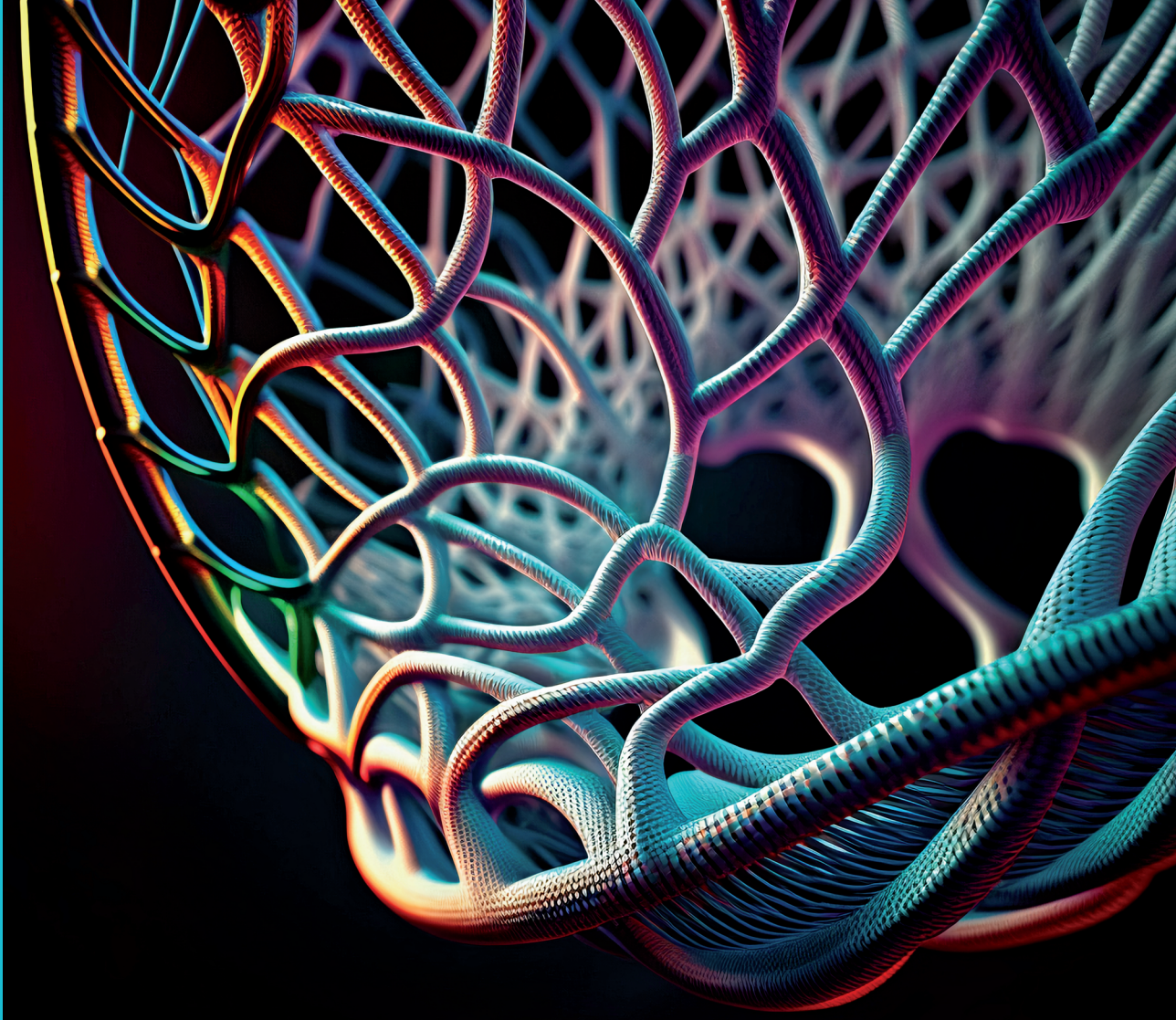

EXERCISE THERAPY FOR PATELLAR TENDINOPATHY

evaluated with quantitative imaging

Stephan Breda

Exercise Therapy For Patellar Tendinopathy Evaluated With Quantitative Imaging

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Colophon
ISBN: 978-94-6361-852-6
Cover-design: Stephan Breda, the Netherlands, 2023
Layout and printing: Optima Grafische Communicatie

Financial support from the National Basketball Association (NBA) and GE Healthcare Orthopaedics and Sports Medicine Collaboration is gratefully acknowledged.

Exercise Therapy for Patellar Tendinopathy Evaluated with Quantitative Imaging

Oefentherapie voor patella tendinopathie
geëvalueerd met kwantitatieve beeldvorming

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof. dr. A.L. Bredenoord

en volgens het besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op:
Dinsdag 27 juni 2023 om 15:30 uur

door

Stephan Jonathan Breda
geboren te Eindhoven

Erasmus University Rotterdam

PROMOTIECOMMISSIE

Promotor:	Prof. dr. E.H.G Oei
Overige leden:	Prof. dr. M.S. Rathleff
	Dr. S. Klein
	Dr. M. van Middelkoop
Co-promotor:	Dr. R.J. de Vos

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General Introduction

PATELLAR TENDINOPATHY

Patellar tendinopathy (PT), also referred to as "Jumper's knee", is a common and often chronic overuse injury of the patellar tendon.[1] Athletes performing repetitive jumping and landing activities, such as basketball and volleyball, are most commonly affected. Prevalence rates of 45% for elite volleyball players and 32% for elite basketball players have been reported.[2] PT is also seen in soccer players and athletes performing track and field activities.[3,4] PT is typically observed in elite sports populations, but it can also occur recreative sports or physical activities that strain the knee extensor muscles.[5] The incidence of PT can fluctuate within seasons or periods of competition, becoming increasingly common among players as the season progresses or when training intensity suddenly increases, for example in preparation for the competitive period.[6] Patients with PT experience pain most commonly at the inferior patellar pole, where the patellar tendon attaches to the patellar bone.[7] Pain is typically worse when initiating activity, eases with physical activity and will then increase again after training or competition (the so called "warm-up" phenomenon).[8] Especially after training with high demanding loads, such as high jumps or explosive cutting manoeuvres, pain can persist for several days.[9] In later stages, pain might also increase after the warm-up period.[10] The pain forces most athletes with PT to diminish their participation in training and impedes athletic performance. It even leads to cessation of sports activities in more than half of athletes.[11] It has also been shown that 58% of the patients with PT encounter problems with participation in physically demanding work.[12] The concerns, frustrations and impact on quality of life and daily functioning in individuals with tendinopathy have been well described.[13] The injury burden of PT is difficult to describe in detail, merely due to lacking data on the number of days of time loss from sports as a measure of severity, which also comprises only one of the many consequences for the individual athlete.[14]

PATHOLOGICAL FINDINGS

Macroscopically, the patellar tendon is composed of collagen fibres ordered in large bundles. The structural organisation in the healthy tendon is highly organised, where the bundles consist of parallelly ordered collagen fibres and fibrils. This organisation imparts tensile strength to the patellar tendon and provides the tendon with its unique structural and functional properties. The bundles, fibres and fibrils are part of the extracellular matrix (ECM) of the patellar tendon, which account for about 80% of the dry weight.[15] The tendon is normally only sparsely populated with cells (tenocytes) and only slightly vascularised. Water is an important non-collagenous matrix substance that interacts with the ECM in order to increase stiffness and resistance against shear and compressive forces.[16] Water is attracted by large and negatively charged molecules called proteoglycans and their glycosaminoglycan (GAG) side chains which are an essential part of the ECM.

