amount of time. In contrast to ultrasound-based

techniques like SWE or SE, it is very easy to use, does not require any operator experience, and does not need complex machine settings or post-processing of the data. However, its limited ability to assess tendons under load and the shallow penetration of its impulse restrict its applicability to superficial tendons and to conditions of relaxation.

In conclusion, this instrument offers great versatility and excellent clinical applicability. Its reliability and construct validity have been confirmed in numerous studies. However, given the nature of the impulse provided, it does not allow for the analysis of tendons under load and is limited to a small number of superficial tendons.

10.3.4 Shear wave tensiometry

The last technology evaluated was shear wave tensiometry, which has been recently developed and implemented in various fields, including gait analysis (Keuler et al., 2019), running (Reiter et al., 2024a), and tendons subjected to pathological processes.

Its advantage lies in its high sensitivity to changes in tendon load, allowing for the analysis of mechanical properties even at high levels of contraction. As shown in Chapter six eight and nine, shear wave tensiometry is not only able to detect differences between tendon after ATR and the healthy contralateral side but also to precisely discriminate the tendon loading during isometric contraction of increasing intensities. Indeed, several examinations confirm that there is a linear relationship between the squared wave speed and the increase in ankle torque reinforcing the consistency of these measure based on a tensioned beam model (Martin et al., 2018, Keuler et al., 2019). Given its high sensitivity in detecting changes during load, and the individual behaviour of tendons between participants found in Chapter six eight and nine, this technology could allow a more accurate investigation of this variability to

understand whether it is normal, as it is a phenomenon also present in healthy participants, or if it could be indicative of a pathological process or even suggest which tendons are more prone to rupture or injury. Together with ultrasonography and dynamometry this is the first technology that is able to detect high level of isometric contractions, up to MVC, with consistent results between studies (Martin et al., 2018, Keuler et al., 2019, Ebrahimi et al., 2020).

Validation studies of this technology have reported similar transient motion of different tissues as the shear wave passes, assuming that skin and subcutaneous tissue motion does not affect the measurement of tendon shear wave velocity (Martin et al., 2018. Salman and Sabra, 2015). However, we cannot exclude that scar tissue immediately under the accelerometers may affect the accuracy of the analysis. Given that this technology is newly developed and used by a small number of research groups, the clinimetric properties have not been tested. The reliability of shear wave tensiometry has been investigated only in Chapter six of this thesis on healthy participants and only intra-rater (intra-session and inter-session) was examined. The results suggest that shear wave tensiometry is a reliable instrument and can be used to detect tendon loading at different ankle torque both within the same session and in different sessions. More research is needed to evaluate inter-rater reliability since the positioning of accelerometers and the generation of the shear wave by a manual impulse could probably introduce some measurement errors if different raters perform the measurement.

Construct validity has been evaluated by determining the relationship between shear wave speed and ankle torque and different studies (Martin et al., 2018, Keuler et al., 2019, Acuna et al., 2019) suggest a linear relationship between these parameters with an increase of wave speed while increasing the ankle torque. To date, comparison between shear wave tensiometry and other technologies has not been performed therefore we cannot establish if a relationship between shear wave speed and tendon strain measured with ultrasonography and

dynamometry or Young's modulus measured with SWE exist. Furthermore, there are no studies that evaluate changes following pathological processes or interventions, so we cannot comment on the responsiveness.

In terms of clinical applicability, unfortunately the shear wave tensiometer it is still a prototype used only for research purposes by a few groups, and as a result, there is no version available on the market. Further technological developments will be necessary to make the tool easier to use and available for clinical settings. The technology behind this device is very simple, but it needs to be refined to become more applicable in different contexts. Moreover, to date, studies are limited to superficial tendon that can be easily approached with the accelerometers on the skin above the tendon. Deeper tendon, where multiple tissues layers are present between the skin and the target tendon are probably not suitable for this type of analysis given that the impulse provided and therefore the propagation of the shear wave cannot be performed without the direct access of the target structure.

With the aim of reducing the complexity of measurements and making the tool applicable to different structures, some technological developments have been made, including the possibility of using a single sensor to evaluate the shear wave speed (Schmitz et al., 2023) and the use of a Kalman filter approach to improve accuracy and reduce the error due to accelerometer positioning (Schmitz et al., 2022).

In conclusion, shear wave tensiometry is a promising technology able to detect tendon loading changes even at high level of isometric contractions, in healthy participants and in people after ATR. Further research on the clinimetric properties of this tool is necessary to better understand its clinical applicability and the possibility of using it outside of the research context.

10.4 Quality of research in the thesis

To assess the quality of the research carried out in this thesis, several risk of bias tools and reporting guidelines were employed to ensure meaningful conclusions could be drawn.

For the cross-sectional studies in Chapter two, three, eight and nine, the STROBE guidelines (von Elm et al., 2007) were used as an evaluation framework. The systematic review in Chapter four was registered with PROSPERO and followed the PRISMA guidelines (Moher et al., 2009). The PICOS framework was applied to establish the eligibility criteria and organise the review questions. A thorough search strategy was implemented across multiple databases, with two independent reviewers conducting the study selection and data extraction. Additionally, the reasons for study exclusions and the number of full-text studies evaluated were documented. Two quality assessment checklists were used to assess the risk of bias of the selected study. The GRRAS (Kottner et al., 2011) was used to assess the quality of the reporting whereas the QAREL (Lucas et al., 2010) evaluated the quality of the design and conduct (internal quality) of the studies.

Additionally, in Chapters five and six where reliability of the tools was assessed the GRRAS checklist was used as a guideline for reporting the results and ICC values were reported following the guidelines of selecting and reporting ICC for reliability research (Koo and Li, 2016).

As suggested by the GRRAS checklist and by other authors (Donner and Eliasziw, 1992, Roberts and McNamee, 1998), ICC values in the reliability studies were always described together with CI as a measure of statistical uncertainty to better describe the range of values that are considered to be plausible for a target population. Moreover, both relative, using ICC, and absolute reliability using SEM and MDC were reported together. The use of a combination

of both relative and absolute reliability has been suggested to have an index of the variance of the measures between subjects but also the true error express in the same units as the measurements of interest (Weir, 2005, Bruton et al., 2000).

10.5 Overall strengths and limitations

All the studies presented in the thesis have provided a general overview of the technologies available for assessing the mechanical properties of the AT. The use of a common rationale across all studies, namely evaluating how the different technologies detect changes in the mechanical properties of the AT in response to load variations, allowed to compare the results of the different studies and understanding which tool was the most useful for this purpose. Particular attention was given to the clinimetric properties, specifically reliability and construct validity, which were deeply evaluated in the various chapters. Additionally, a new promising technology was developed, used to evaluate the clinimetric properties and was implemented in a clinical setting to evaluate participants after ATR treated surgically and conservatively. Finally, as mentioned in the previous section, the methodological quality of the thesis was evaluated through the use of validated checklists for the reporting and the screening of the internal validity.

There are some limitations that need to be acknowledged. Each of the studies in the thesis present with some limitations and has been discussed in the different chapters. Reliability studies presented in Chapter five and six were performed in healthy participants therefore a generalization of these results to people with tendon disease may not be done. As AT was the only tendon evaluated in this thesis, transferring these results to other tendons with different morphology and characteristics may not be possible. The systematic review in Chapter five

focused solely on analyzing the reliability values of the sonoelastography technique. An evaluation of other clinimetric properties, such as validity and responsiveness, would have provided a clearer understanding of the characteristics of these measurements. Chapter six explores only intra-operator reliability; future studies will be needed to understand whether this technology is also reliable when used by different operators. Chapter seven presents a pilot laboratory study with a small sample size of healthy participants, making it uncertain whether these results will be confirmed in a larger sample. Chapter eight and nine which evaluate tendon mechanical properties after ATR did not evaluate tendon resting length following rupture. A greater tendon length has been showed after surgery (Agres et al., 2015, Khair et al., 2022, Zellers et al., 2019) and a lengthening of the tendon cannot be excluded even in ATR treated conservatively. We could therefore not establish if tendon resting length influences shear wave speed values.

10.6 Clinical implication and future research

This thesis has laid the groundwork for a better understanding of the technologies currently used for the evaluation of tendon mechanical properties. Considering the limitations and advantages of these technologies, there is a need for future longitudinal studies to assess the responsiveness of these tools in detecting changes in mechanical properties and whether these can be linked to clinical changes.

If the relationship between clinical features and mechanical properties will be confirmed by future research evaluating the effect of rehabilitation protocols on tendon mechanical properties in people with tendon disorders, it could be helpful to detect which type of exercise can target and modify tendon mechanical properties. Moreover, the association between altered

mechanical properties and risk of ATR is not yet established; longitudinal studies using accurate technology could help to clarify this aspect.

Shear wave tensiometry shows the potential to be an instrument suitable for the evaluation of tendon under load, and future technological development could increase its clinical applicability by simplifying the device and the post processing analysis. Finally, to better characterise the mechanical properties of AT disorders, an understanding of normal values in the general population is required, and therefore normative data studies that take into account gender, age, and physical activity of individuals are expected.

10.7 Conclusion

This thesis showed that each technology used in the assessment of tendon mechanical properties presents advantages and disadvantages, and to date, no technology has shown superiority over another. The choice of the technology used must be made based on the research objective. Given the overview provided in this thesis, a quicker assessment of the most pertinent technology for the purpose of the investigation can be carried out.

The implementation of shear wave tensiometry in clinical studies has been presented, and the results showed that shear wave tensiometry can be used to detect tendon mechanical property changes after ATR. The use of this type of technology, which is able to detect loading changes even at higher load levels, sets the basis for a more extensive evaluation of tendon mechanical properties during load.

Although there is currently no clear relationship between changes in tendon mechanical properties and clinical changes (i.e., pain and disability) in people with tendon disease, this thesis emphasizes the importance of considering this aspect to gain a better understanding of

tendon behaviour under load. With the development of increasingly precise technologies, including shear wave tensiometry, future studies could confirm this relationship. Having a tool capable of accurately tracking mechanical properties during the clinical course could potentially provide us with more information about the loading status and possibly detect adaptation or maladaptation resulting from exercises or pathology.

Clinicians would benefit from technologies that track mechanical property changes during or after their treatments, enabling the customization of interventions based on objective data, thus optimising them for each individual case.

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APPENDICES

Appendix 1 – Schneebeli et al., 2019

Appendix 2 – Schneebeli et al., 2021

Appendix 3 – SE and SWE images example of saturation.

Appendix 4 – Schneebeli et al., 2020a

Appendix 5 – PRISMA Checklist

Appendix 6 – Schneebeli et al., 2020b

Appendix 7 – Schneebeli et al., 2022

Appendix 8 – Schneebeli et al., 2023

Appendix 9 – Ethical Review, Consent Forms and Patient Information Sheets for Chapter Two

Appendix 10 – Ethical Review, Consent Forms and Patient Information Sheets for Chapter Three

Appendix 11 – Ethical Review, Consent Forms and Patient Information Sheets for Chapter Five

Appendix 12 – Ethical Review, Consent Forms and Patient Information Sheets for Chapter Six

Appendix 13 – Ethical Review, Consent Forms and Patient Information Sheets for Chapter Eight

Appendix 14 – Ethical Review, Consent Forms and Patient Information Sheets for Chapter Nine

Appendix 15 – Achilles Tendon Total Rupture Score (ATRS)

Appendix 16 – Tegner Activity Level Scale

Appendix 17 – Poster presented at the IFOMPT conference 2024

Appendix 1 – Schneebeli et al., 2019

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A novel application of strain sonoelastography can detect changes in Achilles tendon elasticity during isometric contractions of increasing intensity

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Abstract

Background: Mechanical and morphological properties of the Achilles tendon are altered in disease and in response to changes in mechanical loading. In the last few years different ultrasound based technologies have been used to detect tendon mechanical properties changes mainly in resting condition. Therefore the aim of this study was to evaluate if strain sonoelastography can identify changes in Achilles tendon elasticity during isometric contractions of increasing intensity.

Methods: This cross-sectional study enrolled 37 healthy volunteers (19 women) with mean (±SD) age of 27.1 (±7.0) years between January and June 2017. Strain sonoelastography images of the Achilles tendon were acquired during an isometric ramp force (0 kg, 0.5 kg, 1 kg, 2 kg, 5 kg and, 10 kg). An external reference material was used to provide a comparison between the examined tissue and a material of constant elasticity. Friedman test with post hoc pairwise comparison were used to determine the correlation between the difference contraction levels.

Results: The median and interquartile range (IQR) values for the strain ratio were 1.61 (1.5–2.9) in a relaxed state and 1.30 (1.07–2.02), 1.00 (0.76–1.66), 0.81 (0.70–1.19), 0.47 (0.39–0.73) and 0.33 (0.28–0.40) for 0.5 kg, 1 kg, 2 kg, 5 kg and 10 kg, respectively revealing increased tendon hardness with increasing contraction intensities. Friedman test revealed significant differences ($p < 0.05$) in the strain ratio between all contractions except between 0.5 kg – 1 kg ($p = 0.41$); 1 kg – 2 kg ($p = 0.12$) and 5 kg – 10 kg ($p = 0.12$).

Conclusion: Strain sonoelastography can detect changes in Achilles tendon elasticity between different contraction intensities. The results provide an original force-elasticity curve for the Achilles tendon in a healthy, asymptomatic population.

Trial registration: The study was approved by the Ethics Committee of Canton Ticino.

Keywords: Strain sonoelastography, Achilles tendon, Elasticity

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Background

The Achilles tendon is the strongest tendon in the body and constitutes a dynamic link between the triceps surae and the calcanous bone [1, 2]. A high mechanical load is applied to the Achilles-gastrocnemius complex and tendon stiffness can increase in response to chronic load [3]. Changes in glycosaminoglycan content, reduction of collagen cross-linking content and alignment of collagen fibers are factors that may alter tendon elasticity [3].

Overuse injuries of the Achilles tendon can occur with excessive loading during physical exercise [4]. Repetitive overload and subsequent microtrauma can lead to inflammation of the tendon sheath or degeneration of the tendon body [5]. The mechanical and morphological properties of the Achilles tendon are altered in disease and in response to changes in mechanical loading, including a reduction in tendon stiffness and a softening of the tendon measured with sonoelastography in individuals with chronic tendinopathy [6, 7].

A healthy Achilles tendon with intact mechanical and morphological properties is expected to become stiffer and harder with increased tensile load during isometric contraction. [8, 9] As shown by Magnusson et al. [10], both deformation and strain of a healthy Achilles tendon increase with an increase in tendon isometric force. Similarly, Lersch et al. [11] demonstrated increased strain of the Achilles tendon when the tendon was subjected to an increased load. Wren et al. [12] showed an increased Young's modulus in a similar in vitro investigation using a servo-hydraulic materials testing machine, and although in vivo and in vitro results are not directly comparable, the Achilles tendon seems to behave similarly.

Shear wave sonoelastography is based on acoustic radiation force impulses through tissue to obtain the elastic modulus (Young modulus, kPa) and is typically employed to measure Achilles tendon elasticity. An ultrasound pulse produces a directional shear wave within the tissues, and the propagation velocity of this wave is calculated using an ultrafast ultrasound tracking technique [13]. However, given that the upper limit of 800 kPa of Young modulus is often reached in the Achilles tendon when the ankle is near 0° of plantar flexion, this measurement technique is not suitable for the evaluation of the tendon in a functional position (near 0° plantar flexion), during usual movement or with additional load [14]. Moreover, signal saturation occurs when the Achilles tendon approaches the 0° plantar flexion or a dorsiflexed position and leads to an underestimation of the shear wave speed [15].

Strain sonoelastography is another ultrasound-based technique that enables the elasticity of musculoskeletal structures to be evaluated [16–18]. Tissue compression with an ultrasound probe is applied to a surface producing a displacement within the tissue. The displacement, which is less pronounced in harder than in softer materials, is calculated by comparing B-mode image pairs before and after compression [19]. A novel method using strain sonoelastography and calculation of a strain ratio was recently developed and provides a semi-quantitative evaluation of the tendon based on the elastography color scale [8]. Combined with an external reference material, this approach can identify changes between a contracted and relaxed state [8], however the accuracy of this novel method to detect small changes in tendon mechanical properties due to load, needs further investigation. The use of an external reference material with known elasticity properties allows the computation of the strain ratio between the tendon color scale and the external material which is not affected by changes during contraction. This method has established reliability [8, 20].

The added value of this methods is the combination of a measure of elasticity, provided by the transverse compression force of the probe, and the progressive longitudinal mechanical load given by the contraction of the triceps surae muscle.

A more comprehensive analysis of the Achilles tendon with evaluation of the tendon under load is warranted as this approach could provide a clearer indication about the functional impairment of tendon structure. Therefore, together with clinical history and standard imaging this technology could ultimately lead to an enhancement of the diagnosis and management of tendinopathy.

Thus, the aim of this study was to evaluate if strain sonoelastography using the strain ratio, can accurately detect changes in Achilles tendon elasticity during isometric contractions of varying intensity in healthy volunteers.

We hypothesized that differences between the selected contraction levels could be identified by a change in strain ratio of the sonoelastography color scale.

Methods

Study population

Thirty-seven healthy participants (19 women) were prospectively enrolled in the study between January to June 2017. The mean (±SD) age, height and weight were 27.1 (±7.0) years, 172.2 (±9.8) cm and 67.5 (±13.2) kg, respectively.

Inclusion criteria for the selection of the sample were: no history of tendon and/or foot injury or surgery; any painful episodes in the lower limb in the last year. Exclusion criteria were: history of connective tissue, endocrine or metabolic diseases; systemic inflammatory disorder; spondyloarthropathy, rheumatoidarthritis, or hypercholesterolemia. Furthermore, those usually taking estrogen or steroid treatment were excluded.

The study was approved by the Ethics Committee of Canton Ticino, conducted according to the Declaration of Helsinki and written informed consent forms were signed by participants. The report of this study adheres

to STROBE (Strengthening The Reporting of Observational Studies in Epidemiology) guidelines.

Mean and standard deviation values of relaxed and contracted strain ratios from a previous study [8] using the same experimental setup were used to calculate the minimal sample size necessary to ensure a statistical power of 90% at the 5% significance level for a two-tailed hypothesis test. The Cohen's d effect size has been calculated using the pooled standard deviation of the previous study [8]. Effect size was very large (d = 1.69). The calculation, performed with STATA 14 (College Station, TX, USA), showed that the minimal sample size of $n = 32$ was required.

Ultrasound and sonoelastography

A MyLab Class C ultrasound device (Esaote, Genoa, Italy) with a linear probe (3–13 MHz) and elastography software were used to perform the measurements. The Achilles tendon was visualized through a custom made external material (Zerdine® CIRS, Norfolk, VA, USA). The properties of the reference material were tested by the manufacturer, the elasticity was 102 kPa, speed of sound was 1580 m/s, and the attenuation coefficient was 0.5 dB/cm/MHz. The external reference material was utilized to guarantee a comparison between the Achilles tendon and a material with known elasticity (102 kPa). Furthermore, the reference material was used as stand-off pads to create a steady contact between the transducer and the skin and to enhance the stability of the sonographer's hand [21].

Light and rhythmic perpendicular compression was applied by the operator with the ultrasound probe on the reference material. A quality indicator graph on a screen in front of the operator was controlled to regulate the amount of the compression across condition and participants. Compression–relaxation cycles were provided for 5 s (approximately 100 frames) for each acquisition, during this time the sonoelastogram remained as stable as possible.

Dynamometry

The torque of the ankle was assessed using a dynamometer connected to a force sensor that operated linearly in the range between 0 and 100 N (Mod. TF2/S; CCT Transducers, Turin, Italy). The force sensor was attached to a wooden board connected to a hinge that allowed natural dorsiflexion and plantar flexion of the ankle (Fig. 1). The board was fixed in order to permit isometric contractions only at a fixed angle of 0° dorsiflexion. The force measured by the force sensor was proportional to the torque exerted at the ankle level. Force signals were amplified using MISO-II (OT Bioelettronica, Turin, Italy; bandwidth 0–80 Hz) and presented to the participants as a real time visual feedback (60 Hz refresh rate) on a PC monitor positioned 50 cm in front of the subjects.

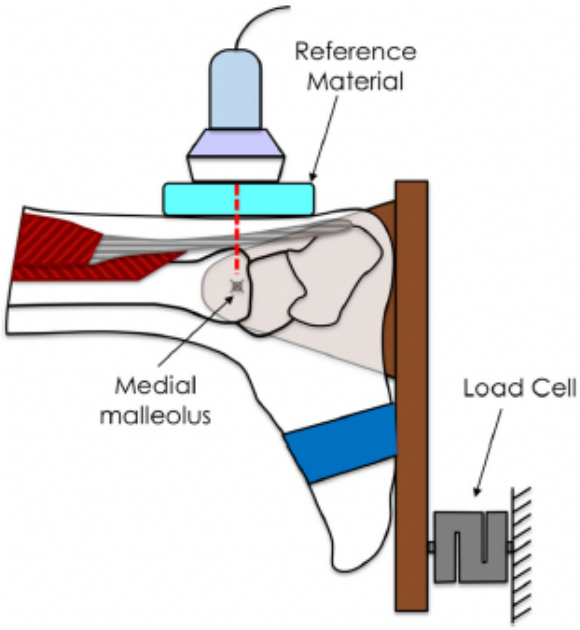


Fig. 1 Schematic of the experimental setup. The foot was securely attached to a dynamometer with a wooden board at a fixed angle of 0° of dorsiflexion. The force measured by the load cell was proportional to the torque exerted at the ankle level. The ultrasound probe was placed in a longitudinal scan at the level of the medial malleolus

Procedure

Participants were asked to lie in a prone position with the foot tightly secured within the dynamometer with the ankle in a neutral position (0° of plantarflexion). Prior to the recordings, the participants practiced the contraction with the instruction to "push on the board as if you were pushing onto the top of your toes") and a contraction of 10 kg (maximum strength required) was performed to verify that the heel remained in contact with the dynamometer and to familiarize the participant with the visual feedback. Heel movement was prevented during the contraction by firmly securing the foot in the dynamometer with two belts over foot and ankle.

Both the left and right Achilles tendon of each participant were evaluated during isometric plantar flexion under increasing contraction intensities (0 kg, 0.5 kg, 1 kg, 2 kg, 5 kg and, 10 kg) performed in a randomised order. Strain sonoelastography of the Achilles tendon, was performed in a longitudinal scan using the Elasto-Dual software (Fig. 3). The external reference material was included in the image and the measurement were performed at the level of the medial malleolus applying an established and reliable method [8].

To guarantee the evaluation of the same tendon part under the different conditions, a reference point on the medial malleolus was drawn and the ultrasound transducer was aligned with the point each time. All the

ultrasound procedures were conducted by the same, well trained operator, with 8 years of ultrasound and elastography experience.

The colour scale of the elastograms ranged from red, showing soft tissue, to blue showing hard tissue, whereas green to yellow indicating medium tissue elasticity. The elastograms were automatically constructed maintaining the same ideal settings during the entire study, as recommended by Havre et al. [22] in a previous study.

Image analysis

The analysis of the 5 s ultrasound clip was leaded using a customized MATLAB® software (MathWorks, Natick, MA, USA). Two different regions of interest (ROI) were drawn on the sonoelastographic images, including the reference material and the Achilles tendon (Fig. 3). The range between soft and hard (from red to blue) was divided into 256 levels (0–255) according to the depth of colour of the sonoelastographic image where blue corresponds to 0 and red to 255. The frames of the entire clip were averaged to extract a single image where the colour distribution was calculated. The median and interquartile range of colours was computed for each acquisition.

Strain ratios were calculated between the Achilles tendon median range of colours and the external reference material median range of colours, comparisons between the different contraction levels were computed for each tendon.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 22 (SPSS, Chicago, IL, USA) was used to perform statistical analysis. Descriptive statistics (mean ± SD) were used to describe the characteristics of the sample. Shapiro-Wilk test was used to evaluate if the data were normally distributed. Non-parametric, independent samples, Mann-Whitney test was then used to assess whether there were significant differences in Achilles tendon elasticity between men and women and between the right and left Achilles tendon.

Since the data were not normally distributed, Friedman test with post hoc pairwise comparison (Wilcoxon signed-rang test) were used to determine the correlation between elasticity measured at different contraction levels. Bonferroni correction was applied and statistical significance was set to $\alpha = 0.05$.

Data are presented as median and interquartile range (IQR).

Results

No significant difference in Achilles tendon strain ratios was observed between men median (IQR) 1.31 (0.96–1.81) and women 2.00 (1.19–2.81) ($p = 0.6$) or between the left 1.48 (1.13–2.06) and right Achilles tendon 1.71 (0.94–2.91) ($p = 0.5$), therefore the data were pooled and further analysed as an entire sample.

The median (IQR) values for the strain ratio were 1.61 (1.5–2.9) in a relaxed state and 1.30 (1.07–2.02), 1.00 (0.76–1.66), 0.81 (0.70–1.19), 0.47 (0.39–0.73) and 0.33 (0.28–0.40) for 0.5 kg, 1 kg, 2 kg, 5 kg and 10 kg, respectively. Friedman test for related samples showed significant ($p < 0.01$) differences between all contraction levels except for 0.5 kg – 1 kg ($p = 0.41$); 1 kg – 2 kg ($p = 0.12$) and 5 kg – 10 kg ($p = 0.12$) (Fig. 2). Detailed pairwise comparison for all the contraction levels are presented in Table 1.

Discussion

This is the first study to evaluate changes in Achilles tendon elasticity using strain sonoelastography during progressive increases in contraction force. The results provide an original force-elasticity curve for the Achilles tendon in a healthy, asymptomatic population (Fig. 2).

This study confirms that strain sonoelastography can detect changes in Achilles tendon elasticity between a relaxed state and all the examined contraction levels; the Achilles tendon progressively become harder across the different contraction levels, and this increment was seen as a reduction of the strain ratio as previously reported in other studies [8, 9]. A previous study [8] with a similar experimental setup showed large variability of the Achilles tendon strain ratio between healthy subjects when measured in the resting state. This variability, similarly to our study, is reduced when load is put on the tendon (see Fig. 2). The large variability seen between participants when the tendon is measured in the relaxed state is likely related to variation in physical activity levels, age and individual anatomical differences. Although tendon elasticity changed across contraction intensities, the contraction levels with similar intensity (0.5 kg – 1 kg ($p = 0.41$); 1 kg – 2 kg ($p = 0.12$) and 5 kg – 10 kg ($p = 0.12$)) revealed similar measures of elasticity thus likely the difference in load was insufficient to change tendon mechanical properties to a significant extent.

Previous studies [23–26] used the Kager Fat pad (KFP) as a medium to calculate the strain ratio in the evaluation of Achilles tendon elasticity. The results showed moderate to good reliability [24] and the authors suggested the use of strain elastography in the evaluation of the Achilles tendon following surgery [23]. However, caution should be taken when measuring strain ratio with a biological tissue such as KFP since other tissues could encounter changes in elasticity due to pathology, recovery or to different measurement conditions. The mechanical properties of the KFP changes following the hardening of the Achilles tendon and this change is not always linear, likely because of anatomical differences between subjects e.g. longer soleus muscle, more connective tissue, or due to the compression of the Achilles

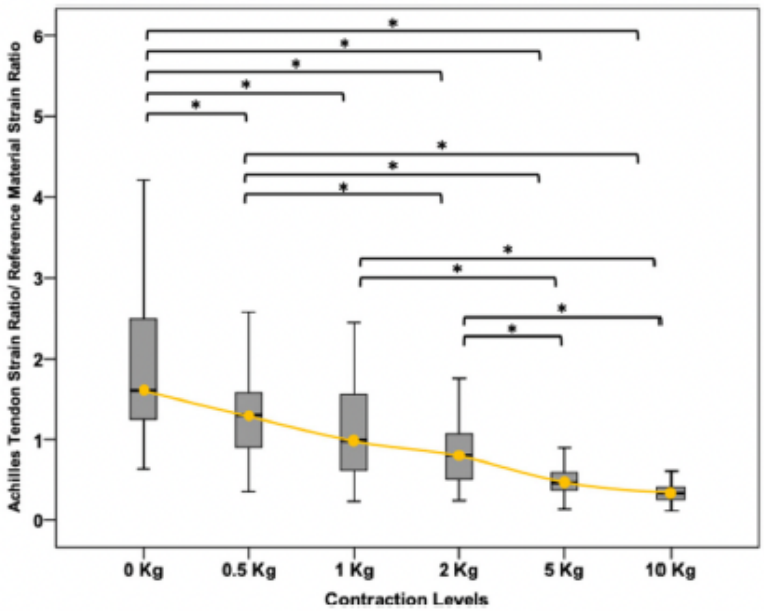


Fig. 2 Force-elasticity curve. Box plot showing the median and interquartile range of values of the entire sample during the different contraction levels. The orange line represent the force-elasticity curve. * $p < 0.01$; statistical significant difference between the different contraction levels

tendon on the underlying tissues. In the current study, we used an external material with a constant elasticity. Figure 3 shows an apparent softening of the reference material as the tendon became harder. The sonoelatography algorithm implemented in the ultrasound machine display the elasticity of the tendon with an "auto-scale" color range. The softest and the hardest structure visible in each of the ROI analyzed are displayed in red and blue respectively. For this reason, we can observe a progressive color change of the reference material (green at 0 kg, red at 10 kg) (see Fig. 3) because the tendon progressively becomes the harder structure within the ROI. However, strain ratios (i.e. ratios between the median colors) have been used as an index of elasticity which is not affected by the "auto--scale" color range.

The findings of the present study are supported by other investigations which measured strain of the Achilles tendon using a strain tracking procedure during maximal voluntary contractions [10, 27]. However, in these studies tendon displacement and tendon strain were measured using the aponeurosis-tendon complex while in the present study we have characterized changes in tendon elasticity with a direct measure of the free tendon. Other ultrasound-based techniques with direct measures of the tendon (i.e. shear wave elastography) have measured an increase of Young modulus (kPa) while the tendon is tensioned by changing the degree of ankle flexion [14, 15]. However in those studies it was suggested that the use of shear wave elastography should be limited to the relaxed tendon to avoid saturation of the signal.

Another promising 2D ultrasound technology, based on a speckle tracking algorithm [28] has been proposed. A non-uniform regional strain behavior of the different layers of the Achilles tendon has been observed. However given the different nature of strain sonoelastography measurement compared to the speckle tracking technique, the results cannot be directly compared.

Future studies which apply strain sonoelastography to evaluate the free tendon in different ankle positions or under different conditions (i.e. varying contraction intensity; functional tasks) are now warranted to better

Table 1 Pairwise comparison for the different contraction levels. Statistical significant results ($p < 0.01$) are represented in bold

Contraction levels (Kg)	Pairwise comparison	Contraction levels (Kg)	Pairwise comparison	Contraction levels (Kg)	Pairwise comparison	Contraction levels (Kg)	Pairwise comparison	Contraction levels (Kg)	Pairwise comparison
0–0.5	**$p < 0.01$**	0.5–1	$p = 0.41$	1–2	$p = 0.12$	2–5	**$p < 0.01$**	5–10	$p = 0.12$
0–1	**$p < 0.01$**	0.5–2	**$p < 0.01$**	1–5	**$p < 0.01$**	2–10	**$p < 0.01$**	–	–
0–2	**$p < 0.01$**	0.5–5	**$p < 0.01$**	1–10	**$p < 0.01$**	–	–	–	–
0–5	**$p < 0.01$**	0.5–10	**$p < 0.01$**	–	–	–	–	–	–
0–10	**$p < 0.01$**	–	–	–	–	–	–	–	–

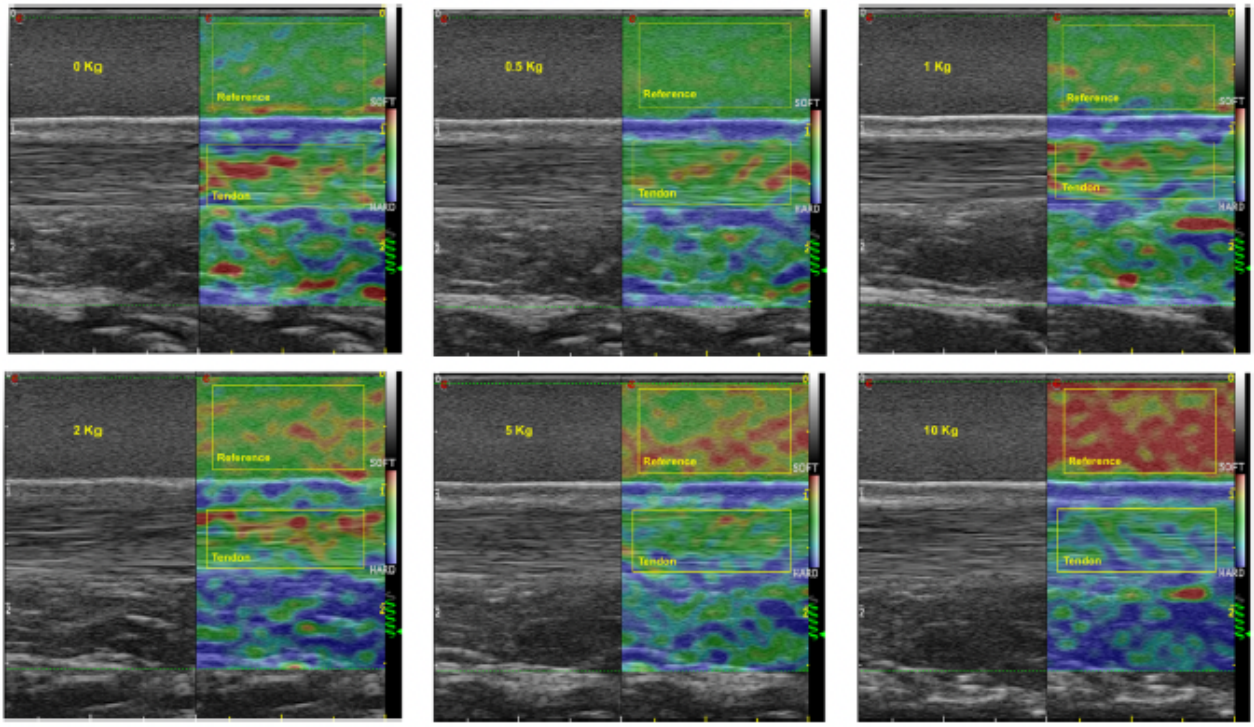


Fig. 3 Achilles tendon sonoelastography during an isometric ramp contraction. Elasto-Dual images of the Achilles tendon during the isometric ramp contraction; the regions of interest (i.e., yellow boxes) define the two tissues examined for the calculation of the strain ratio. The six different boxes represent the different contraction levels

understand and characterize the behavior of the Achilles tendon. Moreover, the addition strain sonoelastography measures of the Achilles tendon during loaded contractions may increase diagnostic capability in Achilles tendinopathy and future research is needed to explore this.

Strain sonoelastography requires manual compression and therefore variation in the level of pressure of the transducer on the skin may affect the results. To reduce such variability, both very high and low pressure was avoided as proposed by Itoh et al. [29] and visual feedback of the applied pressure was provided so that it could be constantly controlled by the experienced operator.

Furthermore, strain ratio employed in this study offers a measure of elasticity provided by a transverse compression force of the ultrasound probe on the tendon structure. Further research is needed to establish the relationship between strain ratio and tendon longitudinal mechanical properties.

Conclusions

Strain sonoelastography can detect changes in Achilles tendon elasticity between different contraction intensities. It was observed that tendon elasticity was not modified between some contraction intensities. The reduction of the strain ratio between the tendon and the reference material indicates a constant increase of tendon elasticity during contractions of increasing intensity and provides an original force-elasticity curve. Future studies, using strain sonoelastography with an external reference material, are now warranted to explore potential changes in Achilles tendon elasticity in those with tendinopathy.

Abbreviations

KFP: Kager Fat Pad; ROI: Region of Interest

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Availability of data and materials

All data generated during this study are included in this published article. Ultrasound images of the entire sample of the current study are available from the corresponding author on reasonable request.

Authors' contributions

AS, FDG, MB, DF conceived the study and contributed to the design. AS, acquired the ultrasound images. AS, CC, RC recruited the participants, performed the data analysis, helped with the interpretation of the results. All authors contributed to preparation and approval of the final manuscript.

Ethics approval and consent to participate
The study was approved by the Ethics Committee of Canton Ticino, conducted according to the Declaration of Helsinki and written informed consent forms were signed by participants.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Insights into Imaging

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Shear wave and strain sonoelastography for the evaluation of the Achilles tendon during isometric contractions

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Abstract

Objectives: Changes in mechanical loading as well as pathology can modify the Achilles tendon mechanical properties and therefore detection of these changes is relevant for the diagnosis and management of Achilles tendinopathy. The aim of this study was to evaluate strain and shear wave sonoelastography for their ability to detect changes in the Achilles tendon mechanical properties during a series of isometric contractions.

Methods: Longitudinal sonoelastography images of the Achilles tendon were acquired from 20 healthy participants using four different ultrasound devices; two implementing strain sonoelastography technology (SE1, SE2) and two, shear wave elastography technology (SWE1, SWE2).

Results: SE1 measured a decreasing strain ratio (tendon become harder) during the different contraction levels from 1.51 (0.92) to 0.33 (0.16) whereas SE2 mesaured a decreasing strain ratio from 1.08 (0.76) to 0.50 (0.32). SWE1 measured decreasing tendon stiffness during contractions of increasing intensity from 33.40 (19.61) to 16.19 (2.68) whereas SWE2 revealed increasing tendon stiffness between the first two contraction levels from 428.65 (131.5) kPa to 487.9 (121.5) kPa followed by decreasing stiffness for the higher contraction levels from 459.35 (113.48) kPa to 293.5 (91.18) kPa.

Conclusions: Strain elastography used with a reference material was able to detect elasticity changes between the different contraction levels whereas shear wave elastography was less able to detect changes in Achilles tendon stiffness when under load. Inconsistent results between the two technologies should be further investigated.

Keywords: Shear wave elastography, Strain elastography, Achilles tendon

Key points

- Achilles tendon disorders are common both in athletes and the general population.
- SWE and SE are ready to use tools to evaluate musculoskeletal structures.
- SE was able to detect elasticity changes between the different contraction levels.
- Inconsistency between SWE and SE should be further investigated.

Background

Achilles tendon (AT) is the thickest tendon in the human body; it connects the triceps surae to the calcaneus bone and produces plantar flexion of the ankle. Injuries of the AT are often related to excessive loading during physical exercise [1]. Moreover, several

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mechanical and morphological changes of the AT occur with aging and in individuals with chronic tendinopathy [2, 3].

Ultrasonography evaluation is usually the first-line imaging examination for patients with suspected Achilles tendinopathy since it is widely available, has a relatively low cost and provides a real-time assessment [4]. Nevertheless, conventional ultrasound images can only provide information about the anatomical and morphological features of the AT and cannot assess tendon mechanical properties. More recently, AT stiffness and elasticity have been evaluated with different ultrasound-based technologies, in particular shear wave sonoelastography (SWE) and strain sonoelastography (SE) [5–10].

SE provides qualitative data of tissue elasticity on colour elastograms, exploiting the displacement determined by the operator through repeated compressions and decompressions with the probe [9]. Given that the force applied by the operator to the tissue is unknown, in order to obtain a semi-quantitative evaluation of tissue elasticity, the ratio between two different region of interest (ROI) within the tissue is calculated. This "strain ratio" is often obtained by using subcutaneous fat [11] or external material [12, 13] as a reference tissue. In contrast, SWE applies an acoustic radiation force via the ultrasound beam to the tissue, in which the propagation velocity correlates with the tissue elasticity which can be quantified (in m/s or kPa) [6, 14].

Ultrasound-based elastography offers both researchers and clinicians a fast, non-invasive, quantitative assessment of tendon mechanical properties. It can be applied in the evaluation of acute and chronic Achilles tendinopathy [15, 16] or to define the response to several different mechanical loads [17] and additionally has the potential to improve the diagnosis of tendon disorders [18].

Although these technologies have been commonly used in research and clinical settings, the reliability of measurements from the AT is still debated [5, 12, 19, 20]. Limits and constraints of both SWE and SE have been reported [21] especially when used to analyse the tendon structure, indicating the importance of a systematic and structured approach. Nevertheless, some studies have confirmed the superiority of SE and SWE in terms of specificity, sensitivity and accuracy compared to conventional ultrasound for diagnosing Achilles tendinopathy [21]. Surprisingly, there has been no attempt to compare the available sonoelastography techniques. Therefore, the aim of this study was to evaluate and compare in vivo mechanical properties of the AT measured during contractions of increasing intensity when using three different SE/SWE devices. Additionally, the study aimed to establish if there is a correlation between the strain ratio methods and SWE in the evaluation of AT stiffness.

Methods

Twenty asymptomatic volunteers (12 males, 8 females, mean age 28.95 ± 4.16 years) were recruited for this repeated measures study. Height (centimetres) and weight (kilograms) were recorded, and the body mass index (BMI) was calculated.

Subjects with a history of tendon injury and/or previous foot surgery or any painful episodes in the lower limbs in the last year, or systemic inflammatory disorders such as rheumatoid arthritis, spondyloarthropathies and hypercolesterolemia were excluded. All participants were informed about the content of the study and signed the informed consent form prior to the experimental procedure. The study was approved by the Ethics Committee of the Policlinico San Matteo, Pavia. (ID: 0579).

Longitudinal sonoelastography images of the left and right AT were performed with three ultrasound devices, using two different systems of SE and SWE technologies. The systems with SE were: Resona 7, Mindray, Shenzhen, China (SE1), and Aplio 500, Toshiba Medical Systems Corp., Tokyo, Japan (SE2). The systems with SWE were: Resona 7, Mindray, Shenzhen, China (SWE1), and Aixplorer; SuperSonic Imagine, Aix-En-Provence, France (SWE2).

All examinations were performed bilaterally using multifrequency linear transducers (14L5 probe for Toshiba, L14-6VU for Mindray and 4–15 MHz, SL15-4 for Aixplorer). The participants were asked to lie in a prone position, exposing both AT, with the legs extended and the feet placed over the examination couch, in contact with a dynamometer (see Fig. 1).

The examination included AT long axis evaluation using B-mode, SE and SWE. Images were acquired at the level of the medial malleolus in order to minimize "bone proximity" hardening artefacts [22, 23]. The participants were instructed to perform contractions of different intensities (0 kg, 0.5 kg, 1 kg, 2 kg, 5 kg and 10 kg) in plantar flexion using an ankle ergometer; the examiner performed one measurement on each tendon at every load. The side of the tendon as well as the sequence of the isometric contractions was randomized.

All evaluations were performed by an experienced musculoskeletal radiologist with 7 years of experience with elastography and experience with all devices used.