Changes that occur on a microscopic level in PT include an increase in the amount of glycosaminoglycans, leading to significant increase in water content in tendons with PT.[17] The upregulation of GAG's and the large aggregating proteoglycan "versican" contributes to an increased ECM volume and an associated increase in water content. These changes are referred to as mucoid degeneration.[17–19] The increase of mucoid ground substance within the collagen fibres separates the collagen bundles, hereby affecting the normal tendon architecture.[20] In addition to the disordered arrangement of collagen fibres, increased vascularity is found on histopathological examination. The spectrum of degenerative changes referred to are classified as hypoxic, hyaline, mucoid or myxoid, fibrocartilage metaplasia and fatty degenerations.[21] Hyaline degeneration is considered as an end-stage process of tendon degeneration, where patients with longer symptom duration tend to have a greater amount of hyaline degeneration.[22] Hyaline degeneration involves intracellular changes in the tenocytes mediated by hypoxemia and is characterised by increased stiffness rather than reduced stiffness in mucoid degeneration.[23] However, in early tendon adaptation to increasing loads, an increase in water content also leads to stiffening of the tendon.[24,25] From gene expression studies in rats, genes involved in ECM components responded differently to different loading of the patellar tendon. After isotonic (dynamic) loading, fibrocartilage markers were increased whereas after isometric (static) loads markers of tendon regeneration were increased.[26] Others described a potential tendon strengthening effect by eccentric exercises that are thought to stimulate mechanoreceptors in tenocytes to produce collagen and thus potentially revert the degenerative tendinosis cycle.[27]

Tendinitis and tendinopathy are two terms that each describe different features of PT. Where the term tendinitis is limited to describing tendon inflammation, tendinopathy has been used as a descriptor of the clinical picture without referring to a specific histopathological condition. Critical reviews finding limited evidence of anti-inflammatory drugs to fully manage the disease burden of PT and a better understanding of the pathophysiological mechanisms occurring in PT have led to a paradigm shift from a classic tissue-based diagnosis. According to the ISTS consensus statement, the broader term tendinopathy is the preferred term for persistent tendon pain and loss of function related to mechanical loading.[1] Moreover, tendinopathy better reflects the complexity of morphologic changes with a predominant pattern of tendon degeneration, with evidence of collagen disorganisation and increase in mucoid ground substance.[28,29]

CLINICAL DIAGNOSIS

Patellar tendinopathy is a clinical diagnosis that is made based on patient history and physical examination. The typical clinical sequelae are focal pain at the inferior pole of the patella and load-dependent symptoms, with increased loads resulting in a greater degree of pain.[8] Despite palpation tenderness along the course of the patellar tendon (Fig 1E) is frequently considered as pathognomonic for diagnosing PT, its role for diagnosing PT has also been

questioned because of lacking specificity for PT.[30] Therefore, appropriate history taking is crucial in the diagnostic process, which is also the result of a paradigm shift from using a classic tissue-based diagnosis.[31]

Clinically, it can be challenging to distinguish tendinopathy from patellofemoral pain due to similar characteristics in their clinical presentation. Patellofemoral pain (PFP) is also a very common knee condition resulting in pain that is provoked by activities of daily living or sports.[32] Pain in PFP is not typically located at the inferior pole of the patella, but presents as pain around or behind the patella (Fig 1D) during activities that involve loading of the patellofemoral joint.[33] Despite exercise therapy has also become a cornerstone treatment in PFP, the approach differs from tendinopathy that is more focussed on improving tendon structure and function. Unlike PT, structural abnormalities of the patellofemoral joint are not associated with PFP.[34] Especially in trials that focus on physical rehabilitation programs to treat anterior knee pain, it is of utmost importance to include homogeneous study populations, to evaluate the therapeutic effect in only one condition. Provocation tests according to the patellofemoral pain consensus statement can be performed to exclude patellofemoral pain, but clear gold standards for diagnosis PFP are lacking due to their unclear pathogenesis.[31,33]

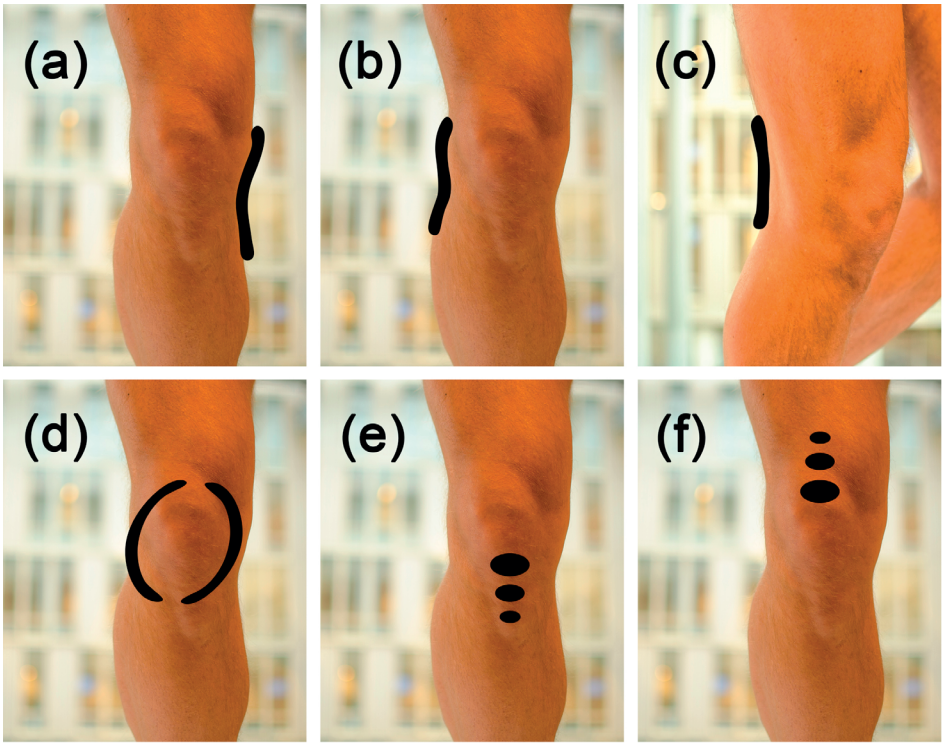

Figure 1: Knee pain map for pain localisation

IMAGING OF PATELLAR TENDINOPATHY

Ultrasound (US) is the most frequently applied imaging modality in routine assessment of the patellar tendon. US is used primarily to confirm the clinical diagnosis and to assess the extent of PT.[35] Ultrasound is very sensitive for detecting increased patellar tendon thickness and hypoechoic areas within the patellar tendon, with loss of the normal structural organisation. The normal ultrasound appearance of the patellar tendon in an asymptomatic individual is illustrated in Fig 2. An example of a patellar tendon in PT is illustrated in Fig 3. Spatial image resolution of US is excellent, exceeding that of magnetic resonance imaging (MRI) and is therefore well suited for evaluation of superficial structures such as the patellar tendon. Power Doppler imaging, which is also an US-based imaging technique is very sensitive for detecting increased tendon vascularity. However, the specificity of these findings for PT is unfortunately low. The prevalence of structural tendon abnormalities on ultrasound in a population of elite basketball players is high, up to 62%.[36] Even in junior basketball players that never reported patellar tendon pain, these ultrasound abnormalities are present in 22%.[37] Therefore, structural tendon abnormalities on imaging are not specific for PT and are also frequently observed in asymptomatic individuals (up to 13% in asymptomatic basketball players and up to 14% in asymptomatic volleyball players).[38,39]

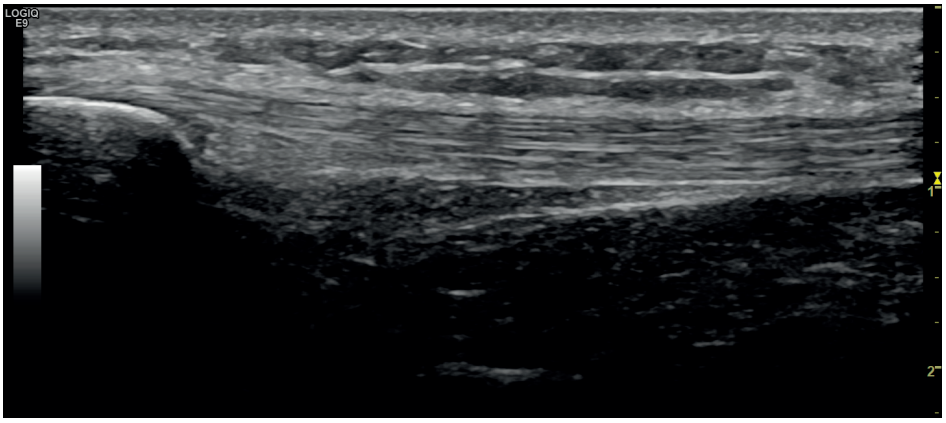

Figure 2: Longitudinal B-mode ultrasound of the patellar tendon in an asymptomatic individual. The inferior patellar border is shown left on the image, characterised by the concave white border and posterior acoustic shadowing due to the reflection of ultrasound waves on bone. The patellar tendon is attached to the inferior patellar border and progresses to the tibial tuberosity on the lower leg (not displayed on the image). The patellar tendon thickness is approximately equal over its entire length and large bundles of collagen fibres are recognised by the parallelly ordered lines within the patellar tendon. Posterior to the patellar tendon is a hypoechoic (dark) tissue, called Hoffa's fatpad.

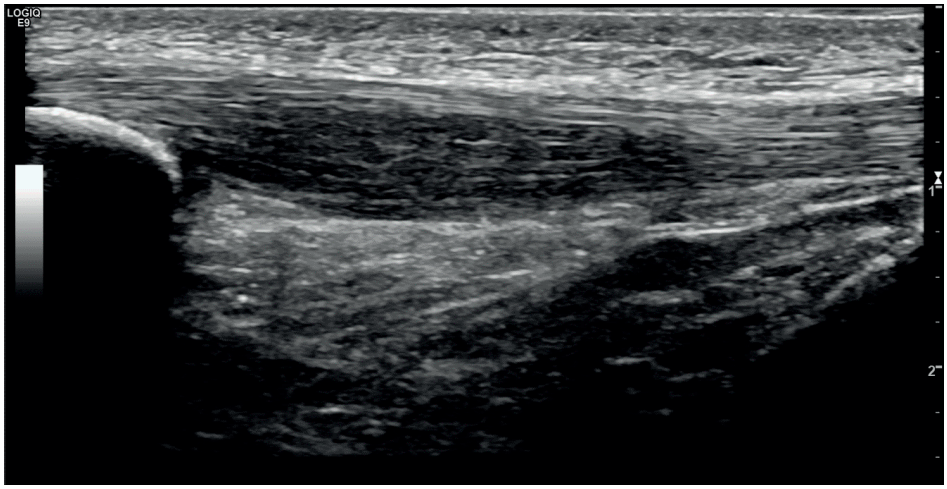

Figure 3: Longitudinal B-mode ultrasound of the patellar tendon in an athlete with PT. The patellar tendon is thickened and reveals hypoechogenic (dark) changes separating the bundles of collagen fibres and hereby affecting the normal tendon architecture.

MRI is used less frequently due to higher cost and more limited availability than US. MRI has additional diagnostic value compared to US to rule out other causes for knee pain than PT, such as osteochondral lesions or meniscal injury.[40] Typical MRI findings of PT are thickening of the proximal patellar tendon and an increased signal intensity in the proximal patellar tendon, which reflects an increased water content (Fig 4).[41] Using MRI, the prevalence of signal changes in the patellar tendon is estimated at 27% in 230 asymptomatic knees.[42]

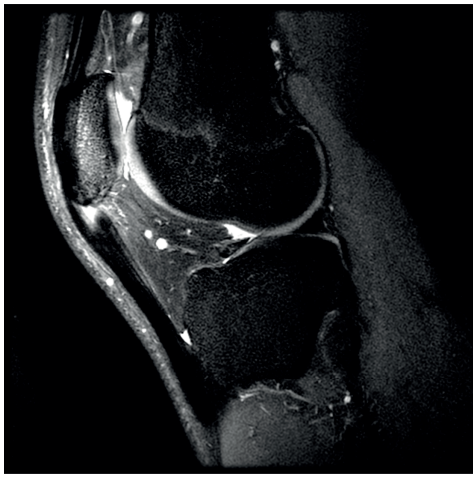

Figure 4: Sagittal MR image of the knee at echo time 4.87 ms (proton density sequence) in an athlete with patellar tendinopathy.

Patellar tendon abnormalities visualised using US in asymptomatic patellar tendons are considered predictive of future PT with a fourfold increased risk.[39,43] For diagnosis of PT on the other hand, the clinical use of these imaging modalities should be targeted within an appropriate clinical context.[44] Imaging can then guide the clinician when the diagnosis is unclear or may help to guide clinical management of PT and to estimate prognosis. For evaluating the effect of therapy of PT, imaging is sometimes used but results should also be interpreted with caution. A systematic review that focussed on the association between clinical and imaging outcomes after therapeutic exercise therapy found only moderate evidence supporting an association of a reduction in tendon thickness and tendon vascularity with improved pain and function.[45]

ADVANCED IMAGING TECHNIQUES

Imaging techniques used in daily clinical routine are often limited to describing morphological changes, but lack the ability to provide insights in structural properties of the patellar tendon in a quantitative way. Advanced imaging methods enable tissue quantification and have a great potential to be applied in the field of sports medicine. To date, advanced imaging techniques are mainly explored in research and not applied routinely in clinical practice.[35] New quantitative imaging techniques show potential to assist in patient management and prognosis. Shear-wave elastography (SWE) is an ultrasound-based imaging technique that can be used to estimate stiffness of the patellar tendon.[46] The assessment of patellar tendon stiffness could potentially correlate better with tendon pain than routine ultrasound because SWE enables to investigate mechanical properties that cannot be seen morphologically. However, first applications of SWE in scientific research show conflicting results. Both increased stiffness and decreased stiffness of the patellar tendon have been reported in patients with PT.[47,48]

Routine MR imaging of tendons is typically limited due to the fast free induction decay of collagen, which also impedes tissue quantification.[49] Because of this fast decaying transverse magnetisations in collagen, tendons and ligaments appear characteristically black with no measurable signal on the acquired MR images. Recent advances in MRI techniques with ultrashort echo time (UTE) sequences overcome these issues by implementing ultrashort echo times that enable to capture signal from tendons.[50] Imaging with UTE MRI can detect changes in the composition and structure of degenerated tendon in patients with PT. Studies implementing UTE-MRI have shown potential to quantify different water pools in cortical bone and tendon.[51,52] UTE-MRI based T2* relaxation times have been used in tendons to quantify their relaxation parameters.[53] It was found that these parameters altered in PT, with patients having significantly higher T2* of the patellar tendon than healthy subjects.[54]

TREATMENT OF PATELLAR TENDINOPATHY

Due to the chronicity of the injury, recovery from PT is often difficult and involves more than taking a brief rest from athletic activities. A common misconception about tendinopathies is that they are self-limiting and take only a few weeks to resolve. Although rest is advised in the Dutch standard of care for general practitioners, exercise therapy is considered to play a critical role in recovery from PT.[55] Yet, the evidence that conservative treatment reduces pain and improves function in athletes with PT is only weak.[56,57] Invasive treatment options, such as injection therapy and surgery, have proven insufficient to manage the disease burden of PT and are sometimes even associated with deterioration of the patellar tendon, such as in corticosteroid injections that increase risk of patellar tendon rupture significantly.[58]

EXERCISE THERAPY FOR PATELLAR TENDINOPATHY

A significant change in the pathophysiological concept of patellar tendinopathy resulted in the first step in the implementation of exercises as treatment for PT rather than rest.[28] From the athlete's perspective, an ideal rehabilitation programme would be easy to perform (resulting in a high compliance), with short term relief of symptoms. This analgesic component of therapy is by far the most important, enabling to continue training and competition and, not least important, joining the social aspect of sport.[13] Additionally, the programme should not interfere substantially with the regular training and competitions.

The boost in favouring exercise therapy for tendinopathy has led to a long track record of studies indicating clinical effectiveness of eccentric exercises.[59,60] The eccentric exercises used for Achilles tendinopathy were automatically adapted for other tendinopathies, such as patellar tendinopathy. A heavy-load and pain-provoking eccentric exercise program became usual care for PT according to the National Institute for Health and Care Excellence (NICE) guidelines.[61,62] However, EET is lacking an immediate improvement in symptoms and could therefore lead to poorer adherence, despite several studies showing a beneficial outcome of EET after 12 weeks.[60,63,64] Although conservative treatment is aimed at improving tendon structure, the results of a systematic review indicate that there is strong evidence to refute any improvement in tendon structure from EET.[65] Also, symptoms typically increase in the first 2 to 4 weeks in response to eccentric loading.[59] And when eccentric exercises were applied in-season, no benefit or even worse outcomes were documented.[66,67]

Isometric exercises have been proposed as alternatives for eccentric exercises to reduce tendon pain in-season, allowing athletes to fulfil their commitments to training and competition.[68] One study found that isotonic exercises (heavy slow resistance training) were as effective as eccentric exercises only with also higher patient satisfaction.[60] Also, the exercises were applicable in-season. Another study that implemented either isometric or isotonic exercises in 20 volleyball and basketball athletes with PT during a 4-week competitive season found

that both protocols were effective for in-season athletes to reduce pain and that isometric exercises produced significantly greater direct analgesia.[68] With these promising results of different exercise protocols that can also be used in-season, a clinical advice was published, proposing a 4-stage exercise protocol with progressive loading.[8] Moreover, this treatment regime was better individualised to the athlete, by using personalised progression criteria that defined progression to the subsequent stage of the exercise protocol. The first stage consisted of isometric loading with the rationale to reduce pain in the highly irritable tendon and preparing the patellar tendon for high isotonic loading. A pain rating of 3/10 or less was defined as acceptable and indicated to initiate the next stage of the 4-stage protocol. Isotonic loading was the second stage and was performed by using a leg-press and seated knee extension machine (as in stage 1) with the rationale to restore strength and to provide a high-load stimulus in order to revert the degenerative cascade of tendinopathy. Subsequently, energy storage loads were added (stage 3) in order to increase the load tolerance of the tendon and to improve power as a progression to return to sport. A 3-day interval was used for this most provocative stage to enable a collagen synthesis response in the tendon. The last stage focussed on sport-specific exercises, promoting a return to sport.