Data acquisition

Specific musculoskeletal presets were used and no ultrasound setting changes were allowed during the study; only simple tuning was allowed (e.g. depth, brightness and contrast) in order to obtain the best possible

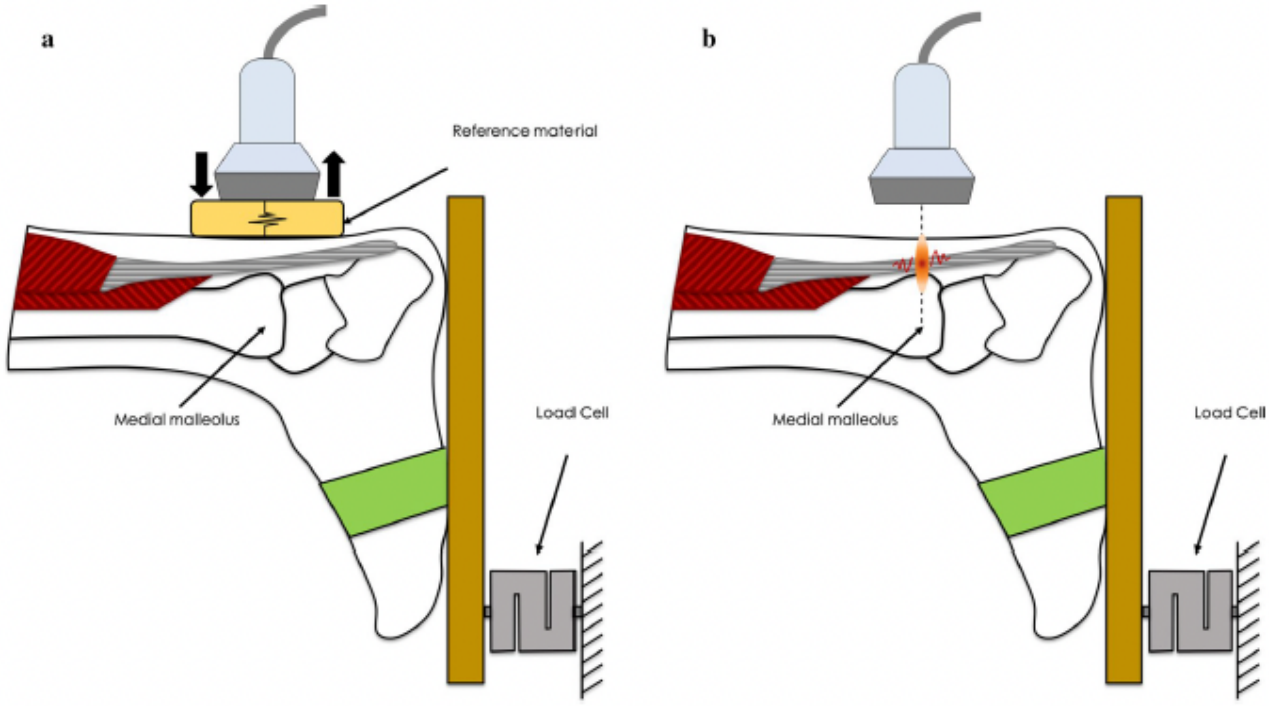


Fig. 1 Schematic of the experimental setup. **a** Strain sonoelastography with reference material **b** Shear Wave sonoelastography. Ultrasound probe was placed in a longitudinal scan at the level of the medial malleolus

image. For the SE analysis, we used an external reference material (Zerdine®, CIRS, Inc., Norfolk) with known elastic properties (elasticity—102 kPa, speed of sound—1580 m/s, and attenuation coefficient—0.5 dB/cm/MHz). The external reference material was placed on the participant's AT, included in the B-mode scans, and used to provide a comparison between the examined tendon and a material in which a constant elasticity was present.

SE images were analysed using a custom-made software; colour scale pixel count was made and colour histograms were extracted from two regions of interest (the reference material and AT). The range between soft and hard (from red to blue) was divided into 256 steps (0–255) according to the ultrasound image colour depth. Strain ratios between the tendon and the reference material were calculated and the comparison between different contraction levels were made. Higher strain ratio between the AT and the reference material indicates a softer tendon. This method has been validated, and reliability established in a previous study [12, 24]. The use of strain ratios with a reference material with known elasticity properties becomes even more relevant when comparing different ultrasound devices.

Shear wave images were analysed on the ultrasound device, and region of interest (ROI) were manually drawn in post-processing and included the full extent of the examined tendon displayable in the saved image. Reliability maps were available in dual screen for both systems and were used to check the quality of the obtained images. The acquired SWE-information was evaluated quantitatively; the shear elastic modulus (Young's modulus) was calculated by the measuring tools of the ultrasound systems in kPa. This procedure was repeated for both AT and at different contraction levels. A higher value obtained with the SWE corresponds to a harder tendon. All images and data were stored in the ultrasound work-stations.

The comparison between different contraction levels for each of the ultrasound devices was made.

Figure 2 shows an example of SE and SWE images for the AT for the 0 kg load condition.

Statistical analysis

The Shapiro–Wilk test was used to test the normal distribution of quantitative variables. Nonparametric, independent samples, Mann–Whitney test was used to assess differences in stiffness of the AT between the left and right side and between men and women.

A nonparametric test (Friedman test with post hoc pair wise comparison) was used to compare differences of stiffness for each of the ultrasound devices. Bonferroni correction was applied and an overall p value less than

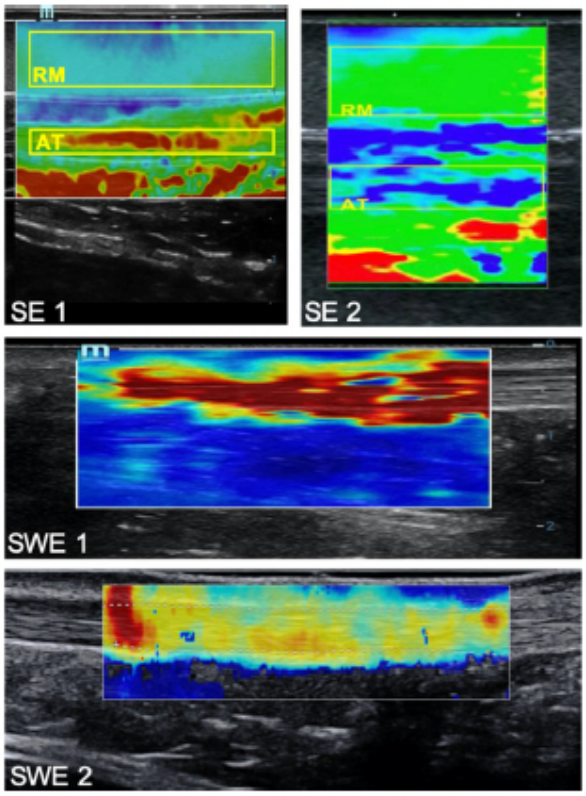


Fig. 2 Example of the Achilles tendon mechanical properties at 0 kg measured with the different sonoelastography devices. SE1, strain elastography Resona 7, Mindray; SE2, strain elastography Aplio 500, Toshiba Medical Systems Corp.; SWE1, shear wave elastography Resona 7, Mindray; SWE2, shear wave elastography Aixplorer; SuperSonic Imagine, RM, reference material; AT, Achilles tendon

0.05 was considered a significant difference. Medians and interquartile ranges (IQR 25th and 75th percentile) were used to report the results. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 22.0 software (SPSS, Chicago, IL, USA).

Results

There were no significant differences in elastographic parameters between genders or between the left and right AT, and therefore, the data were pooled and further analysed as an entire sample. The median age of the participants was 28 years (range 26–41 years), with a sex ratio (M:F) of 12:20. The mean ± SD height, weight and BMI were 173.6 (±7.4) cm, 68.2 (±10.5) kg and 22.5 (±2.35), respectively.

Comparison of the SE strain ratio values

The median (IQR) values for the strain ratio measured at difference contraction levels are represented in Table 1. Evaluation with SE1 revealed a strain ratio of 1.51 (0.92) for the AT in the relaxed position and a progressive decrease of tendon strain ratio (the tendon became progressively harder) during increasing contraction levels, with median (IQR) values of 1.12 (0.49) at 0.5 kg, 0.99 (0.33) at 1 kg, 0.91 (0.37) at 2 kg, 0.50 (0.32) at 5 kg and 0.33 (0.16) at 10 kg. Friedman test for related samples revealed a significant difference ($p < 0.01$) between all contraction levels except for the adjacent levels. (Table 2 and Fig. 3a) Evaluation with SE2 revealed a strain ratio of 1.08 (0.76) for of the AT in the relaxed position, and a progressive decrease of the tendon strain ratio during contractions of increasing intensity, with median values of 1.02 (0.48) at 0.5 kg, 1.02 (0.26) at 1 kg, 0.97 (0.18) at 2 kg, 0.79 (0.37) at 5 kg, and 0.50 (0.32) at 10 kg. Friedman test for related samples, revealed a significant difference ($p < 0.01$) between the highest contraction levels (10 kg and 5 kg) and the other contractions but no difference ($p > 0.05$) between the adjacent and the lowest contraction levels. (Table 2 and Fig. 3b).

Comparison of the SWE Young's modulus (kPa)

Evaluation with SWE1 revealed a median (IQR) elastic modulus of 33.40 (19.61) kPa for the AT in the relaxed position and a progressive decrease of Young's modulus (indicating reduced stiffness) during the progressive contraction levels, with median values of 23.75 (10.12) kPa at 0.5 kg, 19.54 (6.48) kPa at 1 kg, 17.33 (4.41) kPa at 2 kg, 16.56 (4.09) kPa at 5 kg and 16.19 (2.68) kPa at 10 kg. Friedman test for related samples revealed a significant difference ($p < 0.01$) between the lowest contraction levels (0 kg and 0.5 kg) and the other contractions but no

Table 1 Median (IQR) of the strain ratio (tendon/reference material) and Young's modulus (kPa) at different contraction levels

	0 kg	0.5 kg	1 kg	2 kg	5 kg	10 kg
SE 1 (TE/REF)	1.51 (0.92)	1.12 (0.49)	0.99 (0.33)	0.91 (0.37)	0.50 (0.32)	0.33 (0.16)
SE 2 (TE/REF)	1.08 (0.76)	1.02 (0.48)	1.02 (0.26)	0.97 (0.18)	0.79 (0.37)	0.50 (0.32)
SWE 1 (kPa)	33.40 (19.61)	23.75 (10.12)	19.54 (6.48)	17.33 (4.41)	16.56 (4.09)	16.19 (2.68)
SWE 2 (kPa)	428.65 (131.5)	487.9 (121.5)	459.35 (113.48)	393 (83.83)	319.7 (94.75)	293.5 (91.18)

Table 2 Friedman test p values between the different contraction levels for the different technologies

SE2	SE1						SWE2	SWE1					
	0 kg	**0.5 kg**	**1 kg**	**2 kg**	**5 kg**	**10 kg**		**0 kg**	**0.5 kg**	**1 kg**	**2 kg**	**5 kg**	**10 kg**
0 kg	–	1.000	0.405	**0.000**	**0.000**	**0.000**	0 kg	–	0.073	**0.000**	**0.000**	**0.000**	**0.000**
0.5 kg	1.000	–	1.000	**0.002**	**0.000**	**0.000**	0.5 kg	0.625	–	0.475	**0.011**	**0.000**	**0.000**
1 kg	1.000	1.000	–	0.632	**0.000**	**0.000**	1 kg	1.000	1.000	–	1.000	0.127	0.106
2 kg	1.000	1.000	1.000	–	0.062	**0.000**	2 kg	1.000	0.053	0.735	–	1.000	1.000
5 kg	**0.004**	**0.001**	**0.000**	**0.015**	–	0.062	5 kg	**0.000**	**0.000**	**0.000**	**0.008**	–	1.000
10 kg	**0.000**	**0.000**	**0.000**	**0.000**	0.128	–	10 kg	**0.000**	**0.000**	**0.000**	**0.001**	1.000	–

Bold values indicate statistically significant difference between the different contraction levels $p < 0.05$

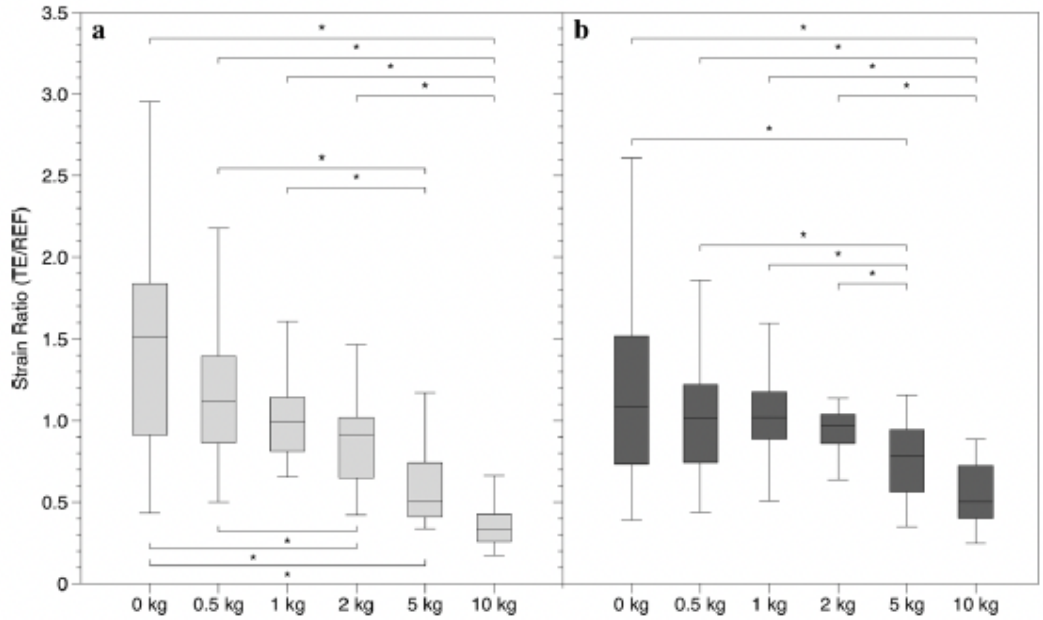


Fig. 3 Strain sonoelastography. Box plot showing the median and IQR strain ratio (TE/REF) values of the entire sample for the different contraction levels **a** SE1 and **b** SE2. *$p < 0.05$; statistical significant difference between the different contraction levels

difference ($p > 0.05$) between the adjacent and the highest contraction levels. (Fig. 4a).

Evaluation with SWE2 showed median (IQR) elastic modulus of 428.65 (131.5) kPa for the AT in the relaxed position and an increase of Young's modulus (higher stiffness) to 487.9 (121.5) kPa at 0.5 kg followed by a progressive decrease of tendon modulus (reduced stiffness) during higher contraction levels, with median values of 459.35 (113.48) kPa at 1 kg, 393 (83.83) kPa at 2 kg, 319.7 (94.75) kPa at 5 kg and 293.5 (91.18) kPa at 10 kg. Friedman test for related samples revealed a significant difference ($p < 0.01$) between the highest contraction levels (10 kg and 5 kg) and the other contractions but no difference ($p > 0.05$) between the adjacent and the lowest contraction levels. (Fig. 4b).

Discussion

This study was undertaken to assess the consistency of SE and SWE in the evaluation of the AT at different contraction levels, to compare the elasticity results using commercially available scanners and to explore the performances using different ultrasound imaging. Different behaviour was observed for the two sonoelastography techniques as well as for the different devices indicating limitations of both techniques.

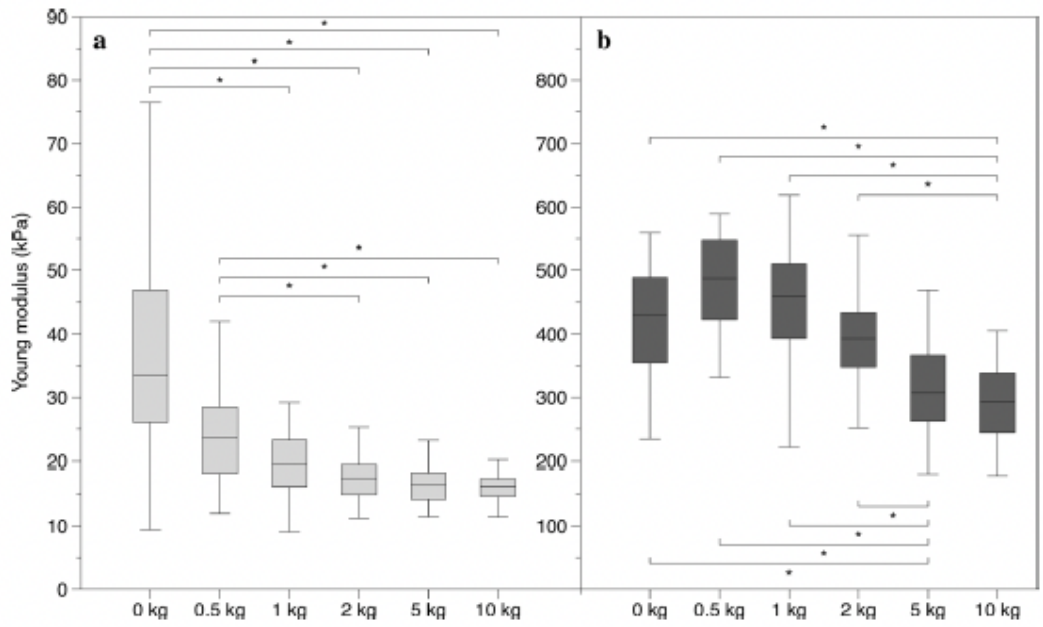


Fig. 4 Shear wave sonoelastography. Box plot showing the median Young's modulus and IQR values of the entire sample for the different contraction levels **a** SWE1 and **b** SWE2. *$p < 0.05$; statistical significant difference between the different contraction levels

The observed differences can be explained by the inconsistent methodological and computational approaches used to estimate tissue stiffness/elasticity. This has important consequences for both researchers and clinicians. Secondary research such as systematic reviews or meta-analysis is also hindered due to the limitations when pooling datasets from different studies. The lack of a reference standard constitutes a barrier for a diffuse application of SE/SWE the clinical practice.

The behaviour of both SE1 and SE2 is similar to previously published studies showing a decrease of the strain ratio values when the tendon becomes harder due to an increase in plantarflexion strength [24] or with supraspinatus contraction [25] and similar results were obtained using a semi-quantitative method with SE [26]. Moreover, these results are in line with a myotonometry evaluation of the AT [27] which showed increased stiffness when the tendon is under load.

As shown by Schneebeli et al. [24], higher variability of strain ratio values between the participants was present in the relaxed position and at low levels of contraction. This variability is reduced when the tendon is put under load. This behaviour is clearly visible in both SE techniques (Fig. 3) and could be explained by inter-individual difference in age, level of activity and anatomical differences (gastrocnemius and soleus length). A lack of accuracy of these techniques in the relaxed position, leading to a large variability in the strain ratio results, cannot be excluded. However, this method has high intra-rater reliability when used in both a relaxed and contracted state [12].

Strain ratio values between SE1 and SE2 appear to be different with SE1, showing a relaxed value of 1.51 (0.92) and a rapid decrease in strain ratio when the tendon is put under load (see Fig. 3), while SE2 showed a starting value of 1.08 (0.76) and similar values at the low contraction levels. Values of SE1 are highly comparable with another study [24] reporting a strain ratio of 1.61 (1.5–2.9) in the relaxed state, 1.30 (1.07–2.02) at 0.5 kg, 1.00 (0.76–1.66) at 1 kg, 0.81 (0.70–1.19) at 2 kg, 0.47 (0.39–0.73) at 5 kg and 0.33 (0.28–0.40) at 10 kg. Pairwise comparison between different contraction levels showed that SE1 could not detect changes between contraction levels of similar intensity and at the beginning of the isometric contraction (0–0.5 kg ($p = 1.000$), 0–1 kg ($p = 0.405$)). Similarly, SE2 could not distinguish the adjacent contraction levels but additionally, differences between low level contraction levels were not detected by this device. Differences were only observed at the higher contraction levels (5 kg, 10 kg). This low sensitivity in the initial phase of the contraction could be attributed to a different colour scale implemented in the device that considers mid-range values (green levels) more so than the higher or lower values.

Conversely, SWE using two different devices showed a different result compared to SE and to the expected biomechanical behaviour. Previous studies evaluating AT at different ankle angles indicate an increase in the shear

modulus and shear wave velocity with an increase in ankle dorsiflexion [5, 8, 19, 28–31].

In this study, SWE 1 showed the opposite behaviour with a decrease in shear modulus with an increase in the contraction level and thus tension on the AT. It could be that the upper limit of the device (66.7 kPa) was surpassed. The implemented algorithm in SWE 1 does not present saturated values as a loss of signal (as for SWE 2) (Additional file 1: Appendix 1).

Moreover, the values obtained with SWE 1 at 0° of ankle plantar flexion (33.40 (19.61)) are extremely low compared to values reported in other studies [5, 32, 33], questioning the possibility of using Mindray shear wave sonoelastography to analyse tendon mechanical properties.

Values reported in Table 2 and Fig. 4a, which indicate a significant difference between different contraction levels, should be interpreted cautiously given the unusual shear modulus values indicating an opposite behaviour of this technology compared to SE and biomechanical studies. Further studies using SWE 1 are needed to evaluate the feasibility of this technology to measure mechanical properties of tendinous structures.

SWE 2 measured an increase of tendon stiffness during isometric plantar flexion from 0 to 0.5 kg load with shear modulus median values ranging from 428.65 (131.5) to 487.9 (121.5). This increment is followed by a progressive decrease of the Young's modulus for isometric plantar flexion at 1, 2, 5 and 10 kg (see Table 1). This behaviour does not reflect tendon biomechanics, and it appears that the upper limit of the device (800 kPa) was reached. SWE 2 images of isometric contraction higher than 0.5 kg revealed signal saturation with a signal loss within the elastogram. This signal loss is probably due to the alignment or the displacement of the fibrillary structure within the AT that could increase the speed of the shear waves or could generate an abnormal propagation of the shear wave that cannot be registered by the device.

The absence of signal within some portion of the AT could have led to a miscalculation of the shear modulus resulting in a reduction of the kPa which was not attributed to the actual behaviour of the tendon. (Additional file 1Appendix 2). Given the upper limit of the shear modulus in these technologies, some authors suggested [5, 32] to limit the evaluation of AT to a relaxed or plantar flexed position and to not put tendon under load by means of a dorsiflexed position or any additional weight.

SWE has been largely used to evaluate the AT, a in natural relaxed position. In 1165 healthy Chinese adults, a Young's modulus of 374.24 ± 106.12 kPa was reported [31]. However, inconsistency between studies exists when tendon is analysed at 0° of plantar flexion as in the present study. Shear modulus varied from 723.1 (kPa) [5] to 174.1 (kPa) [19] with one study reporting 322 (kPa) for the dominant leg and 320 (kPa) for the non-dominant [33]. Chino et al. [32] reported values to those measured with SWE2 in the present study with 430 (± 96) kPa at measured at 10% of the lower limb length and 470 (± 151) kPa at 15% of the lower limb length. The present study reported a median (IQR) value of 428.65 (131.5).

Even though these studies evaluated AT in the free tendon part, differences between results could be attributed to the transducer position along the free tendon or to challenges using this technology to evaluate the tendon under tension as in the 0° ankle position.

Using SWE 1, we measured median (IQR) values of 33.40 (19.61) at 0° of plantar flexion. Since this device, to our knowledge, has never been used to analyse tendinous structures, there are no data to compare to. However, considering the values obtained with other devices, these results appear to be far below the expected kPa values questioning the possibility to compare the results between different ultrasound devices.

The lack of relationship between these two methods may be related to the inherent differences in the parameters measured. SE evaluates tissue elasticity before and after manual compression, while SWE estimates Young's modulus on the basis of the ultrasound propagation shear wave velocity. In addition, SWE is more susceptible to measurement interference due to the anisotropic nature of the tendon.

Considering the fundamental role of load in the development of tendon pathology as well as in the management of tendon rehabilitation, by means of loaded-based exercises, a device which is able to detect changes in the mechanical properties of tendon during tasks that directly challenge the tendinous structure (i.e. contraction) could provide a better understanding of tendon injury and rehabilitation effects. Strain evaluation appears to be the best technique to assess the elastic changes of the AT during isometric plantar flexion, nevertheless SE provides only semi-quantitative values (strain ratios) and this data, unlike Young's modulus, does not represent the tissue intrinsic properties [21]. Moreover, the use of manual compression and reference material required higher technical skills leading to a more operator-dependent procedure.

There are some limitations to the current study. First, the selection of the devices and technology used was limited to those available. Second, the application of SE and SWE was limited to the evaluation of the AT. Generalizability of these findings to other devices and other tendons may not be possible. Further studies, which also evaluate the mechanical properties of pathological tendons, are necessary.

Conclusion

SE with the use of reference material is able to detect changes in AT elasticity when measured in ankle plantar flexion during different contraction levels, and the results are in line with the expected physiological and mechanical behaviour of the tendon. Nevertheless, SE can only provide semi-quantitative (i.e. strain ratio) values and requires higher technical skills for operation. Conversely, SWE measured changes in tendon stiffness which were contradictory to the mechanical characteristics of the AT, probably due to the propagation shear wave velocity and the fibrillary structure of the AT. SE appears more suitable for the evaluation of the AT when under load. Caution should be taken when comparing the results of different devices used to assess the AT. The inconsistency of the results between the different devices may hinder the clinical applicability of SE and SWE.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13244-021-00974-y.

Additional file 1. 1. Example of SWE 1 measurement during isometric contraction from 0 kg to 10 kg. Red values correspond to higher stiffness whereas blue values represent lower stiffness. 2. Example of SWE 2 measurement during isometric contraction from 0 kg to 10 kg. Red values correspond to higher stiffness whereas blue values represent lower stiffness. Signal loss in the Region of Interest are visible after 0.5 kg of isometric contraction.

Abbreviations

AT: Achilles tendon; SE: Strain elastography; SWE: Shear wave elastography; ROI: Region of interest; IQR: Interquartile ranges.

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Authors' contributions

AS, CC, CB, PL and MB designed and planned the study. AS, CC, CB and MVR collected the data. AS, IF, DF and TF analysed the data. All authors were involved in the drafting and revision of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

All participants were informed about the content of the study and signed the informed consent form prior to the experimental procedure. The study was approved by the Ethics Committee of the Policlinico San Matteo, Pavia. (ID: 0579).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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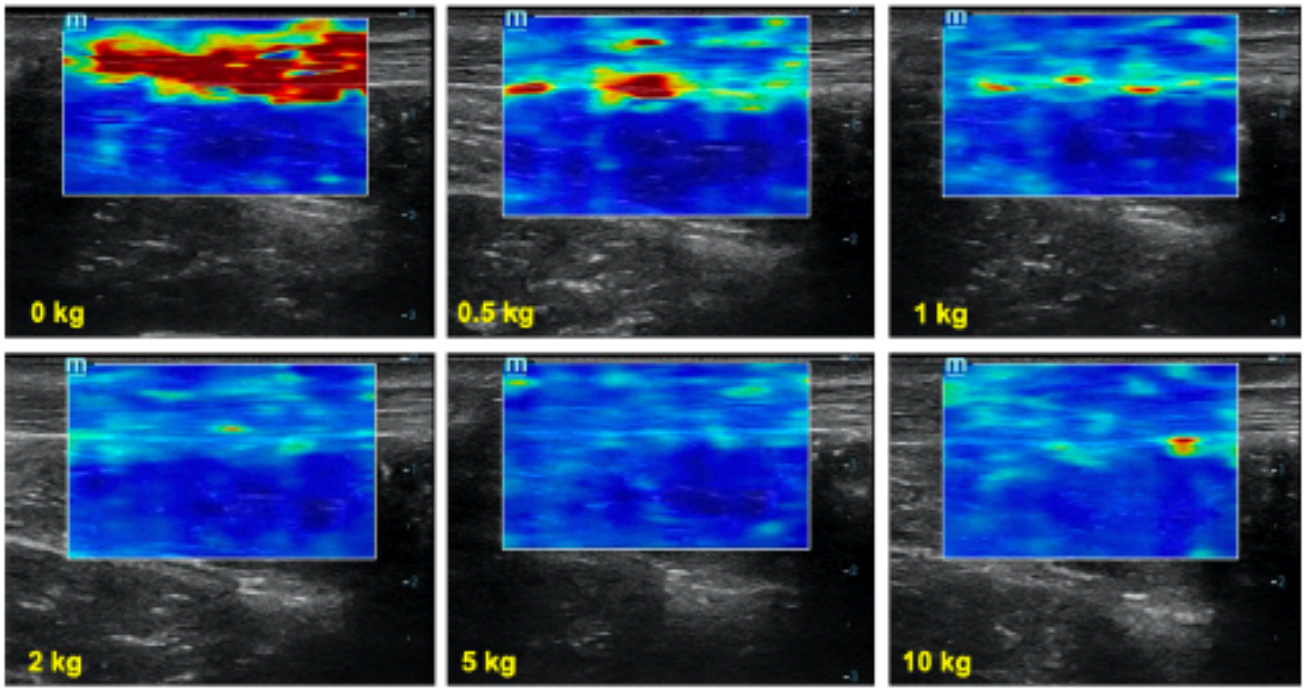
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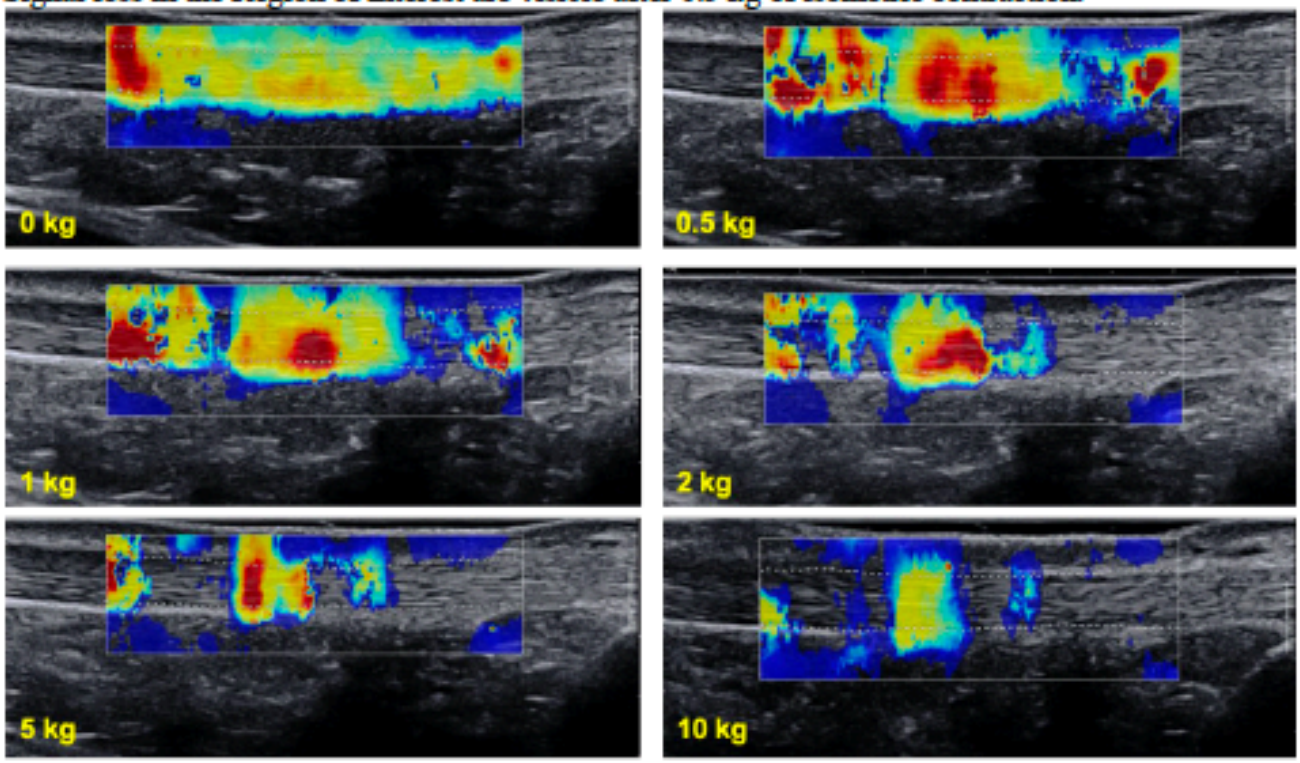
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Appendix 3 – SE and SWE images example of saturation.

1. Example of SWE 1 measurement during isometric contraction from 0kg to 10kg.
Red values correspond to higher stiffness whereas blue values represent lower stiffness.



2. Example of SWE 2 measurement during isometric contraction from 0kg to 10kg.
Red values correspond to higher stiffness whereas blue values represent lower stiffness.
Signal loss in the Region of Interest are visible after 0.5 kg of isometric contraction.



Appendix 4 – Schneebeli et al., 2020a

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● *Original Contribution*

RELIABILITY OF SONOELASTOGRAPHY MEASUREMENTS OF LOWER LIMB TENDON PROPERTIES: A SYSTEMATIC REVIEW

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Abstract—This study investigated the reliability of sonoelastography techniques in quantifying lower limb tendon elasticity. A literature search was conducted using PubMed, Web of Science and CINAHL. The quality of the selected papers was evaluated using the Guidelines for Reporting Reliability and Agreement Studies and the Quality Appraisal Tool for Studies of Diagnostic Reliability checklist. Reliability values were extracted and synthesized. Twenty-four studies were included and were divided by the two main technologies used: strain and shear-wave elastography. The overall methodological quality was questionable; all studies were at risk of bias. Highly variable results ranging from poor to excellent reliability were found for both technologies and for all tendons considered. Intra-rater reliability of strain elastography on the Achilles tendon and shear-wave elastography on the patellar and quadriceps tendon was adequate. Inter-rater, inter-session and inter-machine reliability was insufficient. Caution should be used when interpreting results from sonoelastography studies measuring lower limb tendon elasticity. (E-mail: alessandro.schneebeli@supsi.ch) **© 2020 World Federation for Ultrasound in Medicine & Biology. All rights reserved.**

Key Words: **Achilles tendon, Patellar tendon, Quadriceps tendon, Strain sonoelastography, Shear-wave sonoelastography, Elastography.**

INTRODUCTION

Understanding how tendon mechanical properties, such as elasticity, change as a response to load is crucial to better comprehend the behavior of tendons after exercise or other rehabilitation interventions. Tendons are highly responsive to mechanical stimuli (Magnusson et al. 2008; Heinemeier and Kjaer 2011; Bohm et al. 2015; Wiesinger et al. 2015); therefore, the application or elimination of either tensile strain, compression or shear stress could lead to a change in the tendon's mechanical properties (Docking and Cook 2019). Although the relationship between mechanical changes and pathology or performance is still debated, the importance of measuring these parameters is not (Docking and Cook 2019). Clinicians would benefit from technologies that measure mechanical changes during or after their treatments, and this would lead to (case-by-case optimization) tailoring of the interventions according to objective measurements.

Currently, many different measurement techniques are used to measure tendon mechanical properties, with sonoelastography being the most common technique because it can be used to directly assess free tendons (Coombes et al. 2018; Prado-Costa et al. 2018). Based on the calculation of tissue internal displacement as a response to the application of a stress force, sonoelastography can describe the elastic properties of different materials (Ophir et al. 1991). Two main technologies have exploited this physical phenomenon to estimate mechanical parameters using different excitation application (stress). Shear-wave elastography (SWE) uses a focused radiation force, which induces a shear wave within the tissues (Sandrin et al. 2002; Bercoff et al. 2004). Conversely, strain elastography (SE), or compression elastography, uses a manual generated force to induce an internal displacement of the underneath tissues (Drakonaki et al. 2012). Both SWE and SE return values describing the elastic properties of the material, in the first case a Young's elastic modulus

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(E) or shear elastic modulus (G) while in the latter case a color elastogram, that can be analyzed either qualitatively or semi-quantitatively using strain ratio between two regions of interest (ROI).

The elastogram automatically constructed by the ultrasound device displays different colors, from red (soft) to blue (hard), indicating different elasticity values. Strain ratios are calculated as the mean between the range of color in the target structure divided by a reference structure.

A 2018 review by Prado-Costa et al. analyzing the feasibility and applicability of SWE and SE to assess tendon pathology and injury showed potential application in the evaluation of tendinopathies. However, the authors suggest that a more structured and systematic approach is needed to overcome the limitations of both technologies. Even if these technologies have been largely used to describe elasticity in different tendons and in different conditions, methodological studies aiming to evaluate the reliability of these techniques are scarcely present in the literature, and results are often conflicting.

Reliability, as well as other measurement properties, must be determined before any measurement device or assessment tool can be applied in a clinical or research setting (Koo and Li 2016). When no accepted reference standard is available, as for *in vivo* tendon elasticity measures, and validity or accuracy measures are not possible, reliability studies of high methodological quality become crucial to guarantee the applicability of these measures. Criteria for conducting and reporting robust reliability studies are present within the literature (Lucas et al. 2010; Mokkink et al. 2010; Kottner et al. 2011), and guidelines for the interpretation of results are also available (Shrout and Fleiss 1979; Koo and Li 2016). Nevertheless, to date no attempt to synthesize current knowledge on reliability of sonoelastography measurement has been done. Therefore, the aim of this systematic review was to determine the reliability of sonoelastography techniques for measuring lower limb tendon elasticity and to investigate the quality of these studies.

METHODS

Registration

The present systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (Moher et al. 2009) and was registered in the International Prospective Register of Systematic Reviews (PROSPERO nr. CRD42020148572) on February 3, 2020.

Eligibility criteria

The population, intervention, comparator, outcome and study design (PICOS) framework was used and adapted for this type of study (Akers 2009). Articles were included if the full text article was published in a peer-reviewed journal, if one of the aims of the study was to investigate the reliability of sonoelastography on lower limb tendons, and if the population included healthy individuals or patients with tendon disease (*i.e.,* patients with lower limb tendinopathies or tendon rupture). Studies using animal models were excluded. We also excluded studies using *ex vivo* or human models because this review is focused on the clinical application of the technology. We included observational studies, such as cross-sectional studies and repeated measurement studies. Studies were included if an ethics committee or institutional review board approved the protocol. Observational studies were excluded when reliability was not the primary aim but was investigated in a preliminary or pilot study and was not described in the methods. Randomized controlled trials were excluded. A PRISMA flowchart illustrating the study screening and selection process is presented in Figure 1.

Search strategy

A comprehensive search of the databases MEDLINE (PubMed), Web of Science and CINHAL was conducted by the first reviewer (A.S.) the February 26, 2020. The full electronic search strategy used for PubMed is presented as an example: ("Achilles tendon" OR ("Achilles" AND "tendon") OR ("calcaneal" AND "tendon") OR ("triceps surae" AND "tendon") OR ("gastrocnemius" AND "tendon") OR ("soleus" AND "tendon") OR ("plantarflexor" AND "tendon") OR ("calf" AND "tendon") OR ("patellar" AND "tendon") OR ("patellar" AND "ligament") OR ("hamstring" AND "tendon") OR ("lower extremities" AND "tendon") OR ("lower limb" AND "tendon") OR "tendons") AND ("Elastic modulus" OR "Elasticity" OR "Elastic" OR "viscoelastic" OR ("visco" AND "elastic") OR ("young" AND "modulus" OR "moduli") OR "compliance" OR "lengthening" OR "stiffness" OR "properties" OR "strain" OR "mechanical") AND ("reliability" OR "reliabilities" OR "reproducibility" OR "test-retest").

Additionally, the search strategy was adapted for Web of Science and CINAHL databases. To avoid the exclusion of relevant papers, search filters (*i.e.,* animal studies, type of study, *in vitro*) were not included (Doust et al. 2005). No publication date or language restrictions were applied. Moreover, reference lists of included studies were checked. Studies obtained using the search strategies were exported to EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA) by the first reviewer (A.S.), and duplicates were removed.

Study selection

Two reviewers (A.S. and A.F.) independently screened titles and abstracts to determine which studies met the inclusion and exclusion criteria. Studies whose

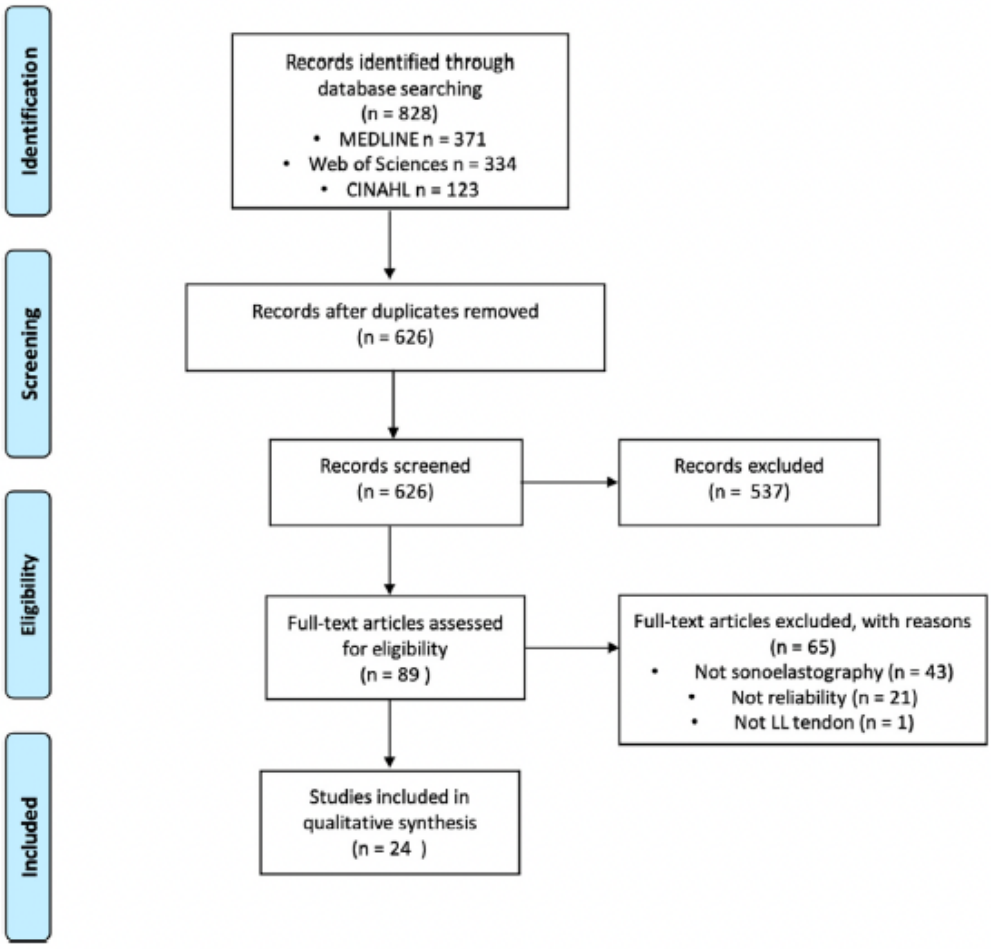


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flowchart of study identification, screening and eligibility. LL, lower limbs.

eligibility could not be established from the screening of title or abstract were searched for full-text review. Any disagreement between reviewers were resolved by consulting a third reviewer (M.B.).

Quality assessment

The included studies were assessed using two different quality assessment tools for reliability studies. To assess the quality of the reporting of the included studies, the Guidelines for Reporting Reliability and Agreement Studies (GRRAS) (Kottner et al. 2011) checklist was used. To guarantee the correct interpretation and synthesis of the results of other studies, adequate and clear reporting was mandatory.