The comparison of eccentric exercises as current usual care versus the newly proposed protocol advocating a more gradual increase in loading of the patellar tendon using individualised progression criteria was a gap of knowledge in patellar tendon research for several years.

AIMS AND OUTLINE

In the JUMPER-study, the largest trial in PT to date, we investigate the effectiveness of newly proposed progressive tendon-loading exercises (PTLE) versus eccentric exercise therapy (EET) as the current standard of clinical care in athletes with patellar tendinopathy (PT). The therapeutic effects are evaluated using both clinical and radiological outcome measures, of which the latter also includes advances imaging modalities that enable tissue quantification. In **Chapter 2** of this thesis, we compare the effectiveness of PTLE with EET in 76 patients with PT. A stratified, investigator-blinded, block-randomised trial was performed with study name "JUMPER-study". In **Chapters 3-7**, we investigate advanced quantitative imaging techniques using both ultrasound and magnetic resonance imaging (MRI) to gain knowledge about the structural changes that occur in PT and to monitor longitudinal changes in tendon structure after exercise therapy.

In **Chapter 3**, we implement shear-wave elastography (SWE) in a case-control study to determine the association between patellar tendon stiffness and PT, and learn about the reliability of SWE. In **Chapter 4**, we evaluate changes of patellar tendon stiffness in athletes with PT who performed exercise therapy using longitudinal SWE measurements. Associations between patellar tendon stiffness and clinical outcome after exercise therapy are also part of this

chapter. In **Chapters 5-7**, we implement ultrashort echo time (UTE) sequences to perform quantitative T2* mapping of the patellar tendon in athletes from the JUMPER-study. In order to perform a specific T2* quantification of the patellar tendon, we describe an optimised image analysis approach in **Chapter 5** that is able to quantify T2* relaxation times in specific tissue compartments of the patellar tendon in which voxels containing comparable water pools are automatically selected for image analysis. For this sophisticated image analysis approach, we evaluate the reliability of mono-exponential, bi-exponential and fractional order fitting methods to quantify UTE relaxometry data. In **Chapter 6**, we evaluate these fitting methods on their dependence of low signal-to-noise ratio's and evaluate the performance of fractional order fitting to describe T2* relaxation in complex heterogeneous tissues. Finally, in **Chapter 7**, we assess the association between T2* relaxation times and clinical outcome in athletes with PT performing exercise therapy.

A general discussion and summary are provided in **Chapter 8** of this thesis.

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2

Effectiveness of progressive tendon-loading exercise therapy in patients with patellar tendinopathy: a randomised clinical trial.

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Br J Sports Med. 2021 May;55(9):501-509.

ABSTRACT

Objective: To compare the effectiveness of progressive tendon-loading exercises (PTLE) with eccentric exercise therapy (EET) in patients with patellar tendinopathy (PT).

Methods: In a stratified, investigator-blinded, block-randomised trial, 76 patients with clinically diagnosed and ultrasound-confirmed PT were randomly assigned in a 1:1 ratio to receive either PTLE or EET. The primary end point was clinical outcome after 24 weeks following an intention-to-treat analysis, as assessed with the validated Victorian Institute of Sports Assessment for patellar tendons (VISA-P) questionnaire measuring pain, function and ability to play sports. Secondary outcomes included the return to sports rate, subjective patient satisfaction and exercise adherence.

Results: Patients were randomised between January 2017 and July 2019. The intention-to-treat population (mean age, 24 years, SD 4); 58 (76%) male) consisted of patients with mostly chronic PT (median symptom duration 2 years). Most patients (82%) underwent prior treatment for PT but failed to recover fully. 38 patients were randomised to the PTLE group and 38 patients to the EET group. The improvement in VISA-P score was significantly better for PTLE than for EET after 24 weeks (28 vs 18 points, adjusted mean between-group difference, 9 (95% CI 1 to 16); p=0.023). There was a trend towards a higher return to sports rate in the PTLE group (43% vs 27%, p=0.13). No significant between-group difference was found for subjective patient satisfaction (81% vs 83%, p=0.54) and exercise adherence between the PTLE group and EET group after 24 weeks (40% vs 49%, p=0.33).

Conclusions: In patients with PT, PTLE resulted in a significantly better clinical outcome after 24 weeks than EET. PTLE are superior to EET and are therefore recommended as initial conservative treatment for PT.

INTRODUCTION

Patellar tendinopathy (PT) is a common chronic tendon injury that is characterised by load-related pain in the patellar tendon.[1] As many as 45% of elite athletes in jumping sports like basketball and volleyball suffer from PT.[2] This often results in prolonged sport absence, which hampers an individual's athletic performance and the health-related benefits of physical activity.[3] It also has been shown that 58% of the patients with PT encounter problems with participation in physically demanding work.[4]

Despite the fact that many risk factors in the aetiology and pathogenesis of PT have been suggested, a direct cause–effect relationship is currently unknown.[5] The nomenclature 'tendinitis' has been replaced by 'tendinopathy',[1] since histopathological studies confirm structural degenerative changes of the tendon tissue as the key feature, with minimal presence of inflammatory cells.[6,7] Anti-inflammatory treatment options are, therefore, discouraged and these have proven ineffective for tendinopathy.[8]

Eccentric exercise therapy (EET) has strong evidence of effectiveness for PT and is also supported in guidelines by the National Institute for Health and Care Excellence (NICE), London, UK.[9,10] However, EET is pain-provoking and the therapeutic effects on pain and functional outcome are debated when applied during the competitive season.[11] A recent review proposed an alternative exercise therapy for PT consisting of progressive tendon-loading exercises (PTLE) within the limits of acceptable pain.[3] To date, it is unknown how the effectiveness of PTLE compares to EET.

The aim of our stratified, single-blinded, block-randomised controlled trial was to compare PTLE and EET based on clinical outcome after 24 weeks in patients with PT.

METHODS

Trial design

The JUMPER study was a stratified, investigator-blinded, block-randomised controlled trial that included recreational, competitive and professional athletes with PT. The trial was conducted at a university medical centre in The Netherlands. The study protocol was registered on ClinicalTrials.gov (ID: NCT02938143) prior to recruitment. All patients provided written informed consent.

Patient involvement

Patients and public were not involved in the trial design and conduct of the study or the choice of outcome measures. Several national sports federations announced the study with additional advertisements in local sport organisations. Healthcare providers were alerted to the study with conference announcements, information on websites, newsletters and emails.

Patients

Inclusion criteria were: age 18–35 years old; history of knee pain localised in the region of the patellar tendon in association with training and competition; performing sports at least three times a week; tenderness on palpation of the corresponding area on the proximal patellar tendon; structural tendon changes on grey scale ultrasound and/or increased tendon vascularity on power Doppler; and Victorian Institute of Sports Assessment for Patellar Tendons (VISA-P) score <80 out of 100 points.[12,13]

Exclusion criteria were: acute knee or patellar tendon injuries, prior knee surgery without full rehabilitation, known presence of inflammatory joint diseases or familial hypercholesterolaemia, daily use of drugs with a putative effect on the patellar tendon in the preceding 12 months (eg, fluoroquinolones), local injection therapy with corticosteroids in the preceding 12 months, previous patellar tendon rupture, daily exercise therapy with a minimum duration of 4 weeks in total in the preceding 12 months, inability to perform an exercise programme, participation in other concomitant treatment programmes, signs or symptoms of other coexisting knee pathology on physical examination or ultrasound/MRI and contraindications for MRI.

Applicant eligibility was assessed with an initial online screening, including the VISA-P questionnaire and a self-reported pain map to assess the location of pain (figure 1).[14] The screening criteria that needed to be fulfilled were VISA-P score <80 points and the reporting of pain exclusively at the inferior pole of the patella or anywhere along the course of the patellar tendon (figure 1E) in association with physical load. The final eligibility assessment in our hospital to confirm eligibility included first, history taking, completing the VISA-P questionnaire and physical examination performed by one sports physician (R-JdV) with 10 years experience. Activity level was measured using the Cincinnati Sports Activity Scale (CSAS).[15] The clinical examination was regarded positive if tenderness at the inferior patellar pole or patellar tendon could be reproduced on palpation and a single-leg squat. Provocation tests according to the patellofemoral pain consensus statement were performed to exclude patellofemoral pain.[16] Second, eligibility was confirmed by using grey scale ultrasound and power Doppler to increase the likelihood of the clinical diagnosis, performed by a radiologist-in-training with 5 years experience (SJB) under supervision of a senior musculoskeletal radiologist with 16 years experience (EHGO). The ultrasound examination was regarded positive if there was presence

of structural and/or hypoechoic changes and/or tendon thickening (anterior–posterior diameter >6 mm) and/or the presence of intratendinous power Doppler flow.[17]

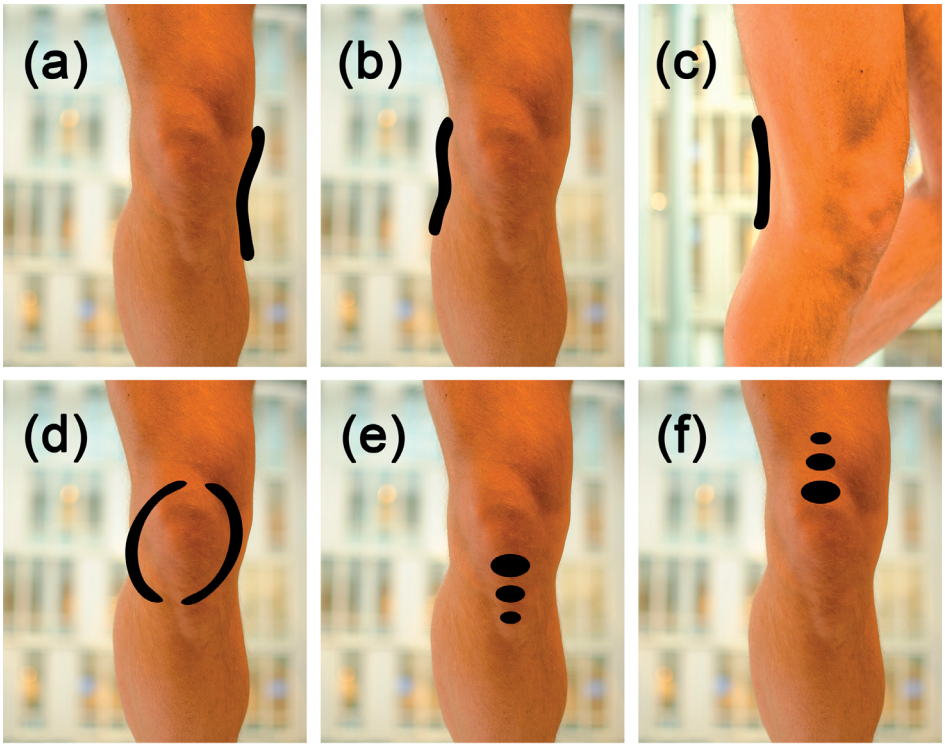

Figure 1: Knee pain map for pain localisation. For the initial eligibility assessment, patients were asked to select one picture describing the location of pain most correctly; either (A) Pain on the medial side of the knee, (B) Pain on the lateral side of the knee, (C) Pain on the backside of the knee, (D) Pain behind and around the patella, (E) Pain directly under the patella or along the course of the patellar tendon or (F) Pain directly above the patella.

Randomisation and blinding

Centralised computer-based randomisation was performed in a 1:1 ratio to PTLE (interventional treatment) or EET (control treatment), using computer-generated block randomisation with a variable block size ranging from 4 to 10. Allocation concealment was ensured by keeping the randomisation list in the care of the sports physician (R-JdV) who was not involved in the follow-up measurements. The allocation sequence was concealed until patients were enrolled and assigned to interventions. The main investigator (SJB) was blinded for the allocated treatment during the entire period of data collection. During the study, patients were requested not to discuss their treatment exercises with the main investigator or the sports physician who instructed the exercise programme. Instead, patients were instructed to consult an independent second sports physician (JZ) if they had any questions regarding the therapy. Stratification was performed to divide the number of patients with early PT (≤6

weeks of symptom duration) from patients with longstanding PT, because it is suggested that early PT has a better prognosis.[18]

Interventions

Patients were randomly assigned to PTLE within the limits of acceptable pain (interventional treatment) or pain-provoking EET (control treatment) during 24 weeks (figure 2). We have provided detailed information regarding the unsupervised exercise programmes in the patient information brochures (online supplemental appendix). Patients could access our dedicated website (http://www.jumperstudie.nl/) with instructional videos that we created in collaboration with a sports physiotherapist (EV).

Patients in the intervention group performed daily isometric (static), isotonic (dynamic), energy-storage (explosive) and sport-specific exercises consecutively, within the limits of acceptable pain (online supplemental appendix). Progressive load was administered based on the individual pain response (Visual Analogue Scale, VAS score ≤3 points on a scale 0–10). This PTLE programme contained four stages, where stage 1 consisted of daily isometric exercises (single-leg leg-press or leg-extension, 5 repetitions of 45 s mid-range (60° knee flexion) quadriceps isometric hold at 70% of maximum voluntary contraction). Stage 2 consisted of the isometric exercises of stage 1 on every first day, and new isotonic exercises performed on every second day. The isotonic exercises were also performed as a single-leg leg-press or leg-extension, and started with 4 sets of 15 repetitions between 10° and 60° of knee flexion and slowly progressed to 4 sets of 6 repetitions with increasing load and knee angles between almost full extension and 90° flexion. Stage 3 consisted of plyometric (energy storage) loading and running exercises (jump squats, box jumps and cutting manoeuvers) on every third day, starting with 3 sets of 10 repetitions using both legs and slowly progressed to 6 sets of 10 repetitions using one leg. Isometric and isotonic exercises were continued on every first and second day, respectively. Stage 4 consisted of sport-specific exercises, which were characteristic for the type of sport (eg, basketball, volleyball). Patients were instructed to gradually return to sport-specific training, performed every 2–3 days to allow for recovery from high tendon-loading exercises. In this stage, the isometric exercises of stage 1 were continued on days that the sport-specific exercises were not performed. Progression to each subsequent stage was defined using individualised progression criteria, based on the level of pain experienced during a pain provocation test that consisted of one single-leg squat. If the VAS-score was 3 or less and exercises of the stage were performed for at least 1 week, progression to the next stage was advised. When all the exercises in stage 4 were performed within the limits of acceptable pain (VAS score ≤3 points), return to competition was recommended. In this phase, stage 1 and 2 maintenance exercises were advised twice per week. The fastest possible time to return to sports was after 4 weeks, according to this PTLE programme. Patients who were allocated to PTLE were financially compensated for a subscription at the gym.