The items covered by GRRAS evaluate if the information about the sample selection, study design, rater characteristics and statistical analysis are properly reported. This 15-item checklist was used, and a quality score was given depending on the number of items reported in the correct section of the article. GRRAS items are described in detail in Figures 2 and 3.

The quality in the design and conduct (internal quality) of the studies was assessed using the quality appraisal tool for studies of diagnostic reliability (QAREL). This checklist was developed by Lucas et al. (2010) with the aim to critically appraise reliability studies. Previous checklists investigating diagnostic accuracy (*i.e.,* the Quality Assessment of Diagnostic Accuracy Studies [QUADAS]) (Whiting et al. 2006) have been developed, nevertheless, when there is no accepted reference standard to relate to, as in the case of elasticity measures, reliability studies become crucial.

The QAREL is an 11-item checklist covering the spectrum of patients, examiners, appropriate test application and statistical analysis specific for reliability studies. QAREL items can be answered as "no," "unclear" and "yes"; additionally, the option "not applicable" can be used in some items. The more "yes" responses, the higher the quality of the study; conversely, a single "no" answer may invalidate the study findings. Five out of 11 items can be scored as "not applicable," therefore the final score of the article will take into account the real

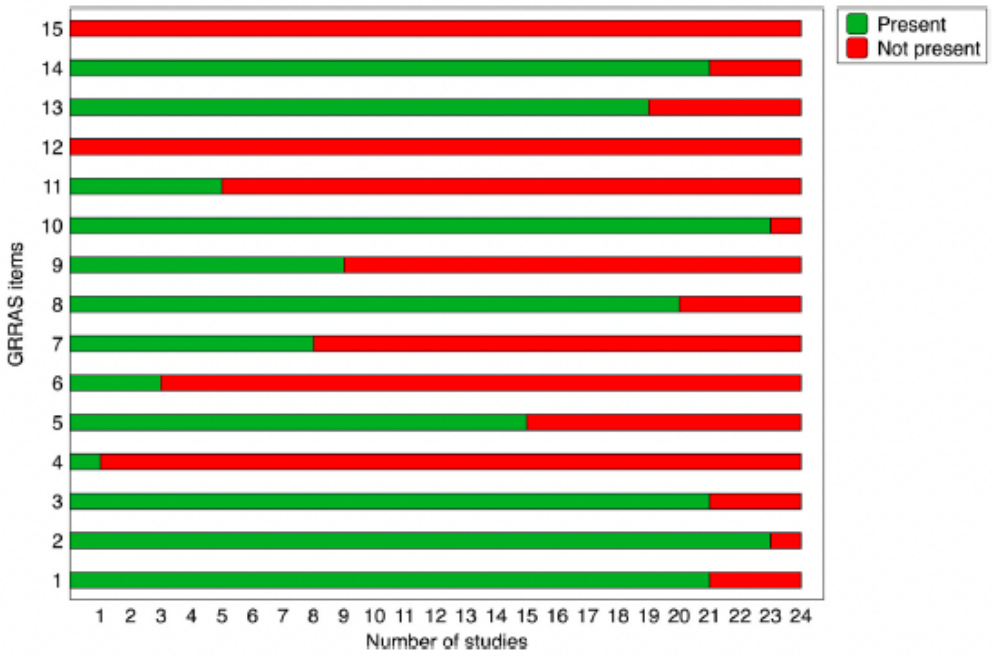


Fig. 2. Bar chart showing the presence of the different Guidelines for Reporting Reliability and Agreement Studies (GRRAS) items in the selected studies (n = 24). Title/abstract; item 1: Identify in title or abstract that interrater/intra-rater reliability or agreement was investigated. Introduction; item 2: Name and describe the diagnostic or measurement device of interest explicitly. Item 3: Specify the subject population of interest. Item 4: Specify the rater population of interest (if applicable). Item 5: Describe what is already known about reliability and agreement and provide a rationale for the study (if applicable). Methods; item 6: Explain how the sample size was chosen. State the determined number of raters, patients/objects, and replicate observations. Item 7: Describe the sampling method. Item 8: Describe the measurement/rating process (*e.g.*, time interval between repeated measurements, availability of clinical information, blinding). Item 9: State whether measurements/ratings were conducted independently. Item 10: Describe the statistical analysis. Results; item 11: State the actual number of raters and patients/objects that were included and the number of replicate observations that were conducted. Item 12: Describe the sample characteristics of raters and patients (*e.g.*, training, experience). Item 13: Report estimates of reliability and agreement including measures of statistical uncertainty. Discussion; item 14: Discuss the practical relevance of results. Auxiliary material; item 15: Provide detailed results if possible (*e.g.*, online).

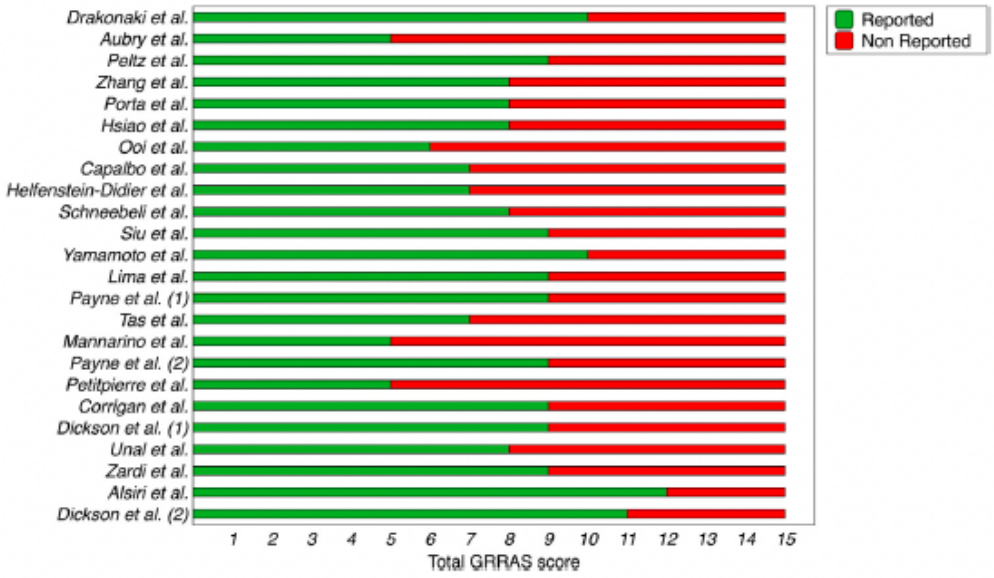


Fig. 3. Bar chart showing the total Guidelines for Reporting Reliability and Agreement Studies (GRRAS) score of the different selected studies.

total value (11 items, not applicable [N/A]). A detailed explanation of all the items is presented in Figure 4. Disagreements in the ratings of the QAREL and the GRRAS checklists among the two reviewers (A.S. and A.F.) were discussed and resolved after consulting with the third reviewer (M.B.).

Data extraction

Information was independently extracted by a reviewer (A.S.) and was controlled by a second reviewer (A.F.). Study characteristics, including number of participants, tendons analyzed, ultrasound device and technique used, reliability type, operators experience and measurement protocol were extracted and collected in a descriptive table (Table 1). Study results are reported in separate tables divided by the type of sonoelastography technique. These tables summarize the condition evaluated and the relative and absolute reliability results.

Relative reliability calculated with intra-class correlation coefficient (ICC) was interpreted as follows:

- ICC values less of than 0.5 indicate poor reliability, values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.9 show good reliability and values greater than 0.9 indicate excellent reliability (Portney and Watkins 2015).
- As suggested by Koo and Li (2016), where 95% confidence interval (CI) of ICC were reported, the rating considers not only the point estimation but the lower and upper limit of the 95% CI.
- A cut-off point of ICC of >0.6 was used to consider the clinical relevance of the measurements (Chinn 1990; Munro 2005).

Where present, agreement or correlation were interpreted as follows:

- Cohen's kappa value for categorical data were interpreted according to the Landis and Koch scale (Landis and Koch 1977), where <0 indicates poor agreement, 0.00–0.20 indicate slight agreement, 0.21–0.40 indicate fair agreement, 0.41–0.60 indicate moderate agreement, 0.61–0.80 indicate substantial agreement and 0.81–1.00 indicate almost perfect agreement.

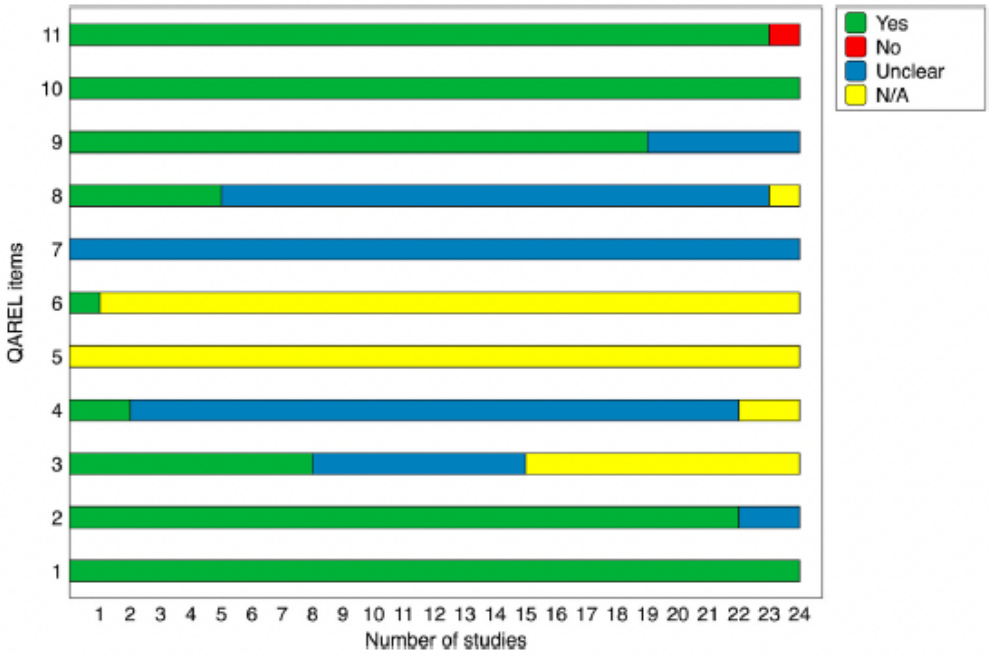


Fig. 4. Bar chart showing the presence of the different QAREL items in the selected studies (n = 24). N/A, not applicable. Item 1: Was the test evaluated in a sample of patients who were representative of those to whom the authors intended the results to be applied? Item 2: Was the test performed by raters who were representative of those to whom the authors intended the results to be applied? Item 3: Were raters blinded to the findings of other raters during the study? Item 4: Were raters blinded to their own prior findings of the test under evaluation? Item 5: Were raters blinded to the results of the reference standard for the target disorder (or variable) being evaluated? Item 6: Were raters blinded to clinical information that was not intended to be provided as part of the testing procedure or study design? Item 7: Were raters blinded to additional cues that were not part of the test? Item 8: Was the order of the examination varied? Item 9: Was the time interval between repeated measurements compatible with the stability (or theoretical stability) of the variable being measured? Item 10: Was the test applied correctly and interpreted appropriately? Item 11: Were appropriate statistical measures of agreement used?

ARTICLE IN PRESS

Table 1. Study characteristics of included articles.

Authors (y)	Subjects	Tendon	SE/SWE	Device	Reliability type	Protocol (measure distance)	Operators (experience)
Drakonaki et al. (2009)	50	AT	SE	Hitachi	Intra-Inter rater	1 session 2 measurements (2 h)	2 musculoskeletal radiologists (NR)
Aubry et al. (2013)	30	AT	SWE	Aixplorer	Inter-rater	1 session 3 measurements (NR)	3 medical doctors (>6 y)
Peltz et al. (2013)	12	AT PT QT	SWE	Aixplorer	Intra-rater	2 sessions D1: 2 measurements (4 h) D2: 2 measurements (4 h) 2 d between D1 and D2	1 trained operator (NR)
Zhang and Fu (2013)	11	PT	SWE	Aixplorer	Intra-Inter rater	1 session 2 measurements (1 h)	1 operator (5 y) and 1 physical therapist (2 y)
Porta et al. (2014)	11	PT	SE	Esaote	Intra-Inter rater	1 session 3 measurements (NR)	2 medical doctors (>8 y)
Hsiao et al. (2015)	5	PT	SWE	Aixplorer	Intra-Inter rater	2 sessions D1: 1 measurement D2: 1 measurement 1 wk between D1 and D2	2 operators (>1 y)
Ooi et al. (2015)	10	AT	SE	Philips	Intra-Inter rater	2 sessions D1: 1 measurement D2: 1 measurement 1 wk between D1 and D2	2 sonographer (>10 and >20 y)
Capalbo et al. (2016)	40	AT	SE	Hitachi	Inter-rater	NR	2 radiologists (10 and 4 y)
Helfenstein-Didier et al. (2016)	7	AT	SWE	Aixplorer	Intra-rater	1 session 5 measurements (immediate)	1 operator (NR)
Schneebeli et al. (2015)	24	AT	SE	Esaote	Intra-rater	1 session 2 measurements (1 min)	1 physical therapist (NR)
Siu et al.(2016)	36	AT	SWE	Aixplorer	Intra-Inter rater	1 session 3 measurements (NR)	3 sonographer (>1 y)
Yamamoto et al. (2017)	25	AT	SE	Hitachi	Intra-Inter rater	1 session 3 measurements (NR)	2 medical doctors (7 and 8 y)
Lima et al. (2017)	24	AT	SWE	Aixplorer	Intra-rater Inter-session	2 sessions D1: 1 measurement D2: 1 measurement 1 wk between D1 and D2	1 operator (NR)
Payne et al. (2017)	8	AT	SE	Siemens	Intra-rater Inter-session	6 sessions D1: 5 measurements (1 h) D2-D6: 1 measurement	1 operator (NR)
Tas et al. (2017)	12	PT	SWE	Siemens	Intra-rater Inter-rater Inter-session	2 sessions D1: 2 measurements (20 min) D2: 1 measurement 1 wk between D1 and D2	1 radiologist and 1 physical therapist with different experience (5-1 y)
Mannarino et al. (2018)	23	PT	SWE	Aixplorer	Intra-rater Inter-session	2 sessions D1: 2 measurements D2: 2 measurements 1 wk between D1 and D2	1 operator (NR)
Payne et al. (2018)	14	AT	SWE	Siemens	Intra-rater Inter-session	6 sessions D1: 5 measurements (1 h) D2-D6: 1 measurement	1 sport scientist (3 y)
Petitpierre et al. (2018)	15	AT	SWE	Aixplorer	Inter-rater	1 session 2 measurements (NR)	2 radiologists (6 and 3 y)

(continued on next page)

Table 1 (*Continued*)

Authors (y)	Subjects	Tendon	SE/SWE	Device	Reliability type	Protocol (measure distance)	Operators (experience)
Corrigan et al. (2019)	20	AT	SWE	Ultrasonix	Intra-rater	2 sessions D1: 4 measurements (30 min; 2/4 h) D2: 1 measurement 2 wk between D1 and D2	1 operator (NR)
Dickson et al. (2019)	20	PT QT	SE	GE	Intra-Inter rater	1 session 6 measurements (NR)	3 operators (12, 7 and 0 y)
Ünal et al. (2019)	42	AT	SE	Toshiba and Hitachi	Intra-Inter rater Inter-machine	2 sessions D1: 2 measurements with 2 devices D2: 2 measurements with 2 devices 10 d between D1 and D2	2 operators (NR)
Zardi et al. (2019)	18	PT	SWE	Esaote	Intra-rater	1 session 2 measurements (15 min)	1 sonographer (>10 y)
Alsiri et al. (2020)	18	QT AT	SE	GE	Intra-rater	1 session 2 measurements (1 h)	1 physical therapist (4 y)
Dickson et al. (2020)	20	PT QT	SE	GE and Esaote	Intra-Inter rater Inter-machine	1 session 8 measurements (15 min)	2 operators (12 and 0 y)

AT = Achilles tendon; D = day; NR = not reported; PT = patellar tendon; QT = quadriceps tendon; SE = strain elastography; SWE = shear-wave elastography.

- Correlation between measures using Spearman's rank was considered weak when r_s <0.3, moderate when r_s = 0.31–0.70 and strong when r_s >0.71 (Dancey and Reidy 2002).

Absolute reliability by mean of standard error of measurement (SEM), coefficient of variation (CV) and Bland and Altman plots were reported in the Tables 2–5 when presented in the studies.

RESULTS

Literature search and selection of studies

The initial electronic search through MEDLINE, Web of Science and CINHAL identified 828 potentially eligible articles. After the removal of duplicates, 626 articles were screened by title and abstracts with an agreement between the two reviewers of K = 0.73. Eighty-nine full text articles were assessed for eligibility. Twenty-four studies met all the inclusion criteria and were included in the final qualitative synthesis (Fig. 1). The agreement on the full-text screening between the two reviewers was K = 0.97. The majority of the studies were excluded after full-text screening for the following reasons: not using sonoelastography, not assessing reliability and not examining a tendon of the lower limb.

Characteristics of included studies

Characteristics of included studies are presented in Table 1. The number of participants included in the included studies ranged from a minimum of 5 to a maximum of 50. In the majority of the studies, participants were healthy (n = 23). Only one study evaluated reliability in patients with Achilles tendinopathy (Ooi et al. 2015). In the included studies, the following tendons were evaluated: Achilles tendon (AT) (n = 15); patellar tendon (PT) (n = 5); PT and quadriceps tendon (QT) (n = 3); and AT, PT and QT (n = 1).

Two major sonoelastography techniques were evaluated; SE (n = 11) and SWE (n = 13). Nine out of 11 studies using SE analyzed the values by mean of the strain ratio. Strain ratio is defined as the elasticity ratio between the tendon and another material (*i.e.,* fat tissue [n = 5], subcutaneous tissue [n = 2] and an external reference material [n = 2]). Of those, three studies added the evaluation of the color scale by mean of the color grading.

One study used only color grading (Capalbo et al. 2016), and another study used the percentage of displacement between the compressions (Payne et al. 2017).

Nine out of 13 studies using SWE calculated the elasticity values by the mean of shear modulus measured in kPa or mPa, whereas 2 studies used velocity of the

Table 2. Strain elastography reliability results on Achilles tendon.

Autors (y)	Parameters	Conditions	Intra-rater reliability		Inter-session reliability		Inter-rater reliability	
			Relative	Absolute	Relative	Absolute	Relative	Absolute
Drakonaki et al. (2009)	Strain ratio (Tendon/fat)	Axial	ICC 0.43 • OP1 0.45 • OP2	CV % 39% 37%			ICC 0.41 •	CV % 30%
		Longitudinal	0.78 • OP1 0.66 • OP2	30.5% 30.1%			0.51 •	29.6%
Ooi et al. (2015)	Strain ratio (Tendon/fat)	Longitudinal	ICC 0.87 •				ICC 0.79 •	
	Color grading		Cohen K 0.70				Cohen K 0.70	
Capalbo et al. (2016)	Color grading	Longitudinal Left Right					Cohen K 0.89 0.91	
Schneebeli et al. (2016)	Strain ratio (Tendon/ reference material)	Longitudinal Relaxed Contracted	ICC (95%CI) 0.87 (0.75-0.93) • • 0.94 (0.90-0.97) • •	MD (LoA) 0.13 (0.73/-0.47) 0.00 (0.16/-0.17)				
Yamamoto et al. (2016)	Strain ratio (Tendon/ reference material)	Longitudinal	ICC (95%CI) 0.93 (0.89-0.96) • • OP1 0.87 (0.80-0.92) • • OP2	SEM 0.06 0.07			Spearman rank 0.61	
Payne et al. (2017)	% of displacement	Longitudinal Fixed Relaxed Axial Fixed Relaxed	ICC 0.11 (-0.07-0.54) • • 0.06 (-0.12-0.49) • • 0.00 (-0.16-0.38) • • 0.00 (-0.19-0.31) • •	CV% 111.5% 105.7% 112.4% 53.6%	ICC 0.01 (-0.14-0.40) • • 0.10 (-0.08-0.53) • • 0.02 (-0.14-0.43) • • 0.11 (-0.10-0.55) • •	CV% 92.8% 80.8% 80.4% 60.9%		
Ünal et al. (2019)	Strain ratio (tendon/fat)	Longitudinal Hitachi Toshiba Hitachi-Toshiba	ICC (95%CI) 0.98 (0.95-0.99) • • OP1 0.98 (0.96-0.99) • • OP2 0.97 (0.92-0.99) • • OP1 0.96 (0.93-0.98) • • OP2		ICC(95%CI) 0.85 (0.26-0.95) • •		ICC (95%CI) 0.84 (0.74-0.89) • • M1 0.81 (0.70-0.88) • • M2 0.73 (0.57-0.83) • • M1 0.75 (0.61-0.84) • • M2	
Alsiri et al. (2020)	Strain ratio (tendon/subc. fat) Strain index	Longitudinal Lower SI Higher SI	ICC (95%CI) 0.82 (0.53-0.93) • • 0.91 (0.76-0.97) • • 0.91 (0.78-0.97) • •	MD (LoA) -0.33(2.70/-3.24) 0.00(0.03/-0.02) 0.02(0.15/-1.12)				
	Color Pixel %	Red pixel % Green pixel % Blue pixel %	0.99 (0.97-1.00) • • 0.91 (0.77-0.97) • • 0.94 (0.85-0.98) • •	-0.33(3.51/-4.17) -2.07(20.07/-24.21) 2.41(25.36/-20.54)				

Color dots in the table describes the ICC value. • poor reliability, • moderate reliability, • good reliability, • excellent reliability. When 2 dots are present, they indicate the lower and upper limit of the 95%CI.
Abbreviations: ICC, Intraclass correlation coefficient; CI, confidence interval; CV, coefficient of variation; OP, operator; MD, mean difference; LoA, limit of agreement; SEM, standard error of measurement; SI, strain index; M, measurement.

shear-wave propagation (m.s-1). Two studies (Aubry et al. 2013; Hsiao et al. 2015) used both parameters; shear modulus and shear-wave speed.

Type of reliability and raters

In 19 of 24 studies, the primary study aim was to test the reliability, whereas in five of 24 studies, reliability was a secondary aim. In these latter studies, the primary aim was quantification of tendon elasticity (n = 4) and the effect of exercise on tendon elasticity (n = 1).

Intra-rater reliability was assessed in 21 studies, inter-rater reliability was assessed in 14 studies, intra-rater inter-session reliability was assessed in five studies and inter-machine reliability was assessed in two studies. In the majority of the studies (n = 22), ICC was used to analyze the relative reliability, while in two studies (Capalbo et al. 2016; Petitpierre et al. 2018), reliability was assessed using Cohen k or *p* values. Of the 22 studies using ICC, only 12 studies reported the 95% CI despite the recommendation to do so in reporting guidelines (Koo and Li 2016). Other studies used *p* values (n = 4), only the point value of ICC (n = 6) or the ICC range (n = 1). After formal request of additional data, authors of five studies (Helfenstein-Didier et al. 2016; Payne et al. 2017, 2018; Dickson et al. 2019, 2020) provided 95% CI for ICC values.

Table 3. Strain elastography reliability results on patellar and quadriceps tendon.

Autors (y)	Parameters	Conditions	Intra-rater reliability		Inter-session reliability		Inter-rater reliability	
			Relative	Absolute	Relative	Absolute	Relative	Absolute
Porta et al. (2014)	Strain ratio (tendon/subcutaneous tissue)	Longitudinal	ICC (95%CI)				ICC (95%CI)	
		Proximal	0.79 (0.63-0.90) • • OP1				0.64 (0.31-0.84) • •	
			0.75 (0.56-0.88) • • OP2					
		Middle	0.65 (0.43-0.83) • • OP1				0.59 (0.24-0.81) • •	
			0.74 (0.55-0.87) • • OP2					
		Distal	0.71 (0.50-0.85) • • OP1				0.53 (0.15-0.77) • •	
			0.67 (0.44-0.83) • • OP2					
Dickson et al. (2019)	Strain ratio (tendon/fat)	Longitudinal						
			ICC				ICC	
		PQT	0.49 (0.07-0.76) • • OP1				0.10 (-0.05-0.34) • • M1	
		DQT	0.43 (0.00-0.73) • • OP1				0.25 (-0.60-0.39) • • M1	
		PPT	0.85 (0.66-0.94) • • OP1				0.15 (-0.07-0.45) • • M1	
		MPT	0.13 (-0.33-0.53) • • OP1				0.08 (-0.10-0.35) • • M1	
		DPT	0.91 (0.78-0.96) • • OP1				0.10 (-0.05-0.33) • • M1	
		PQT	0.30 (-0.16-0.65) • • OP2				0.14 (-0.14-0.50) • • M2	
		DQT	-0.20 (-0.58-0.26) • • OP2				0.38 (-0.08-0.45) • • M2	
		PPT	0.49 (0.07-0.76) • • OP2				0.11 (-0.10-0.40) • • M2	
		MPT	0.44 (0.01-0.74) • • OP2				0.18 (-0.02-0.45) • • M2	
		DPT	0.41 (0.08-0.76) • • OP2				0.22 (0.00-0.50) • • M2	
		PQT	0.17 (-0.29-0.56) • • OP3					
		DQT	0.01 (-0.43-0.44) • • OP3					
		PPT	0.40 (-0.01-0.72) • • OP3					
		MPT	0.21 (-0.24-0.59) • • OP3					
		DPT	0.22 (-0.24-0.60) • • OP3					
	Color grading		Mean % agreement				Mean % agreement	
		PQT	72%				60% M1 / 57% M2	
		DQT	77%				50% M1 / 48% M2	
		PPT	83%				83% M1 / 83% M2	
		MPT	82%				68% M1 / 80% M2	
		DPT	93%				87% M1 / 93% M2	
Dickson et al. (2020)	Strain ratio (tendon/fat)	Longitudinal			Pearson and Spearman		t-Test #	
			ICC		(p values)&		(p values)	
		PQT	0.49 (0.07-0.76) • • OP1 G *		0.575 OP1 M1		**<0.001** G M1	
		DQT	0.43 (0.00-0.73) • • OP1 G *		0.794 OP1 M1		**<0.001** G M1	
		PPT	0.85 (0.66-0.94) • • OP1 G *		0.267 OP1 M1		0.896 G M1	
		MPT	0.13 (-0.33-0.53) • • OP1 G *		0.711 OP1 M1		**0.03** G M1	
		DPT	0.91 (0.78-0.96) • • OP1 G *		0.138 OP1 M1		0.36 G M1	
		PQT	0.17 (-0.30-0.56) • • OP2 G *		0.574 OP2 M1		0.086 G M2	
		DQT	0.01 (-0.43-0.44) • • OP2 G *		0.846 OP2 M1		**<0.001** G M2	
		PPT	0.40 (-0.01-0.72) • • OP2 G *		0.122 OP2 M1		0.765 G M2	
		MPT	0.21 (-0.24-0.59) • • OP2 G *		0.901 OP2 M1		**0.048** G M2	
		DPT	0.22 (-0.24-0.60) • • OP2 G *		0.493 OP2 M1		0.09 G M2	
		PQT	0.27 (-0.19-0.63) • • OP1 E		0.963 OP1 M2		0.575 E M1	
		DQT	0.51 (0.10-0.77) • • OP1 E		0.324 OP1 M2		0.213 E M1	
		PPT	0.48 (0.05-0.75) • • OP1 E		0.224 OP1 M2		0.455 E M1	
		MPT	0.67 (0.32-0.85) • • OP1 E		0.369 OP1 M2		**0.035** E M1	
		DPT	0.15 (-0.31-0.60) • • OP1 E		0.619 OP1 M2		0.25 E M1	
		PQT	0.35 (-0.10-0.68) • • OP2 E		0.983 OP2 M2		0.533 E M2	
		DQT	0.20 (-0.26-0.58) • • OP2 E		0.964 OP2 M2		0.092 E M2	
		PPT	0.46 (0.04-0.75) • • OP2 E		0.092 OP2 M2		0.615 E M2	
		MPT	0.41 (-0.03-0.71) • • OP2 E		0.756 OP2 M2		**0.044** E M2	
		DPT	0.57 (0.18-0.80) • • OP2 E		0.441 OP2 M2		0.145 E M2	
	Color grading		Mean % agreement		Mean % agreement		Mean % agreement	
		PQT	81% G / 63% E		58%		68% G / 63% E	
		DQT	85% G / 75% E		64%		53% G / 53% E	
		PPT	80% G / 80% E		86%		80% G / 93% E	
		MPT	83% G / 88 % E		81%		73% G / 95 % E	
		DPT	95% G / 80 % E		64%		95% G / 70 % E	

Color dots in the table describes the ICC value. • poor reliability, • moderate reliability, • good reliability, • excellent reliability. When 2 dots are present they indicate the lower and upper limit of the 95%CI.
& significant values indicated inter-machine association.
# significant values **(bold)** indicated no inter-rater reliability.
* same dataset as Dickson et al. 2019 OP1 and OP3.

Table 4. Shear-wave elastography reliability results on Achilles tendon.

Autors (y)	Parameters	Conditions	Intra-rater reliability		Inter-session reliability		Inter-rater reliability	
			Relative	Absolute	Relative	Absolute	Relative	Absolute
Aubry et al. (2013)	Velocity (m.s-1)	Axial					ICC	
		P1 max PF					0.15 ●	
		P2 45° PF					0.06 ●	
		P3 0° PF					0.29 ●	
		P4 45° DF					0.19 ●	
		Longitudinal					ICC	
		P1 max PF					0.46 ●	
		P2 45° PF					0.22 ●	
		P3 0° PF					-0.01 ●	
		P4 45° DF					0.03 ●	
	Shear modulus (kPa)	Axial					ICC	
		P1 max PF					0.16 ●	
		P2 45° PF					0.02 ●	
		P3 0° PF					0.31 ●	
		P4 45° DF					0.17 ●	
		Longitudinal					ICC	
		P1 max PF					0.43 ●	
		P2 45° PF					0.01 ●	
		P3 0° PF					-0.02 ●	
		P4 45° DF					0.04 ●	
	Anisotropy Coefficent (A)	Longitudinal					ICC	
		P1 max PF					0.21 ●	
		P2 45° PF					0.10 ●	
		P3 0° PF					0.23 ●	
		P4 45° DF					0.20 ●	
Peltz et al. (2013)	Shear modulus (kPa)	Longitudinal	ICC					
		Achilles Left	0.54 ● D1 T1					
			0.31 ● D1 T2					
			0.66 ● D2 T1					
			0.82 ● D2 T2					
		Achilles Right						
			0.19 ● D1 T2					
			0.00 ● D1 T2					
			0.11 ● D2 T1					
			0.37 ● D2 T2					
Helfenstein-Didier et al. (2016)	Compression modulus (MPa)	Longitudinal	ICC	CV% and SEM				
		45°	0.42 (0.05-0.83) ● ●	0.81% and 2.14				
		35°	0.73 (0.40-0.94) ● ●	0.60% and 2.04				
		25°	0.85 (0.60-0.97) ● ●	0.48% and 1.37				
	Shear modulus (kPa)							
		45°	1.00 (1.00-1.00) ● ●	0.07% and 10.69				
		35°	1.00 (1.00-1.00) ● ●	0.05% and 6.45				
		25°	1.00 (1.00-1.00) ● ●	0.05% and 3.5				
Siu et al. (2016)	Shear modulus (kPa)	Longitudinal	ICC	CV %			ICC	CV %
			0.85 ● OP1	0.09%			0.59 ●	0.13%
			0.84 ● OP2	0.1%				
			0.80 ● OP3	0.11%				
Lima et al. (2017)	Shear modulus (kPa)	Longitudinal	ICC	CV %	ICC			
		Left	0.93 ●	23%	0.42 ●			
		Right	0.82 ●	25%	0.60 ●			
Payne et al. (2018)	Velocity (m.s-1)	Longitudinal	ICC	CV%; SEM and MDC	ICC	CV%; SEM and MDC		
		Fixed	0.71 (0.50-0.83) ● ●	4.9%; 0.23 and 0.65	0.67 (0.44-0.81) ● ●	5.2%; 0.27 and 0.76		
		Relaxed	0.54 (0.21-0.73) ● ●	2.9%; 0.19 and 0.51	0.55 (0.24-0.73) ● ●	3.1%; 0.20 and 0.55		
		Axial						
		Fixed	0.62 (0.29-0.78) ● ●	3.9%; 0.19 and 0.53	0.78 (0.62-0.87) ● ●	4.4%; 0.17 and 0.46		
		Relaxed	0.71 (0.50-0.82) ● ●	6.0%; 0.26 and 0.71	0.85 (0.74-0.91) ● ●	6.3%; 0.19 and 0.53		
Petitpierre et al. (2018)	Shear modulus (kPa)	Longitudinal PF					p values	
		MTJ					0.163	
		Pre insertional					0.153	
		Enthesis					0.075	
		Longitudinal DF						
		Body					0.236	
		Pre insertional					0.070	
		Enthesis					0.096	
		Axial PF						
		MTJ					0.305	
		Body					0.304	
		Enthesis					0.273	
		Axial DF						
		MTJ					0.134	
		Body					0.096	
		Enthesis					0.169	
Autors (y)	Parameters	Conditions	Intra-rater reliability		Inter-session reliability		Inter-rater reliability	
			Relative	Absolute	Relative	Absolute	Relative	Absolute
Corrigan et al. (2019)	Static and dynamic shear modulus. (kPa) Viscosity (Pa*s)	Longitudinal	ICC (95%CI)					
		Static modulus	0.70 (0.39-0.87) ● ●					
		Dynamic modulus	0.86 (0.72-0.94) ● ●					
		Viscosity	0.86 (0.72-0.94) ● ●					

Color dots in the table describes the ICC value. ● poor reliability, ● moderate reliability, ● good reliability, ● excellent reliability. When 2 dots are present they indicate the lower and upper limit of the 95%CI.

Abbreviations: ICC, Intraclass correlation coefficient; CI, confidence interval; CV, coefficient of variation; SEM, standard error of measurement; MDC, minimal detectable change; OP, operator; PF, plantar flexion; DF, dorsi flexion; MTJ, musculotendinious junction.

Table 5. Shear-wave elastography reliability results on patellar and quadriceps tendon.

Autors (y)	Parameters	Contitions	Intra-rater reliability		Inter-session reliability		Inter-rater reliability	
			Relative	Absolute	Relative	Absolute	Relative	Absolute
Peltz et al. (2013)	Shear modulus (kPa)	Longitudinal	ICC					
		Patellar Left	0.90 • D1 T1					
			0.49 • D1 T2					
			0.40 • D2 T1					
			0.67 • D2 T2					
		Patellar Right	0.45 • D1 T1					
			0.74 • D1 T2					
			0.24 • D2 T1					
			0.23 • D2 T2					
		Quadriceps Left	0.67 • D1 T1					
			0.80 • D1 T2					
			0.79 • D2 T1					
			0.81 • D2 T2					
		Quadriceps Right	0.67 • D1 T1					
			0.61 • D1 T2					
			0.87 • D2 T1					
			0.67 • D2 T2					
Zhang and Fu (2013)	Shear modulus (kPa)	Longitudinal Proximal	ICC (95%CI) 0.98 (0.93–0.99) • •	SEM / MDC (kPa) 1.54 / 4.27			ICC (95%CI) 0.97 (0.93–0.98) • •	SEM / MDC (kPa) 1.64 / 4.54
Hsiao et al. (2015)	Shear modulus (kPa)	Longitudinal	ICC (95%CI)				ICC (95%CI)	
		Proximal	0.87 (0.58–0.97) • • OP1				0.74 (0.04–0.94) • •	
			0.83 (0.32–0.96) • • OP2					
		Middle	0.97 (0.87–0.99) • • OP1				0.82 (0.28–0.96) • •	
			0.99 (0.96–1.00) • • OP2					
		Distal	0.84 (0.47–0.96) • • OP1				0.78 (0.13–0.95) • •	
			0.88 (0.51–0.97) • • OP2					
Tas et al. (2017)	Velocity (m.s-1)	Longitudinal	ICC (95%CI)	CV% / SEM	ICC (95%CI)	CV% / SEM	ICC (95%CI)	CV% / SEM
			0.92 (0.82–0.97) • • OP1	6.5% / 0.48	0.83 (0.57–0.95) • • OP1	7.5% / 0.56	0.71 (0.32–0.88) • •	9.3% / 0.70
			0.91 (0.80–0.96) • • OP2	5.9% / 0.44	0.81 (0.57–0.93) • • OP2	7.1% / 0.51		
Mannarino et al. (2018)	Shear modulus (kPa)	Longitudinal	ICC (95%CI)	CV%	ICC (95%CI)	CV%		
		Dominant	0.89 (0.55–0.92) • • D1	40.19%	0.65 (0.09–0.87) • •	41.26%		
			0.93 (0.80–0.97) • • D2	62.79%				
		Non-dominant	0.89 (0.61–0.97) • • D1	62.98%	0.63 (0.07–0.85) • •	48.19%		
			0.90 (0.65–0.97) • • D2	48.37%				
Zardi et al. (2019)	Shear modulus (kPa)	Longitudinal	ICC (95%CI)	CV (M1/M2)				
		Quadriceps	1.00 (0.99–1.00) • •	0.527 / 0.528				
		Patellar	0.99 (0.98–1.00) • •	0.623 / 0.629				

Absolute reliability was assessed in 13 of 24 studies, with SEM (n = 4), CV (n = 9), mean difference (MD) with upper and lower limit of agreement (n = 2) and smallest detectable changes (n = 1).

In the majority of studies, the rater was described as a general operator, and their profession was not reported (n = 11), whereas seven studies declared the raters to be a radiologist or sonographer, four studies involved medical doctors as raters, two studies involved a physical therapist and one study involved a sport scientist. The years of ultrasound experience of the raters ranged from 0 y (novice) to more than 20 y (senior). Ten of 24 studies did not report the raters' years of experience.

Methodological and reporting quality

Reporting quality (GRRAS). The mean score for all the selected studies was 7.9 out of 15 items, with a lowest score of 5/15 (Aubry et al. 2013; Mannarino et al. 2018; Petitpierre et al. 2018) and a highest score of 12/15 (Alsiri et al. 2020). None of the included studies provided auxiliary material to detail the results of the study; therefore item 15 was not reported in any article.

Item 12, regarding the description in the results section of the rater and subject characteristics, was not reported in any of the included studies. However, in 15 of the selected studies, this information was reported in the methods section.

There were a high number of studies missing on one or more of the following items: item 4: only one study (Dickson et al. 2020) specified the rater population of interest in the introduction; item 6: only three studies (Yamamoto et al. 2016; Ünal et al. 2019; Alsiri et al. 2020) explained in the methods how sample size was chosen; item 7: eight of 24 studies described the sampling methods; item 11: five of 24 studies stated, in the results section, the actual number of raters and patients included.

Detailed scores for each item are reported in Figure 2. Conversely, a large amount of the studies included (>21) reported the items regarding the description of the study design (item 1) and of the technology included (item 2), specified the subject population of interest (item 3), described the statistical analysis (item 10) and discussed the practical relevance of the results (item 14). All the items of the

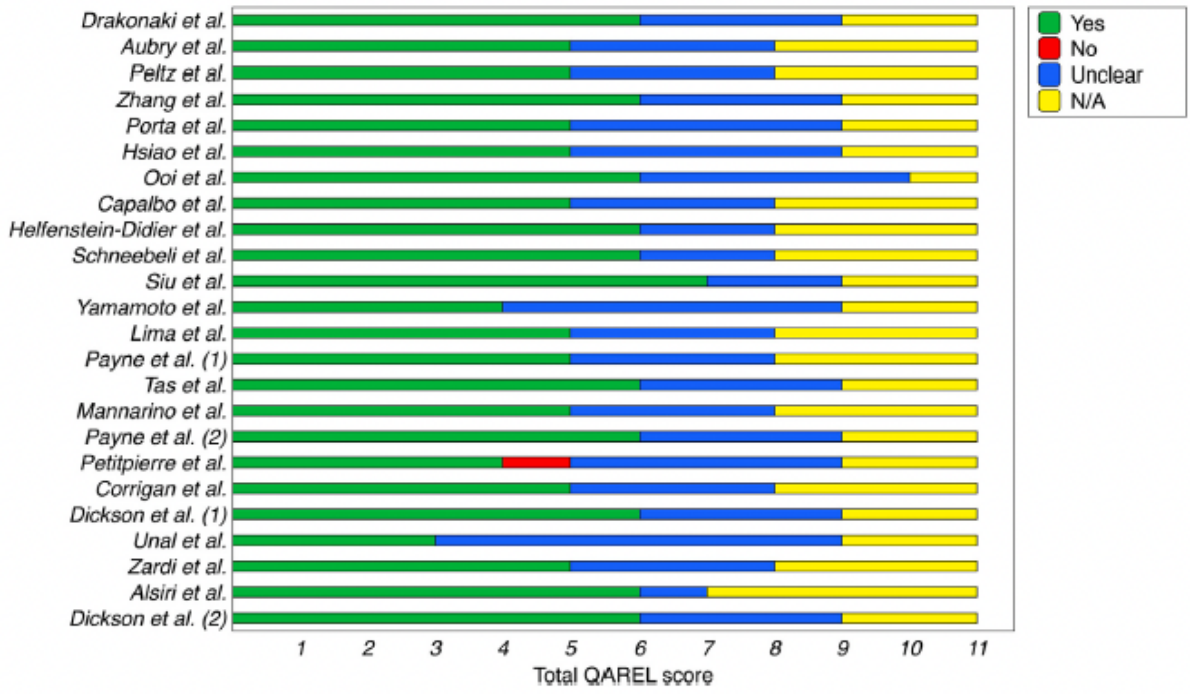


Fig. 5. Bar chart showing the total QAREL score of the different selected studies.

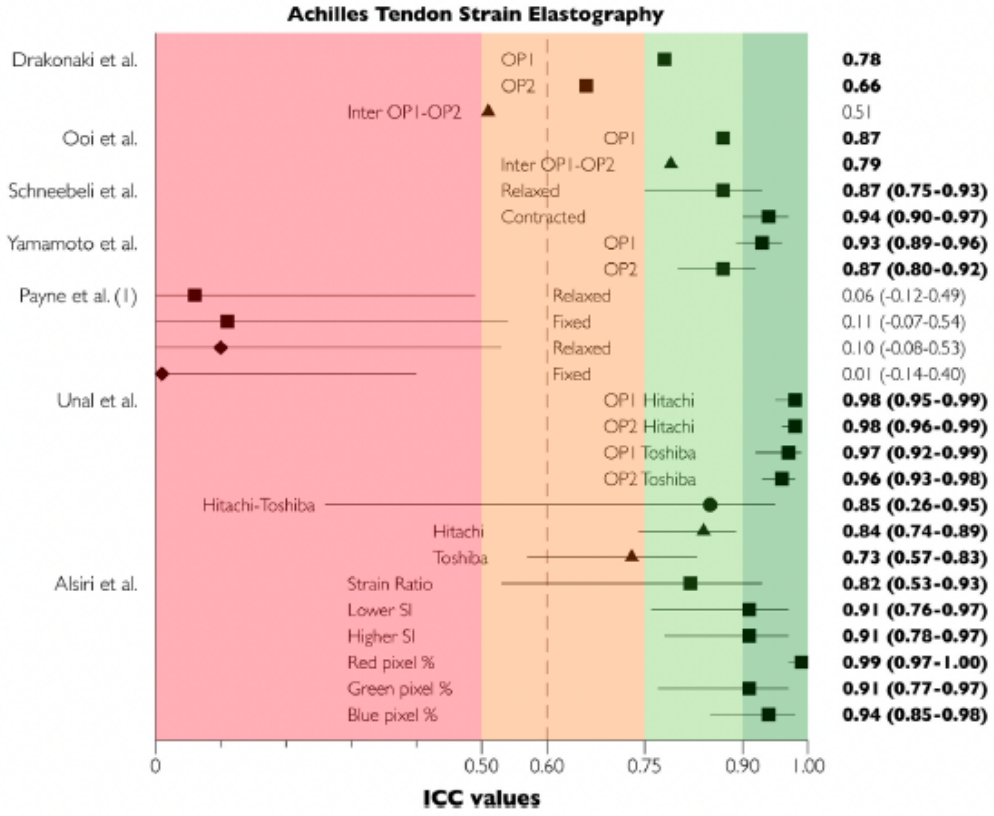


Fig. 6. Forest plot representing the intra-class correlation coefficient (ICC) values of the study analyzing strain elastography (SE) reliability in the Achilles tendon in the longitudinal scan. Dotted line, ICC = 0.6 clinical relevance threshold. Red, orange, light green and dark green areas represent poor, moderate, good and excellent reliability values, respectively. ■; Intra-rater reliability ▲; Inter-rater reliability ◆; Inter-session reliability ●; Inter-machine reliability OP, operator; SI, strain index.

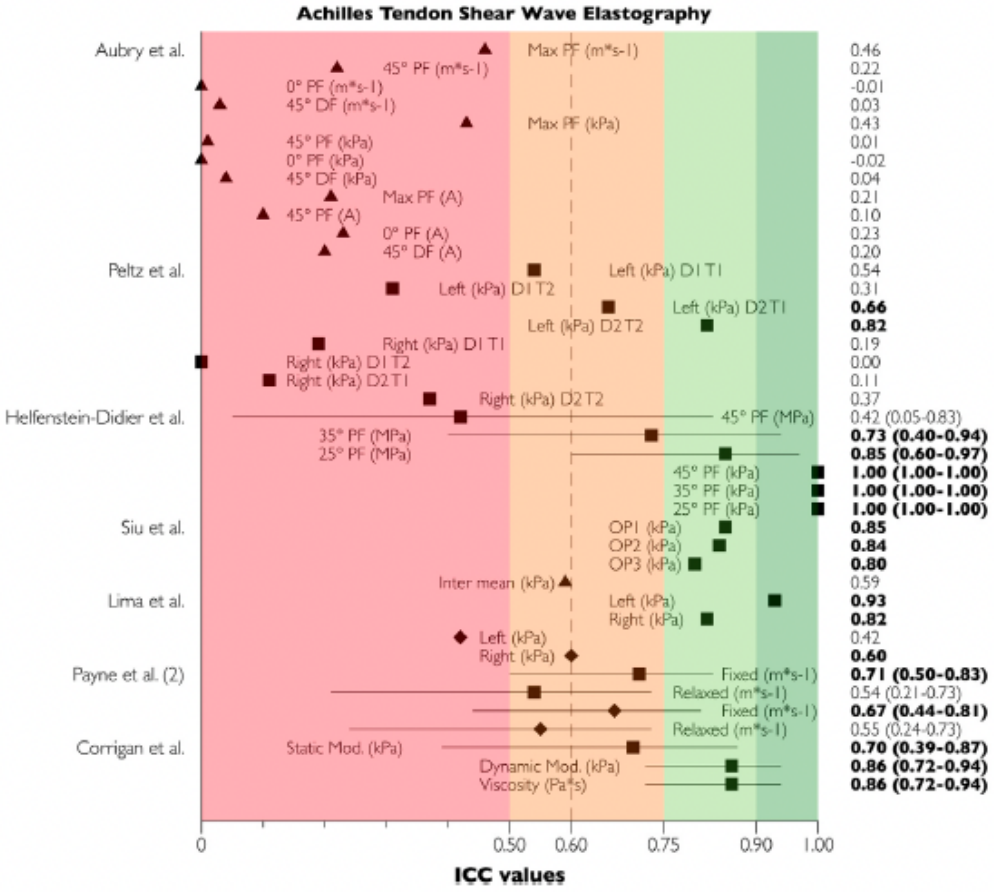


Fig. 7. Forest plot representing the intra-class correlation coefficient (ICC) values of the study analyzing shear-wave elastography (SWE) reliability in the Achilles tendon in the longitudinal scan. Dotted line, ICC = 0.6 clinical relevance threshold. Red, orange, light green and dark green areas represent poor, moderate, good and excellent values, respectively. ■; Intra-rater reliability ▲; Inter-rater reliability ◆; Inter-session reliability A, anisotropy coefficient; D, day; DF, dorsi flexion; Mod., modulus; OP, operator; PF, plantar flexion; T, trial.

GRRAS scale divided for each study are reported in the Figure 3. The mean agreement between the two reviewers scoring on the GRRAS scale was 95.8%. Disagreement on one item of three different studies were resolved by the third reviewer.

Methodological quality (QAREL). The QAREL checklist was used to appraise the methodological quality of the included studies. Item 5 regarding the blinding of the disease status was rated N/A in all studies whereas item 7 regarding the blinding of additional cues was rated as unclear in all studies. Once the N/A score was removed, the maximum score possible ranged from 7–10. The maximum of "yes" answers were obtained by Siu et al. (Siu et al. 2016) with a score of 7 of 9. A minimum of one and a maximum of six "unclear" answers were reported in all 24 studies selected, indicating uncertainty in the methodological quality, exposing all the studies to a possible risk of bias. Detailed scores for each item are reported in Figure 4.

The study that presented with the highest "yes" answers net of the total score is the study of Alsiri et al. (2020), with only one "unclear" answer. One study (Petitpierre et al. 2018) obtained a "no" answer for the item 11 regarding the appropriate statistical analysis. As defined by Lucas et al. (2010), the items rated as "no" can invalidate the study and compromise the findings. Therefore, the aforementioned study was not included in the qualitative syntheses of the present review.

QAREL items divided for each study are reported in Figure 5. The mean agreement was 96.2% between the two reviewers scoring on the QAREL checklist. Disagreement on one item of two different studies were resolved by the third reviewer.

Reliability

The heterogeneity of the analyzed studies precluded a quantitative analysis; therefore a qualitative analysis was performed, dividing the studies by the type of technology used (SE or SWE) and the tendon analyzed

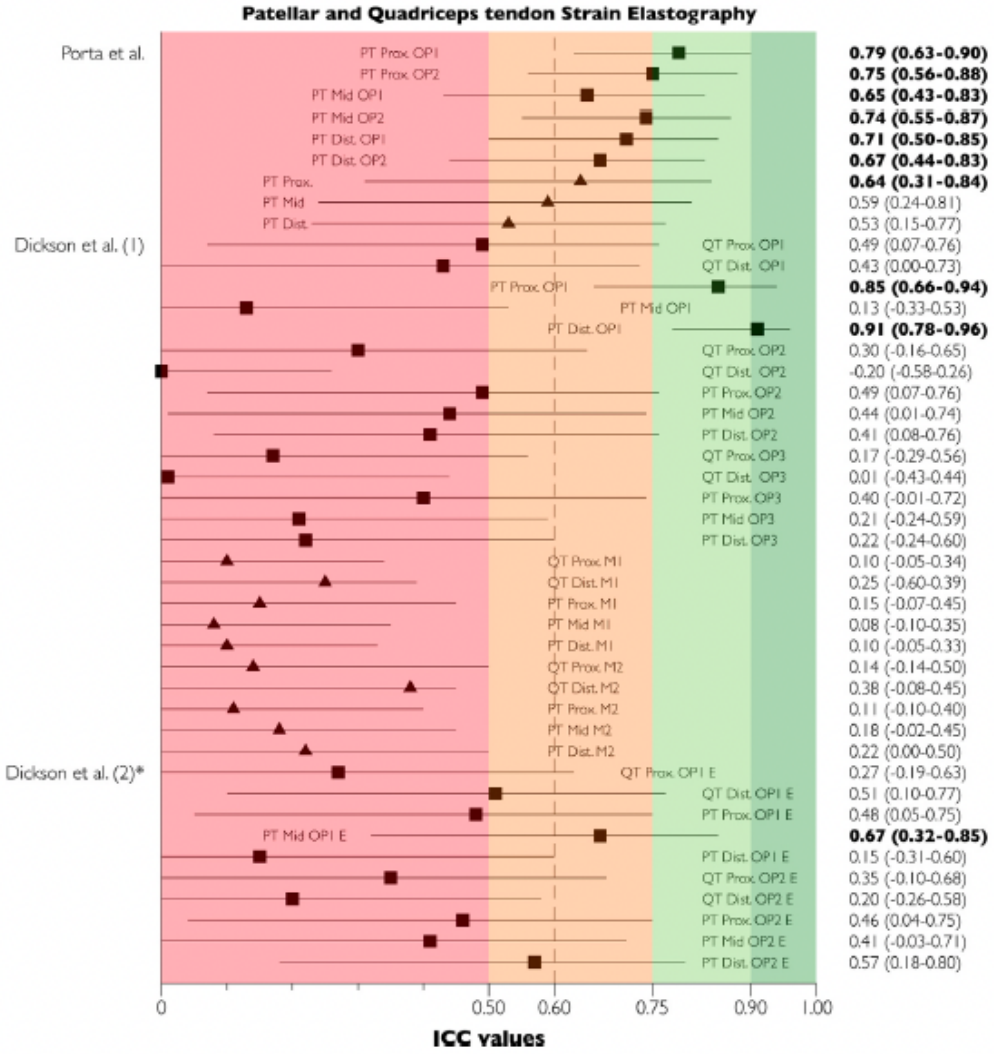


Fig. 8. Forest plot representing the intra-class correlation coefficient (ICC) values of the study analyzing strain elastography (SE) reliability in the patellar and quadriceps tendons in the longitudinal scan. Dotted line, ICC = 0.6 clinical relevance threshold. Red, orange, light green and dark green areas represent poor, moderate, good and excellent reliability values, respectively. ■; Intra-rater reliability ▲; Inter-rater reliability D, day; Dist., distal; Dom., dominant; E, Esaote ultrasound, N-Dom, non-dominant; OP, operator; Prox., proximal; PT, patellar tendon; QT, quadriceps tendon. * For GE ultrasound values of this study, see Dickson et al. (1) OP1 and OP3.

(AT, PT and QT). Relative and absolute reliability for the different tendons and technologies are reported in Tables 2–5. A visual representation of relative reliability with ICC values is presented in Figures 6–9.

The qualitative synthesis of the studies was performed considering the following criteria:

- The ICC punctual value has to be ≥ 0.6.
- The lower limit of the 95% CI has to exceed 0.5.

If one of these criteria was not fulfilled, this study was considered to have inconclusive reliability. Moreover, where 95% CI were not reported, the study was cautiously evaluated.

SE: Achilles tendon. Eight studies evaluated the reliability of AT elasticity measures using SE. Moderate to excellent intra-rater reliability was found for the longitudinal measurement of strain ratio; results ranged from an ICC of 0.66–0.99. Inter-rater reliability was moderate to good (ICC = 0.51–0.84), with some studies showing values below the 0.6 threshold.

A moderate inter-rater correlation was also found in one study (r_s 0.61) (Yamamoto et al. 2016). Another study (Ünal et al. 2019) analyzing the inter-machine reliability showed an ICC of 0.85 (0.26–0.95), indicating good reliability but with very large 95% CI. Agreement on the color grading of SE images was considered substantial ($\kappa = 0.70$) for intra-rater evaluation and was

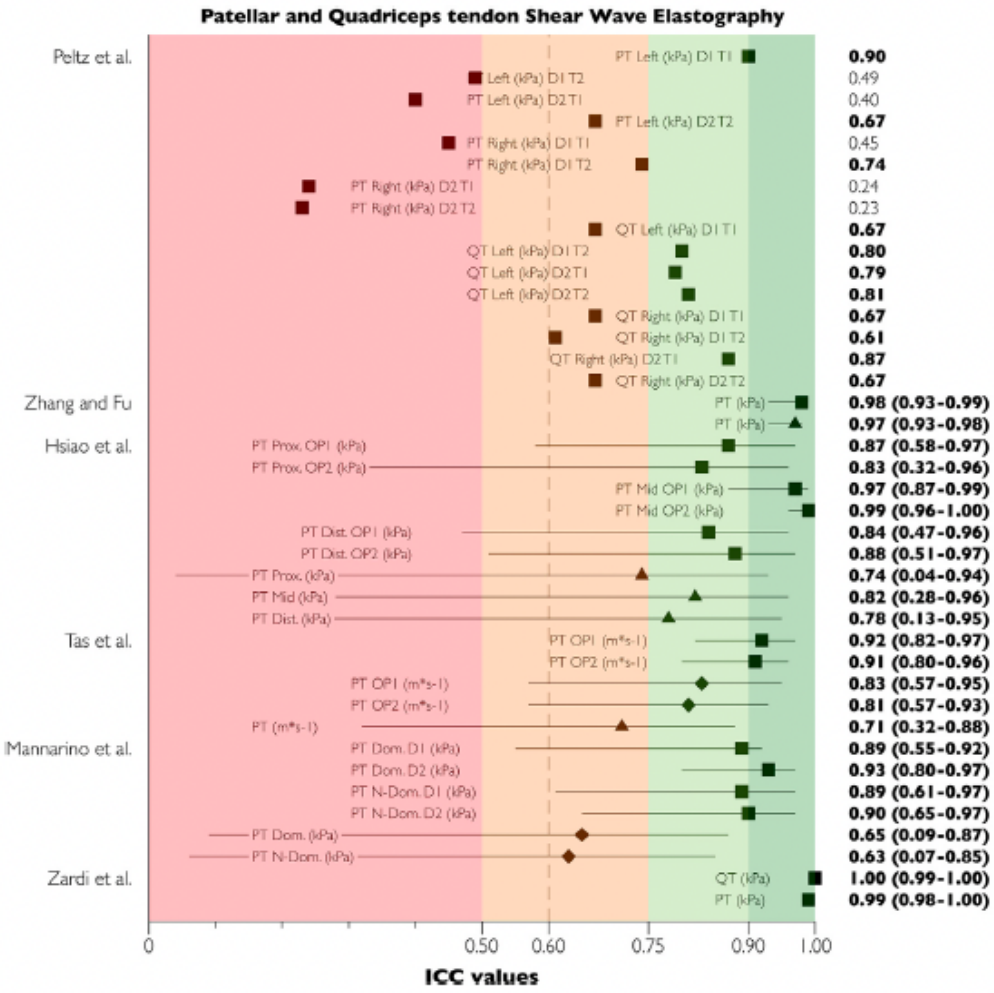


Fig. 9. Forest plot representing the intra-class correlation coefficient (ICC) values of the study analyzing shear-wave elastography (SWE) reliability in the patellar and quadriceps tendons in the longitudinal scan. Dotted line, ICC = 0.6 clinical relevance threshold. Red, orange, light green and dark green areas represent poor, moderate, good and excellent reliability values, respectively. ■; Intra-rater reliability ▲; Inter-rater reliability ◆; Inter-session reliability D, day; Dist., distal; Dom., dominant; N-Dom, non-dominant; OP, operator; Prox., proximal; PT, patellar tendon; QT, quadriceps tendon; T, trial.

considered substantial to almost perfect ($\kappa = 0.70-0.91$) for inter-rater evaluation.

Poor reliability was found for intra-rater (ICC = 0.06–0.11) and for inter-session (ICC = 0.01–0.10) when using the percent of displacement values (Payne et al. 2017). Axial scan using SE was evaluated in two studies (Drakonaki et al. 2009; Payne et al. 2017), showing poor intra- and inter-rater reliability (ICC < 0.45).

Overall, intra- and inter-rater reliability for AT elasticity measured with SE strain ratios in a longitudinal scan was adequate. Inter-machine reliability tested in one study reported inconclusive results. Color grading intra- and inter-rater agreement was substantial.

SE: patellar and quadriceps tendons. Two studies (Dickson et al. 2019, 2020) shared part of the data set; therefore, intra-rater reliability values obtained with the GE ultrasound device were reported only for the study by Dickson et al. (2019), eliminating the other study (Dickson et al. 2020).

PT strain ratio was evaluated in three studies, showing intra-rater reliability values ranging from poor to good (ICC = 0.40–0.85) for the proximal, (ICC = 0.13–0.67), middle (ICC = 0.15–0.91) and distal part of the tendon. Inter-rater reliability ranged from poor to moderate (ICC = 0.11–0.64) for the proximal (ICC = 0.08–0.60), middle (ICC = 0.22–0.96) and distal part of the tendon.

Inter-rater agreement of strain ratio using a *t*-test (*p* values) (Dickson et al. 2020) revealed mixed results with good values only documented for the proximal and distal part of the PT (Table 3). Inter-machine association using strain ratios was evaluated in one study (Dickson et al. 2020) showing significant results, indicating no association between the two ultrasound devices for the PT.

Mean percent of agreement on the color grading for PT was >80% for intra-rater, between 68% and 95% for inter-rater and between 64% and 86% for inter-machine (Dickson et al. 2019, 2020).

QT strain ratio was evaluated in two studies revealing poor intra-rater (ICC<0.5) and inter-rater (ICC<0.5) reliability and no inter-machine association ($p > 0.05$). Mean percent of agreement on the color grading for QT was between 63% and 85% for intra-rater, between 48% and 68% for inter-rater and between 58% and 64% for inter-machine (Dickson et al. 2019, 2020).

Overall, reliability of SE measures using strain ratios on the PT was adequate only for intra-rater reliability when measured in the proximal part of the PT and if analyzed by expert operators. QT measures were not reliable. Intra-rater agreement in the color grading was good for the PT and QT. Inter-rater agreement was adequate in the PT and lower on the QT.

SWE: Achilles tendon. Eight studies evaluated the reliability of using SWE to measure AT elasticity in a longitudinal scan. Results indicated poor to excellent intra-rater reliability (ICC = 0.17–1.00) for the elasticity or shear modulus (kPa), moderate intra-rater reliability (ICC = 0.54–0.71) for velocity ($m.s^{-1}$) and poor to good intra-rater reliability (ICC = 0.42–0.85) for compression modulus (MPa). In two studies (Aubry et al. 2013; Helfenstein-Didier et al. 2016), reliability results were also divided according to angle of the ankle when the measurements were performed (Table 4). Inter-rater reliability was poor to moderate (ICC = −0.02 to 0.59) for shear modulus (kPa) and poor (ICC < 0.5) for velocity ($m.s^{-1}$). Inter-session reliability was poor to moderate (ICC = 0.42–0.60) for shear modulus (kPa) and moderate (ICC = 0.55–0.67) for velocity ($m.s^{-1}$).

One study (Payne et al. 2018) showed moderate to good intra-rater and inter-session reliability for velocity axial values (ICC = 0.62–0.85), whereas another study (Aubry et al. 2013) showed poor inter-rater axial values (ICC <0.5) for shear modulus and for velocity.

Overall, inter-rater and inter-session reliability of SWE measures for AT was inconclusive.

Intra-rater reliability was conflicting, with some studies indicating good reliability and others poor reliability.

SWE: patellar and quadriceps tendon. Six studies evaluated intra-rater reliability of PT measurements with poor to excellent results (ICC = 0.45–1.00) for shear modulus (kPa) and excellent intra-rater reliability (ICC = 0.91–0.92) for velocity ($m.s^{-1}$). Inter-session reliability was moderate (ICC = 0.63–0.65) for shear modulus (kPa) and good (ICC = 0.81–0.83) for velocity (m.s-1). Inter-rater reliability ranged from moderate to excellent (ICC = 0.71–0.97) for both shear modulus and velocity.

Two studies evaluated the QT intra-rater reliability, one with moderate results (ICC = 0.72–0.77) (Peltz et al. 2013) and the other with excellent results (ICC = 0.99–1.00) (Zardi et al. 2019). Overall, intra-rater reliability of SWE was satisfactory for the PT and QT. Inter-rater and inter-session reliability results were conflicting.

DISCUSSION

The present systematic review aimed to synthesize the evidence regarding the reliability of sonoelastography for the assessment of lower limb tendon mechanical properties. Reliability and validity are prerequisites to the clinical applicability of a measure. These measurement properties should be confirmed before this technology is used in clinical settings. The results of this systematic review suggest that reliability is highly variable across the studies, and therefore the use of this technology in a clinical setting should be further evaluated in high-quality reliability studies. Furthermore, other clinimetric properties (*i.e.,* validity and responsiveness) should be further investigated.

Twenty-four articles were included and reviewed in subgroups of studies divided by technology used and tendons analyzed. High heterogeneity was found between studies even when using the same technology on the same tendon. Different joint angles and position, different probe orientation (longitudinal or axial scan), different parameters used to calculate elasticity and different ultrasound devices used challenged the possibility of comparing results between studies. Nevertheless, a qualitative synthesis was conducted, and overall, there was a large variability of the results regardless of the technology used or the tendon analyzed with variable reliability findings; these conflicting results could be attributed to the low methodological quality of the included studies.

As expected, intra-rater reliability results were superior to inter-rater or inter-session values, confirming that this type of ultrasound-based technology, whether with qualitative or quantitative elastogram analysis, is particularly dependent on the operator's manual skills and experience (Prado-Costa et al. 2018). However, we cannot exclude that the lower reliability found for inter-rater and inter-session is related to the paucity of studies analyzing this type of reliability. Different results were found between the lower limb tendons, suggesting that the reliability of sonoelastography could be influenced by the structural and morphologic characteristics of the tissues evaluated.

Very wide 95% confidence intervals of the ICC values were found across the majority of the studies, questioning

the sample size used. The use of inadequate sample size is confirmed by the low score on the GRRAS scale (item 6).

The quality of the reporting in the selected papers was poor, with only two studies with more than 10 out of 15 points on the GRRAS scale (Alsiri et al. 2020; Dickson et al. 2020). The majority of the studies lacked a description of the raters and patients of interest in the definition of the sampling methods and the calculation of the sample size.

Although the reviewed papers were designed specifically to evaluate reliability, many were not reported adequately. Moreover, the comparison between studies and the replication of an individual study is compromised by the lack of detailed reporting of the procedures. Furthermore, even the methodological quality of the studies included, screened with the QAREL checklist, showed a possible risk of bias owing to shortcomings in the study design.

Considering the real total score without "N/A" answers, the majority of the included studies (17 out of 24) scored at maximum 2 or 3 points less than the possible highest value. Nevertheless, in almost all of the included studies, one or more items were scored as "unclear," indicating possible methodological bias (Fig. 5). The lack of clarity in the experimental design mainly concerned the blinding of the raters to the finding of other raters (item 3), the blinding to their own prior findings (item 4), the blinding to additional cues that were not part of the test (item 7) and the varied order of examination (item 8). The "unclear" score did not invalidate the study but made it vulnerable to possible bias. These limitations may be attributed to insufficient reporting rather than real methodological bias. Given the low quality in reporting and the possible methodological bias present in all studies, caution should be used in the interpretation of the results.

Future studies evaluating reliability should adhere to validated quality assessment tools to improve methodological quality and reporting of the results.

SE: Achilles tendon

The majority of the included studies showed that SE has acceptable (ICC >0.6) intra-rater reliability except for one study (Payne et al. 2017) that showed very low reliability values. High intra-rater reliability values were found when the AT was analyzed using semi-quantitative analysis using strain ratio with an external reference material (Schneebeli et al. 2016; Yamamoto et al. 2016). Variable results (moderate to excellent) were obtained when using strain ratio for the Kager fat pad (Drakonaki et al. 2009; Ooi et al. 2015; Ünal et al. 2019) or subcutaneous fat (Alsiri et al. 2020) and low results when using the percent of displacement calculation (Payne et al. 2017).

Inter-rater results were variable (moderate to high) between studies, with one study presenting results lower than the threshold of 0.6 (Drakonaki et al. 2009) and two studies with moderate to good reliability (Ooi et al. 2015; Ünal et al. 2019).

Overall, both intra- and inter-rater SE measurements of the AT appear reliable when using semi-quantitative strain ratio analysis. Conversely, calculating the percent of displacement in SE seems unreliable (Payne et al. 2017). When analyzing the tendon qualitatively with color grading, the agreement is substantial to almost perfect.

In addition to strain ratio measurements, Alsiri et al. (2020) presented another method to quantify SE images using the color pixel analysis. This method is based on the quantification of the percentages of each color in the SE image. Intra-rater reliability of this method on the AT appeared higher than the strain ratio measure. However, caution should be used in the analysis of elastograms without an external reference material not affected by changes in elasticity owing to pathology, recovery or different measurement conditions. A simple count of the color pixel within the same structure disregards the algorithm implemented in SE ultrasound devices that uses an "auto scale" color range (Schneebeli et al. 2019).

Ünal et al. (2019) evaluated the inter-machine reliability, showing variable results ranging from ICC of 0.26–0.95. Given this result, the author suggests evaluating the tendon separately for each device. The latter study emphasizes one of the major limitations of SE. The semi-quantitative analysis obtained by a color scale may differ depending on the algorithm implemented by different companies and from the amount of compression with the probe permitted by different devices.

The differences between devices in the generation of the color scale may hinder the clinical applicability of SE. Caution should be taken when comparing results obtained from different devices on the same structure.

SE: patellar and quadriceps tendon

In contrast to the AT, SE using strain ratios on the PT and QT have questionable intra- and inter-rater reliability results. 95% CI of the reliability measurement often fell below the 0.6 threshold, indicating poor to moderate reliability and weak clinical relevance.

Porta et al. (2014) showed moderate to good intra-rater reliability with almost all the CI values below 0.6 and poor inter-rater reliability. Two studies (Dickson et al. 2019, 2020) reported mixed results with measurements on some part of the PT appearing to be reliable when measured by an expert rater. Overall, the results of those studies indicate poor reliability except for the proximal PT when analyzed by expert operators.

When using color grading, agreement between operators appears to be better compared with using semi-quantitative analysis (Dickson et al. 2019, 2020).

Operator experience seems to play an important role to be able to measure the PT and QT in a reliable way. The different reliability values obtained with SE on the AT, QT and PT could be attributed to differences in anatomy between tendons, where the first two are tendons with one bone insertion and muscle while the latter is attached to a bony structure on both sides. Compression with the ultrasound probe on a "free" tendon rather than on a more solid structure with the proximity of prominent bone projection, as for PT, could affect reliability results. Furthermore, the different structures used for the strain ratio, subcutaneous tissue (Porta et al. 2014) and Hoffa fat pad (Dickson et al. 2019, 2020) could have led to a difference in reliability compared with AT measurements using an external reference material (Schneebeli et al. 2016; Yamamoto et al. 2016) or Kager fat pad (Drakonaki et al. 2009; Ooi et al. 2015; Ünal et al. 2019; Alsiri et al. 2020).

To date, only three studies with a small sample size are present in the literature. Given the high variability of these results, further studies with high methodological quality are needed to establish the reliability of SE when measuring these tendons.

SWE: Achilles tendon

SWE measurements of the AT showed conflicting results with two studies (Aubry et al. 2013; Peltz et al. 2013) showing poor to moderate intra- and inter-rater reliability for longitudinal and axial scans. One of these studies (Peltz et al. 2013) indicated a reliability slightly over the 0.6 threshold but only for the left tendon.

Two other studies (Helfenstein-Didier et al. 2016; Corrigan et al. 2019) revealed moderate to excellent intra-rater reliability for compression and shear modulus (Helfenstein-Didier et al. 2016) except for the compression modulus at 45° and 35° plantarflexion and moderate to excellent intra-rater reliability for dynamic modulus and viscosity (Corrigan et al. 2019) with inconclusive results for the static modulus.

Furthermore, two studies (Siu et al. 2016; Lima et al. 2017) showed good to excellent intra-rater reliability but poor or moderate inter-rater (Siu et al. 2016) and inter-session reliability (Lima et al. 2017). Finally, Payne et al. (2018) showed acceptable intra-rater reliability in the longitudinal scan when the ankle was fixed at 0° plantarflexion, but doubtful reliability for the relaxed position. Surprisingly, this study showed higher values (moderate to high) when the tendon was analyzed in the axial scan.

Indeed, waves propagate along the fibers, as for longitudinal scan, more easily than across the fiber, as for axial scan. Moreover, during an axial scan, inhomogeneous compression with the edges of the probe could occur, which may affect the reliability. Considering these results, further studies are needed to better understand the value of axial scans in the analysis of tendon elasticity.

Although the majority of the SWE studies used the Aixplorer ultrasound equipment, two studies (Payne et al. 2018; Corrigan et al. 2019) analyzed AT with a different SWE device but obtained similar results to the other studies. Overall the results indicated relatively good intra-rater reliability but poor inter-rater and inter-session reliability.

The main reasons for the lack of inter-rater reliability are, according to the authors, because of the difficulties in the stabilization of the ankle joint position (Aubry et al. 2013; Peltz et al. 2013) and measurement bias related to positioning, the direction of the transducer or to the positioning of the ROI (Aubry et al. 2013). Moreover, anisotropic changes of the tendon owing to a slightly different position of the ankle can occur. Furthermore, some authors (Aubry et al. 2013; DeWall et al. 2014; Chino and Takahashi 2015) suggested that the higher shear modulus achievable with this technology (600−800 kPa) was not sufficient to calculate tendon elasticity in a position near to 0° plantarflexion or in dorsiflexion because of saturation of the signal.

SWE: patellar and quadriceps tendon

The six studies evaluating the PT and QT with SWE showed high intra- and inter-rater reliability with all the point values of ICC of more than 0.6, except for the PT in the study of Peltz et al. (2013). Inter-session reliability was also considered moderate to high in two studies (Tas et al. 2017; Mannarino et al. 2018).

Two studies (Zhang and Fu 2013; Zardi et al. 2019) reported excellent intra- and inter-rater reliability values for PT and QT. Nevertheless, considering the 95% CI of all the ICC results (Fig. 9), the majority of the included studies, especially for inter-rater and inter-session reliability, presented CI values substantially lower than 0.5 and therefore should be considered as poor reliability. These values are often neglected by authors and readers but are critical when analyzing and interpreting ICC values. Indeed, the CI gives the range within which the true ICC value is supposed to be, and this could be at any point between the lower and the higher limits. Therefore, the true ICC value could largely be lower than the estimate value (Shrout and Fleiss 1979; Koo and Li 2016). Considering this large confidence interval, Hsiao et al. (Hsiao et al. 2015) concluded that the only suitable part of the PT to make SWE evaluation is the mid tendon and that inter-rater reliability should be cautiously interpreted. Overall, intra-rater reliability was adequate for PT and QT but dubious for inter-rater and inter-session. According to the authors, the reason for this variability between studies could be attributed to the difference in the ROI placement and size. Furthermore, some authors

(Drakonaki et al. 2012; Chen et al. 2013; Hsiao et al. 2015) suggested that another possible cause of heterogeneity in the results are the saturation of the signal with high shear modulus (kPa) values and the excessive noise signal when measuring soft tissue near bone. Finally, the small sample size present in some of these studies may have led to an increased 95% CI.

Limitations

To improve the quality of the included articles, the search was restricted to full peer-reviewed published papers; relevant grey literature may have been excluded. The high heterogeneity of the included studies, which used varying joint angles, tendon portion, conditions, ultrasound scan, extracted parameters and statistical methods, made generalization of the results difficult. Graphical synthesis of the results was done in a sub-portion of the data of the included studies. Given the high heterogeneity of the data reported, especially regarding the parameter used to calculate elasticity, a quantitative synthesis with meta-analysis was not possible. This systematic review included only reliability measures on lower limb tendons and therefore the results may not be generalized to other tendons. Other measurement properties apart from reliability (*i.e.,* validity, diagnostic accuracy, sensitivity, specificity) were not evaluated in this systematic review; different sonoelastography measurement properties need to be reviewed in the future. Moreover, the majority of the studies assessed tendon in healthy participants, and therefore it is not possible to generalize these results to a clinical context in the assessment of pathologic tendons.

CONCLUSIONS

Although sonoelastography measures of lower limb tendons are commonly used in research and clinical settings, overall the reliability of these measures remains highly variable across studies. SE on AT is reliable when using strain ratio, and good agreement was found in the color grading analysis, but this was not the case for the PT.

The reliability of SWE measurements were highly variable between studies; nevertheless, it seems to be more reliable on PT than on AT, especially if different operators are compared. However, weakness in the reporting and possible methodological bias were present in all studies, making it difficult to recommend one technology over another. The interpretation of reliability results was often over-estimated given the lack of consideration of the confidence interval. The lack of inter-rater, inter-session and inter-machine reliability found in this systematic review raises important doubts about the clinical applicability of these technologies. Caution should be used when interpreting results from sonoelastography measures.

Further reliability studies of high methodological quality are needed to better understand the value of these technologies in the assessment of lower limb tendon mechanical properties to transfer the use of these measures in clinical settings to provide meaningful information about tendon status.

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Appendix 5 – PRISMA Checklist

Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMAreporting guidelines, and cite them as:

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

		Reporting Item	Page Number
Title			
	#1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	2
Introduction			
Rationale	#3	Describe the rationale for the review in the context of what is already known.	3

		each meta-analysis.	
Risk of bias across studies	#15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	#16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
Results			
Study selection	#17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	#18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citation.	6
Risk of bias within studies	#19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	7-8
Results of individual studies	#20	For all outcomes considered (benefits and harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	8-10
Synthesis of results	#21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	8-10
Risk of bias across studies	#22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	#23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
Discussion			
Summary of Evidence	#24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers	10-12

Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	#26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
Funding			
Funding	#27	Describe sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review.	14

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Appendix 6 – Schneebeli et al., 2020b

BMJ Open Sport & Exercise Medicine

Myotonometry for the evaluation of Achilles tendon mechanical properties: a reliability and construct validity study

Alessandro Schneebeli [1,2], Deborah Falla [2], Ron Clijsen [1,3], Marco Barbero [1]

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ABSTRACT

Objective This study evaluates the intra-rater and inter-rater reliability of the MyotonPRO and its construct validity for the assessment of Achilles tendon stiffness.

Design Reliability and construct validity study.

Methods Forty healthy participants were assessed using the MyotonPRO by two raters on two different occasions. Tendon was evaluated in three different positions (relaxed, 0° plantarflexion and standing) and during different isometric contractions (range 0–3 kg). Reliability was calculated using intraclass correlation coefficient (ICC and 95% CI) standard error of measurement and minimal detectable change. Construct validity was evaluated between the different positions and the different contraction intensities using Friedman test.

Results Intra-rater reliability was very high $ICC_{2,k}$ 0.87–0.98. The reliability of the 0.5 kg contraction was moderate with an $ICC_{2,k}$ of 0.59. Inter-rater reliability ranged from high to very high with an $ICC_{2,k}$ of 0.76–0.86. The reliability of the 0.5 kg, 1 kg contraction and the standing position was moderate with an $ICC_{2,k}$ of 0.55, 0.54 and 0.56 respectively. Inter-session reliability ranged from high to very high with an $ICC_{2,k}$ of 0.70–0.89. The reliability of the 0.5 kg contraction was moderate with an $ICC_{2,k}$ of 0.54. Construct validity was demonstrated between different contraction levels and different positions.

Conclusion MyotonPRO is a reliable tool for the evaluation of Achilles tendon stiffness during different contraction levels and in different positions. Construct validity was supported by changes of tendon stiffness during the explored conditions. MyotonPRO can be implemented, as a ready to use device, in the evaluation of tendon tissue mechanical properties.

Summary box

- Achilles tendon stiffness can be measured with MyotonPRO. High intra-rater, inter-rater and inter-session reliability has been found in different position and during isometric contractions.
- The interest in measuring tendon stiffness is growing for its clinical and research relevance. A reliable and ready to use device has been presented in this study. MyotonPRO could be implemented in the evaluation of Achilles tendon mechanical properties.
- Stiffness of healthy Achilles tendons has been assessed, reliability in patient with tendinopathies could be different.

INTRODUCTION

The Achilles tendon (AT) is one of the most commonly injured structures in the lower limb, both in athletes and the general population.[1 2] Tendinopathy of AT can alter the mechanical, material and morphological properties of the tendon structure with a decrease of stiffness and young modulus and an increase of tendon cross-sectional area and diameter.[3 4]

Healthy tendon is highly responsiveness to mechanical loading.[5] Adaptation of tendon has been shown following different loading protocols, and the intensity of the exercise (ie, high loading magnitude) and the intervention duration (>12 weeks) appear to contribute the most to changes in the mechanical properties of the tendon. The change in tendon stiffness appears to be largely due to adaptations in the material rather than morphological properties of the tendon.[5] That is, early changes in young modulus is apparent following loading protocols whereas changes in tendon hypertrophy appear as longer-term adaptations to mechanical loading.[6]

Tendon responses to loading, unloading and ageing have been evaluated in a recent review revealing adaptability of the tendon tissue with an increase in stiffness when loaded and reduced stiffness when unloaded.[3] Nevertheless, conflicting results has been reported when evaluating the in vivo effects of ageing on tendon stiffness, with some authors suggesting a decrease in modulus[3 7–11] and others reporting unchanged tendon stiffness with ageing.[12 13]

Given the clinical and research interest in evaluate tendon stiffness as a parameter to describe tendon behaviour and tendon health, different measurement techniques have been developed. Once recent, non-invasive, ready to use technology is the

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MyotonPRO (Muomeetria, Tallinn, Estonia). This device is a handheld myotonometer producing a mechanical impulse to the skin overlying the target structure. The oscillation of the tissues underneath the probe permits calculation of the viscoelastic properties of the tissue.[14–16] One parameter that can be extracted with this device is dynamic stiffness (N/m), which has been used in different studies to characterise the behaviour of different musculoskeletal tissues. This device has recently been used to evaluate tendon stiffness[17–20] with a recent work showing decreased stiffness over the tendinopathic region of the tendon in people with Achilles tendinopathy and a significant difference in tendon stiffness between weight-bearing and non-weight-bearing positions.

The reliability of the MyotonPRO has been demonstrated for the evaluation of muscle stiffness,[15 21–23] however, the reliability of MyotonPRO for measuring AT stiffness requires further investigation,[17 18 24 25] especially regarding the capability of this device to measure the tendon in different conditions. In contrast to muscle, values of AT stiffness are extremely high and even higher when tested under load.[19] Being able to quantify AT mechanical properties with a ready to use and affordable device which provides a reliable and valid evaluation of the tendon under different conditions, would provide new opportunities to characterise the mechanical behaviour of the AT, for example, in people with Achilles tendinopathy or following an intervention.

This study evaluates the intra-rater and inter-rater reliability of using the MyotonPRO to measure stiffness of asymptomatic AT in different position and during increasing load and to determine the construct validity of this device for measuring tendon stiffness.

METHODS

The study was conducted between January and July 2019 at the University of Applied Sciences and Arts of Southern Switzerland. The study reporting adheres to the Guidelines for Reporting Reliability and Agreement Studies.[26]

A convenience sample of 40 healthy participants (18 women, 22 men, aged 33.8±14.2 years) were prospectively recruited trough public announcement at the University. Their mean (±SD) height and weight were 172.2 (±8.2) cm and 71.7 (±12) kg. Health-related physical activity was monitored using the International Physical Activity Questionnaires Short form (IPAQ)[27]; 23 participants were categorised as high, 15 as moderate and 2 as having low physical activity levels. Participants were excluded if they had a history of tendon or foot injury or surgery; connective tissue, metabolic or endocrine disease. Furthermore, participants with systemic inflammatory disorders, rheumatoid arthritis, spondyloartropathy or hypercholesterolaemia were excluded.

Sample size was estimated according to Walter *et al*[28] using the following parameters: two replicates, p0=0.6, p1=0.80, α=0.05 and β=0.2. The optimal sample size was 39.1, and we rounded up to 40 participants.

Procedures

The AT mechanical properties were randomly analysed by two independent operators who were both physiotherapists with a minimum of 4 hours of training with the MyotonPRO prior to the study. Two measurement sessions were planned within 7 days. During the first session, the two operators consecutively performed the measures in order to evaluate the intra-rater and inter-rater reliability. The second session was used to evaluate inter-session reliability.

Testing location and room temperature (21°C–23°C) was kept constant across sessions. Participants were asked to maintain the same activity level between the two testing days.

The resistance of the soft tissues to the deformation induced by the MyotonPRO is calculated from an acceleration graph representing the damped natural oscillation of the tissues. Dynamic stiffness, calculated in N/m, is computed by multiplying the maximum acceleration of the oscillation graph to the mass of the probe divided by the maximum displacement of the tissue; higher values represent a stiffer tissue.

Both the left and right AT were evaluated at the most central point of the tendon following a trajectory from the most central component of the medial malleolus as this point has been suggested as the most prevalent region for tendinopathy.[29] Furthermore, a previous study using MyotonPRO to evaluate stiffness of the AT in people with Achilles tendinopathy and asymptomatic controls showed that changes in mechanical parameters are more likely to be detected from 8 to 12 cm from the plantar aspect of the heel, corresponding to the free tendon part.[19]

MyotonPRO was setup with a multiscan sequence of 5 impulses (1 s apart), a short duration (15 ms) impulse involving minimal mechanical force with a precompression of 0.18 N and an impulse of 0.40 (total=0.58 n) was exerted on the tendon.

Measurements ware taken in three different positions; standing, a relaxed position and during isometric contractions of the plantar flexors of increasing intensities, in order to evaluate construct validity (figure 1). As the triceps surae contracts to increase plantarflexor force, the passive tension within the tendon increases as shown in previous studies.[30] Since tendon stiffness and tendon displacement are directly related to plantarflexor strength[31] and ankle angle,[32] myonotometry values are expected to increase with increasing muscle contraction and with increased plantarflexion. To illustrate this construct, stiffness of the AT was compared across the five different contraction levels and between the three different positions. Testing in the three different positions as well as the sequence of the isometric contractions were randomised using a random number table.

Isometric contractions

The participants were positioned in prone with the foot secured within a dynamometer with the ankle in

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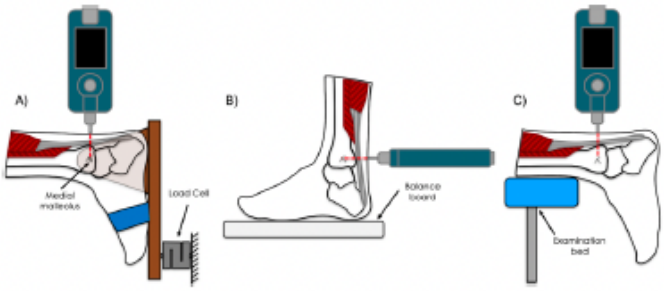


Figure 1 Schematic of the experimental setup. (A) Isometric contractions: the foot was securely attached to a dynamometer with a wooden board at a fixed angle of 0° of dorsiflexion. The force measured by the load cell was proportional to the torque exerted at the ankle level. (B) Standing position: participants were asked to stand on a Wii balance board (Nintendo, Kyoto, Japan) with the centre of mass centred on the centre of board with the feet equally spaced. (C) Relaxed position: the feet were hanging freely over the edge of the examination bed. MyotonPRO was applied to the most central point of the tendon at the level of the medial malleolus.