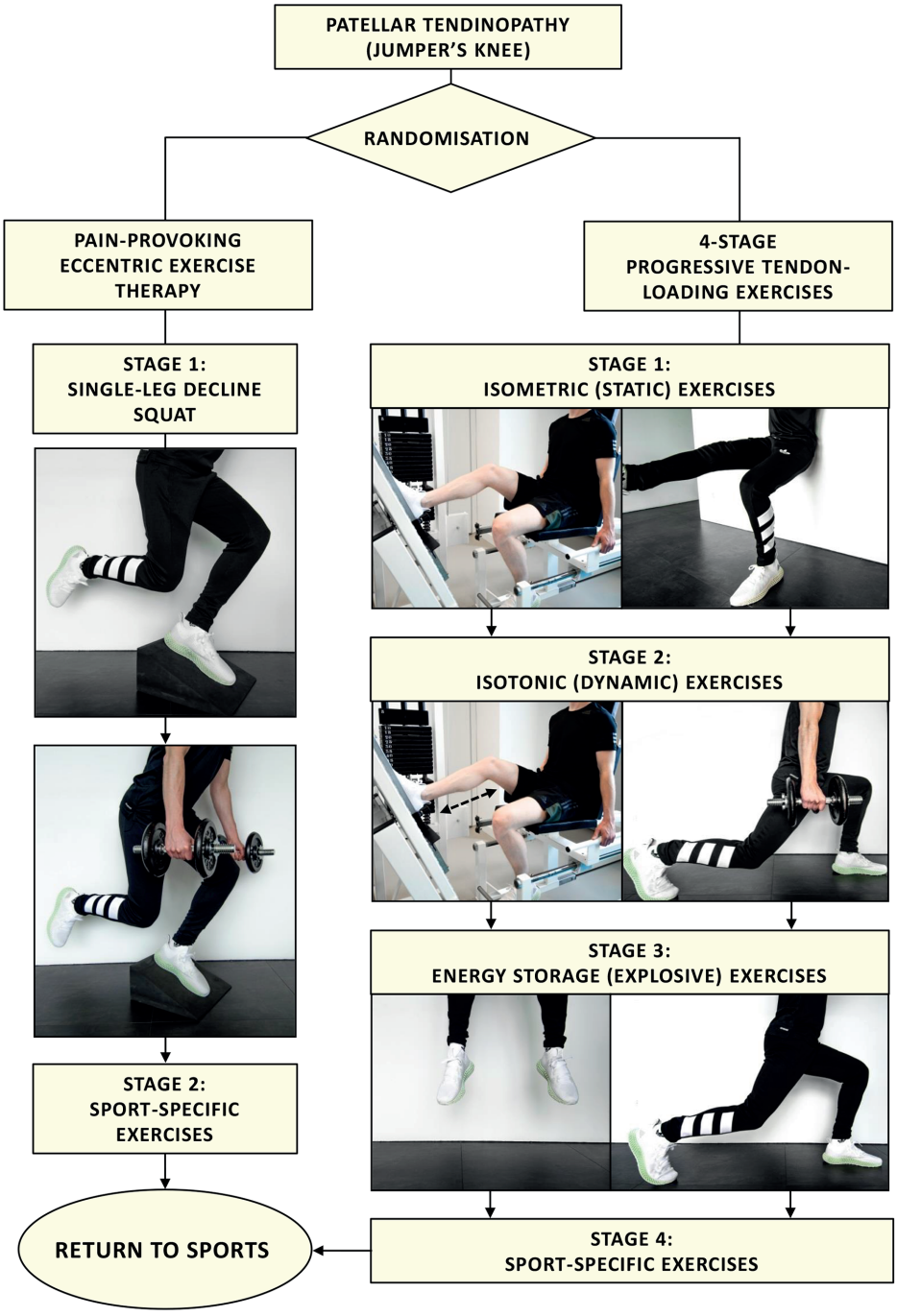

Figure 2: Exercise therapy performed in the PLTE group (intervention) and EET group (control). The exercises illustrated are exemplary images. The complete exercise programme is available in online supplemental appendix. EET, eccentric exercise therapy; PTLE, progressive tendon-loading exercises.

The control treatment was pain-provoking EET, performed twice daily for a duration of 12 weeks (first stage). The eccentric exercises were performed on a decline board with a 25° slope, as described previously.[19] Stage 1 of the EET consisted of a single-leg decline squat, where the downward component (eccentric phase) was performed with the symptomatic leg and the upward component (concentric phase) mainly performed using the contralateral leg. Patients were instructed to perform the exercises with pain (VAS score ≥5 points on a scale 0–10 during the exercises).[11] Additional load in a backpack was advised to increase the intensity of the exercise if no or only minimal pain was experienced when performing the exercises. Stage 2 was initiated if there was complete adherence to stage 1 exercises and when there was acceptable pain during eccentric exercises with additional weights (VAS score ≤3 points on a scale 0–10, the amount of weights was not specified). Stage 2 exercises consisted of sport-specific exercises, which were characteristic for the type of sport. Maintenance exercises consisted of stage 1 exercises twice a week. Patients in the EET group were allowed to return to sports after 4 weeks. We advised to do this if a single-leg squat could be performed within the limits of acceptable pain (VAS score ≤3 points on a scale 0–10). The decline board with a 25° slope was provided for patients allocated to EET.

Patients in both study arms were instructed to perform exercises targeting risk factors for PT in addition to the allocated tendon-specific exercises.[20,21] These exercises targeting risk factors included flexibility exercises of quadriceps, hamstrings, gastrocnemius and soleus muscles, strength exercises for the hip abductor muscles and hip extensor muscles using an elastic resistance band, calf-muscle strengthening exercises and core-stability exercises. The resistance band was provided to each participant. All patients with bilateral symptoms were motivated to perform the exercises for both legs.

All patients received detailed advice and education on tendon care by a sports physician (R-JdV). This included explanation of the condition, expected management, the positive influence of exercise therapy and the positive effects of a gradual return to sports. Specific attention was given to the relation between load and pain using the pain-monitoring model.[22] Modification of all athletic activity (intensity, duration, frequency and type of load) was advised for activities that result in considerable patellar tendon pain, namely either significantly reduced or even avoided for at least 4 weeks. We stimulated to perform (sports) activities within the limits of acceptable pain (VAS score ≤3 points on a scale 0–10).

Outcomes

The primary outcome was the VISA-P questionnaire.[12] This validated and injury-specific questionnaire incorporates pain, function and ability to play sports. A VISA-P score of 100 indicates no pain, maximum function and unrestricted ability to play sports. The VISA-P

questionnaire was self-administered without assistance at baseline, 12 weeks and 24 weeks, after a brief explanation of the questionnaire by the main investigator (SJB).

Secondary outcomes were the return to sports rate, subjective patient satisfaction and exercise adherence. Return to sports was designated as return to desired sports at pre-injury level; return to desired sports, but not at preinjury level; return to sports, but not to desired sport; and no return to sports.[23] Subjective patient satisfaction was categorised into excellent, good, moderate and poor.[23] Exercise adherence was reported descriptively as a percentage of the total number of prescribed training sessions completed. Additional secondary outcomes included the reasons for not performing the tendon-specific exercises and exercises targeting risk factors, number of registered training or match days, pain scores, questionnaires, functional tests and commonly used and advanced imaging methods (online supplemental appendix). All outcomes were collected by one trained examiner (SJB).

At baseline, patients with bilateral symptoms were asked to choose the most painful knee for reporting pain scores. In these cases, all clinical and radiological outcome parameters were obtained for this specific side. At each follow-up visit, patients were reminded to report outcome measures for this initially chosen side. Adverse events were monitored during the trial period. Any adverse events that occurred were discussed at the follow-up visits, and patients were requested to report any adverse events that occurred in-between the follow-up visits by telephone or email to the main investigator (SJB). The use of cointerventions during the study period was discouraged.

Statistical methods

The statistical analysis plan was uploaded on ClinicalTrials.gov before completion of the study. The sample size was calculated at 76 patients to detect a predefined minimum clinically important difference (MCID) of 13 points for the VISA-P questionnaire (power 0.80, two-sided significance level 0.05, and accounting for 10% lost to follow-up).[24] Statistical analyses following an intention-to-treat approach were performed by the main investigator (SJB) under supervision of a biomedical statistician (JZ). Normality of the data was checked visually with Q-Q plots and tested statistically using the Shapiro-Wilk test. Longitudinal data were analysed using generalised estimating equations (GEE), to test for between-group differences in primary and secondary outcomes. In order to test for these between-group differences in relation to the time course of the dependent variables, we included the interaction term 'study arm*visit' in the GEE-model. The visit variable defined the time point at which the measurements were performed (baseline, 12 weeks, 24 weeks). Predefined adjustments were made for baseline variables age, sex, body mass index, symptom duration and CSAS. Bonferroni adjustment was applied for multiple comparisons to reduce the chance of obtaining false-positive results. We performed an additional analysis of the percentage of patients that

achieved the MCID of 13 points or better for the VISA-P.[24] Categorical variables were analysed using Fisher's exact test. Return to sports was dichotomised into return to desired sports at preinjury level and no return to desired sports at preinjury level.[23] The influence of symptom duration prior to intervention on the dichotomised return to sports and subjective patient satisfaction was investigated using adjusted binary logistic regression analysis. Patient satisfaction was dichotomised into satisfied (excellent/good) and dissatisfied (moderate/poor).[23] Adherence to the tendon-specific exercises and exercises targeting risk factors were registered using a weekly online questionnaire. The daily adherence to the tendon-specific exercises and exercises targeting risk factors of the preceding week was registered as a percentage. Imputation of missing data was not performed, because the missingness of data was assumed to occur not at random. Namely, missingness in the outcome depends on the difference between the pain-provoking EET group and the PTLE exercises within the limits of pain, and is related to the true value of the outcome.[25] Instead, post hoc sensitivity analyses were performed following three scenarios (online supplemental appendix). In the worst-case scenario for PTLE, the single missing participant from the PTLE group was assigned the worst outcome of this treatment group (VISA-P score of 43 points and 49 points at 12 weeks and 24 weeks, respectively) while all missing patients from the EET group were assigned the best outcome of their treatment group (VISA-P score of 91 points and 100 points at 12 weeks and 24 weeks, respectively). Statistical analysis was performed using IBM SPSS software V.25 (IBM). Statistical significance was defined as a $p<0.05$.