0° of dorsiflexion/plantarflexion. Different intensities of isometric contractions of the plantar flexors were performed (0, 0.5, 1, 2 and 3 kg). The torque at the ankle joint was evaluated using a dynamometer connected to a force sensor operating in a 0–100 n range (CCT Transducers, Turin, Italy). The force sensor was attached to a wooden board connected to a hinge that enabled natural movement of the ankle joint in dorsiflexion and plantarflexion (figure 1A). The board was then fixed in order to permit isometric contractions only at a defined angle of 0° dorsiflexion. The force detected by the sensor was proportional to the torque exerted at the ankle level. Force signals were amplified using MISO-II (OT Bioelettronica, Turin, Italy) and visual feedback was provided to the participants.

A practice phase prior to the recording was conducted by asking the patient to familiarise with the visual feedback and perform contractions with the instruction to 'push on the board as if you want to reach a tip-toe position'. During this practice phase, the lift of the heel was controlled. In order to prevent the detachment of the heel from the board, the foot and ankle were tightly secured in the dynamometer with two belts.

Standing

For the analysis in the standing position, participants were asked to stand on a Wii-Balance board (Nintendo, Kyoto, Japan) with the centre of mas on the middle of the board with the feet equally spaced (figure 1B). Visual feedback was provided by the BrainBLOX Software (University of Colorado, Boulder, Colorado, USA) to the participant in order to ensure that the centre of mass remained in the same position. Participants were asked to rest their hands on a fixed box which ensured the stability of the standing position and avoided oscillation of the centre of mass during the measurement that could affect the tension of the triceps surae muscle-tendon complex.

Relaxed position

The measurements in the relaxed position were performed with the participants in prone on an examination bed and the feet hanging freely over the edge (figure 1C). The participants were instructed not to move their feet during the measurement.

Statistical analysis

Statistical Package for the Social Sciences (SPSS V.24) was used to perform statistical analysis. Descriptive statistics (mean±SD) were used to describe the demographic characteristics of the sample. The distribution of the values was assessed using the Shapiro-Wilk test. Given the non-normal distribution of the data, non parametric, independent samples, Mann-Whitney test was used to assess whether there were significant differences in AT mechanical properties between men and women, between participants with different physical activity levels based on their IPAQ score.

Intra-rater and inter-rater reliability was assessed using intraclass correlation coefficient ($ICC_{2,k}$) and the absolute reliability was calculated using standard error of measurement (SEM) and minimal detectable change (MDC).[33]

Furthermore, a cut-off point of ICC >0.6 was used to consider the clinical relevance of the measurements.[34 35]

Construct validity was tested analysing the correlations between the five different contraction levels and the three different positions using Friedman test with post hoc pairwise comparison Bonferroni correction was applied and statistical significance was set to α=0.05. Data are presented as median and IQR.

Patient and public involvement statement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

RESULTS

No significant difference in AT stiffness was observed between men and women (p=0.6) or between participants with different physical activity levels based on their IPAQ score (p=0.9), therefore, the data were pooled and further analysed across the sample. Table 1 reports the descriptive statistics for the sample in the different conditions.

A total of eighty AT of 40 healthy participants were assessed by the two physical therapists.

Intra-rater reliability was very high with an $ICC_{2,k}$ of 0.95 for 0 kg, 0.87 for 1 kg, 0.95 for 2 kg, 0.94 for 3 kg, and 0.98 and 0.87 for the relaxed and standing positions respectively. The intra-rater reliability of measuring AT stiffness during the 0.5 kg contraction was moderate with an $ICC_{2,k}$ of 0.59.

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Table 1 Descriptive statistics

		Sample (mean±SD)			Stiffness N/m (median IQR)						
	N	Age (year)	Height (cm)	Weight (kg)	0 kg	0.5 kg	1 kg	2 kg	3 kg	Relax	Standing
Total	40	33.8	172.2	71.7	1043.0	1096.5	1110.5	1180.5	1381.5	771.0	1596.0
		14.2	8.2	12.0	132.3	62.0	121.3	255.5	214.3	105.3	339.3
Men	22	35.6	177.7	77.4	1057.5	1089.5	1086.5	1117.5	1333.0	792.0	1577.5
		13.8	5.6	10.6	144.0	65.0	132.3	143.3	198.3	124.0	337.3
Women	18	32.4	167.6	67.0	1041.0	1099.5	1129.5	1284.0	1435.5	753.0	1616.5
		15.1	6.9	11.0	139.0	89.5	129.8	279.8	201.3	83.3	363.5

Sample characteristics and stiffness values.

Inter-rater reliability between the two raters ranged from high to very high with an $ICC_{2,k}$ of 0.76 for 0 kg, 0.79 for 2 kg, 0.81 for 3 kg and 0.86 for the relaxed position. The inter-rater reliability of measuring AT stiffness during the 0.5 kg, 1 kg contraction and the standing position was moderate with an $ICC_{2,k}$ of 0.55, 0.54 and 0.56, respectively.

Inter-session reliability ranged from high to very high with an $ICC_{2,k}$ of 0.88 for 0 kg, 0.70 for 1 kg 0.86 for 2 kg, 0.78 for 3 kg, 0.89 and 0.75 for the relaxed and standing positions, respectively. The inter-session reliability of measuring AT stiffness during the 0.5 kg contraction was moderate with an $ICC_{2,k}$ of 0.54.

Table 2 reports the relative reliability with ICC and 95% CI and absolute reliability with SEM and MDC.

Changes in AT stiffness between the different conditions were calculated using Friedman test for related samples. Significant differences ($p<0.01$) were found between all contraction levels except for 0–0.5 kg ($p=0.9$); 0.5–1 kg ($p=0.9$); 1–2 kg ($p=0.7$) and between the different positions (figure 2).

DISCUSSION

The present study evaluated the absolute and relative reliability of the myotonometry to measure the stiffness of AT in different conditions. Even though the MyotonPRO was developed to evaluate the stiffness and tone of skeletal muscle, the present study shows the transferability of this technology and that measuring stiffness of tendon tissue is feasible and reliable. Intra-rater and inter-rater reliability ranged from high to very high in most of the tested conditions. Moreover, stiffness changes between the different contraction intensities and the different positions was detected, demonstrating the construct validity of this device.

One of the conditions in the current study was assessing AT stiffness with the person in a relaxed position with the feet hanging freely over the edge of the examination bed. A previous study[25] also showed high intra-rater reliability when the AT was evaluated in a relaxed position (ICC: 0.80 in healthy participants). A further study evaluating the effect of dorsiflexion of the ankle joint on tendon stiffness[18] showed high to very high intra-reliability and inter-reliability when measured in a relaxed position (ICC >0.88). Our results strengthen these previous observations by confirming high to very high intra and inter-rater reliability (ICC >0.86), now demonstrated in a larger sample. The stiffness values vary slightly between studies with an average of 873 N/m reported by Finnamore *et al*,[25] 776.11±71.70 reported by Liu *et al*,[18] and 771±105.3 N/m observed in the present study. Nevertheless, collectively the current and previous findings confirm that MyotonPRO is a reliable device to evaluate AT stiffness in a relaxed position on the same day, between different days and between different operators.

Stiffness values increased from 1043±132.3 N/m when tendon was assessed in a 0° ankle dorsiflexion

Table 2 Absolute and relative reliability for the different conditions

	Intra-rater			Inter-rater			Inter-session		
	ICC (95% CI)	SEM	MDC	ICC (95% CI)	SEM	MDC	ICC (95% CI)	SEM	MDC
0 kg	0.95 (0.92 to 0.97)	19.3	53.5	0.76 (0.62 to 0.84)	43.2	119.6	0.88 (0.82 to 0.93)	30.5	84.6
0.5 kg	0.59 (0.36 to 0.74)	40	111	0.55 (0.30 to 0.72)	50.2	139.1	0.54 (0.29 to 0.71)	49.8	137.9
1 kg	0.87 (0.80 to 0.92)	36	99.8	0.54 (0.28 to 0.71)	66.2	183.5	0.70 (0.54 to 0.81)	56.1	155.6
2 kg	0.95 (0.91 to 0.97)	39.3	109	0.79 (0.67 to 0.87)	83.3	231	0.86 (0.78 to 0.91)	65.8	182.5
3 kg	0.94 (0.91 to 0.96)	47.7	132.1	0.81 (0.69 to 0.88)	85.9	238.2	0.78 (0.66 to 0.86)	92.7	256.9
Relax	0.98 (0.97 to 0.99)	10.8	30	0.86 (0.78 to 0.91)	30.5	84.6	0.89 (0.83 to 0.93)	24.7	68.4
Standing	0.87 (0.89 to 0.92)	70.7	196.1	0.56 (0.29 to 0.73)	130.1	360.5	0.75 (0.60 to 0.84)	101.5	281.3

CI, confidence interval; ICC, intraclass correlation coefficient; MDC, minimal detectable change; SEM, standard error of measurement.

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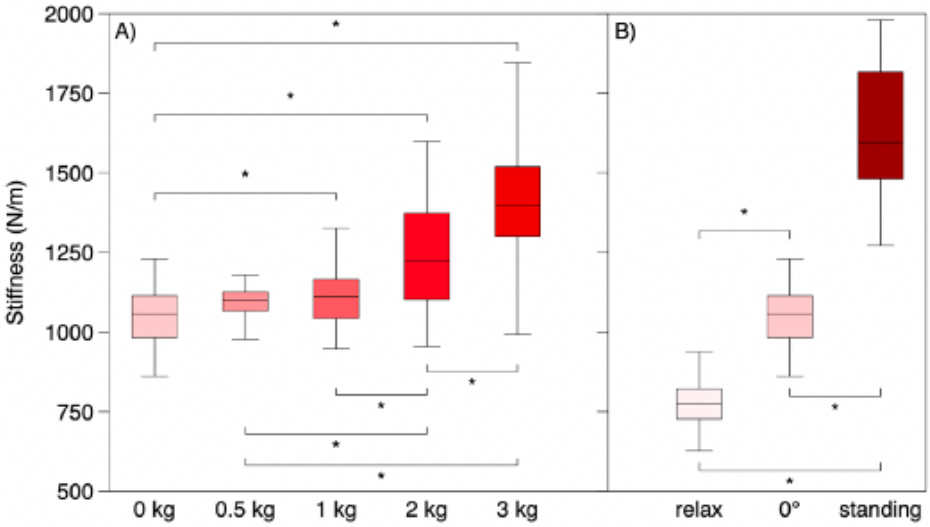


Figure 2 Construct validity. Box plot showing the stiffness median and IQR values of the entire sample for the different contraction levels (A) and for the different positions (B). *p<0.01; statistical significant difference between the different conditions.

position with 0 kg of contraction to 1381±214 N/m for the isometric contraction at 3 kg. The ICC values showed high to very high intra-rater and inter-rater reliability for the majority of the isometric contraction levels (see table 2). Moderate intra-rater and inter-rater reliability was found for the 0.5 kg contraction level and the level of reliability did not exceed the cut-off point of ICC =0.6 considered as the threshold for clinical relevance.[34] The low reliability for the contraction at 0.5 kg is likely due to the difficulty in maintaining the force feedback stable during such a low contraction of the plantar flexors. A previous study[18] evaluating AT stiffness at different ankle angles showed similar results to the present study with an average stiffness of 1143 N/m at 0° of dorsiflexion compared with 1043±132 N/m found in the current study. Liu *et al*[18] did not examine reliability at different ankle angles, however, the data reported in this article demonstrated a statistically significant increase in tendon stiffness due to the change in ankle dorsiflexion angle from 1143 N/m at 0° to 1329 N/m at 30°. These results are in line with the present study, which showed a significant increase in tendon stiffness with contractions of increasing intensity. Thus, the MyotonPRO can reliably detect changes in AT stiffness whether the tendon is stretched from contraction of the triceps surae muscle or stretched as a result of a change in the angle of the ankle.

Another study[20] analysing the tissue properties of the AT and plantar fascia in healthy volunteers found slightly different stiffness values when the tendon was measured at 0° of dorsiflexion. The article reports a mean (±SD) of 848 (±95.73) N/m and 847.3 (±101.5) N/m for the left and right AT, respectively, whereas we observed higher values with an average stiffness of 1043±132 N/m.

Tendon structural and mechanical adaptations are strongly related to the load magnitude exerted to the musculotendinous complex[3 5] and the majority of interventions targeting pathological tendon tissue are loading-based exercise regimens.[36–40] The current results support the evaluation of the tendon tissue behaviour during load with a reliable and easy to use device could be helpful to detect possible mechanical adaptation following different rehabilitation protocol.

Stiffness of the AT was also evaluated in standing position in this study to verify the feasibility of MyotonPRO to analyse the tendon in a weight-bearing position. Intra-rater reliability was very high and inter-session reliability was high. Conversely inter-rater reliability in the standing position was moderate. It is important to note, however, that in the standing position the average stiffness values were 1596 (±339) N/m which is approaching the upper limit that the device is able to detect. The lower reliability could be a consequence of the measurement threshold of the device such that when it is close to the higher limit, there were difficulties in providing a mechanical impulse strong enough to give a proper oscillation wave. Morgan *et al*[19] found similar results in a population of healthy participants in a weight-bearing position. Despite the possible technical limitation of analysing tendon stiffness in a weight-bearing position, the results demonstrate good intra-rater reliability but only moderate inter-rater reliability.

This is the first study to evaluate changes in AT stiffness between different contraction levels using the MyotonPRO. The results confirm a significant difference in tendon stiffness between the different contraction levels. Although stiffness changes can be detected across different contractions, the levels with similar intensity (0–0.5 kg (p=0.9); 0.5–1 kg (p=0.9); 1–2 kg (p=0.7)) showed similar stiffness values likely as the difference between consecutive contraction levels was not sufficient to change the mechanical properties of the tendon. These results are consistent with those reported in a previous sonoelastography evaluation[41] showing an increase of tendon elastography colour scale index when the AT was

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gradually put under tension by isometric contractions of increasing intensity. In further support of the construct validity, pairwise comparisons showed a difference in AT stiffness between the different positions (relaxed, 0° ankle angle and standing). Similarly, a previous study using shear wave sonoelastography[42] showed an increase in wave velocity, indicating a hardening of the AT, when the ankle angle changed from a plantarflexed position to 0° of dorsiflexion.

There are some limitations of this study which should be noted. Healthy participants were recruited and stiffness was evaluated in only one point of the tendon and it is therefore unknown whether variation may exist in different regions of the tendon. Another potential limitation was the selection of the contraction intensities. The upper limit of this ramp was chosen because after a certain amount of load (approximately 5 kg) the device cannot detect stiffness values. The small changes between the different contraction levels could be not sufficient to fully describe the behaviour of the tendon during load.

CONCLUSIONS

MyotonPRO is a reliable tool to measure AT stiffness in different conditions including when the tendon is in a relaxed position and under load. Reliability is confirmed for the same rater, between different days and between two raters. Construct validity was supported by changes of tendon stiffness during the explored contractions and ankle positions. MyotonPRO can be implemented, as a ready to use device, in the evaluation of tendon tissue mechanical properties.

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Appendix 7 – Schneebeli et al., 2022

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Technical and measurement report

Measurement of Achilles tendon loading using shear wave tensiometry: A reliability study

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ABSTRACT

Background: Shear wave tensiometry is a recent promising technology which can be used to evaluate tendon loading. Knowing the clinimetric features (e.g., reliability) of this technology is important for use in clinical and research settings.

Objectives: To evaluate the inter-session reliability of a novel shear wave tensiometer for the assessment of Achilles tendon loading. A further aim was to test the construct validity of this device by evaluating its precision in detecting Achilles tendon loading changes induced by a plantar flexor isometric contraction of increasing intensity.

Method: Ten healthy participants were recruited. Five measurements were performed at different time points to evaluate inter-session reliability. Shear wave speed along the Achilles tendon was evaluated during different isometric contractions using a shear wave tensiometer composed of an array of four accelerometers fixed on the tendon, ranging from 4 to 8.5 cm from the calcaneal insertion of the tendon. Test-retest, intra- and inter-session reliability were determined using intraclass correlation coefficient ($ICC_{3,1}$). Absolute reliability was calculated using the standard error of measurement and minimal detectable change.

Results: Test-retest reliability was good to excellent ($ICC_{3,1}$ 0.87–0.99) for each of the contraction levels examined. Intra-session reliability was good to excellent ($ICC_{3,1}$ 0.85–0.96) and inter-session reliability was also good to excellent ($ICC_{3,1}$ 0.75–0.93) for each of the contraction levels.

Conclusions: This study confirms the reliability of this novel device. Future studies analyzing participants with Achilles tendinopathy are needed to evaluate the capability of shear wave tensiometry to detect transient changes in loading due to pathology.

1. Introduction

Increased mechanical stimuli on tendinous structures may lead to changes in the mechanical, material and morphological properties of the tendon; tendon stiffness appears to be modified by changes in the material rather than morphological properties of the tendon (Bohm et al., 2015). A recent study evaluating tendon responses to unloading, loading, and aging showed that tendon tissue is highly adaptable, with increased stiffness when loaded and decreased stiffness when unloaded (Magnusson and Kjaer, 2019). Some authors suggest that tendinopathic changes in the Achilles tendon (AT) leads to decreased tendon axial stiffness (Arya and Kulig, 2010; Chang and Kulig 2015; Child et al., 2010; Helland et al., 2013) and shear stiffness as measured with elastography (Aubry et al., 2015; Coombes et al., 2018).

Different loading protocols have demonstrated an effect on tendon adaptation, with the intensity of the exercise (high loading magnitude) and the length of the intervention (>12 weeks) contributing the most to improvements in tendon mechanical properties (Bohm et al., 2015).

Different assessment techniques have been developed in response to clinical and research interests in evaluating tendon mechanical properties to be able to characterize tendon response to loading and tendon health status. Recently, a promising technology known as shear wave tensiometry, has been developed and validated (Martin et al., 2018). This technology uses accelerometers to measure wave propagation

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along the tendon generated by a tapping device in order to measure muscle-tendon loading. The principle behind this technology is based on the concept that squared tendon wave speed varies in proportion to the axial stress in the tissue (Martin et al., 2018). Recent studies have demonstrated a relationship between AT wave speed and ankle kinetics during locomotion (Martin et al., 2018; Keuler et al., 2019) and different tendon loading between older and younger adults during walking (Ebrahimi et al., 2020).

Evaluation of the inter-session reliability of this device is important to apply this measure with confidence in a clinical setting and in longitudinal studies. Therefore, the aim of this study was to evaluate the inter-session reliability of a novel shear wave tensiometer for the assessment of AT loading. An additional aim was to test the construct validity of this device by evaluating its precision in detecting transient changes in tendon loading induced by a plantar flexor isometric contraction of increasing intensity.

2. Materials and methods

The study was conducted between May and July 2021 at the University of Applied Sciences and Arts of Southern Switzerland. The study was approved by the Ethics Committee of Canton Ticino (ID:2021–00611/CE3844) and written informed consent was provided by the participants. Reporting of this study adheres to the Guidelines for Reporting Reliability and Agreement Studies (Kottner et al., 2011).

2.1. Participants

Ten (5 male and 5 female) healthy, asymptomatic participants were prospectively recruited. Participants were excluded if they had a history of foot or tendon injury or surgery, metabolic, connective tissue or endocrine disease. Participants with systemic inflammatory disorders, spondyloartropathy, rheumatoid arthritis, or hypercholesterolemia were excluded.

The size of the sample was estimated according to Walter et al., (1998) using the following parameters: five replicates, $\rho 0 = 0.6$, $p1 = 0.9$, $\alpha = 0.05$, and $\beta = 0.2$. The ideal sample size was 6.4. Given the choice of healthy participants and the non-invasive procedures, 10 were recruited. p0 was selected according to the clinical relevance threshold for the reliability measurement in clinics (0.6) (Munro 2005) whereas p1 of 0.9 was chosen after a structured pilot study involving four healthy participants.

2.2. Study procedures

A test-retest without repositioning of the participant and the device (test-retest) followed by a third measure where the participants were asked to stand up and come back to the examination bed (intra-session) was performed on the first day.

Two between day measures were performed following 1 week and 2 weeks (inter-session).

Participants were asked to maintain the same activity level throughout the entire study.

Wave speed along the AT (m/s) was measured using four accelerometers placed longitudinally on the AT during a ramp of isometric contractions with a randomized level of intensity corresponding to 0–1.75–3.5 - 7–17.5–35 Nm of the ankle joint torque. The participants were positioned in prone with the foot secured within a dynamometer with the ankle in 0° of dorsiflexion/plantarflexion (Fig. 1).

Prior to the first session, the participants attended a practice session to learn how to perform the isometric contraction and familiarize themselves with the visual feedback. The instruction 'push on the board as if you want to reach a tip-toe position' was given. Detachment of the heel from the dynamometer was monitored by the investigator and a tight fixation of the foot and ankle was ensured by two belts.

The detection software acquired a set of 10 repeated measures for each of the contraction levels for both the left and right AT for each participant. The mean of these 10 measurements were used to determine the reliability values. The same test location and times were maintained throughout the study.



Fig. 1. Image of the experimental setup. The participant was positioned in prone with the foot secured within a dynamometer with the ankle in 0° of dorsiflexion/plantarflexion. Force feedback was presented to the participants in real time. The bottom right box shows a detailed image of the tapping device and accelerometers.

2.3. Equipment

2.3.1. Accelerometers

The shear wave tensiometer was composed of an array of four accelerometers (Analog Devices, ADXL202JE) which were fixed with double adhesive tape on the tendon, equally spaced at a distance of 15 mm (Fig. 1). The most distal accelerometer was positioned 4 cm to the calcaneal insertion of the tendon (previously identified with ultrasound imaging - US). US was also used to check whether all the accelerometers were placed on the tendon and not on the musculotendinous junction.

The signals were acquired using a Sessantaquattro (OTBioelettronica, Torino, Italy) with a sampling frequency of 10 kHz. The signals were analyzed in order to identify the propagation velocity of the mechanical waves on the tendon, based on the delay between the waves.

Since the four accelerometers were equally spaced and given the hypothesis that the wave propagates at a constant speed, the delay between the waveforms detected by adjacent accelerometers was expected to be constant. The technique for propagation velocity estimation is based on the estimation of this delay using the cross-correlation function between pairs of signals. Once the average delay from each possible pair of signals was determined, the propagation velocity was calculated as the ratio between the inter-accelerometer distance and the average delay (Farina et al. 2001).

The algorithm is the same used in the field of surface electromyography for the computation of muscle fiber conduction velocity (Farina et al. 2001; Farina et al., 2004). The outcome variable was one propagation speed value (m/s) for each tap provided to the tendon (Fig. 2).

2.3.2. Tapper

The mechanical impulse was generated by a custom developed tapper based on an electromagnetic transductor. A current impulse was used to activate an electromagnet, which attracts the iron arm connected to a wooden stick. In its rest position the wooden stick was held a few millimetres away from the tendon. The tapping frequency was set to 4 Hz. The opening and closing of the switch was controlled by a microcontroller (Arduino UNO, Italy) programmed to provide intermittent

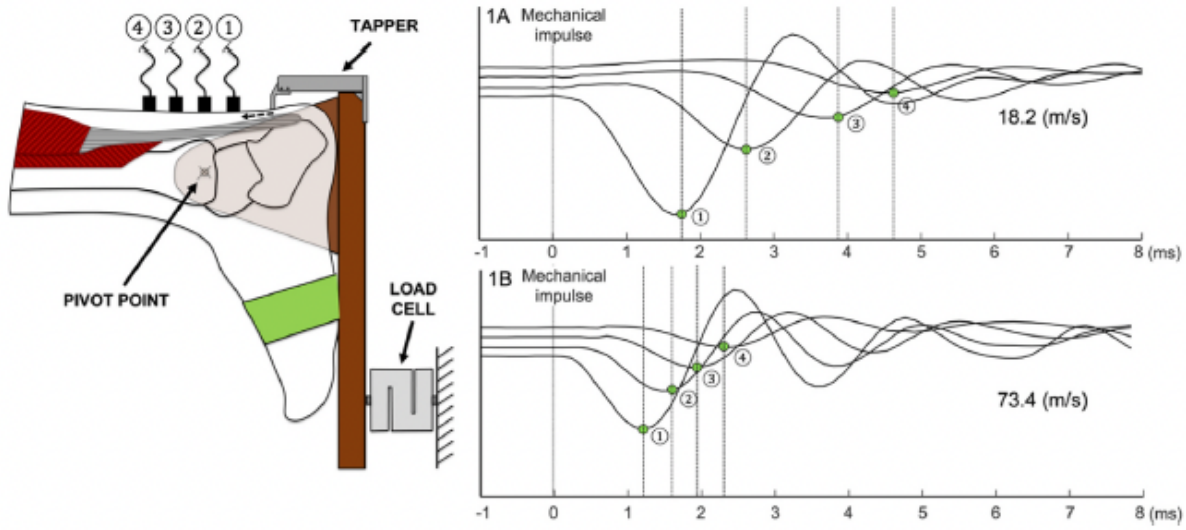


Fig. 2. Schematic of the shear wave tensiometer. The tapper device was mounted on the dynamometer and placed on the Achilles tendon at 2 cm from the calcaneus insertion. The four accelerometers (1–4) were attached to the skin in series with a 15 mm inter-accelerometer distance. Shear wave speed signals of the Achilles tendon at 0 Nm (1A) and at 35 Nm of isometric ankle torque (1B). The propagation velocity of the wave was calculated based on the delay between the waves passing from the accelerometers.".

pulses with constant time intervals (250 ms). The tapper was positioned 2 cm proximally from the end of the calcaneal bone. This location was checked by means of US.

2.3.3. Force feedback

Participants performed different intensities of isometric contractions of the plantar flexors (0–1.75–3.5 - 7–17.5–35 Nm). The torque of the ankle was assessed using a dynamometer connected to a force sensor that operated linearly in the range between 0 and 100N (Mod. TF2/S; CCT Transducers, Turin, Italy). The force sensor was attached to a wooden board connected to a hinge that allowed natural dorsiflexion and plantar flexion of the ankle. The board was fixed in order to permit isometric contractions only at a fixed angle of 0° dorsiflexion. The force measured by the force sensor was proportional to the torque exerted at the ankle level. Force signals were amplified using MISO-II (OT Bioelettronica, Turin, Italy; bandwidth 0–80 Hz) and presented to the participants as real time visual feedback. A practice phase prior to the recording was conducted in order to familiarize the participant with the visual feedback and practice the contractions.

2.4. Statistical analysis

Descriptive statistics, mean ± SD, were determined to characterize the demographics of the sample. Statistical Package for Social Sciences (SPSS v. 26) was used for statistical analysis.

Test-retest, intra-session and inter-session reliability was calculated using intraclass correlation coefficient ($ICC_{3,1}$) based on a single-rater (k = 1), absolute agreement, 2-way mixed effect model. Absolute reliability was calculated using the standard error of measurement (SEM) and minimal detectable change (MDC) (Atkinson and Nevill 1998). An ICC >0.6 was used to consider the clinical relevance of the measurements (Munro 2005). Inter-measurement variability was calculated using the coefficient of variation % (CoV%) of the 10 measurements for each participant and contraction level.

The distribution of the data was determined using Shapiro-Wilk test and non-parametric independent samples, Mann-Whitney test was performed to assess significant differences in AT wave speed between men and women and between the dominant and non-dominant leg.

A linear regression model was used for each participant to test the linear relationship between squared wave speed and ankle joint torque to determine construct validity. The goodness of fit of the subject specific model was assessed using the coefficient of determination (R^2).

Wave speed values are presented as median and IQR.

3. Results

Data from 10 healthy participants (5 female) were analyzed. Their mean (±SD) age, height and weight were 31 (6.9) years, 173 (8.2) cm and 65 (9.3) kg respectively.

Data were pooled and analyzed across the entire sample given that no significant difference in AT wave speed was observed between men and women ($p = 1.000$) or between the left and right side ($p = 0.853$). Wave speed values at the different contraction levels and inter-measurement variability are reported in Table 1.

Test-retest reliability was good to excellent with a minimum value of $ICC_{3,1}$ 0.87 and a maximum of $ICC_{3,1}$ 0.99 considering all contraction levels. Intra-session reliability was good to excellent with a minimum value of $ICC_{3,1}$ 0.85 and a maximum of $ICC_{3,1}$ 0.96 considering all contraction levels. Inter-session reliability was also good to excellent with a minimum value of $ICC_{3,1}$ 0.75 and a maximum of $ICC_{3,1}$ 0.93 considering all contraction levels. The measure at 17.5 Nm showed good reliability but the lower limits of 95% CI were below the cut-off point of >0.6 considered to be the clinically relevant threshold. Reliability data with 95% CI and absolute reliability calculated with SEM and MDC are reported in detail in Table 1.

Linear regression models showed that squared wave speed was quite accurately predicted by ankle joint torque for each of the participants ($R^2 = 0.991 \pm 0.01$ and 0.992 ± 0.01, mean ± SD, for the left and right tendon respectively) (Fig. 3) For every Nm of torque increase, the squared wave speed increased by 139 (m^2s^{-2}) on average among the participants. The ankle joint torque-wave speed relationship was however variable across participants, ranging from a minimum value of 84.9 to a maximum of 211.7 (m^2s^{-2}).

4. Discussion

The purpose of this study was to evaluate the reliability of a shear wave tensiometer for the evaluation of AT loading at different contraction levels. The results showed that this device is highly reliable (ICC>0.75) not only when a test-retest without repositioning of the accelerometers was performed but also with the repositioning (intra-session) and between different sessions (inter-session).

Table 1
Shear wave speed values of the sample, inter-measurement variability, absolute and relative reliability values for the different contraction levels.

Ankle torque	Shear wave speed values (m/s)	Inter-measurement variability	Test-retest reliability			Intra-session reliability			Inter-session reliability		
Nm	Median (IQR)	Cov (%)	ICC	SEM	MDC	ICC	SEM	MDC	ICC	SEM	MDC
0	21.53 (4.4)	2.3%	0.99 (0.98–0.99)	0.3	0.8	0.96 (0.91–0.99)	0.6	1.8	0.93 (0.86–0.97)	0.9	2.5
1.75	27.24 (6.3)	2.8%	0.95 (0.87–0.98)	0.8	2.3	0.92 (0.79–0.97)	1.2	3.4	0.83 (0.65–0.93)	1.9	5.1
3.5	31.3 (5.8)	2.6%	0.94 (0.84–0.98)	1.0	2.7	0.95 (0.86–0.98)	0.9	2.6	0.84 (0.65–0.93)	1.9	5.3
7	36.08 (6.8)	2.4%	0.96 (0.89–0.98)	1.0	2.7	0.85 (0.62–0.94)	2.0	5.4	0.81 (0.60–0.92)	2.3	6.4
17.5	54.6 (9.2)	2.5%	0.93 (0.83–0.97)	1.7	4.6	0.90 (0.75–0.96)	2.0	5.7	0.75 (0.48–0.89)	3.4	9.5
35	76.33 (22.6)	2.1%	0.87 (0.67–0.95)	4.7	13.1	0.90 (0.75–0.96)	3.7	10.3	0.84 (0.66–0.93)	4.7	12.9

Abr.: ICC, intraclass correlation coefficient; CI, coefficient interval; SEM, standard error of measurement; MDC, minimal detectable change; CoV, coefficient of variation; IQR, interquartile range.

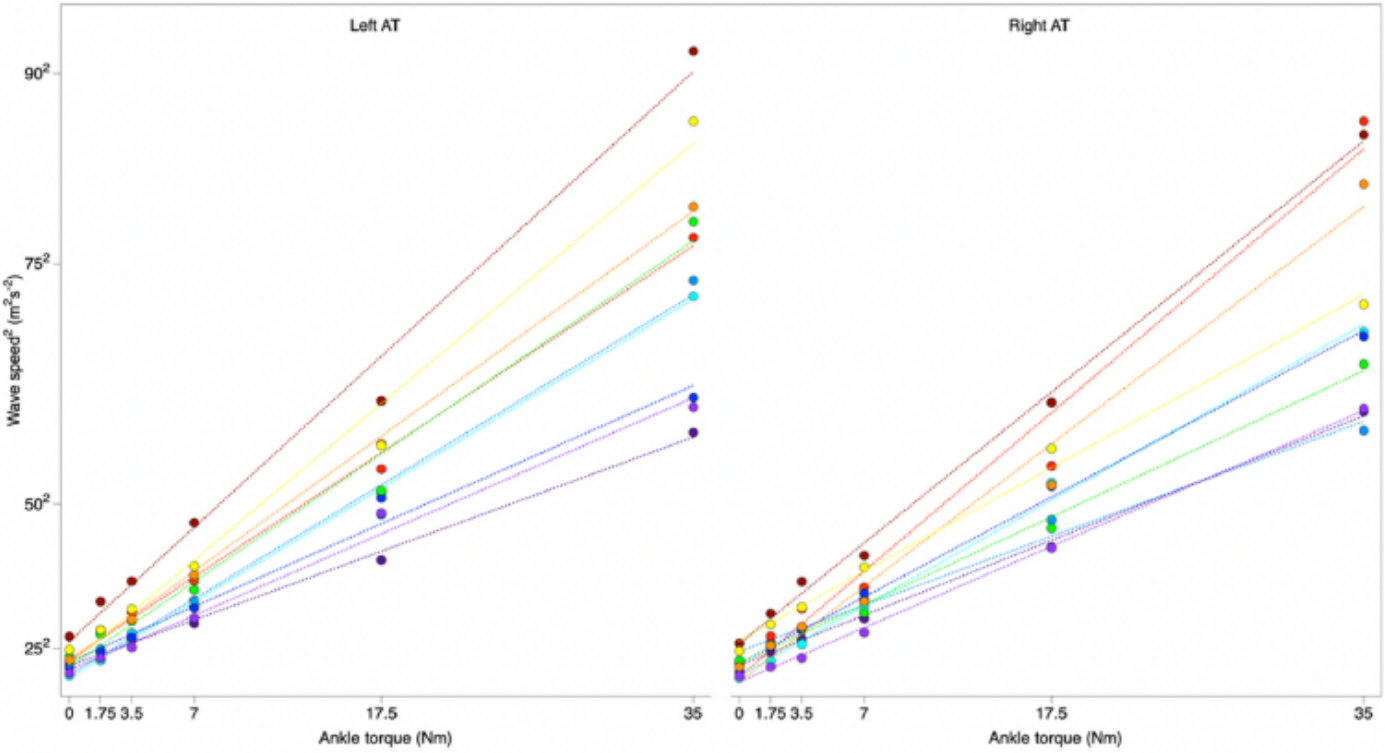


Fig. 3. Scatter plot showing the squared shear wave speed values of each of the participants tendons (n = 20) for the different levels of ankle torque. The two panels show the values of the left and right tendon (AT). Each dot is the average of three sessions and each colour represents a participant. Lines represent the linear regression for each tendon (R^2).(For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article)

Every contraction level assessed in the study (from 0 to 35 Nm) resulted in high reliability values showing that this instrument is precise even when the tendon is under load and is subject to a transient loading change. Moreover, absolute reliability calculated with the SEM and MDC showed a very small error when compared to the shear wave speed values obtained in the different contraction levels.

As the plantar flexor force increase, AT should increase its strain and its stiffness (Kjaer 2004; Magnusson et al., 2003), and therefore an increment in the shear wave speed should be found when the tendon is gradually put under load by isometric contractions to confirm this construct. Construct validity of the measurement was confirmed, and indeed for each participant the coefficient of determination (R^2) was very high ($R^2 = 0.991 \pm 0.01$ and 0.992 ± 0.01, mean ± SD, for the left and right tendon respectively) indicating that the increase in the squared wave speed was strongly correlated with the increase of the ankle joint torque.

Despite this strong relationship, highly variable results were found between participants showing possible individual behavior of the tendon during load. Further studies are needed to better understand these changes.

This novel technology has been previously validated and used to assess AT loading during gait (Martin et al., 2018). Only a few studies (Martin et al., 2018 Keuler et al., 2019) tested this device during isometric contractions and the results are comparable with the present study with a wave speed that varies from 15 to 20 (m/s) when the muscles were relaxed, to 60 to 80 (m/s) when maximal contractions were performed.

In the present study, values ranged from 21.53 m/s (IQR 4.4) with no

contraction to 76.33 m/s (IQR 22.6) with a 35 Nm contraction. The device used in the current study consisted of 4 accelerometers in series with an inter-accelerometer distance of 1.5 cm which allows a larger (4.5 cm) portion of the Achilles free tendon to be assessed compared to previous studies which analyzed 1 cm of the tendon. (Keuler et al., 2019; Ebrahimi et al., 2020; Acuna et al., 2019). Considering that it was not possible to assume a constant wave speed between accelerometers pairs, due to possible variation of the tendon cross-sectional area or wave dispersion, a larger spatial sampling with multiple detection points allowed us to average the wave speed.

4.1. Methodological considerations

There are some limitations of this study that need to be acknowledged. Firstly, the study evaluated a novel shear wave tensiometer under controlled conditions, and therefore the results cannot be generalized to other types of shear wave tensiometers. Sample size was estimated for the calculation of the reliability values, therefore values of the correlation between contraction levels with this sample size could be underpowered. Moreover, the results cannot be generalized to other tendons or to different conditions.

5. Conclusions

This study confirms the reliability and construct validity of shear wave tensiometry. Future studies analyzing participants with Achilles tendon pathology (i.e., tendinopathies or tendon rupture) are needed to evaluate the capability of shear wave tensiometry for use in clinical practice.

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Declaration of competing interest

None.

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Appendix 8 – Schneebeli et al., 2023

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Shear Wave Tensiometry Can Detect Loading Differences Between Operated and Unaffected Achilles Tendon

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Abstract

Background: The clinically relevant healing process of a ruptured and repaired Achilles tendon (AT) can last more than a year. The purpose of this cross-sectional study was to test if shear wave tensiometry is able to detect AT loading changes between a surgically managed AT rupture versus the unaffected contralateral tendon. Our secondary aims were to evaluate differences in mechanical properties when measured with myotonometry and morphological properties of the tendons measured with ultrasonographic imaging.

Methods: Twenty-one patients with surgically treated AT ruptures were investigated 12-37 months after surgery. Tendon load was measured using a shear wave tensiometer composed of an array of 4 accelerometers fixed on the tendon. Shear wave speed along the Achilles tendon was evaluated at different levels of ankle torque for both the operated and the unaffected side. Mechanical properties of the tendons were evaluated using MyotonPRO and morphological properties using ultrasonographic imaging. Friedman test was used to assess differences in AT wave speed, stiffness, thickness, and cross-sectional area between the operated and the unaffected tendon.

Results: We found a significant shear wave speed difference between sides at every ankle joint torque ($P < .05$) with a large effect size for the lowest ankle torque and small to medium effect sizes for higher ankle torque. Stiffness, thickness, and cross-sectional area of the operated tendon remained significantly higher compared to the unaffected side.

Conclusion: In this cohort, we found that shear wave tensiometry can detect differences between operated and unaffected AT during a standardized loading procedure. The shear wave speed along the operated tendon, as well as the mechanical and morphologic properties, remains higher for 1-3 years after a rupture.

Level of Evidence: Level III, case-control study.

Keywords: Shear wave tensiometry, Achilles tendon rupture

Introduction

Achilles tendon (AT) ruptures are common musculoskeletal injuries, and their annual incidence is rising[20] with 5 to 50 events per 100 000 persons.[13] Pathological processes affecting the AT can alter the mechanical and morphological properties of the tendon structure, resulting in a modification of the stiffness, Young modulus, tendon cross-sectional area (CSA), and diameter.[25,29] In AT rupture, the extended period of immobilization and the development of scar tissue after surgery can noticeably alter the collagen synthesis/degradation within the tendon[14]; a larger proportion of type III collagen is present in the operated tendon, which can affect the mechanical properties by weakening the tendon and decreasing its tensile strength.[16]

The healing process of a ruptured AT can last more than a year,[12,36] and several studies have shown that during this period the tendon structure and mechanical properties are altered.[11,14,39] However, despite the growing interest in assessing the mechanical properties of tendons during the healing process, still limited and conflicting data are available. Some studies show decreased tendon stiffness[5,11,14,27,38] whereas others show increased stiffness[1,2] compared to the unaffected side up to 2-6 years after rupture. To date, no gold standard device exists to evaluate the mechanical

properties of tendons, and all technologies have their advantages and disadvantages.

Recently, a technology using accelerometers to measure wave propagation along the tendon was developed and validated in order to define tendon mechanical properties.[26] This technology, called shear wave tensiometry, is based on the concept that the axial stress within the tissue affects the squared tendon wave speed.[26] Further work have shown a relationship between AT wave speed and ankle kinematics, as well as different tendon loading during walking in participants of different ages.[7,17,26] Moreover, the reliability and construct validity of this technology has been demonstrated.[31]

Given that investigating the tendon's mechanical changes during the clinical course of a rupture can help to better understand the tissue healing process of tendons, in this study we aimed to test if shear wave tensiometry is able to detect AT loading changes between a surgically managed AT after rupture and the unaffected contralateral tendon. Our secondary aims were to evaluate differences in mechanical properties when measured with myotonometry and morphological properties of the tendons measured with ultrasonographic imaging.

Materials and Methods

This cross-sectional study was conducted at the orthopaedic department of the Ente Ospedaliero Cantonale. The study was approved by the Ethics Committee of Canton Ticino (ID:2022-01707/CE4192) and written informed consent was provided by the participants. Because no previous study investigating AT after surgery based on measurements taken with this technology was available, the sample size calculated based on a pilot to ensure a statistical power of 80% at the 5% significance level for a 2-tailed hypothesis test was n=20.

The study reporting adheres to the STROBE guidelines for observational studies.[37]

Participants

The database of the Ente Ospedaliero Cantonale was retrospectively screened to search for participants who underwent unilateral surgery of the Achilles tendon following AT rupture between 2018 and 2021.