RESULTS

Between January 2017 and July 2019, a total of 272 applications from potentially eligible athletes with suspected PT were screened, of which 101 athletes were invited for eligibility assessment. Twenty-seven of these athletes were excluded, leaving 76 eligible patients remaining for inclusion (figure 3). The intention-to-treat population consisted of patients with a median (IQR) symptom duration of 2 years (1-4) and 42% had bilateral symptoms. Most patients (82%) underwent prior treatment for PT but failed to recover fully. There were no between-group differences in baseline characteristics, except for a longer symptom duration in the intervention group (119 vs 78 weeks) and more ultrasound-assessed erosions of the inferior patellar border (45% vs 18%) in the intervention group (table 1). An equal majority of the patients (82% in both groups) received therapy prior to the time of study commencement, of which physical therapy was part of the prior therapy in 74% of patients in both groups. Nine patients (12%) were lost to follow-up; 1 in the intervention group and 8 in the control group. Only one of the patients was included for the stratum early tendinopathy (≤6 weeks of symptom duration).

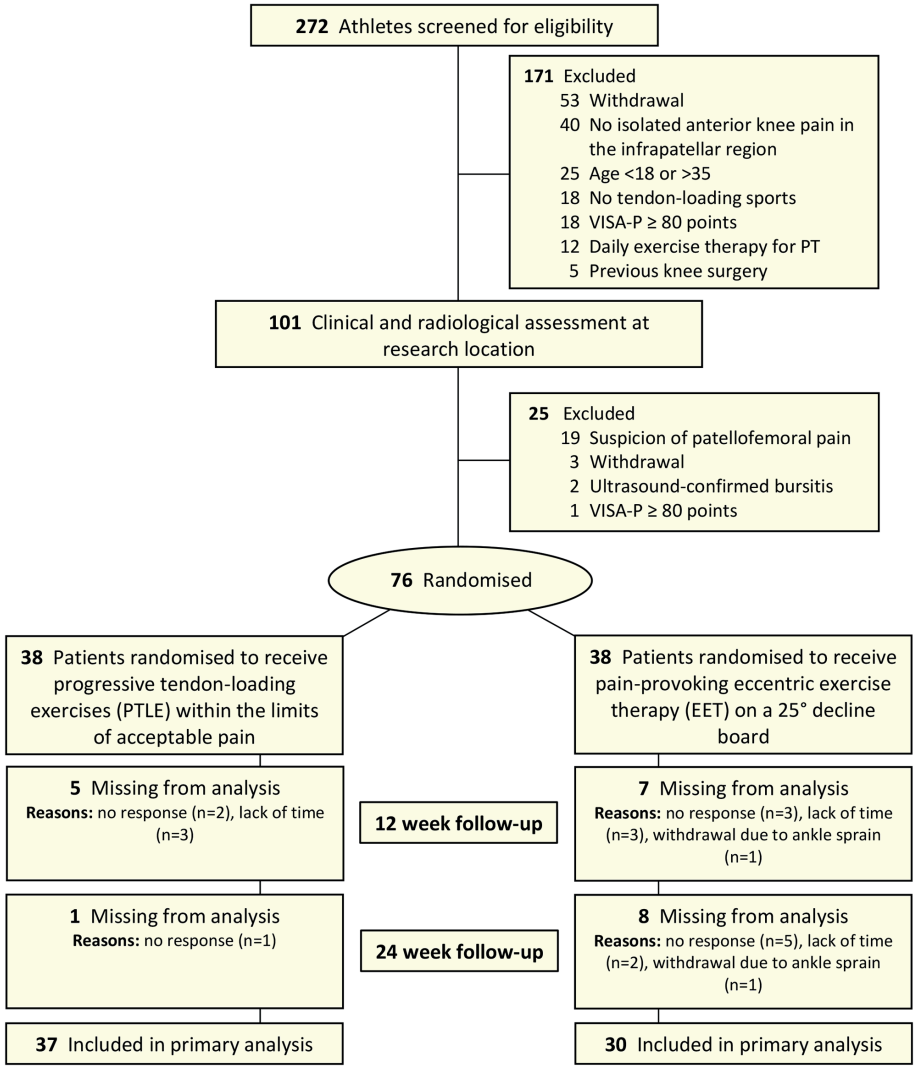

Figure 3: The CONSORT flow diagram. CONSORT, Consolidated Standards of Reporting Trials; PT, patellar tendinopathy; VISA-P, Victorian Institute of Sports Assessment for Patellar Tendons.

Table 1. Baseline Characteristics of the Progressive Tendon-loading Exercise (PTLE) and Eccentric Exercise Therapy (EET) Groups[a]

Characteristics	PTLE group (n = 38)	EET group (n = 38)
Age, mean (SD), years	24 (3.5)	24 (4.2)
Sex, male	31 (82)	27 (71)
BMI, mean (SD)	23.8 (2.5)	24.1 (3.2)
Symptom duration, median [IQR], weeks	119 [64-273]	78 [40-169]
VISA-P score, mean (SD)	55 (13.1)	56 (13.2)

Table 1. Baseline Characteristics of the Progressive Tendon-loading Exercise (PTLE) and Eccentric Exercise Therapy (EET) Groups[a] (*continued*)

Characteristics	**PTLE group (n = 38)**	**EET group (n = 38)**
Cincinnati Sports Activity Scale (CSAS), prior to onset of PT		
Level I (4 to 7 days/week)		
100	10 (26)	7 (18)
95	0 (0)	0 (0)
90	0 (0)	0 (0)
Level II (1 to 3 days/week)		
85	23 (61)	27 (71)
80	5 (13)	4 (11)
Sports participation in desired sport at the time of study commencement, n (%)		
Equal	10 (26)	9 (24)
Reduced	14 (37)	15 (40)
Ceased	14 (37)	14 (37)
Affected side		
Unilateral, left/right, n (%)	10 (53) / 9 (47)	16 (64) / 9 (36)
Bilateral, n (%)	19 (50)	13 (34)
Interventions at the time of study commencement, n (%)		
None	8 (21)	5 (13)
Patellar strap	14 (37)	18 (47)
Foot orthoses	14 (37)	9 (24)
Medical taping	8 (21)	6 (16)
Knee sleeve	5 (13)	2 (5)
Ankle brace	2 (5)	5 (13)
Paracetamol pain killers	3 (8)	3 (8)
NSAIDs pain killers	2 (5)	3 (8)
Knee brace	2 (5)	1 (3)
Cooling	2 (5)	1 (3)
Warming	2 (5)	1 (3)
Prior therapy, n (%)		
None	6 (16)	6 (16)
Physical therapy	28 (74)	28 (74)
Eccentric exercises	6 (16)	5 (13)
Shock-wave therapy	6 (16)	4 (11)
Percutaneous needle electrolysis	2 (5)	5 (13)
Dry needling	4 (11)	2 (5)
Rest	2 (5)	3 (8)
Corticosteroid injections	1 (3)	2 (5)
NSAIDs	1 (3)	1 (3)

Table 1. Baseline Characteristics of the Progressive Tendon-loading Exercise (PTLE) and Eccentric Exercise Therapy (EET) Groups[a] (*continued*)

Characteristics	**PTLE group (n = 38)**	**EET group (n = 38)**
PRP-injections	0 (0)	1 (3)
Histamine iontophoresis	1 (3)	0 (0)
Referral		
Sports Physician	11 (29)	9 (24)
Physiotherapist	16 (42)	21 (55)
General Practitioner	0 (0)	3 (8)
Orthopaedic surgeon	1 (3)	2 (5)
Self-referral	10 (26)	3 (8)
US-assessment		
Patellar tendon thickness, mm ± SD	8.2 ± 2.7	8.6 ± 2.0
Intratendinous Doppler flow, n (%)	33 (87)	36 (95)
Hypoechoic regions, n (%)	38 (100)	38 (100)
Tendon calcifications, n (%)	9 (24)	11 (29)
Patellar erosions, n (%)	17 (45)	7 (18)

[a]Data are presented as No. (%) unless otherwise specified.
Abbreviations: SD, standard deviation; BMI, body mass index, calculated as weight in kilograms divided by height in meter squared; IQR, interquartile range; VISA-P, Victorian Institute of Sports Assessment questionnaire for patellar tendons; CSAS, Cincinnati Sports Activity Scale; NSAIDs, non-steroidal anti-inflammatory drugs; PRP; platelet-rich plasma; US, ultrasound; mm, millimetres.