Inclusion criteria:

- Unilateral open repair AT tenorrhaphy following complete AT rupture
- Surgery >1 year and <4 years
- Age ≥18 years
- Time from rupture to surgery < 3 weeks

Exclusion criteria:

- Arthrodesis of one of the upper foot/ankle joints
- History of problems with the contralateral AT (ie, Achilles tendinopathy, previous AT rupture, pain in the AT for more than 1 month)
- Other surgical interventions involving scar tissue on the posterior part of the leg or AT
- History of connective tissue, metabolic, and endocrine diseases
- Systemic inflammatory disorders, rheumatoid arthritis, spondyloarthropathy, or diabetes
- Currently using systemic antibiotics (fluoroquinolones, ie, ciproxin) and steroids

Clinical Outcomes

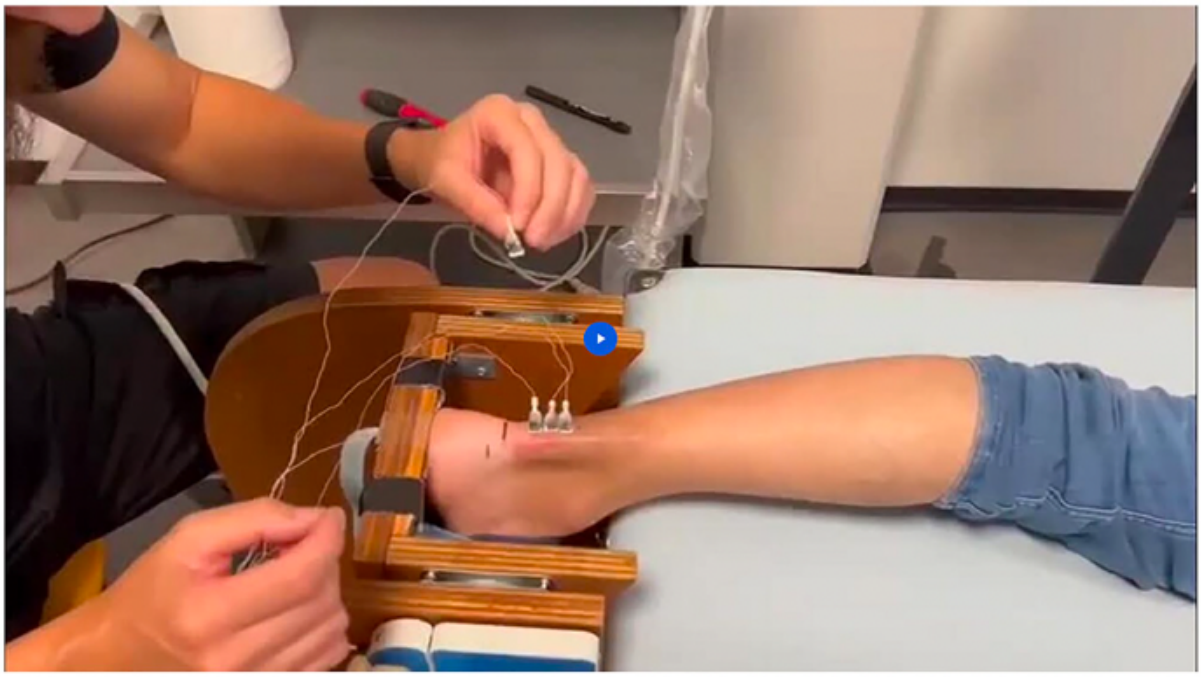
Participants were asked to complete a validated questionnaire designed to evaluate clinical features of AT conditions, the Achilles tendon total rupture score (ATRS).[35] The Tegner activity level scale was used to evaluate differences in the level of physical activity before and after surgery.[34]

Ankle dorsiflexion range of motion was measured bilaterally using a simplified version of the weightbearing ankle lunge test.[4] Range of motion was quantified using a smartphone application (GetmyROM, Interactive Medical Production, LCC) with the smartphone placed 2 cm below the tibial tuberosity. The maximal calf circumference was measured with the subject seated with the knee at 90 degrees.

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Shear wave tensiometry (Video 1). Tendon loading was measured with a shear wave tensiometer consisting of 4 accelerometers (Analog Devices, ADXL202JE) in series fixed on the skin posterior to the tendon with adhesive tape and equally spaced at a distance of 10 mm. The accelerometers were positioned on the skin posterior to the AT following ultrasonographic imaging to ensure the correct position on the free part of the AT (3-6 cm to the calcaneal insertion) and not on the musculotendinous junction. The small impulse needed to elicit the wave propagation along the tendon was performed manually with a reflex hammer. This technique has been previously tested in a pilot study with 10 participants and the convergent validity with an automatic impulse confirmed. A set of 5 repeated measures (1 per second) for each of the contraction levels for both left and right AT of each subject was acquired, and the mean of these 5 measurements was used to perform the calculation of the tendon wave speed. Within- and between-session reliability of this technology has been evaluated in a previous study, which found good to excellent reliability (intraclass correlation coefficient 0.75-0.96).[31]



Video 1. Experimental setup for shear wave tensiometer evaluation.

A Sessantaquattro (OTBioelettronica, Torino, Italy) with a sampling frequency of 10 kHz was used to acquire the signals. The signals were analyzed based on the time delay between the different waves provided by the accelerometers and the propagation of the mechanical wave on the tendon. The technique for estimating propagation velocity used the cross-correlation function between signal pairs.[8,9] Each impulse corresponded to a propagation speed value (m/s) (Figure 1). The participants were in a prone position with the foot firmly fixed in a dynamometer at 0 degrees of plantarflexion (Figure 2). Ten different isometric contractions of increasing intensity (0-35 Nm) were performed. Ankle torque was assessed with a dynamometer connected to a force sensor (Mod.TF2/S; CCT Transducers, Turin, Italy) operating in a 0- to 100-N range. A MISO-II (OT Bioelettronica, Turin, Italy) was used to present the force signal to the participants as a real-time visual feedback.

Participants were instructed to push on the dynamometer as if they want to stand on their tiptoes.

Myotonometry. Tendon mechanical properties were measured with a MyotonPRO (Muomeetria, Tallinn, Estonia) following a predefined protocol.[32] The affected and unaffected AT were measured in 2 different regions of the free tendon (distal part: at 3 cm; proximal part: at 6 cm from the calcaneal insertion) with the participants' feet hanging freely over the edge of the examination bed.

Ultrasonographic imaging. Thickness and CSA were measured at 0 degrees plantarflexion using an ultrasonograph (MyLab25 gold, Esaote, Genoa, Italy) with a 13- to 4-MHz linear array (LA523). Thickness images were acquired using a longitudinal scan from 2 to 7 cm from

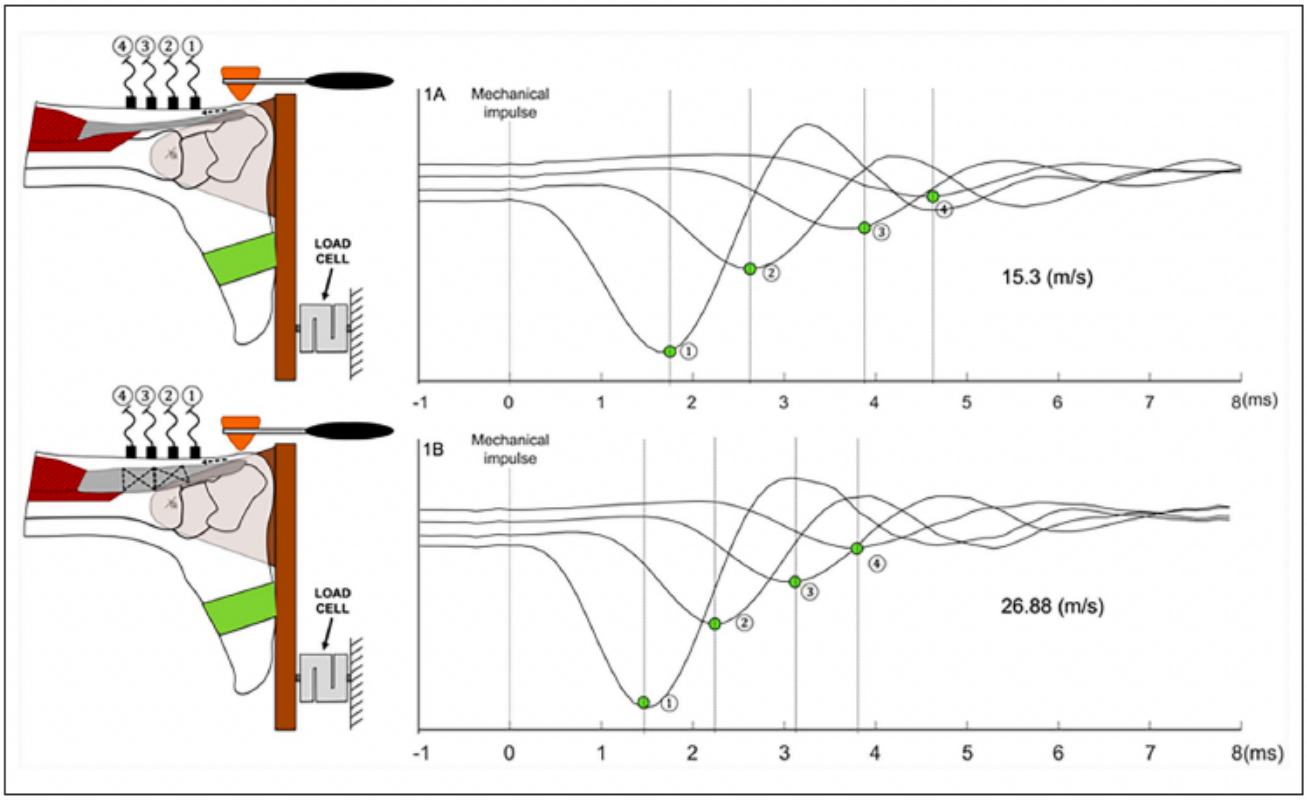


Figure 1. Schematic of the shear wave tensiometer. The impulse was provided at 2 cm from the calcaneal insertion. The 4 accelerometers (1-4) were attached to the skin in series with a 10-mm interaccelerometer distance. Shear wave speed signals of the (A) unaffected Achilles tendon and of the (B) operated Achilles tendon at 0 Nm. The propagation velocity of the wave was calculated based on the delay between the waves passing from the accelerometers.

the calcaneal insertion whereas CSA images were acquired using a transverse scan at 3 and 6 cm from the calcaneal insertion.

Statistical Analysis

The distribution of the data was assessed using the Shapiro-Wilk test, and because of non normality, the non-parametric related sample Friedman test was used for AT wave speed between tendons (SPSS, version 28). Post hoc pairwise comparison Bonferroni correction was applied, and statistical significance was set to $P < .05$. Effect size was calculated using the Kendall W, results were evaluated using the Cohen interpretation guidelines, with 0.2, 0.5, and 0.8 representing small, medium, and large effect, respectively.[6] For each tendon, a linear regression model was used to test the relation between squared wave speed and ankle joint torque. The model's goodness of fit was assessed using the coefficient of determination (R^2). Wave speed values were presented as median and interquartile range (IQR). Friedman test was also used to assess differences between the operated and unaffected tendons for the additional outcomes.

Correlations between shear wave speed values and clinical outcomes (ATRS, Tegner scale, and time after surgery) were performed using Spearman correlation (ρ).

Results

Twenty-three participants were screened for eligibility, 1 participant was excluded because of a recent injury of the contralateral tendon and 1 participant was excluded because of technical difficulties during the placement of the accelerometers on the AT (patient suffered from foot hyperhidrosis). Thus, 21 male participants were analyzed. Participants had a mean age of 47.3 ± 14.2 years, and the mean time from surgery was 20.3 ± 8.1 months (range 12-37). All the sutures were performed with Krackow or Kyrchmeyer-Kessler technique, using PDS 0 suture and PDS 4-0 to close the paratenon.

Clinical Outcomes

The Tegner activity level scale showed that 57% of the participants returned to an equal level of sport activity compared with before the operation. The ATRS showed a mean

score of 88/100 ± 14.7, with the lowest value of 40 and the highest value of 100. ATRS (ρ = 0.19), Tegner activity level scale (ρ = 0.15), and time after surgery (ρ = 0.11) were not correlated with shear wave speed values.

Mean ankle dorsiflexion range of motion was significantly higher for the unaffected AT compared to the operated AT ($P = .039$), with 41.6 ± 4.4 degrees vs 39.4 ± 4.5 degrees range of motion, respectively. Mean calf circumference was also significantly higher for the leg on the unaffected side compared to the leg of the operated side ($P < .01$), with 39.7 ± 3.3 cm vs 36.6 ± 2.4 cm respectively.

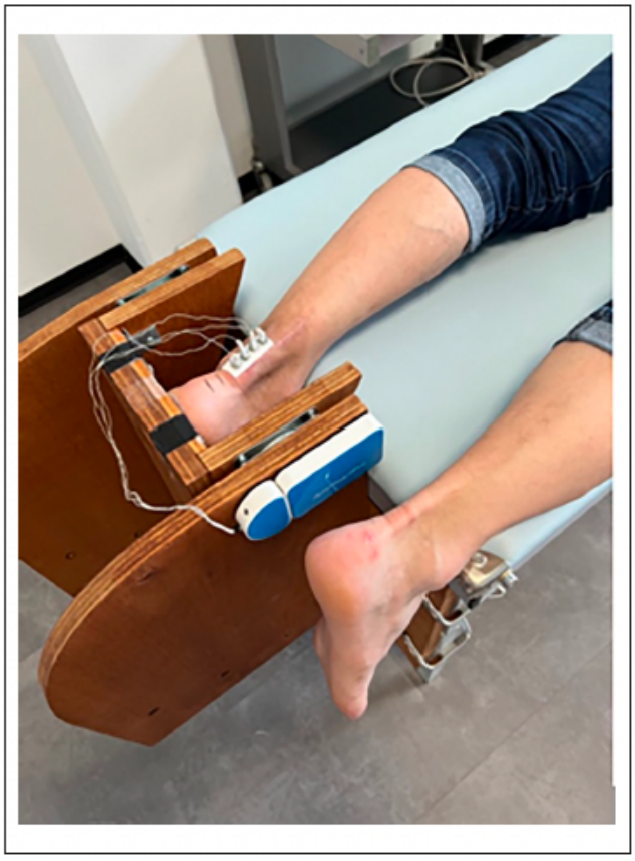


Figure 2. Image of the experimental setup. The participant was placed in a prone position, with the foot securely held within a dynamometer, maintaining the ankle at 0 degrees of dorsiflexion/plantarflexion. The accelerometers were attached to the skin with a 10-mm interaccelerometer distance.

Shear Wave Tensiometry

Shear wave speed values between the operated and the unaffected AT at different ankle joint torques are reported in Table 1 and Figure 3. Friedman test showed a significant difference between sides at every ankle joint torque ($P < .05$) with a large effect size for the lowest ankle torque (0-21 Nm) and small to medium effect sizes for higher ankle torque (24.5-35 Nm). The linear regression model calculated for every AT during the different ankle torque conditions showed a mean coefficient of determination (R^2) of 0.97 ± 0.02 for the unaffected side and 0.93 ± 0.05 for the operated side, indicating a linear fit between wave speed and ankle torque for both the operated and the unaffected side, with no difference between the 2 tendons ($P = .127$). The slope of the regression lines was similar between sides (mean of 0.79 ± 0.28 for the unaffected and 0.74 ± 0.14 for the operated side; $P = .513$), indicating a similar behavior of the shear wave speed during contraction for both AT (Figure 4).

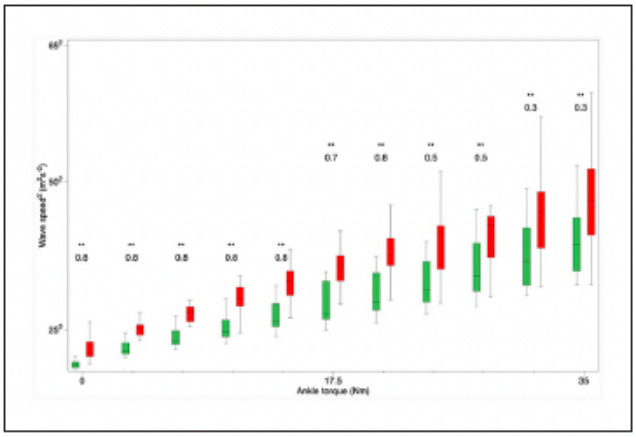


Figure 3. Box plot showing the median (interquartile range) squared shear wave speed of the entire sample at different ankle torques. Green boxes and red boxes represent the unaffected and the operated side, respectively.
**$P < .05$; numbers below represent the effect size.

Table 1. Shear Wave Speed Values of the Entire Sample at Different Ankle Torques.

SWS	0 Nm		3.5 Nm		7 Nm		10.5 Nm		14 Nm		17.5 Nm		21 Nm		24.5 Nm		28 Nm		31.5 Nm		35 Nm	
	H	OP	H	OP	H	OP	H	OP	H	OP	H	OP	H	OP	H	OP	H	OP	H	OP	H	OP
Median (m/s)	13.30	18.21	18.92	25.43	21.91	28.97	24.58	31.88	26.92	35.31	28.85	38.06	31.23	39.66	33.69	43.03	36.19	44.16	38.66	46.02	41.30	47.48
IQR	3.28	4.91	3.92	2.79	4.03	3.46	5.14	4.05	5.81	5.46	7.86	5.19	7.75	4.61	8.49	7.26	9.01	7.45	9.49	10.97	9.14	10.10
P[a]	**<.001**		**<.001**		**<.001**		**<.001**		**<.001**		**<.001**		**<.001**		**.001**		**.001**		**.016**		**.016**	
Effect size	0.80		0.80		0.80		0.80		0.80		0.70		0.80		0.50		0.50		0.30		0.30	

Abbreviations: H, Healthy tendon; OP, Operated tendon; SWS, shear wave speed.
[a]Boldface indicates significance ($P < .05$).

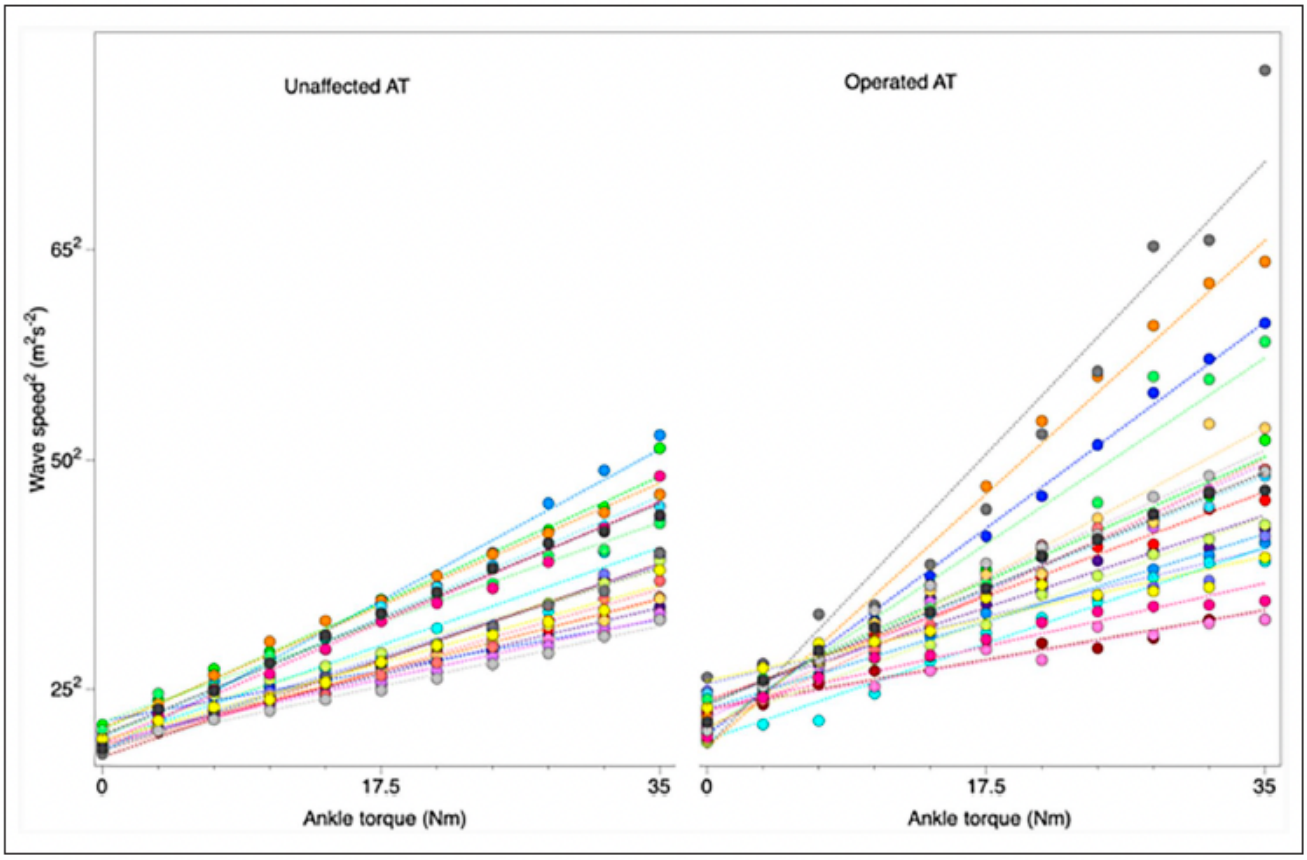


Figure 4. Scatter plot showing the relationship between wave shear wave speed and ankle torque. Left panel shows the unaffected AT whereas the right panel shows the operated AT. Lines represent the linear regression for each tendon.

Myotonometry

Stiffness of the AT measured in the distal part with MyotonPRO showed a median (IQR) of 813 N/m (124) for the unaffected side and 919 N/m (61.5) for the operated AT, indicating an increased stiffness of the operated AT ($P < .01$). The stiffness in the proximal part was higher in the operated AT with 844 N/m (73.3) compared to the unaffected AT with 838 N/m (119) ($P = .03$).

Ultrasonographic Imaging

The median (IQR) thickness was 5.15 mm (1.5) and 13.2 mm (2.2) for the unaffected and the operated AT, respectively ($P < .01$) (Figure 5). The CSA median (IQR) values for the unaffected AT were 62.4 mm^2 (7.3) and 56.1 mm^2 (9.1) in the distal and proximal part, respectively, whereas for the operated AT they were 176 mm^2 (40) and 196 mm^2 (43) ($P < .01$).

Discussion

The present study represents the first investigation assessing tendon loading using shear wave tensiometry in a cohort of individuals who underwent AT surgery. The sample evaluated consisted of 21 male participants with a mean time from surgery of approximately 20 months, and generally low levels of disability except for 2 participants with an ATRS score < 60. The results are comparable with other studies that showed that people generally report low levels of disability 1 year[3] or several years after surgery.[30] A recent large randomized trial[28] involving 526 patients with AT rupture showed a preinjury ATRS score of 93.9 ± 15 suggesting that our current sample had a score comparable to that of a healthy population. Nevertheless, the Tegner activity level scale showed that only 57% of the participants had returned to an equal level of sport activity compared with before the operation. Thus, although our sample showed that the level of disability in their daily life (measured with the ATRS) had almost returned to the normal values, when asked about high demand performance in sport, half of the participants had not returned to their preinjury level. The lack of complete recovery could be explained by persistent abnormalities detected in the operated tendon or by changes in behavior toward higher-demand activities. Calf circumferences of the operated leg was significantly smaller that the unaffected leg; thus, muscle trophism asymmetry

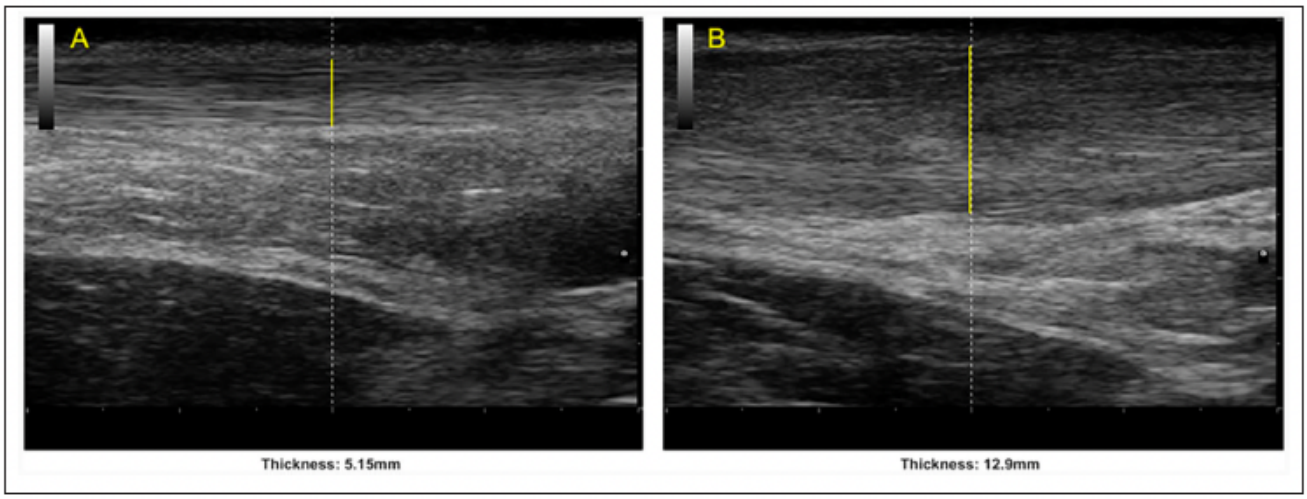


Figure 5. Longitudinal ultrasonographic images of the unaffected (A) and operated (B) Achilles tendon.

appears to persist over time. Indeed Rosso et al[30] showed similar results 7.5 years after AT rupture (37.9 cm for the affected and 39.2 for the unaffected AT). In addition, a different range of motion between the 2 ankles was found, albeit of small magnitude.

Differences in shear wave speed between tendons have been found across all the torque levels evaluated, with a higher effect size (0.8) at lower torque and small effect size (0.3-0.5) at higher torque levels. The operated tendons showed a higher shear wave speed compared to the contralateral unaffected tendons at every ankle torque evaluated (Table 1). These results build on previous studies[17,26] using shear wave speed during isometric contractions in healthy participants. Values ranged from 15 to 20 m/s with the muscles relaxed and from 60 to 80 m/s during a maximal contraction, and provide important new information on the debate about mechanical changes of the tendon after AT rupture repair. Previous studies found decreased stiffness[5,11,14,27,38] whereas other studies reported increased tendon stiffness[1,2] compared to the unaffected side 2-6 years after rupture. This variation could partially be explained by the time point of evaluation. It appears that in the healing phase after surgery (<1 year) the tendon has less stiffness, which progressively increases toward normal value or even exceeds the values of the unaffected tendon in the later phases, as identified in the current work. Indeed, shear wave speed values remain higher even in participants examined long time after surgery (in this study up to 37 months). However, no significant correlations were found between shear wave speed and time elapsed since surgery, ATRS and Tegner activity level scale.

One possible explanation is that mechanical properties and clinical features are not closely interrelated; alternatively, it is likely that the sample size was not large enough to achieve sufficient statistical power, and the findings of this study must be considered to be preliminary. The behavior of the tendon shear wave speed and its relationship with the distance from the surgery, clinical features (ATRS and Tegner activity level scale), or level of injury is currently unclear and should be further investigated.

Several parameters have been used to describe the mechanical properties of tendons and therefore not all results are directly comparable given the different technology used. In the current study, we use tendon tension/loading as an index to measure the axial stress as the shear wave speed is proportional to the axial stress in the tissue. During isometric contraction of increased intensity, force/torque, AT axial strain, and stiffness should all increase.[19,24] In this study and previous studies,[26,31] shear wave speed increases when tension is put on the AT by an isometric contraction. However, because of the possible relationship between stiffness and tension measured with shear wave tensiometry, the previously ruptured and surgically repaired AT appears stiffer than the healthy contralateral tendon. This finding is also supported by the myotonometry results, which found increased stiffness (N/m) in the operated AT compared to the unaffected side both in the most distal and proximal region of the tendon. Similarly, Bravo-Sanchez et al[2] found increased stiffness in the operated tendon.

Several potential explanations exist for the distinct loading values observed. Changes in collagen type have been shown in tendon following surgery, with a greater proportion of type III collagen in repaired tendon when compared to unaffected tendons that contain mainly type I collagen.[23] Type I collagen has more tensile strength than type III; therefore, the composition of the tendon can influence its capacity to tolerate load[22] and the tendon's mechanical properties.[16,21] Thus the higher proportion of type III collagen relative to type I might stiffen the tendon.[2,33] Differences between the operated and the unaffected tendon were also

present in the morphological properties measured with ultrasonographic imaging. Tendon thickness and CSA remain higher in the operated tendon even after more than 1 year postsurgery. These results are in line with other studies showing increased tendon thickness and CSA in the longer term after the surgery.[2,11,14,18] Indeed, operated tendons are characterized by a round irregular area of increased size[33] with disorganized collagen fiber due to scar maturation and remodeling. Morphological parameters can influence the mechanical parameters as the tendon shear wave speed is directly correlated to the tendon CSA.[26]

The linear relationship between squared shear wave speed and ankle torque has been evaluated to test the consistency of the tensioned beam model.[26] As previously shown in healthy participants,[31] squared AT wave speed increases linearly with the increment of ankle torque. In the present study the coefficient of determination R^2 of both the operated and unaffected tendon was close to 1 (0.93 and 0.97, respectively), showing a close linear relationship between shear wave speed and ankle torque (Figure 4). Moreover, tendon loading is highly variable between participants, especially with higher ankle torque; IQR values increased as torque increases, showing different tendon behavior between participants as previously shown in healthy participants.[31] This variability is particularly noticeable for the operated tendon (Figure 4) where the values are more evenly spread, especially at higher ankle torque. This is probably due to different muscular activation patterns between plantarflexor muscles in different individuals. As previously shown in other studies,[10,15,18] the contribution of flexor hallucis longus muscles and of the soleus can change after AT ruptures. Furthermore, calf muscle trophism in the operated limb as well as muscle maximal voluntary contraction remain significantly lower long term after the injury[18,30]; collectively, these factors can contribute to different muscle activity patterns. The different contribution of the plantarflexor muscles cannot be distinguished by the tensiometer that measures AT wave speed.

This study presents some limitations. First, the exact surgical procedure as well as the rehabilitation protocol has not been systematically recorded; all participants underwent open repair surgery, however, it remains unclear if the outcomes measured were affected by slight variations in operational treatments or rehabilitation protocols. Also, and critically important to consider, is that this study was of 21 male patients—both a small sample size and one that is hard to generalize.

Another aspect is the acquisition of the tensiometry values from 0 to 35 Nm of ankle torque at 0 degrees of plantarflexion; we cannot exclude that the results may be different at different ankle torque levels or at different ankle angles. Lastly, different loading between the 2 tendons could be related to the different resting length of the tendon after the suture. Two factors can influence the residual length of the operated AT, the position in which the tendon is sutured and the lengthening that possibly occurs during the rehabilitation phase. When this type of surgery is performed, the foot is positioned in the equinus to facilitate the approaching of the 2 tendon stumps.

Previous studies showed greater tendon resting length[1,18,39] in the operated tendon compared to the unaffected side. However, the tendon resting length was not assessed in this study, and therefore we cannot establish whether tendon length influences shear wave speed. Future studies to evaluate the relationship between shear wave speed and tendon resting length could be relevant. Further studies are also needed to better understand the clinical relevance of shear wave tensiometry in measuring tendon loading and guiding the treatment of AT rupture. Having an instrument able to precisely detect changes in tendon loading responses over time not only holds the potential to enhance our understanding of tendon behavior during the healing phase but also can support clinicians in developing patient-specific rehabilitation protocols.

Conclusion

Shear wave tensiometry can precisely detect differences between operated and unaffected AT during a standardized loading procedure. The shear wave speed along the operated tendon remains higher in the long-term after a rupture. This study represents the first step toward the implementation of this technology in clinical settings in order to monitor the evolution of the mechanical properties of the AT over time for patients affected by AT rupture and other tendon pathologies.

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Ethical Approval

Ethical approval for this study was obtained from the Ethics Committee of Canton Ticino (ID:2022-01707/CE4192).

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. ICMJE forms for all authors are available online.

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Appendix 9 – Ethical Review, Consent Forms and Patient Information Sheets for Chapter Two

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Prof. Marco Barbero
Ricercatore responsabile Area Riabilitazione
Dipartimento sanità SUPSI
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Bellinzona
14 marzo 2014

Ns. riferimento Vs. riferimento

Ripetibilità dell'elastografia nel valutare l'elasticità del tendine d'Achille in soggetti sani e soggetti con tendinopatie; Rif.CE 2752

Egregio Professor Barbero ,

il Comitato etico cantonale ha esaminato il progetto di ricerca sopra citato, oggetto della sua domanda di autorizzazione riguardante il protocollo di studio sopracitato

☐ procedura normale ☒ procedura semplificata ☐ valutazione successiva

Il Comitato etico ha fondato la sua valutazione sui documenti elencati esaustivamente nell'allegato "Formulario di base" del 7.10.2013, che costituisce parte integrante della presente decisione.

La versione del protocollo valutata e approvata dal Comitato Etico è la versione 3 del 12.02.2014.

Il Comitato etico è giunto alla seguente **decisione**:

☒ **A positiva**
☐ **B positiva con raccomandazioni**
☐ **C per principio positiva ma vincolata a condizioni**
È necessaria una valutazione successiva da parte del Comitato etico ☐
È sufficiente una comunicazione scritta al Comitato etico ☐
☐ **D negativa** (con motivazione e spiegazione per la valutazione successiva)
☐ **E non entrata in materia (con motivazione)**

La decisione vale anche per gli altri sperimentatori segnalati nella domanda di esame che rientrano nel settore di competenza del Comitato etico.

1. **Lo studio risponde ai requisiti etici usuali e non dà luogo a obiezioni.**
2. **Il Comitato etico concede pertanto l'autorizzazione all'esecuzione dello studio.**
3. **La tassa di esame del protocollo ammonta a fr.300 La polizza di versamento le sarà inviata separatamente dal Centro sistemi informativi.**

Contro la presente decisione è dato ricorso entro 15 giorni da questa notifica; l'atto di ricorso deve essere indirizzato al Comitato etico cantonale che lo trasmetterà in seguito al Consiglio di Stato.

Augurandole una buona ricerca porgiamo, egregio Professore, i più cordiali saluti.

PER IL COMITATO ETICO CANTONALE

Il Presidente:

Giovan Maria Zanini

Allegato:

- "Formulario di base" del 7.10.2013

Scuola universitaria professionale
della Svizzera italiana

SUPSI

Informazione per i volontari

Progetto ELASTO. Ripetibilità dell'elastografia nel valutare l'elasticità del tendine d'Achille in soggetti sani e soggetti con tendinopatie.

Gentile volontario,

legga per cortesia attentamente il contenuto di questo foglio informativo riguardante lo studio al quale Le è stato proposto di partecipare. Non esiti ad interpellarci qualora non comprendesse qualche cosa o desiderasse ulteriori informazioni.

Scopo dello studio
Le è stato chiesto di partecipare a questo studio perché si vuole indagare ripetibilità dell'elastografia, uno strumento di misura non invasivo che permette di valutare l'elasticità di muscoli e tendini.
Questo studio è condotto nel rispetto delle leggi svizzere e dei principi etico-morali riconosciuti dalla comunità scientifica internazionale.
La Sua partecipazione a questo studio è volontaria. Se rinunciasse a partecipare a questo studio non dovrà temere alcuno svantaggio. Lo stesso vale qualora ritirasse il Suo consenso in un secondo momento, possibilità che manterrà per tutta la durata dello studio. Che rinunci a partecipare allo studio o che revochi il suo consenso, in entrambi i casi non sarà tenuto a giustificarsi. Qualora decidesse di ritirarsi, i dati raccolti fino a quel momento saranno comunque utilizzati.

Scelta dei partecipanti allo studio
Lo studio è uno studio su misure ripetute. Saranno convocati 24 soggetti sani e 15 soggetti con tendinopatia del tendine d'Achille. I partecipanti sani saranno esclusi qualora riportino: operazioni o dolori al tendine d'Achille; patologie metaboliche o del tessuto connettivo; patologie infiammatorie sistemiche; artrite reumatoide; spondiloartropatie; ipercolesterolemia; assunzione di steroidi o estrogeni.
I partecipanti volontari con tendinopatia del tendine d'Achille saranno esclusi qualora riportino: patologie metaboliche o del tessuto connettivo; patologie infiammatorie sistemiche; artrite reumatoide; spondiloartropatie; ipercolesterolemia; assunzione di steroidi o estrogeni.

Descrizione e svolgimento dello studio
Lo studio avrà una durata complessiva di circa 30 minuti.
Durante la sessione verrà sottoposto a dei test diagnosici per identificare la presenza/assenza di tendinopatie del tendine d'Achille, questi test consistono nella palpazione del tendine d'Achille per identificare eventuali zone dolorose. La seconda parte dello studio consisterà in un indagine ecografica del tendine d'Achille, il Suo tendine verrà analizzato con l'ausilio di un ecografo, inizialmente per valutare alcuni parametri morfologici e poi per valutare l'elasticità del tendine. Per questa seconda valutazione l'operatore farà delle piccole compressioni, quasi impercettibili, con la sonda ecografica sul tendine analizzato. Per facilitare l'acquisizione delle immagini Le verrà appoggiato sulla pelle un panetto in gel per ecografia (CIRS, Norfolk, Virginia - USA) che verrà rimosso subito dopo l'esame.
Prima dell'inizio dei test riceverà una breve istruzione su come comportarsi durante l'esperimento. L'esperimento si svolgerà da prono su un lettino da fisioterapia, con i piedi in posizione rilassata al di fuori del lettino. La posizione da mantenere durante la procedura sperimentale è confortevole e non le creerà fastidi. Durante lo studio dovrà indossare pantaloncini corti o pantaloni che permettano di essere sollevati per lasciare libero il polpaccio.
Durante l'esecuzione dell'esame Le saranno poste alcune domande di carattere anamnestico e generale.

Benefici e rischi della partecipazione allo studio
La partecipazione a questo studio clinico non Le apporterà alcun beneficio.
Grazie alla Sua partecipazione altre persone potranno beneficiare dei risultati.
La partecipazione allo studio non comporta alcun rischio per la Sua salute. L'ecografo è uno strumento di valutazione che non emette radiazioni ionizzanti e quindi privo di alcun tipo di rischio per la salute.

Confidenzialità dati
In questo studio vengono registrati alcuni dati personali (età, sesso, peso, altezza). Questi dati sono resi anonimi e sono accessibili soltanto agli specialisti per l'elaborazione scientifica. Gli specialisti competenti del promotore (o i loro incaricati) potranno verificare lo svolgimento dello studio nell'ambito del cosiddetto monitoring o audit. Questi specialisti e i membri delle autorità competenti possono accedere ai Suoi dati originali nell'ambito delle ispezioni. Parimenti il comitato etico competente può prendere visione dei dati originali. La confidenzialità è strettamente tutelata durante tutto lo svolgimento dello studio e al momento dei controlli menzionati. Il Suo nome non sarà mai pubblicato in alcun modo in rapporti o pubblicazioni che si baseranno sullo studio.
Le procedure menzionate nel presente foglio informativo sono gratuite per tutti i soggetti partecipanti allo studio. La partecipazione allo studio non causa costi supplementari legati alla partecipazione né per Lei né per la Sua cassa malati.

Per la partecipazione a questo studio clinico non riceverà alcuna indennità.

In caso di dubbi, urgenze, eventi inaspettati o indesiderati che sorgessero durante lo studio o dopo la sua conclusione, può rivolgersi in ogni momento alle persone di contatto indicate qui sotto:

Persone da contattare
Sperimentatori: Alessandro Schneebeli, Marco Barbero
Presso il Dipartimento Sanità della SUPSI
Stabile Piazzetta, via Violino.
CH-6928 Manno
Tel +41 (0) 58 6666435 / 6666437
Email: alessandro.schneebeli@supsi.ch ; marco.barbero@supsi.ch

Se desiderasse ulteriori informazioni sui suoi diritti in qualità di soggetto partecipante a questo studio, o per qualsiasi altra domanda di carattere generale, può rivolgersi a:

Ufficio del farmacista cantonale
Via Maspoli
6850 Mendrisio
tel. 091 816 59 41

Scuola universitaria professionale
della Svizzera italiana

SUPSI

Consenso scritto del volontario sano per la partecipazione ad uno studio clinico

- Legga attentamente il presente formulario.
- Non esiti a pormi delle domande qualora non comprendesse qualche cosa o desiderasse ulteriori informazioni.

Numero dello studio:	
Titolo dello studio:	Ripetibilità dell'elastografia nel valutare l'elasticità del tendine d'Achille in soggetti sani e soggetti con tendinopatie.
Promotore (indirizzo completo):	
Luogo dello studio:	Dipartimento Sanità della SUPSI. Stabile Piazzetta, via Violino 6928 Manno
Sperimentatore Cognome e nome:	Marco Barbero, Alessandro Schneebeli
Volontario Cognome e nome: Data di nascita:	☐ uomo ☐ donna

- Sono stato/a informato/a dallo sperimentatore sia oralmente che per scritto in merito allo scopo, lo svolgimento dello studio, gli effetti attesi, gli svantaggi e i vantaggi, nonché gli eventuali rischi.
- Ho letto e capito l'informazione scritta per i volontari sani del 07/10/2013 consegnatami concernente lo studio sopraccitato. Ho ottenuto una risposta adeguata a tutte le mie domande relative alla partecipazione a questo studio. Mi viene consegnato il modulo informativo scritto per i soggetti partecipanti e ricevo una copia del mio consenso informato scritto.
- Ho avuto tempo a sufficienza per decidere di partecipare.
- So che i miei dati personali saranno inoltrati ad istituzioni esterne soltanto in forma anonima e per fini di ricerca. Acconsento al fatto che gli specialisti competenti del committente dello studio, delle autorità e del comitato etico cantonale accedano ai miei dati originali a fini di valutazione e controllo, tuttavia in stretta osservanza della confidenzialità di tali dati.
- Partecipo a questo studio volontariamente. Posso ritirare in ogni momento e senza giustificazione il mio consenso alla partecipazione allo studio.
- Sono consapevole che durante lo studio devono essere rispettate le esigenze e le limitazioni menzionate nell'informazione per i pazienti. Nell'interesse della mia salute lo sperimentatore può escludermi dallo studio in ogni momento. Ho inoltre informato lo sperimentatore sui trattamenti concomitanti presso un altro medico e sull'assunzione di medicamenti (prescritti dal medico o acquistati di mia iniziativa).

Luogo, data	Firma del/la paziente

Dichiarazione dello sperimentatore: dichiaro di aver spiegato al/la volontario in questione la natura, l'importanza e la portata dello studio. Garantisco di adempiere agli obblighi inerenti a questo studio. Se in qualsiasi momento dello studio venissi a conoscenza di aspetti che potrebbero influenzare la disponibilità del/la volontario a partecipare allo studio, provvederò a informarla/lo immediatamente.

Luogo, data	Firma del/la sperimentatore

Appendix 10 – Ethical Review, Consent Forms and Patient Information Sheets for Chapter Three

Fondazione IRCCS
Policlinico San Matteo

Sistema Socio Sanitario
Regione Lombardia

DIREZIONE SCIENTIFICA

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U.O.C. DIREZIONE MEDICA DI PRESIDIO – SEDE
U.O.C. S.I.T.R.A. – SEDE

Oggetto: Studio "Valutazione delle proprietà meccaniche del tendine di Achille durante contrazione con elastografia shearwave e strain: confronto tra vari devices", promosso dall'U.O.C. Radiologia

Si comunica che lo studio in oggetto è stato autorizzato con decreto dirigenziale n.0570 del 20/08/2020 e che, pertanto, può considerarsi formalmente avviato.

Si ricorda che lo studio dovrà essere condotto in osservanza a quanto stabilito dal "Regolamento per la disciplina delle sperimentazioni cliniche e delle attività di ricerca per conto terzi", e che, ai sensi dell'art. 11 di quest'ultimo, al termine dello studio dovrà essere trasmessa all'Ufficio di Segreteria del Comitato Etico (c/o Direzione Scientifica) una relazione sui risultati conseguiti dallo stesso.

Si ricorda, infine, l'obbligo di provvedere all'inserimento nell'apposito data-base delle relazioni annuali e finale (da trasmettere a questi uffici anche su supporto cartaceo) e dei dati relativi ai pazienti arruolati.

Distinti saluti.

IL RESPONSABILE DEL PROCEDIMENTO

Dr. Franco Marazza

RESPONSABILE DEL PROCEDIMENTO: DR. FRANCO MARAZZA
RESPONSABILE DELL'ISTRUTTORIA: DR.SSA CRISTINA FIOCCHI

Appendix 11 – Ethical Review, Consent Forms and Patient Information Sheets for Chapter Five

c/o Ufficio di sanità
Via Orico 5
telefono 091 814 30 57
fax 091 814 44 47

www.ti.ch/CE

Funzionario incaricato Gutacker

telefono 091 814 30 57
e-mail michaela.gutacker@ti.ch

Repubblica e Cantone
Ticino

Comitato etico cantonale
6501 Bellinzona

Prof. Marco Barbero
SUPSI - DEASS
Stabile Piazzetta
Via Violino 11
6928 Manno

Bellinzona
29.08.2018

Ns. riferimento Vs. riferimento

Lettera di decisione del Comitato etico del Canton Ticino

Project-ID	2018-01483 / CE 3391
Titolo del progetto	Intra and inter-rater reliability of myotonometry in quantifing Achilles tendon stiffness.
Studio master/tesi di:	Schneebeli, Alessandro
Sperimentatore principale e promotore	Prof. Marco Barbero
Centro(i)	SUPSI DEASS, Manno

Tipo di procedura

☒ Procedura ordinaria ☐ Procedura semplificata ☐ Procedura presidenziale

Decisione

Prof. Marco Barbero, SUPSI DEASS, Manno

- ☒ Autorizzato
- ☐ Autorizzato con requisiti
- ☐ Attualmente non può ancora essere autorizzato
- ☐ Non può essere autorizzato
- ☐ Non entrata in materia

Note :

Testo informativo: non trattandosi di una sperimentazione clinica, la preghiamo di togliere la parola clinico in tutto il testo (pagina 2 e pagina 4).

Classificazione

☒ Progetto di ricerca secondo ORUm Categoria: A
- ☒ ricerca con persone
- ☐ Riutilizzo di materiale biologico e di dati sanitari personali
- ☐ con persone decedute

☐ con embrioni e feti
☐ con radiazioni ionizzanti
☐ cambiamento della categoria secondo ORUm, art. 48, cpv. 2

Tassa

Ammontare: 300.- CHF
La polizza di versamento sarà inviata separatamente dal Centro sistemi informativi all'indirizzo da voi indicato.

Rimedi di diritto

Contro la presente decisione è dato ricorso entro 15 giorni da questa notifica; l'atto di ricorso deve essere indirizzato al Comitato etico cantonale che lo trasmetterà in seguito al Consiglio di Stato.

Copia per informazione a

☐ UFSP
☐ Altro(i)

Con i migliori saluti.

PER IL COMITATO ETICO CANTONALE

Il Presidente:

Giovan Maria Zanini

Allegati: -Obblighi del richiedente
-Documenti inoltrati
-Composizione della commissione d'etica

Allegati

Obblighi del richiedente (promotore o sperimentatore)

Sottomissione dei documenti: documenti nuovi o revisionati del progetto di ricerca sono da trasmettere unicamente via portale BASEC nella pagina specifica del progetto già esistente. Vanno eliminati i documenti obsoleti e sostituiti con quelli nuovi e le date e le versioni vanno modificate di conseguenza. I documenti revisionati devono essere trasmessi con le modifiche evidenziate (track changes) e nella versione pulita (clean). Il documento informativo scritto / dichiarazione di consenso, il protocollo e gli emendamenti al protocollo devono essere salvati in una modalità che permetta le ricerche all'interno del documento (PDF navigabile) o la loro scansione deve essere fatta con la modalità OCR (Optical Character Recognition). Nella lettera accompagnatoria datata e firmata dovranno esserci le risposte ad eventuali quesiti posti. I documenti revisionati vanno trasmessi anche alle autorità competenti, se del caso.

Nota: La commissione etica competente esamina nell'ambito del processo di autorizzazione il documento informativo / la dichiarazione di consenso scritti in una delle lingue ufficiali svizzere tedesco, francese o italiano. La commissione etica prende solamente atto di documenti informativi / delle dichiarazioni di consenso scritti in un'altra lingua. Lo sponsor o la direzione del progetto è responsabile della correttezza della traduzione.

Obblighi di notifica: Si applicano gli obblighi di notifica e autorizzazione descritti nelle Ordinanze (es. notifiche di eventi indesiderati gravi, interruzione anticipata del progetto di ricerca e autorizzazioni di modifiche essenziali). Il rapporto finale è da trasmettere alla Commissione etica competente entro un anno dalla fine o dall'interruzione del progetto di ricerca.

Obbligo di registrazione: In caso di sperimentazione clinica il promotore ha l'obbligo di registrare il progetto in un registro primario OMS o nel registro della 'US national library of medicine' (clinicaltrials.gov). Dal registro primario il promotore otterrà un numero di identificazione che dovrà inserire in BASEC, nella sezione SNCTP completata al momento dell'inoltro della richiesta di autorizzazione. Il trasferimento automatico dei dati nello 'Swiss National Clinical Trials Portal' (SNCTP) avverrà dopo autorizzazione da parte della Commissione etica e previo accordo del richiedente. Le informazioni sulla sperimentazione clinica sono disponibili al pubblico in entrambi i registri. Inoltre swissethics pubblica sul suo sito alcune informazioni (titolo, tipo di progetto, nome della Commissione etica direttiva) dei progetti approvati ad eccezione delle sperimentazioni cliniche di fase I.

La Commissione etica cantonale opera in ottemperanza alle ICH-GCP.

Nota: Istruzioni dettagliate sull'inoltro tramite il portale BASEC sono disponibili nel portale stesso.

Significato delle diverse decisioni

Autorizzato: la ricerca può essere effettuata nel rispetto delle condizioni quadro del protocollo di studio sottomesso e nel rispetto delle basi legali applicabili.
Autorizzazioni di progetti di ricerca con agenti terapeutici delle categorie B e C sono accettati a condizione che:

1. eventuali carenze constatate dall'autorità federale (Swissmedic/UFSP/UFAM) non richiedano modifiche alla documentazione valutata dal comitato etico e che
2. sia stata ottenuta l'autorizzazione delle autorità federali (Swissmedic/UFSP/UFAM)

Autorizzato con requisiti: la ricerca può essere effettuata nel rispetto delle condizioni quadro del protocollo di studio sottomesso e nel rispetto delle basi legali applicabili. I requisiti vincolanti sono da soddisfare entro 30 giorni e in ogni caso prima del reclutamento del primo paziente. La documentazione rielaborata viene valutata in procedura presidenziale.

Attualmente non può ancora essere autorizzato: Questo significa che: la ricerca non può essere iniziata. Siete pregati di rispondere alle domande e soddisfare le condizioni poste dal Comitato etico e di risottomettere la documentazione rielaborata.

Non può essere autorizzato: la ricerca non può essere effettuata. È possibile una nuova sottomissione.

Non entrata in materia: il Comitato etico non è legalmente competente per l'autorizzazione. È possibile che sia responsabile un altro ente, oppure che la sperimentazione possa essere effettuata senza autorizzazione.

Documenti inoltrati per il centro coordinatore

Prof. Marco Barbero, SUPSI DEASS, Manno

nome del documento	data del documento	versione
1. Cover Letter		
cover-MyoRel.docx	10/08/2018	
3. Participant information sheet and informed consent (ICF)		
informazione-myorel_AS.docx	10/08/2018	1.0
4. Study plan (protocol), signed and dated		
hro-research-plan-myorel_AS.docx	10/08/2018	1.0
5. CRF (Case Report Form)		
Case-form_1.0.xlsx	10/08/2018	1.0
6. Investigator's CV, dated		
cv-barbero-short.pdf	05/01/2016	
10. Insurance		
see doc/cat: **4**, page/ref: **15**		
11. Other documents handed over to study participants		
No other documents handed over to study participants		
12. Details on nature and scope/value of compensation for participants		
There is no compensation for the participation in this study		
14. Information on secure handling of biological material and personal data, and in particular on the storage thereof		
see doc/cat: **4**, page/ref: **14/15**		
39. Miscellaneous / Varia		
handleiding MyotonPRO User Manual (3).pdf	01/06/2013	6th

Composizione della commissione d'etica nella seduta del 28.08.2018

Il Comitato etico si è riunito nella composizione riportata qui sotto ed era perciò in numero legale (in ottemperanza all'Art. 5, Org-LRUm)

					Partecipante alla decisione	
	Nome e cognome	Posizione professionale/titolo	m	f	Si	no
Presidente	**Giovan Maria Zanini**	Farmacista cantonale, Dipartimento sanità e socialità, Mendrisio	☒	☐	☒	☐
Vice presidenti	Dr. med. **Mario Lazzaro**	Specialista FMH in medicina interna, Ospedale Regionale di Bellinzona e Valli, Bellinzona	☒	☐	☒	☐
	Dr. med. **Hans-Rudolf Schwarzenbach**	Specialista FMH in medicina interna generale, Melide	☒	☐	☐	☒
Membri	Dr. med. **Sonja Bernasconi-Guastalla**	Specialista FMH in medicina generale, Studio medico, Balerna	☐	☒	☐	☒
	Lic. Phil. **Guenda Bernegger**	Laureata in filosofia, Master in Medical Humanities, Massagno	☐	☒	☒	☐
	Dr. sc. nat. **Marco Bissig**	Farmacista, Ospedale Regionale di Lugano	☒	☐	☒	☐
	Dr. theol. **Ernesto Borghi**	Esperto di cultura religiosa presso l'ASP e presidente dell'Ass. Biblica della Svizzera Italiana	☒	☐	☒	☐
	Avv. **Patrizia Bottinelli-Cancellara**	Giurista presso il Dipartimento della sanità e della socialità, Bellinzona	☐	☒	☒	☐
	PD Dr. med. **Guido Domenighetti**	Specialista FMH in medicina interna, malattie polmonari e medicina intensiva, Ospedale regionale La Carità, Locarno	☒	☐	☒	☐
	PD Dr. med. **Christian Garzoni**	Specialista FMH in malattie infettive e medicina interna, studio medico, Lugano	☒	☐	☐	☒
	Irma König	Infermiera diplomata, Ospedale Regionale Bellinzona e Valli, Bellinzona	☐	☒	☐	☒
	Lic. oec. **Costanzo Limoni**	Economista specializzato in biostatistica, Docente di statistica presso USI Lugano (Net-Mega) e (EMAP), studio di consulenza	☒	☐	☐	☒
	PD Dr. sc. nat. **Orlando Petrini**	Libero docente al Politecnico federale di Zurigo, studio di consulenza, Breganzona	☒	☐	☒	☐
	Prof. Dr. med. **Marco Pons**	Specialista FMH in medicina interna e pneumologia, Ospedale Regionale di Lugano, Sede Civico, Lugano	☒	☐	☐	☒
	Dr. med. **Vito Spataro**	Specialista FMH medicina interna, oncologia-ematologica, Studio medico, Bellinzona	☒	☐	☒	☐
	PD Dr. med. **Hans Stricker**	Specialista FMH medicina interna e angiologia, Ospedale Regionale La Carità, Locarno	☒	☐	☒	☐
	Dr. med. **Rafael Traber**	eMBA specialista FMH psichiatria e psicoterapia, direttore di Settore (Sottoceneri e Sopraceneri) Organizzazione sociopsichiatrica cantonale, Lugano	☒	☐	☒	☐
	Michela Tomasoni	Infermiera diplomata, Laurea in scienze della formazione, Gordola	☐	☒	☒	☐
	Avv. **Tiziano Veronelli**	Consulente giuridico del Gran Consiglio, Bellinzona	☒	☐	☒	☐

[1] Il Comitato etico è organizzato e opera in conformità alle GCP-ICH, alle normative applicabili e alla dichiarazione di Helsinki

Scuola universitaria professionale
della Svizzera italiana

SUPSI

Informazione per i partecipanti

Titolo del progetto: Intra and inter-rater reliability of myotonometry in quantifing Achilles tendon stiffness.

Gentile partecipante,

legga per cortesia attentamente il contenuto di questo foglio informativo riguardante lo studio al quale Le è stato proposto di partecipare. Non esiti ad interpellarci qualora non comprendesse qualche cosa o desiderasse ulteriori informazioni.

Con il presente documento La invitiamo a partecipare al nostro studio concernente l'elasticità del tendine d'Achille

Scopo dello studio

Le è stato chiesto di partecipare a questo studio perché si vuole indagare la ripetibilità di un nuovo strumento di misura dell'elasticità dei tessuti, MyotonPRO.
Questo studio è condotto nel rispetto delle leggi svizzere e dei principi etico-morali riconosciuti dalla comunità scientifica internazionale.
La Sua partecipazione a questo studio è volontaria. Se rinunciasse a partecipare a questo studio non dovrà temere alcuno svantaggio. Lo stesso vale qualora ritirasse il Suo consenso in un secondo momento, possibilità che manterrà per tutta la durata dello studio. Che rinunci a partecipare allo studio o che revochi il suo consenso, in entrambi i casi non sarà tenuto a giustificarsi. Qualora decidesse di ritirarsi, i dati raccolti fino a quel momento saranno comunque utilizzati.

Scelta dei partecipanti allo studio

In questo studio pilota saranno convocati 40 volontari sani.

I partecipanti sani saranno esclusi qualora riportino: operazioni al piede o al tendine d'Achille o episodi di dolore al tendine d'Achille. Patologie metaboliche o del tessuto connettivo; patologie infiammatorie sistemiche; artrite reumatoide; ipercolesterolemia; assunzione di steroidi o estrogeni.

Descrizione e svolgimento dello studio

Lo studio avrà una durata complessiva di circa 40 minuti, suddivisi in due giornate di analisi.
I volontari verranno sottoposti a 3 misure di elasticità dei tendini d'Achille due in posizione prona e una in piedi.
Le due misurazioni in posizione prona verranno prese con il piede rilassato, ovvero libero di muoversi al di fuori del lettino e con il piede a 0° di flessione plantare grazie ad una gabbietta che permette di mantenere una posizione fissa del piede.
Le misure di elasticità verranno effettuate con un miotonometro (MyotonPRO, Muomeetria Ltd., Tallinn, Estonia) ovvero uno strumento non invasivo che tramite una piccola percussione determina la risposta elastica dei tessuti.
Entrambi i tendini d'Achille (destro e sinistro) verranno analizzati da due operatori cosi da permettere una valutazione della ripetibilità inter-operatore.

Prima dell'inizio dei test riceverà una breve istruzione su come comportarsi durante l'esperimento. Durante lo studio dovrà essere scalzo e indossare pantaloncini corti o pantaloni che permettano con facilità l'accesso al tendine d'Achille (non troppo stretti a livello della caviglia)
Durante l'esecuzione dell'esame, ai soggetti saranno poste alcune domande di carattere anamnestico e generale (età, sesso, peso, altezza).

Benefici e rischi della partecipazione allo studio

La partecipazione a questo studio clinico non Le apporterà alcun beneficio e non comporta alcun rischio per la Sua salute. Grazie alla Sua partecipazione altre persone potranno beneficiare dei risultati.

Diritti dei partecipanti allo studio

La Sua partecipazione a questo studio è volontaria. Se ora decide di partecipare, potrà comunque ritirarsi in qualsiasi momento dallo studio senza addurre alcuna motivazione.
Lo studio prevede la rilevazione di dati medici sulla Sua persona. Se decide di ritirarsi dallo studio in un secondo momento, i dati non verranno più presi in considerazione ai fini del nostro studio.

Confidenzialità dati

In questo studio vengono registrati alcuni dati personali (età, sesso, peso, altezza). Questi dati vengono codificati e sono accessibili soltanto agli specialisti per l'elaborazione scientifica. Gli specialisti competenti del promotore (o i loro incaricati) potranno verificare lo svolgimento dello studio nell'ambito del cosiddetto monitoring o audit. Questi specialisti e i membri delle autorità competenti possono accedere ai Suoi dati originali nell'ambito delle ispezioni. Parimenti il comitato etico competente può prendere visione dei dati originali. La confidenzialità è strettamente tutelata durante tutto lo svolgimento dello studio e al momento dei controlli menzionati. Il Suo nome non sarà mai pubblicato in alcun modo in rapporti o pubblicazioni che si baseranno sullo studio.

Le procedure menzionate nel presente foglio informativo sono gratuite per tutti i soggetti partecipanti allo studio. La partecipazione allo studio non causa costi supplementari legati alla partecipazione né per Lei né per la Sua cassa malati.

Per la partecipazione a questo studio clinico non riceverà alcuna indennità.

In caso di dubbi, urgenze, eventi inaspettati o indesiderati che sorgessero durante lo studio o dopo la sua conclusione, può rivolgersi in ogni momento alle persone di contatto indicate qui sotto:

Significato del consenso

Le pagine seguenti contengono informazioni approfondite, che costituiscono parte integrante del documento informativo. Sottoscrivendo la dichiarazione di consenso, accetta i contenuti dell'intero documento.

Persone da contattare

Sperimentatori: Alessandro Schneebeli, Marco Barbero, Corrado Cescon, Silvia Trentin.
Presso il Dipartimento Economia Aziendale, Sanità e Sociale (DEASS) della SUPSI
Stabile Piazzetta, via Violino.
CH-6928 Manno
Tel +41 (0) 58 666 64 35 / 666 64 37
Email: alessandro.schneebeli@supsi.ch marco.barbero@supsi.ch; corrado.cescon@supsi.ch

Se desiderasse ulteriori informazioni sui suoi diritti in qualità di soggetto partecipante a questo studio, o per qualsiasi altra domanda di carattere generale, può rivolgersi a:

Farmacista cantonale: Gian Maria Zanini
Presso l'Ufficio del farmacista cantonale
Via Agostino Maspoli 6
6850 Mendrisio
Tel +41 (0)91 816 59 41
Fax +41 (0)91 816 59 49
Email: dss-ufc@ti.ch

Scuola universitaria professionale
della Svizzera italiana

SUPSI

Consenso scritto del volontario sano per la partecipazione ad uno studio clinico

- Legga attentamente il presente formulario.
- Non esiti a porci delle domande qualora non comprendesse qualche cosa o desiderasse ulteriori informazioni.

Numero dello studio:	
Titolo dello studio:	INTRA AND INTER-RATER RELIABILITY OF MYOTONOMETRY IN QUANTIFING ACHILLES TENDON STIFFNESS.
Luogo dello studio:	SUPSI DEASS - Stabile Piazzetta, Via Violino, Manno
Sperimentatore Cognome e nome:	Alessandro Schneebeli, Marco Barbero, Corrado Cescon, Silvia Trentin
Volontario Cognome e nome:	.....
Data di nascita:	...../...../.....
Sesso:	☐ uomo ☐ donna

- Sono stato/a informato/a dallo sperimentatore sia oralmente che per scritto in merito allo scopo, lo svolgimento dello studio, gli effetti attesi, gli svantaggi e i vantaggi, nonché gli eventuali rischi.
- Ho letto e capito l'informazione scritta per i volontari sani del 10.08.2018 consegnatami concernente lo studio sopraccitato. Ho ottenuto una risposta adeguata a tutte le mie domande relative alla partecipazione a questo studio. Mi viene consegnato il modulo informativo scritto per i soggetti partecipanti e ricevo una copia del mio consenso informato scritto.
- Ho avuto tempo a sufficienza per decidere di partecipare.
- So che i miei dati personali saranno inoltrati ad istituzioni esterne soltanto in forma anonima e per fini di ricerca. Acconsento al fatto che gli specialisti competenti del committente dello studio, delle autorità e del comitato etico cantonale accedano ai miei dati originali a fini di valutazione e controllo, tuttavia in stretta osservanza della confidenzialità di tali dati.
- Partecipo a questo studio volontariamente. Posso ritirare in ogni momento e senza giustificazione il mio consenso alla partecipazione allo studio.
- Sono consapevole che durante lo studio devono essere rispettate le esigenze e le limitazioni menzionate nell'informazione per i pazienti. Nell'interesse della mia salute lo sperimentatore può escludermi dallo studio in ogni momento. Ho inoltre informato lo sperimentatore sui trattamenti concomitanti presso un altro medico e sull'assunzione di medicamenti (prescritti dal medico o acquistati di mia iniziativa).

Luogo, data	Firma del/la volontario/a:

Dichiarazione dello sperimentatore: dichiaro di aver spiegato al/la volontario in questione la natura, l'importanza e la portata dello studio. Garantisco di adempiere agli obblighi inerenti a questo studio. Se in qualsiasi momento dello studio venissi a conoscenza di aspetti che potrebbero influenzare la disponibilità del/la volontario a partecipare allo studio, provvederò a informarla/lo immediatamente.

Luogo, data	Firma del/la sperimentatore:

Appendix 12 – Ethical Review, Consent Forms and Patient Information Sheets for Chapter Six

c/o Ufficio di sanità
Via Orico 5
telefono 091 814 30 57
fax 091 814 44 47

www.ti.ch/CE

Funzionario incaricato: Beatrice Giberti Gai

telefono 091 814 30 57
e-mail beatrice.giberti-gai@ti.ch

Repubblica e Cantone
Ticino

Comitato etico cantonale
6501 Bellinzona

Prof. Marco Barbero
SUPSI - DEASS - 2rLab
Stabile Piazzetta Via Violino 11
6928 Manno

Bellinzona
16.04.2021

Ns. riferimento Vs. riferimento

Lettera di decisione del Comitato etico del Canton Ticino

Project-ID	2021-00611 CE 3844
Titolo del progetto	Measurement of Achilles tendon mechanical properties using shear wave tensiometer: an intra-rater reliability study
Studio master/tesi di:	Schneebeli, Alessandro
Direzione del progetto	Prof. Marco Barbero
Promotore	Prof. Marco Barbero
Centro(i)	• Prof. Marco Barbero, SUPSI - DEASS - 2rLab, Manno

Decisione

- x Autorizzato
- ☐ Autorizzato con requisiti
- ☐ Attualmente non può ancora essere autorizzato
- ☐ Non può essere autorizzato
- ☐ Non entrata in materia

Note

Nel testo informativo vi segnaliamo un'incongruenza, che vi preghiamo di correggere:

pagina 1 capitolo "Scopo dello studio" ultima riga si legge *"Qualora decidesse di ritirarsi, i dati raccolti fino a quel momento saranno comunque utilizzati"* mentre poi alla pagina 2 nel capitolo "Diritti dei partecipanti" si legge esattamente il contrario. È corretta la prima versione.

Vi preghiamo di inviarci il testo modificato con la versione e la data aggiornati.

Classificazione

☒ Progetto di ricerca secondo ORUm — Categoria: A

- ☒ ricerca con persone
- ☐ Riutilizzo di materiale biologico e di dati sanitari personali
- ☐ con persone decedute
- ☐ con embrioni e feti

☐ con radiazioni ionizzanti

Tipo di procedura

x Procedura ordinaria ☐ Procedura semplificata ☐ Procedura presidenziale

Elenco dei membri del Comitato etico cantonale presenti alla riunione (si veda allegato).

Il Comitato etico cantonale opera in ottemperanza alle norme ICH-GCP.

Tassa

Ammontare: CHF 200.--

La polizza di versamento sarà inviata separatamente dal Centro sistemi informativi all'indirizzo da voi indicato.

Rimedi di diritto

Contro la presente decisione è dato ricorso entro 15 giorni da questa notifica; l'atto di ricorso deve essere indirizzato al Comitato etico cantonale che lo trasmetterà in seguito al Consiglio di Stato.

Copia per informazione a

☐ UFSP

☐ Altro(i)

Con i migliori saluti.

PER IL COMITATO ETICO CANTONALE

Il Presidente:

p.c. Redazione Culto.

Giovan Maria Zanini

Allegati: -Obblighi del richiedente
-Significato delle diverse decisioni
-Elenco dei documenti
-Elenco dei membri del Comitato etico cantonale presenti alla riunione

Allegati

Obblighi del richiedente (promotore o direzione del progetto)

Sottomissione dei documenti: documenti nuovi o revisionati del progetto di ricerca sono da trasmettere unicamente via portale BASEC nella pagina specifica del progetto già esistente. Vanno eliminati i documenti obsoleti e sostituiti con quelli nuovi e le date e le versioni vanno modificate di conseguenza. I documenti revisionati devono essere trasmessi con le modifiche evidenziate (track changes) e nella versione pulita (clean). Il documento informativo scritto / dichiarazione di consenso, il protocollo e gli emendamenti al protocollo devono essere salvati in una modalità che permetta le ricerche all'interno del documento (PDF navigabile) o la loro scansione deve essere fatta con la modalità OCR (Optical Character Recognition). Nella lettera accompagnatoria datata e firmata dovranno esserci le risposte ad eventuali quesiti posti. I documenti revisionati vanno trasmessi anche alle autorità competenti, se del caso.

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Significato delle diverse decisioni

Autorizzato: La ricerca può essere effettuata nel rispetto delle condizioni quadro del protocollo di studio sottomesso e nel rispetto delle basi legali applicabili. Sono da rispettare gli altri obblighi di autorizzazione (Swissmedic/UFSP).

Autorizzato con requisiti: La ricerca può essere effettuata nel rispetto delle condizioni quadro del protocollo di studio sottomesso e nel rispetto delle basi legali applicabili. I requisiti vincolanti sono da soddisfare entro 30 giorni. La documentazione rielaborata viene valutata in procedura presidenziale. Sono da rispettare gli altri obblighi di autorizzazione (Swissmedic/UFSP).

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Non può essere autorizzato: La ricerca non può essere effettuata nella forma presente. È possibile una nuova sottomissione.

Non entrata in materia: Si veda sopra la motivazione, ad esempio il Comitato etico non è legalmente competente per l'autorizzazione o la ricerca non è soggetta ad autorizzazione.

Documenti inoltrati per il centro coordinatore

Prof. Marco Barbero, SUPSI - DEASS - 2rLab, Manno

nome del documento	data del documento	versione
1. Cover Letter		
taptend-cover-letter.docx	15/03/2021	
3. Participant information sheet and informed consent (ICF)		
informazione-taptend.docx	10/03/2021	1.0
4. Study plan (protocol), signed and dated		
taptend-hro-research-plan-version-1.docx	15/03/2021	1.0
5. CRF (Case Report Form)		
taptend-case-report-form-1-0.xlsx	10/03/2021	1.0
6. Investigator's CV, dated		
cv-barbero.docx	10/01/2021	
11. Other documents handed over to study participants		
No other documents handed over to study participants		
12. Details on nature and scope/value of compensation for participants		
There is no compensation for the participation in this study		
14. Information on secure handling of biological material and personal data, and in particular on the storage thereof		
see doc/cat: **4**, page/ref: **12**		

Riunione del 13 aprile 2021: Il Comitato etico si è riunito nella composizione riportata qui sotto ed era perciò in numero legale (in ottemperanza all'Art. 5, Org-LRUm)

	Nome e cognome	Posizione professionale/titolo	m	f	Partecipante alla decisione: Si	Partecipante alla decisione: no
Presidente	**Giovan Maria Zanini**	Farmacista cantonale, Dipartimento della sanità e della socialità, Mendrisio	☒	☐	☒	☐
Vice presidente	Dr. med. **Hans-Rudolf Schwarzenbach**	Specialista FMH in medicina interna generale, studio medico, Melide	☒	☐	☒	☐
Membri	Don **Charles Komlan Mawulawoe Azanshi**	Parroco e cappellano all'Ospedale Regionale di Lugano (Civico), Dottore in bioetica	☒	☐	☒	☐
	Lic. Phil. **Guenda Bernegger**	Laureata in filosofia, Master in Medical Humanities, Massagno	☐	☒	☒	☐
	Dr. sc. nat. **Marco Bissig**	Farmacista, Ospedale Regionale di Lugano	☒	☐	☒	☐
	Avv. **Patrizia Bottinelli-Cancellara**	Giurista presso il Dipartimento della sanità e della socialità, Bellinzona	☐	☒	☒	☐
	PD Dr. med. **Guido Domenighetti**	Specialista FMH in medicina interna, malattie polmonari e medicina intensiva, Ospedale Regionale La Carità, Locarno	☒	☐	☒	☐
	Dr. med., PhD **Tanja Fusi-Schmidhauser**	Specialista FMH in medicina interna e medicina palliativa, caposervizio Ospedale Regionale Lugano - Civico e Italiano, Lugano	☐	☒	☒	☐
	PD Dr. med. **Christian Garzoni**	Specialista FMH in malattie infettive e medicina interna, studio medico, Lugano	☒	☐	☒	☐
	Angelica Jäggli	Vicepresidente ACSI, Lugano	☐	☒	☒	☐
	Irma König	Infermiera diplomata, Ospedale Regionale Bellinzona e Valli, Bellinzona	☐	☒	☐	☒
	Prof. Dr. med. **Pietro Majno-Hurst**	Primario e capo dipartimento chirurgia e chirurgia viscerale , Ospedale Regionale di Lugano - Civico e Italiano, Lugano	☒	☐	☒	☐
	PD Dr. sc. nat. **Orlando Petrini**	Libero docente al Politecnico federale di Zurigo, studio di consulenza, Breganzona	☒	☐	☐	☒
	Dr. med. **Vito Spataro**	Specialista FMH medicina interna, oncologia-ematologica, Studio medico, Bellinzona	☒	☐	☐	☒
	PD Dr. med. **Hans Stricker**	Specialista FMH medicina interna e angiologia, Ospedale Regionale La Carità, Locarno	☒	☐	☒	☐
	Dr. med. **Rafael Traber**	eMBA specialista FMH psichiatria e psicoterapia, direttore di Settore (Sottoceneri e Sopraceneri) Organizzazione sociopsichiatrica cantonale, Lugano	☒	☐	☒	☐
	Avv. **Tiziano Veronelli**	Segretario generale del Gran Consiglio, Bellinzona	☒	☐	☐	☒

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SUPSI

Informazione per i partecipanti

Titolo del progetto: Measurement of Achilles tendon mechanical properties using shear wave tensiometer: an intra-rater reliability study

Gentile partecipante,

legga per cortesia attentamente il contenuto di questo foglio informativo riguardante lo studio al quale Le è stato proposto di partecipare. Non esiti ad interpellarci qualora non comprendesse qualche cosa o desiderasse ulteriori informazioni.

Con il presente documento La invitiamo a partecipare al nostro studio concernente l'elasticità del tendine d'Achille

Scopo dello studio

Le è stato chiesto di partecipare a questo studio perché si vuole indagare la ripetibilità di un nuovo strumento di misura dell'elasticità dei tendini chiamato tensiometro.

Questo studio è condotto nel rispetto delle leggi svizzere e dei principi etico-morali riconosciuti dalla comunità scientifica internazionale.

La Sua partecipazione a questo studio è volontaria. Se rinunciasse a partecipare a questo studio non dovrà temere alcuno svantaggio. Lo stesso vale qualora ritirasse il Suo consenso in un secondo momento, possibilità che manterrà per tutta la durata dello studio. Che rinunci a partecipare allo studio o che revochi il suo consenso, in entrambi i casi non sarà tenuto a giustificarsi. Qualora decidesse di ritirarsi, i dati raccolti fino a quel momento saranno comunque utilizzati.

Scelta dei partecipanti allo studio

In questo studio di ripetibilità saranno convocati 10 volontari sani.

I partecipanti sani saranno esclusi qualora riportino: operazioni al piede o al tendine d'Achille o episodi di dolore al tendine d'Achille. Patologie metaboliche o del tessuto connettivo; patologie infiammatorie sistemiche; artrite reumatoide; ipercolesterolemia; assunzione di steroidi o estrogeni.

Descrizione e svolgimento dello studio

Lo studio avrà una durata complessiva di circa 40 minuti, suddivisi in tre giornate di analisi.
I volontari verranno sottoposti a 2 misure di elasticità dei tendini d'Achille in posizione prona.
Le due misurazioni verranno prese durante delle contrazioni muscolari di diversa intensità e con il piede a 0° di flessione plantare grazie ad una gabbietta che permette di mantenere una posizione fissa del piede.
Le misure di elasticità verranno effettuate con un tensiometro, ovvero uno strumento non invasivo che tramite un lieve impulso determina la risposta elastica dei tessuti grazie a degli accelerometri posizionati sul tendine.
L'impulso verrà effettuato grazie ad una bacchetta in legno a livello centrale del tendine d'Achille.

Entrambi i tendini d'Achille (destro e sinistro) verranno analizzati da un operatore esperto nell'utilizzo di questo strumento in tre diversi momenti cosi da permettere una valutazione della ripetibilità intra-operatore.

Prima dell'inizio dei test riceverà una breve istruzione su come comportarsi durante l'esperimento. Durante lo studio dovrà essere scalzo e indossare pantaloncini corti o pantaloni che permettano con facilità l'accesso al tendine d'Achille (non troppo stretti a livello della caviglia)

Durante l'esecuzione dell'esame, ai soggetti saranno poste alcune domande di carattere anamnestico e generale (età, sesso, peso, altezza).

Benefici e rischi della partecipazione allo studio

La partecipazione a questo studio clinico non Le apporterà alcun beneficio e non comporta alcun rischio per la Sua salute. Grazie alla Sua partecipazione altre persone potranno beneficiare dei risultati.

Diritti dei partecipanti allo studio

La Sua partecipazione a questo studio è volontaria. Se ora decide di partecipare, potrà comunque ritirarsi in qualsiasi momento dallo studio senza addurre alcuna motivazione.
Lo studio prevede la rilevazione di dati medici sulla Sua persona. Se decide di ritirarsi dallo studio in un secondo momento, i dati raccolti fino a quel momento saranno comunque utilizzati.

Confidenzialità dati

In questo studio vengono registrati alcuni dati personali (età, sesso, peso, altezza). Questi dati vengono codificati e sono accessibili soltanto agli specialisti per l'elaborazione scientifica. Gli specialisti competenti del promotore (o i loro incaricati) potranno verificare lo svolgimento dello studio nell'ambito del cosiddetto monitoring o audit. Questi specialisti e i membri delle autorità competenti possono accedere ai Suoi dati originali nell'ambito delle ispezioni. Parimenti il comitato etico competente può prendere visione dei dati originali. La confidenzialità è strettamente tutelata durante tutto lo svolgimento dello studio e al momento dei controlli menzionati. Il Suo nome non sarà mai pubblicato in alcun modo in rapporti o pubblicazioni che si baseranno sullo studio.

Le procedure menzionate nel presente foglio informativo sono gratuite per tutti i soggetti partecipanti allo studio. La partecipazione allo studio non causa costi supplementari legati alla partecipazione né per Lei né per la Sua cassa malati.

Per la partecipazione a questo studio clinico non riceverà alcuna indennità.

In caso di dubbi, urgenze, eventi inaspettati o indesiderati che sorgessero durante lo studio o dopo la sua conclusione, può rivolgersi in ogni momento alle persone di contatto indicate qui sotto:

Significato del consenso

Le pagine seguenti contengono informazioni approfondite, che costituiscono parte integrante del documento informativo. Sottoscrivendo la dichiarazione di consenso, accetta i contenuti dell'intero documento.

Persone da contattare

Sperimentatori: Alessandro Schneebeli, Marco Barbero, Corrado Cescon.
Presso il Dipartimento Economia Aziendale, Sanità e Sociale (DEASS) della SUPSI
Stabile Piazzetta, via Violino.
CH-6928 Manno
Tel +41 (0) 58 666 64 35 / 666 64 37
Email: alessandro.schneebeli@supsi.ch marco.barbero@supsi.ch; corrado.cescon@supsi.ch

Se desiderasse ulteriori informazioni sui suoi diritti in qualità di soggetto partecipante a questo studio, o per qualsiasi altra domanda di carattere generale, può rivolgersi a:

Farmacista cantonale: Gian Maria Zanini
Presso l'Ufficio del farmacista cantonale
Via Agostino Maspoli 6
6850 Mendrisio
Tel +41 (0)91 816 59 41
Fax +41 (0)91 816 59 49
Email: dss-ufc@ti.ch

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SUPSI

Consenso scritto del volontario sano per la partecipazione ad uno studio clinico

- Legga attentamente il presente formulario.
- Non esiti a porci delle domande qualora non comprendesse qualche cosa o desiderasse ulteriori informazioni.

Numero dello studio:	
Titolo dello studio:	**Measurement of Achilles tendon mechanical properties using shear wave tensiometer: an intra-rater reliability study**
Luogo dello studio:	SUPSI DEASS - Stabile Piazzetta, Via Violino, Manno
Sperimentatore Cognome e nome:	Alessandro Schneebeli, Marco Barbero, Corrado Cescon,
Volontario Cognome e nome:	.....
Data di nascita:	...../...../.....
Sesso:	☐ uomo ☐ donna

- Sono stato/a informato/a dallo sperimentatore sia oralmente che per scritto in merito allo scopo, lo svolgimento dello studio, gli effetti attesi, gli svantaggi e i vantaggi, nonché gli eventuali rischi.
- Ho letto e capito l'informazione scritta per i volontari sani del 10.08.2018 consegnatami concernente lo studio sopraccitato. Ho ottenuto una risposta adeguata a tutte le mie domande relative alla partecipazione a questo studio. Mi viene consegnato il modulo informativo scritto per i soggetti partecipanti e ricevo una copia del mio consenso informato scritto.
- Ho avuto tempo a sufficienza per decidere di partecipare.
- So che i miei dati personali saranno inoltrati ad istituzioni esterne soltanto in forma anonima e per fini di ricerca. Acconsento al fatto che gli specialisti competenti del committente dello studio, delle autorità e del comitato etico cantonale accedano ai miei dati originali a fini di valutazione e controllo, tuttavia in stretta osservanza della confidenzialità di tali dati.
- Partecipo a questo studio volontariamente. Posso ritirare in ogni momento e senza giustificazione il mio consenso alla partecipazione allo studio.
- Sono consapevole che durante lo studio devono essere rispettate le esigenze e le limitazioni menzionate nell'informazione per i pazienti. Nell'interesse della mia salute lo sperimentatore può escludermi dallo studio in ogni momento. Ho inoltre informato lo sperimentatore sui trattamenti concomitanti presso un altro medico e sull'assunzione di medicamenti (prescritti dal medico o acquistati di mia iniziativa).

Luogo, data	Firma del/la volontario/a:

Dichiarazione dello sperimentatore: dichiaro di aver spiegato al/la volontario in questione la natura, l'importanza e la portata dello studio. Garantisco di adempiere agli obblighi inerenti a questo studio. Se in qualsiasi momento dello studio venissi a conoscenza di aspetti che potrebbero influenzare la disponibilità del/la volontario a partecipare allo studio, provvederò a informarla/lo immediatamente.

Luogo, data	Firma del/la sperimentatore:

Appendix 13 – Ethical Review, Consent Forms and Patient Information Sheets for Chapter Eight

c/o Ufficio di sanità
Via Orico 5
telefono 091 814 30 57
fax 091 814 44 47

www.ti.ch/CE

Funzionario incaricato: Gai

telefono 091 814 30 57
e-mail beatrice.giberti-gai@ti.ch

Repubblica e Cantone
Ticino

Comitato etico cantonale
6501 Bellinzona

Alessandro Schneebeli
SUPSI DEASS
Stabile piazzetta
Via Violino
6928 Manno

Bellinzona
13.10.2022

Ns. riferimento Vs. riferimento

Lettera di decisione del Comitato etico del Canton Ticino

Project-ID	2022-01707; Rif. CE 4192
Titolo del progetto	ACHILLES TENDON SHEAR WAVE SPEED AFTER SURGERY: A CROSS SECTIONAL STUDY.
Studio master/tesi di:	Schneebeli, Alessandro
Direzione del progetto	Alessandro Schneebeli
Promotore	SUPSI-DEASS, Prof. Marco Barbero
Centro(i)	• Alessandro Schneebeli, SUPSI-DEASS, Manno

Decisione

- ☒ Autorizzato
- ☐ Autorizzato con requisiti
- ☐ Attualmente non può ancora essere autorizzato
- ☐ Non può essere autorizzato
- ☐ Non entrata in materia

Classificazione

☒ Progetto di ricerca secondo ORUm — Categoria: A

- ☒ ricerca con persone
- ☐ Riutilizzo di materiale biologico e di dati sanitari personali
- ☐ con persone decedute
- ☐ con embrioni e feti
- ☐ con radiazioni ionizzanti

Tipo di procedura

☒ Procedura ordinaria ☐ Procedura semplificata ☐ Procedura presidenziale

Elenco dei membri del Comitato etico cantonale presenti alla riunione (si veda allegato).

Il Comitato etico cantonale opera in ottemperanza alle norme ICH-GCP.

Tassa

Ammontare: CHF 200.--

La polizza di versamento sarà inviata separatamente dal Centro sistemi informativi all'indirizzo da voi indicato.

Rimedi di diritto

Contro la presente decisione è dato ricorso entro 15 giorni da questa notifica; l'atto di ricorso deve essere indirizzato al Comitato etico cantonale che lo trasmetterà in seguito al Consiglio di Stato.

Copia per informazione a

- ☐ UFSP
- ☒ Promotore SUPSI-DEASS, marco.barbero@supsi.ch
- ☐ Altro(i)

Con i migliori saluti.

PER IL COMITATO ETICO CANTONALE

Il Presidente:

p.S. Beatrice Ghisletta

Giovan Maria Zanini

Allegati:
-Obblighi del richiedente
-Significato delle diverse decisioni
-Elenco dei documenti
-Elenco dei membri del Comitato etico cantonale presenti alla riunione

Allegati

Obblighi del richiedente (promotore o direzione del progetto)

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Significato delle diverse decisioni

Autorizzato: La ricerca può essere effettuata nel rispetto delle condizioni quadro del protocollo di studio sottomesso e nel rispetto delle basi legali applicabili. Sono da rispettare gli altri obblighi di autorizzazione (Swissmedic/UFSP).

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Non entrata in materia: Si veda sopra la motivazione, ad esempio il Comitato etico non è legalmente competente per l'autorizzazione o la ricerca non è soggetta ad autorizzazione.

Documenti inoltrati per il centro coordinatore

Alessandro Schneebeli, SUPSI-DEASS, Manno		
nome del documento	data del documento	versione
1. Cover Letter		
tapsurg-cover-letter.pdf	19/09/2022	
3. Participant information sheet and informed consent (ICF)		
informazione-pazienti-lugano-tapsurg-versione-1-0.docx	19/09/2022	1
informazione-pazienti-bellinzona-tapsurg-versione-1-0.docx	19/09/2022	1
4. Study plan (protocol), signed and dated		
hro-research-plan-tapsurg-version-1-0.docx	19/09/2022	1
5. CRF (Case Report Form)		
tapsurg-case-report-form-1-0.xlsx	19/09/2022	1
6. Investigator's CV, dated		
curriculum-vitae-short-alessandro-schneebeli-9-2022.pdf	20/09/2022	
11. Other documents handed over to study participants		
No other documents handed over to study participants		
12. Details on nature and scope/value of compensation for participants		
There is no compensation for the participation in this study		
14. Information on secure handling of biological material and personal data, and in particular on the storage thereof		
see doc/cat: 4, page/ref: 9		

Riunione dell'11 ottobre 2022. Il Comitato etico si è riunito nella composizione riportata qui sotto ed era perciò in numero legale (in ottemperanza all'Art. 5, Org-LRUm)

					Partecipante alla decisione	
	Nome e cognome	**Posizione professionale/titolo**	**m**	**f**	**Si**	**no**
Presidente	**Giovan Maria Zanini**	Farmacista cantonale, Dipartimento della sanità e della socialità, Mendrisio	☒	☐	☒	☐
Vice presidente	Dr. med. **Hans-Rudolf Schwarzenbach**	Specialista FMH in medicina interna generale, studio medico, Melide	☒	☐	☒	☐
Membri	Don **Charles Komlan Mawulawoe Azanshi**	Parroco e cappellano all'Ospedale Regionale di Lugano (Civico), Dottore in bioetica	☒	☐	☒	☐
	Lic. Phil. **Guenda Bernegger**	Laureata in filosofia, Master in Medical Humanities, Massagno	☐	☒	☒	☐
	Dr. sc. nat. **Marco Bissig**	Farmacista, Ospedale Regionale di Lugano	☒	☐	☒	☐
	Avv. **Patrizia Bottinelli-Cancellara**	Giurista presso il Dipartimento della sanità e della socialità, Bellinzona	☐	☒	☐	☒
	PD Dr. med. **Guido Domenighetti**	Specialista FMH in medicina interna, malattie polmonari e medicina intensiva, Ospedale Regionale La Carità, Locarno	☒	☐	☒	☐
	Dr. med., PhD **Tanja Fusi-Schmidhauser**	Specialista FMH in medicina interna e medicina palliativa, caposervizio Ospedale Regionale Lugano - Civico e Italiano, Lugano	☐	☒	☐	☒
	PD Dr. med. **Christian Garzoni**	Specialista FMH in malattie infettive e medicina interna, studio medico, Lugano	☒	☐	☒	☐
	Angelica Jäggli	Vicepresidente ACSI, Lugano	☐	☒	☒	☐
	Irma König	Infermiera diplomata, Ospedale Regionale Bellinzona e Valli, Bellinzona	☐	☒	☒	☐
	Prof. Dr. med. **Pietro Majno-Hurst**	Primario e capo dipartimento chirurgia e chirurgia viscerale , Ospedale Regionale di Lugano - Civico e Italiano, Lugano	☒	☐	☐	☒
	Msc in Statistics **Emiliano Soldini**	Docente-ricercatore senior, SUPSI, Manno	☒	☐	☒	☐
	Dr. med. **Vito Spataro**	Specialista FMH medicina interna, oncologia-ematologica, Studio medico, Bellinzona	☒	☐	☒	☐
	PD Dr. med. **Hans Stricker**	Specialista FMH medicina interna e angiologia, Ospedale Regionale La Carità, Locarno	☒	☐	☒	☐
	Dr. med. **Rafael Traber**	eMBA specialista FMH psichiatria e psicoterapia, direttore di Settore (Sottoceneri e Sopraceneri) Organizzazione sociopsichiatrica cantonale, Lugano	☒	☐	☒	☐
	Avv. **Tiziano Veronelli**	Segretario generale del Gran Consiglio, Bellinzona	☒	☐	☒	☐

[1] Il Comitato etico è organizzato e opera in conformità alle GCP-ICH, alle normative applicabili e alla dichiarazione di Helsinki

Scuola universitaria professionale
della Svizzera italiana

SUPSI

Differenze di proprietà meccaniche tra tendine d'Achille operato e non operato.

Gentile Signora, egregio Signore,

Ci rivolgiamo a Lei per chiederle se è disposta a collaborare al nostro progetto di ricerca.

La sua partecipazione è volontaria. Tutti i dati rilevati nell'ambito di questo progetto sono sottoposti a severe disposizioni in materia di protezione dei dati.

Il progetto di ricerca viene svolto da SUPSI. In caso di interesse la informiamo volentieri sui risultati emersi dal progetto di ricerca.

Perché svolgiamo questo progetto di ricerca?

- In ambito clinico c'è un crescente interesse nel misurare le proprietà meccaniche dei tendini in quanto rilevanti per il possibile sviluppo di problematiche dolorose. Diversi strumenti sono stati sviluppati con lo scopo di misurare queste proprietà.
- Con il nostro progetto di ricerca intendiamo indagare se la tensiometria, una tecnica non invasiva per misurare la tensione dei tendini, riesca a intercettare cambiamenti di tensione tra il suo tendine operato e quello non operato.

Cosa deve fare in caso di partecipazione?

- Se decide di partecipare, le verrà chiesto di sottoporti ad un test che comprende delle misure su entrambi i tendini di Achille. Le misure vengono effettuate su un lettino e le verrà chiesto di fare delle contrazioni del muscolo polpaccio. Durante queste contrazioni verranno dati dei lievi impulsi (quasi impercettibili) sul tendine di Achille per misurare la tensione del tendine. Inoltre le chiederemo di compilare dei questionari per comprendere lo stato di salute del suo tendine.
- Durata: circa 30-45 minuti.
- Numero e impegno delle visite: la vostra partecipazione si limita a questo unico incontro.

Quali sono i benefici e i rischi correlati?

Benefici

- La partecipazione a questo progetto di ricerca ma non le apporterà nessun beneficio diretto.
- Con la vostra partecipazione potrete aiutare futuri pazienti, che potrebbero usare la stessa tecnica una volta che sarà dimostrata affidabile.

Rischi e incomodi

- Lo studio non le arrecherà nessun rischio. Con la sua firma in calce al documento dichiara di acconsentire alla partecipazione volontaria, e di aver compreso i contenuti dell'intero documento.

Informazione dettagliata

1. Scopo e selezione

Nel presente documento informativo definiamo il nostro progetto di ricerca come *sperimentazione*. Se lei dovesse partecipare a questa sperimentazione, viene definita/o come una/un *partecipante alla sperimentazione*.

Prima che una tecnica per valutare i pazienti sia applicata, deve essere studiata scientificamente su partecipanti a una sperimentazione. La sperimentazione ha quindi lo scopo di verificare se la tensiometria riesce a distinguere una diversa tensione tra il tendine precedentemente operato e quello non operato. La tensiometria è una tecnica non invasiva che si basa sulla lettura di un onda che si propaga nel tendine attraverso degli accelerometri.

Ci rivolgiamo a Lei in quanto possono partecipare tutti le persone che siano state sottoposte ad una chiurgia tendinea a seguito di una rottura del tendine d'Achille.

2. Informazioni generali

Questo strumento è stato sviluppato con lo scopo di descrivere le proprietà meccaniche dei tendini e comprendere il comportamento di queste strutture quando sottoposte ad un carico.
Alcuni studi hanno valutato la precisione e l'affidabilità di questo strumento su soggetti senza problematiche tendinee con buoni risultati.
In particolare, verranno misurati:

- Lo stato di tensione a riposo dei suoi tendini.
- Lo stato di tensione dei suoi tendini durante diverse contrazioni del muscolo polpaccio.

Lo scopo principale di questo studio è stabilire se questa tecnologia è in grado di intercettare cambiamenti di tensione tra il tendine operato e quello non operato.
Questa sperimentazione si svolge nel rispetto della legislazione svizzera e delle direttive in vigore a livello internazionale. La sperimentazione è stata esaminata e autorizzata dalla commissione d'etica competente.
Una descrizione di questa sperimentazione è reperibile anche alla pagina Internet dell'Ufficio federale della sanità pubblica all'indirizzo www.kofam.ch

3. Svolgimento

Se acconsente a partecipare allo studio, le verrà richiesto di:

- Compilare alcuni questionari relativo allo stato di salute attuale del suo tendine.
- Sottoporsi ad un test che comprende la misurazione dello stato di tensione dei suoi tendini in condizioni di rilassamento e durante delle contrazioni del muscolo polpaccio.

Tutte queste misure richiederanno circa 30-45 minuti. Tutte le procedure rispetteranno le disposizioni cantonali e federali in vigore per limitare la trasmissione del nuovo Coronavirus.

4. Benefici

La partecipazione a questo progetto di ricerca, ma non le apporterà nessun beneficio diretto.
Con la vostra partecipazione potrete aiutare futuri pazienti, che potrebbero usare la stessa tecnica una volta che sarà stata dimostrata affidabile.

5. Volontarietà e obblighi

La sua partecipazione a questa sperimentazione è volontaria. Se lei non dovesse partecipare a questa sperimentazione, o decide in seguito di revocare la sua decisione, non dovrà in alcun modo motivare la sua decisione. I suoi trattamenti medici sono garantiti a prescindere dalla sua decisione.

Se lei volesse partecipare a questa sperimentazione è pregata di:

- Seguire le richieste che le verranno fatte dal ricercatore

- Informare il ricercatore su eventuali disagi o nuovi dolori.

6. Rischi e incomodi
Lo studio non arrecherà nessun rischio.

7. Risultati
Se lo desidera verrà informata/o sui risultati e sulle conclusioni dello studio.

8. Confidenzialità dei dati personali e del materiale biologico
Tutti i dati raccolti saranno resi anonimi, e nessuno potrà ricondurre a lei i dati, una volta che avrete lasciato la stanza nella quale vengono acquisiti.

8.1. Elaborazione dei dati e codifica
Per la presente sperimentazione vengono registrati ed elaborati i dati relativi alla sua salute, in parte in forma codificata. Ciò significa che tutti i dati che potrebbero identificarla (p. es. nome, data di nascita ecc.) vengono cancellati e sostituiti da un codice. Le persone che non hanno accesso a questi codici non possono risalire a lei.
Solo poche persone specialiste hanno accesso ai dati non codificati e solo per svolgere compiti necessari per la sperimentazione. Queste persone sono sottoposte all'obbligo di riservatezza. Avrà il diritto di consultare i suoi dati di al termine dello studio.

8.2. Protezione dei dati e protezione del materiale biologico
Tutte le disposizioni sulla protezione dei dati vengono rispettate rigorosamente. I suoi dati potrebbero dover essere trasmessi in forma anonima, ad esempio per una pubblicazione, e potrebbero essere messi a disposizione di altri ricercatori, sempre anonimizzati.

8.3. Protezione dei dati in caso di riutilizzo
I suoi dati verranno utilizzati esclusivamente per questo progetto.

8.4. Diritto di consultazione in caso di controlli
La presente sperimentazione può essere sottoposta a verifica da parte dalla commissione d'etica competente o dal promotore che organizza la sperimentazione. Lo sperimentatore dovrà in tal caso mettere a disposizione i suoi dati ai fini di tali controlli. Tutte le persone sono tenute a osservare la più assoluta confidenzialità.

9. Ritiro dalla sperimentazione
Potrà decidere di ritirarsi dalla sperimentazione in qualsiasi momento. In tal caso, i dati rilevati fino a quel momento saranno comunque valutati in forma anonima.

10. Indennità
Per la partecipazione a questa sperimentazione non le sarà versata alcuna indennità.

11. Responsabilità
Nonostante questa sperimentazione non presenti alcun rischio prevedibile, SUPSI secondo le disposizioni di legge è responsabile per tutti i danni che possono insorgere nell'ambito di questa sperimentazione.

12. Finanziamento
La sperimentazione è finanziata completamente da SUPSI.

13. Persona/e di contatto

Può porre in ogni momento domande in merito alla sperimentazione. Anche in caso di incertezze o emergenze che dovessero insorgere durante o dopo la sperimentazione, può rivolgersi a:

Alessandro Schneebeli
Via Violino 11
6928 Manno
tel: 058 666 64 43
e-mail: alessandro.schneebeli@supsi.ch

Organo di consulenza:

Se desidera rivolgersi a un organo indipendente esterno alla sperimentazione, può rivolgersi a:

Ufficio del Farmacista cantonale
tel. 091 816.59.41
e-mail: dss-ufc@ti.ch

Tale organo non ha alcun legame con i ricercatori addetti alla sperimentazione. Il tuo caso sarà trattato in modo assolutamente confidenziale.

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Dichiarazione di consenso

Dichiarazione di consenso scritta per la partecipazione a una sperimentazione clinica
Legga attentamente il presente formulario. Non esiti a porre domande se qualcosa non le è chiaro o se desidera una spiegazione. Per la partecipazione alla sperimentazione è necessario il suo consenso scritto.

Numero BASEC:	2022-01707
Titolo della sperimentazione (in termini scientifici e semplici):	Differenze di proprietà meccaniche tra tendine d'Achille operato e non operato.
Istituzione responsabile (promotore con indirizzo):	SUPSI DEASS Stabile Piazzetta, Via Violino 11 6928 Manno
Luogo di svolgimento:	Ente Ospedaliero Cantonale Servizio di Ortopedia e Traumatologia 6900 Lugano
Sperimentatore nel luogo di svolgimento: Nome e cognome in stampatello:	Alessandro Schneebeli
Partecipante: Nome e cognome in stampatello: Data di nascita:	

- Sono stata/o informata/o dalla sperimentatrice sottoscritta/dallo sperimentatore sottoscritto oralmente e per scritto in merito allo scopo, allo svolgimento della sperimentazione, ai possibili vantaggi e svantaggi nonché agli eventuali rischi.
- Partecipo alla sperimentazione volontariamente. Accetto il contenuto del documento informativo scritto a me consegnato. Ho avuto tempo a sufficienza per prendere la mia decisione.
- Ho ricevuto risposte esaustive alle mie domande relative alla partecipazione a questa sperimentazione. Posso conservare il documento informativo scritto sulla sperimentazione e ricevo una copia della mia dichiarazione di consenso scritta.
- Acconsento al fatto che le specialiste/gli specialisti competenti del promotore della sperimentazione e della commissione d'etica competente possano accedere ai miei dati non codificati a fini di esame e controllo, tuttavia in stretta osservanza della confidenzialità.
- Posso ritirarmi dalla partecipazione alla sperimentazione in qualsiasi momento senza fornire motivazioni. Il suo successivo trattamento medico è garantito a prescindere dalla partecipazione alla sperimentazione. I dati e i campioni di materiale biologico rilevati fino al ritiro saranno ancora analizzati nell'ambito della sperimentazione.
- Sono a conoscenza del fatto che eventuali danni riconducibili alla sperimentazione saranno coperti da un'assicurazione stipulata da SUPSI.

Luogo, data	Firma della/del partecipante alla sperimentazione

Conferma della sperimentatrice/dello sperimentatore: con la presente dichiaro di aver spiegato alla/al partecipante in questione la natura, l'importanza e la portata della sperimentazione. Garantisco di adempiere tutti gli obblighi inerenti a questa sperimentazione secondo il diritto vigente in Svizzera. Se nel corso della sperimentazione dovessi venire a conoscenza di aspetti che potrebbero influenzare la disponibilità della/del partecipante a partecipare alla sperimentazione, provvederò a informarla/o immediatamente.

Luogo, data	Nome e cognome in stampatello della sperimentatrice/dello sperimentatore Firma della sperimentatrice/dello sperimentatore

Appendix 14 – Ethical Review, Consent Forms and Patient Information Sheets for Chapter Nine

c/o Ufficio di sanità
Via Orico 5
telefono 091 814 30 57
fax 091 814 44 47

www.ti.ch/CE

Repubblica e Cantone
Ticino

Funzionario incaricato
Gai

telefono 091 814 30 57
e-mail beatrice.giberti-gai@ti.ch

Comitato etico cantonale
6501 Bellinzona

Alessandro Schneebeli
SUPSI-DEASS
Stabile piazzetta
Via Violino
6928 Manno

Bellinzona
16.01.2023

Ns. riferimento Vs. riferimento

Lettera di decisione del Comitato etico del Canton Ticino

Modifica essenziale:	Emendamento protocollo
sottomessa il	21.12.2022 e 13.01.2023
Project-ID	2022-01707; Rif. CE 4192
Titolo del progetto	ACHILLES TENDON SHEAR WAVE SPEED AFTER SURGERY: A CROSS SECTIONAL STUDY.
Studio master/tesi di	Schneebeli, Alessandro
Direzione del progetto	Alessandro Schneebeli
Promotore	SUPSI-DEASS, Prof. Marco Barbero
Centro(i)	Alessandro Schneebeli, SUPSI-DEASS, Manno

Tipo di procedura

☐ Procedura semplificata ☒ Procedura presidenziale

Decisione

Alessandro Schneebeli, SUPSI-DEASS, Manno

☒ Autorizzato
☐ Autorizzato con requisiti
☐ Attualmente non può ancora essere autorizzato
☐ Non può essere autorizzato

Tassa

Ammontare CHF100.--
La polizza di versamento sarà inviata separatamente dal Centro sistemi informativi all'indirizzo da voi indicato.

Rimedi di diritto

Contro la presente decisione è dato ricorso entro 30 giorni da questa notifica; l'atto di ricorso deve essere indirizzato al Comitato etico cantonale che lo trasmetterà in seguito alla speciale Commissione di ricorso nominata ad hoc dal Consiglio di Stato secondo l'Art.10b della Legge sulla

promozione della salute e il coordinamento sanitario.

Copia per informazione a

- ☐ UFSP
- ☒ Promotore SUPSI-DEASS, marco.barbero@supsi.ch
- ☐ Altro(i)

La Commissione etica opera in ottemperanza alle ICH-GCP.

Con i migliori saluti.

PER IL COMITATO ETICO CANTONALE

Il Presidente:

p.a. Beatrice [illegible]

Giovan Maria Zanini

Allegati: -Significato delle diverse decisioni
-documenti inoltrati il 21.12.2022 e il 13.01.2023

Allegati

Significato delle diverse decisioni

Autorizzato: la ricerca può continuare conformemente alla modifica essenziale inoltrata.

Autorizzato con requisiti: la ricerca può continuare conformemente alla modifica essenziale inoltrata. I requisiti vincolanti sono da soddisfare entro 30 giorni.

Attualmente non può ancora essere autorizzato: la ricerca non può continuare conformemente alla modifica essenziale inoltrata. Siete pregati di rispondere alle domande e soddisfare le condizioni poste dal Comitato etico e di risottomettere la documentazione rielaborata.

Non può essere autorizzato: la ricerca non può essere continuata conformemente alla modifica essenziale inoltrata. È possibile una nuova sottomissione.

Documenti inoltrati il 21.12.2022 e il 13.01.2023

Alessandro Schneebeli, SUPSI-DEASS, Manno

nome del documento	categoria	data del documento	versione
tapsurg-cover-letter-emendamento.docx	1. Cover Letter	21/12/2022	
informazione-pazienti-lugano-tapsurg-versione-2-0-conservativi-track-changes.docx	3. ICF	21/12/2022	2
informazione-pazienti-bellinzona-tapsurg-versione-2-0-conservativi-track-changes.docx	3. ICF	21/12/2022	2
informazione-pazienti-bellinzona-tapsurg-versione-2-0-conservativi-clean.docx	3. ICF	21/12/2022	2
informazione-pazienti-lugano-tapsurg-versione-2-0-conservativi-clean.docx	3. ICF	21/12/2022	2
hro-research-plan-tapsurg-version-2-0-clean.docx	4. Study plan	11.01.2023	2.0

Scuola universitaria professionale
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SUPSI

Differenze di proprietà meccaniche tra tendine d'Achille lesionato e non lesionato.

Gentile Signora, egregio Signore,

Ci rivolgiamo a Lei per chiederle se è disposta a collaborare al nostro progetto di ricerca.

La sua partecipazione è volontaria. Tutti i dati rilevati nell'ambito di questo progetto sono sottoposti a severe disposizioni in materia di protezione dei dati.

Il progetto di ricerca viene svolto da SUPSI. In caso di interesse la informiamo volentieri sui risultati emersi dal progetto di ricerca.

Perché svolgiamo questo progetto di ricerca?

- In ambito clinico c'è un crescente interesse nel misurare le proprietà meccaniche dei tendini in quanto rilevanti per il possibile sviluppo di problematiche dolorose. Diversi strumenti sono stati sviluppati con lo scopo di misurare queste proprietà.
- Con il nostro progetto di ricerca intendiamo indagare se la tensiometria, una tecnica non invasiva per misurare la tensione dei tendini, riesca a intercettare cambiamenti di tensione tra il suo tendine lesionato e quello non lesionato.

Cosa deve fare in caso di partecipazione?

- Se decide di partecipare, le verrà chiesto di sottoporti ad un test che comprende delle misure su entrambi i tendini di Achille. Le misure vengono effettuate su un lettino e le verrà chiesto di fare delle contrazioni del muscolo polpaccio. Durante queste contrazioni verranno dati dei lievi impulsi (quasi impercettibili) sul tendine di Achille per misurare la tensione del tendine. Inoltre le chiederemo di compilare dei questionari per comprendere lo stato di salute del suo tendine.
- Durata: circa 30-45 minuti.
- Numero e impegno delle visite: la vostra partecipazione si limita a questo unico incontro.

Quali sono i benefici e i rischi correlati?

Benefici

- La partecipazione a questo progetto di ricerca ma non le apporterà nessun beneficio diretto.
- Con la vostra partecipazione potrete aiutare futuri pazienti, che potrebbero usare la stessa tecnica una volta che sarà dimostrata affidabile.

Rischi e incomodi

- Lo studio non le arrecherà nessun rischio. Con la sua firma in calce al documento dichiara di acconsentire alla partecipazione volontaria, e di aver compreso i contenuti dell'intero documento.

Informazione dettagliata

1. Scopo e selezione

Nel presente documento informativo definiamo il nostro progetto di ricerca come *sperimentazione*. Se lei dovesse partecipare a questa sperimentazione, viene definita/o come una/un *partecipante alla sperimentazione*.

Prima che una tecnica per valutare i pazienti sia applicata, deve essere studiata scientificamente su partecipanti a una sperimentazione. La sperimentazione ha quindi lo scopo di verificare se la tensiometria riesce a distinguere una diversa tensione tra il tendine precedentemente lesionato e quello non lesionato. La tensiometria è una tecnica non invasiva che si basa sulla lettura di un onda che si propaga nel tendine attraverso degli accelerometri.

Ci rivolgiamo a Lei in quanto possono partecipare tutti le persone che siano state sottoposte ad un trattamento conservativo (non chirurgico) a seguito di una rottura del tendine d'Achille.

2. Informazioni generali

Questo strumento è stato sviluppato con lo scopo di descrivere le proprietà meccaniche dei tendini e comprendere il comportamento di queste strutture quando sottoposte ad un carico.
Alcuni studi hanno valutato la precisione e l'affidabilità di questo strumento su soggetti senza problematiche tendinee con buoni risultati.
In particolare, verranno misurati:

- Lo stato di tensione a riposo dei suoi tendini.
- Lo stato di tensione dei suoi tendini durante diverse contrazioni del muscolo polpaccio.

Lo scopo principale di questo studio è stabilire se questa tecnologia è in grado di intercettare cambiamenti di tensione tra il tendine lesionato e quello non lesionato.
Questa sperimentazione si svolge nel rispetto della legislazione svizzera e delle direttive in vigore a livello internazionale. La sperimentazione è stata esaminata e autorizzata dalla commissione d'etica competente.
Una descrizione di questa sperimentazione è reperibile anche alla pagina Internet dell'Ufficio federale della sanità pubblica all'indirizzo www.kofam.ch

3. Svolgimento

Se acconsente a partecipare allo studio, le verrà richiesto di:

- Compilare alcuni questionari relativo allo stato di salute attuale del suo tendine.
- Sottoporsi ad un test che comprende la misurazione dello stato di tensione dei suoi tendini in condizioni di rilassamento e durante delle contrazioni del muscolo polpaccio.

Tutte queste misure richiederanno circa 30-45 minuti. Tutte le procedure rispetteranno le disposizioni cantonali e federali in vigore per limitare la trasmissione del nuovo Coronavirus.

4. Benefici

La partecipazione a questo progetto di ricerca, ma non le apporterà nessun beneficio diretto.
Con la vostra partecipazione potrete aiutare futuri pazienti, che potrebbero usare la stessa tecnica una volta che sarà stata dimostrata affidabile.

5. Volontarietà e obblighi

La sua partecipazione a questa sperimentazione è volontaria. Se lei non dovesse partecipare a questa sperimentazione, o decide in seguito di revocare la sua decisione, non dovrà in alcun modo motivare la sua decisione. I suoi trattamenti medici sono garantiti a prescindere dalla sua decisione.

Se lei volesse partecipare a questa sperimentazione è pregata di:

- Seguire le richieste che le verranno fatte dal ricercatore

- Informare il ricercatore su eventuali disagi o nuovi dolori.

6. Rischi e incomodi
Lo studio non arrecherà nessun rischio.

7. Risultati
Se lo desidera verrà informata/o sui risultati e sulle conclusioni dello studio.

8. Confidenzialità dei dati personali e del materiale biologico
Tutti i dati raccolti saranno resi anonimi, e nessuno potrà ricondurre a lei i dati, una volta che avrete lasciato la stanza nella quale vengono acquisiti.

8.1. Elaborazione dei dati e codifica
Per la presente sperimentazione vengono registrati ed elaborati i dati relativi alla sua salute, in parte in forma codificata. Ciò significa che tutti i dati che potrebbero identificarla (p. es. nome, data di nascita ecc.) vengono cancellati e sostituiti da un codice. Le persone che non hanno accesso a questi codici non possono risalire a lei.
Solo poche persone specialiste hanno accesso ai dati non codificati e solo per svolgere compiti necessari per la sperimentazione. Queste persone sono sottoposte all'obbligo di riservatezza. Avrà il diritto di consultare i suoi dati di al termine dello studio.

8.2. Protezione dei dati e protezione del materiale biologico
Tutte le disposizioni sulla protezione dei dati vengono rispettate rigorosamente. I suoi dati potrebbero dover essere trasmessi in forma anonima, ad esempio per una pubblicazione, e potrebbero essere messi a disposizione di altri ricercatori, sempre anonimizzati.

8.3. Protezione dei dati in caso di riutilizzo
I suoi dati verranno utilizzati esclusivamente per questo progetto.

8.4. Diritto di consultazione in caso di controlli
La presente sperimentazione può essere sottoposta a verifica da parte dalla commissione d'etica competente o dal promotore che organizza la sperimentazione. Lo sperimentatore dovrà in tal caso mettere a disposizione i suoi dati ai fini di tali controlli. Tutte le persone sono tenute a osservare la più assoluta confidenzialità.

9. Ritiro dalla sperimentazione
Potrà decidere di ritirarsi dalla sperimentazione in qualsiasi momento. In tal caso, i dati rilevati fino a quel momento saranno comunque valutati in forma anonima.

10. Indennità
Per la partecipazione a questa sperimentazione non le sarà versata alcuna indennità.

11. Responsabilità
Nonostante questa sperimentazione non presenti alcun rischio prevedibile, SUPSI secondo le disposizioni di legge è responsabile per tutti i danni che possono insorgere nell'ambito di questa sperimentazione.

12. Finanziamento
La sperimentazione è finanziata completamente da SUPSI.

13. Persona/e di contatto

Può porre in ogni momento domande in merito alla sperimentazione. Anche in caso di incertezze o emergenze che dovessero insorgere durante o dopo la sperimentazione, può rivolgersi a:

Alessandro Schneebeli
Via Violino 11
6928 Manno
tel: 058 666 64 43
e-mail: alessandro.schneebeli@supsi.ch

Organo di consulenza:

Se desidera rivolgersi a un organo indipendente esterno alla sperimentazione, può rivolgersi a:

Ufficio del Farmacista cantonale
tel. 091 816.59.41
e-mail: dss-ufc@ti.ch

Tale organo non ha alcun legame con i ricercatori addetti alla sperimentazione. Il tuo caso sarà trattato in modo assolutamente confidenziale.

Scuola universitaria professionale
della Svizzera italiana

SUPSI

Dichiarazione di consenso

Dichiarazione di consenso scritta per la partecipazione a una sperimentazione clinica
Legga attentamente il presente formulario. Non esiti a porre domande se qualcosa non le è chiaro o se desidera una spiegazione. Per la partecipazione alla sperimentazione è necessario il suo consenso scritto.

Numero BASEC:	2022-01707
Titolo della sperimentazione (in termini scientifici e semplici):	Differenze di proprietà meccaniche tra tendine d'Achille lesionato e non lesionato.
Istituzione responsabile (promotore con indirizzo):	SUPSI DEASS Stabile Piazzetta, Via Violino 11 6928 Manno
Luogo di svolgimento:	Ente Ospedaliero Cantonale Servizio di Ortopedia e Traumatologia 6900 Lugano
Sperimentatore nel luogo di svolgimento: Nome e cognome in stampatello:	Alessandro Schneebeli
Partecipante: Nome e cognome in stampatello: Data di nascita:	

- Sono stata/o informata/o dalla sperimentatrice sottoscritta/dallo sperimentatore sottoscritto oralmente e per scritto in merito allo scopo, allo svolgimento della sperimentazione, ai possibili vantaggi e svantaggi nonché agli eventuali rischi.
- Partecipo alla sperimentazione volontariamente. Accetto il contenuto del documento informativo scritto a me consegnato. Ho avuto tempo a sufficienza per prendere la mia decisione.
- Ho ricevuto risposte esaustive alle mie domande relative alla partecipazione a questa sperimentazione. Posso conservare il documento informativo scritto sulla sperimentazione e ricevo una copia della mia dichiarazione di consenso scritta.
- Acconsento al fatto che le specialiste/gli specialisti competenti del promotore della sperimentazione e della commissione d'etica competente possano accedere ai miei dati non codificati a fini di esame e controllo, tuttavia in stretta osservanza della confidenzialità.
- Posso ritirarmi dalla partecipazione alla sperimentazione in qualsiasi momento senza fornire motivazioni. Il suo successivo trattamento medico è garantito a prescindere dalla partecipazione alla sperimentazione. I dati e i campioni di materiale biologico rilevati fino al ritiro saranno ancora analizzati nell'ambito della sperimentazione.
- Sono a conoscenza del fatto che eventuali danni riconducibili alla sperimentazione saranno coperti da un'assicurazione stipulata da SUPSI.

Luogo, data	Firma della/del partecipante alla sperimentazione

Conferma della sperimentatrice/dello sperimentatore: con la presente dichiaro di aver spiegato alla/al partecipante in questione la natura, l'importanza e la portata della sperimentazione. Garantisco di adempiere tutti gli obblighi inerenti a questa sperimentazione secondo il diritto vigente in Svizzera. Se nel corso della sperimentazione dovessi venire a conoscenza di aspetti che potrebbero influenzare la disponibilità della/del partecipante a partecipare alla sperimentazione, provvederò a informarla/o immediatamente.

Luogo, data	Nome e cognome in stampatello della sperimentatrice/dello sperimentatore Firma della sperimentatrice/dello sperimentatore

Appendix 15 – Achilles Tendon Total Rupture Score (ATRS)

Italian version of the Achilles tendon Total Rupture Score (ATRS)

ID paziente: _____

Lato affetto: _____

Data esame: _____

ISTRUZIONI: Questo questionario intende valutare le limitazioni/difficoltà che Lei prova a causa della lesione del Suo tendine di Achille.
Risponda a ciascuna domanda, quantificando le Sue limitazioni/difficoltà da 0 a 10 (solo una risposta per ciascuna domanda).
Ricordi: **0=grave limitazione, 10=nessuna limitazione**.
Marchi il numero che meglio rispecchia il Suo livello di impedimento.

1. Ha delle limitazioni dovute alla **diminuzione della forza** del polpaccio/tendine di Achille/piede?

0	1	2	3	4	5	6	7	8	9	10

Grave limitazione — Nessuna limitazione

☐

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2. Ha delle limitazioni dovute alla **stanchezza** al polpaccio/tendine di Achille/piede?

0	1	2	3	4	5	6	7	8	9	10

Grave limitazione — Nessuna limitazione

☐

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3. Ha delle limitazioni dovute alla **rigidità** del polpaccio/tendine di Achille/piede?

0	1	2	3	4	5	6	7	8	9	10

Grave limitazione — Nessuna limitazione

☐

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4. Ha delle limitazioni dovute al **dolore** al polpaccio/tendine di Achille/piede?

0	1	2	3	4	5	6	7	8	9	10

Grave limitazione — Nessuna limitazione

☐

Vascellari, A., et al. 2018. Cross-cultural adaptation and multi-centric validation of the Italian version of the Achilles tendon Total Rupture Score (ATRS). Knee Surg Sports Traumatol Arthrosc,26, 854-861.

5. Ha difficoltà nello svolgimento delle Sue **attività quotidiane abituali**?

0	1	2	3	4	5	6	7	8	9	10

Grave limitazione Nessuna limitazione

☐

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6. Ha difficoltà quando **cammina** su una superficie irregolare?

0	1	2	3	4	5	6	7	8	9	10

Grave limitazione Nessuna limitazione

☐

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7. Ha difficoltà quando sale rapidamente le **scale** o cammina in **salita**?

0	1	2	3	4	5	6	7	8	9	10

Grave limitazione Nessuna limitazione

☐

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8. Ha difficoltà durante le attività che includono la **corsa**?

0	1	2	3	4	5	6	7	8	9	10

Grave limitazione Nessuna limitazione

☐

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9. Ha difficoltà durante le attività che includono i **salti**?

0	1	2	3	4	5	6	7	8	9	10

Grave limitazione Nessuna limitazione

☐

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10. È limitato quando esegue **lavori pesanti**?

0	1	2	3	4	5	6	7	8	9	10

Grave limitazione Nessuna limitazione

☐

Punti Totali _____

Vascellari, A., et al. 2018. Cross-cultural adaptation and multi-centric validation of the Italian version of the Achilles tendon Total Rupture Score (ATRS). Knee Surg Sports Traumatol Arthrosc,26, 854-861.

Appendix 16 – Tegner Activity Level Scale

TEGNER ACTIVITY LEVEL SCALE

Indicare negli spazi sottostanti il livello più alto di attività a cui si partecipava prima dell'infortunio e il livello più alto a cui si è in grado di partecipare attualmente.

PRIMA DELL'INFORTUNIO: Livello ___ **ATTUALE: Livello ___**

Livello 10→ Sport agonistici - calcio, football, rugby (élite nazionale)

Livello 9→ Sport agonistici - calcio, football, rugby (divisioni inferiori), hockey su ghiaccio,lotta, ginnastica, pallacanestro, pallavolo

Livello 8→ Sport agonistici , squash o badminton, atletica leggera (salto, ecc.),sci alpino

Livello 7→ Sport agonistici: tennis, corsa, automobilismo, pallamano.

Sport ricreativi - calcio, football, rugby, hockey su ghiaccio, pallacanestro, pallavolo, squash, corsa.

Livello 6→ Sport ricreativi - tennis e badminton, pallamano, squash, sci alpino, jogging almeno 5 volte.

Livello 5→ Lavoro - lavori pesanti (edilizia, ecc.)
Sport agonistici - ciclismo, sci di fondo,
Sport ricreativi: jogging su terreno irregolare almeno due volte alla settimana.

Livello 4→ Lavoro - lavoro moderatamente pesante (ad es. guida di camion, ecc.)

Livello 3→ Lavoro - lavoro leggero (infermieristica, ecc.)

Livello 2→ Lavoro - lavoro leggero
Camminare su terreni irregolari è possibile, ma non è possibile portare lo zaino o fare escursioni.

Livello 1 → Lavoro sedentario (segreteria, ecc.)

Livello 0 → Congedo per malattia o pensione di invalidità a causa di problemi di salute

Y Tegner and J Lysolm. Rating Systems in the Evaluation of Knee Ligament Injuries. Clinical Orthopedics and Related Research. Vol. 198: 43-49, 1985.

Appendix 17 – Poster presented at the IFOMPT conference 2024

University of Applied Sciences and Arts of Southern Switzerland
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Università della Svizzera italiana

IFOMPT 2024 crossing bridges 4–6 July Basel

DIFFERENCES IN SHEAR WAVE SPEED BETWEEN SURGICALLY AND CONSERVATIVELY TREATED ACHILLES TENDONS FOLLOWING RUPTURE

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[2] Centre of Precision Rehabilitation for Spinal Pain (CPR Spine), School of Sport, Exercise Rehabilitation Sciences, College of Life Environmental Sciences, University of Birmingham, Birmingham, UK.
[3] Service of Orthopaedics and Traumatology, Department of Surgery, EOC, Lugano, Switzerland.
[4] Faculty of Biomedical Sciences, Università della Svizzera Italiana, Lugano, Switzerland.

Background and Aim

- Achilles Tendon rupture (ATR) is a frequently occurring musculoskeletal injury, with an annual occurrence rate ranging from 5 to 50 cases per 100,000 individuals, potentially leading to significant disability. To date, clinical outcomes at 12 months post-injury appear to be comparable between those who undergo surgery and those who receive conservative treatment.
- Shear wave tensiometry is a recently described technology that uses accelerometers to measure wave propagation along the tendon to define tendon mechanical properties. This technology is based on the concept that the axial stress within the tissue affects the squared tendon wave speed.
- The aim of this cross-sectional study was to evaluate shear wave speed (SWS) differences between surgically and conservatively treated ATR.

Materials and Methods

- Fifteen participants who underwent unilateral open repair Achilles tendon (AT) tenorrhaphy and fifteen participants with acute ATR treated conservatively were retrospectively identified (from 1 to 5 years since ATR).
- Tendon loading was measured using a shear wave tensiometer consisting of four accelerometers fixed on the tendon following an ultrasound imaging procedure to ensure proper positioning. The wave propagation along the tendon was manually elicited using a reflex hammer. Five repeated measurements were taken during isometric contraction of increasing intensity (0-35 Nm ankle torque) on both the left and right AT of each participant. The SWS was calculated based on the time delay between the different waves detected by the accelerometers and the mechanical wave propagation on the tendon.
- Tendon thickness and cross-sectional area (CSA) were assessed using ultrasound imaging, ankle dorsiflexion range of motion and calf circumference were also measured.

Table 1

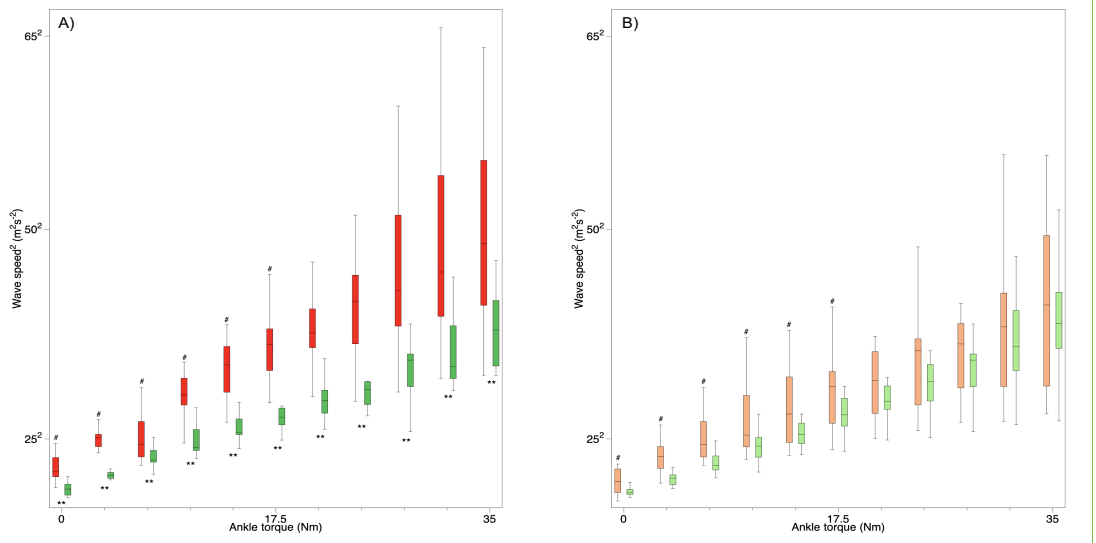
	SURGERY (n=15)			CONSERVATIVE (n=15)			between groups diff. (p)
Age	53.3±11.5			53.5±8.4			0.806
ATRS (0-100)	89.3±12.0			80.4±12.8			0.202
Side	**OP**	**H**	**between side diff. (p)**	**RUP**	**H**	**between side diff. (p)**	
SWS (m/s) @ 0Nm	18.2(4.5)	13.3 (3.7)	**<0.001**	15.7 (6.8)	12.2 (1.9)	0.071	**0.015**
SWS (m/s) @ 17.5Nm	38.3 (5.0)	28.6 (2.6)	**<0.001**	33.1 (7.4)	29.0 (4.2)	0.782	**0.017**
SWS (m/s) @ 35Nm	47.5 (13.1)	41.3 (7.4)	**0.016**	42.7 (13.6)	40.7 (6.1)	0.405	0.300
Thickness (mm)	13.6 (1.9)	5.6 (1.3)	**<0.001**	11 (2.5)	5.4 (1.3)	**<0.001**	**0.005**
CSA (mm2)	178 (36.5)	66 (7.9)	**<0.001**	141 (45.5)	68.2 (19.2)	**<0.001**	**0.023**
ROM (°)	40 (6.5)	43 (5)	**0.033**	39 (5.5)	38 (7.5)	0.248	0.838
Calf Circ. (cm)	37 (4)	41 (4.5)	**0.002**	37 (3.25)	38 (3)	**0.001**	0.902

Acronyms: OP, operated tendon; H, healthy tendon; RUP, ruptured tendon; ATRS, Achilles tendon total rupture score.

Results

- The SWS differences between the affected and unaffected sides were significant only in the SURGERY group with the sutured tendon showing a higher SWS for every contraction level. The CONSERVATIVE group showed a similar SWS behavior between the affected and unaffected side.
- The unaffected tendon of both groups showed a similar SWS while the injured tendon of the CONSERVATIVE group showed a constantly lower SWS compared to the SURGERY group, especially at lower contraction levels. (Figure 1)
- Difference between SURGERY and CONSERVATIVE group were found also for tendon thickness and CSA.

Figure 1



*Box plot showing shear wave speed difference between tendons at different ankle torque for A) SURGERY group and B) CONSERVATIVE group. Red and orange box plots represent the ruptured tendon whereas green and light green represent the healthy tendon. ** p<0.05, statistical significant difference between side; # p<0.05, statistical significant difference between groups*

Conclusions

Achilles tendon surgery after ATR influences SWS values more than conservative treatment. Values remain higher in the operated tendon even in the long term after surgery. The relationship between SWS and clinical features should be further investigated.
An instrument capable of detecting changes in tendon loading responses over time has the potential to improve our comprehension of tendon behavior during the healing process and aid clinicians in tailoring rehabilitation protocols for individual patients.

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