Primary outcome

The estimated mean VISA-P score improved significantly from 56 (95% CI 52 to 61) at baseline to 84 (95% CI 79 to 89); p<0.001 at 24 weeks in the PTLE group and from 57 (95% CI 53 to 62) to 75 (95% CI 69 to 82); p<0.001 in the EET group (figure 4). The parameter estimate for the 'study arm*visit' interaction using GEE was statistically significant (p=0.023), indicating a different course over time of the VISA-P score between both study arms. The adjusted mean between-group difference in VISA-P score was not significant at 12 weeks (1 (95% CI −6 to 8); p=0.69) and significant at 24 weeks (9 (95% CI 1 to 16); p=0.023), in favour of the PTLE group. Unadjusted VISA-P scores are listed in table 2 and the individual data points of the VISA-P scores are illustrated in figure 5. After performing sensitivity analyses to assess the influence of missing data, except from the worst case scenario, the findings were consistent with those from the primary analysis and thus, leading to a similar conclusion on the treatment effect (online supplemental table S2). After 12 weeks, 16 patients (49%) in the PTLE group and 17 patients (55%) in the EET group achieved the previously reported MCID of 13 points or better for the VISA-P score.[24] After 24 weeks, 32 patients (87%) in the PTLE group and 23 patients (77%) in the EET group achieved the MCID or better. The between-group difference for patients achieving the MCID or better was not statistically different at both 12 weeks (p=0.40) and 24 weeks (p=0.24).

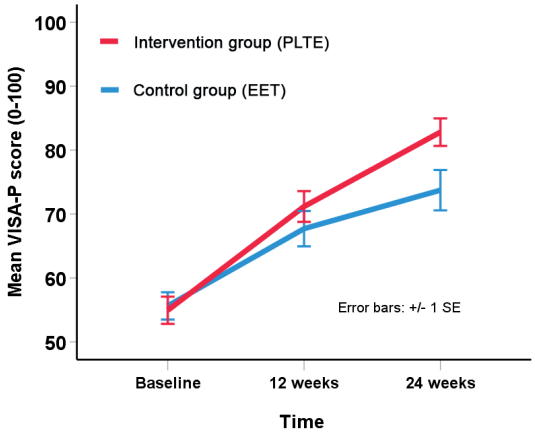

Figure 4: The unadjusted time course of mean VISA-P score in the PTLE group (intervention) and EET group (control). Abbreviations: PTLE, progressive tendon-loading exercises; EET, eccentric exercise therapy. The error bars represent ±1 SE.

Table 2. Main Outcome Measures at 12 and 24 Weeks in the Progressive Tendon-loading Exercise (PTLE) and Eccentric Exercise Therapy (EET) Groups

	PTLE group (n = 38)	**EET group (n = 38)**	**Adjusted mean between-group difference**
Primary Outcome Measure			
VISA-P score, estimated mean (95% CI)[1]			
12 weeks	72.1 (67.0 to 77.2)	70.7 (65.0 to 76.3)	1.4 (-5.5 to 8.3)
24 weeks	84.0 (79.3 to 88.6)	75.2 (69.0 to 81.5)	**8.7 (1.2 to 16.2)**
VISA-P score, unadjusted mean (SD)	**PTLE group (n = 38)**	**EET group (n = 38)**	**Unadjusted mean between-group difference**
Baseline	55.0 ± 13.1	55.6 ± 13.2	-0.6
12 weeks	71.2 ± 13.8	67.7 ± 15.4	3.5
24 weeks	82.8 ± 13.1	73.7 ± 17.3	9.1
Secondary Outcome Measures			
Return to sports, n (%)[2]	**PTLE group (n = 38)**	**EET group (n = 38)**	
No return to sports	2 (6)	3 (10)	
Return to sport, but not in the desired sports	6 (16)	3 (10)	
Return to desired sports, but not at pre-injury level	13 (35)	16 (53)	
Return in the desired sports at pre-injury level	16 (43)	8 (27)	
Subjective patient satisfaction, n (%)[3]			
Poor	1 (3)	1 (3)	
Moderate	6 (16)	4 (13)	
Good	16 (43)	22 (73)	
Excellent	13 (38)	3 (10)	

Table 2. Main Outcome Measures at 12 and 24 Weeks in the Progressive Tendon-loading Exercise (PTLE) and Eccentric Exercise Therapy (EET) Groups (*continued*)

Adherence (%), tendon-specific exercises, estimated mean (95% CI)[1]	**PTLE group (n = 38)**	**EET group (n = 38)**	Adjusted mean between-group difference
0-12 weeks	47.0 (32.7 to 61.2)	53.1 (41.3 to 64.8)	-6.1 (-25.8 to 13.6)
0-24 weeks	40.2 (29.2 to 51.1)	48.6 (36.2 to 60.9)	-8.4 (-25.1 to 8.3)
Adherence (%), exercises targeting risk factors, estimated mean (95% CI)[1]			
0-12 weeks	27.5 (19.4 to 35.6)	28.2 (17.8 to 38.5)	-0.7 (-13.1 to 11.7)
0-24 weeks	21.4 (12.2 to 30.5)	21.6 (10.1 to 33.2)	-0.3 (-14.3 to 13.7)

Abbreviations: PTLE, progressive tendon-loading exercise therapy; EET, eccentric exercise therapy; VISA-P, Victorian Institute of Sports Assessment questionnaire for patellar tendons; CI, confidence interval; SD, standard deviation.

[1]The mean estimated VISA-P score (95% CI) and mean estimated adherence to tendon-specific exercises and exercises targeting risk factors are denoted for the PTLE and EET group. These scores and the adjusted mean between-group differences were calculated using Generalised Estimating Equations (GEE) with adjustments for the following pre-defined baseline variables: age, sex, BMI, symptom duration and Cincinnati Sports Activity Scale. Positive mean adjusted between-group differences favour the PTLE-group. A statistically significant adjusted mean between-group difference was found after 24 weeks (*P*=.023). No significant adjusted mean between-group differences were found for adherence to tendon-specific exercises after 12 weeks (*P*=.54) and 24 weeks (*P*=.33) and for adherence to exercises targeting risk factors after 12 weeks (*P*=.91) and 24 weeks (*P*=.97).

[2]The number of participants (%) is denoted for the PTLE and EET group. For analysis purposes, return to sports was dichotomised into "return to desired sports at pre-injury level" and "no return to desired sports at pre-injury level". No statistically significant differences were found between both treatment groups after 12 (*P*=.12) and 24 weeks (*P*=.13).

[3]The number of participants (%) is denoted for the PTLE and EET group. For analysis purposes, subjective patient satisfaction was dichotomised into "satisfied" and "dissatisfied". No statistically significant differences were found between both treatment groups after 12 weeks (*P*=.14) and 24 weeks (*P*=.54).

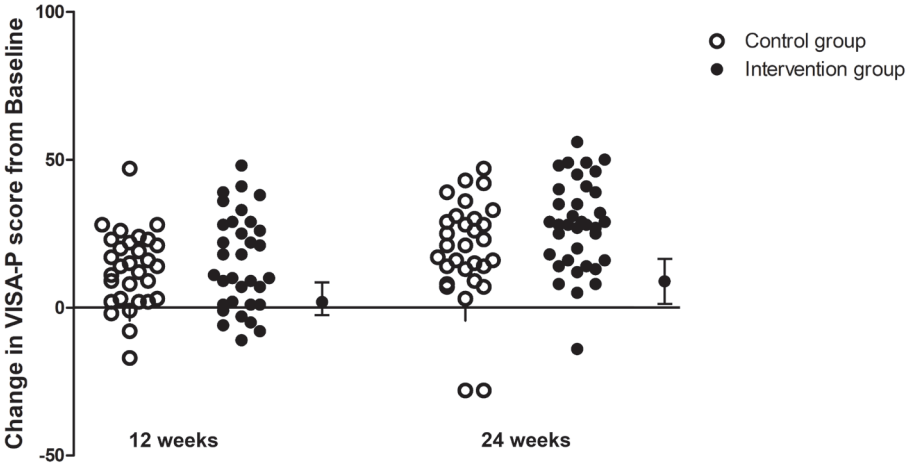

Figure 5: Individual changes in the VISA-P score from baseline in patients in the PLTE group (intervention) and EET group (control). Unadjusted individual changes in VISA-P score are shown after 12 weeks and 24 weeks exercise therapy. Adjusted mean between-group differences from baseline to 12 and 24 weeks are shown with 95% Cis. EET, eccentric exercise therapy; PLTE, progressive tendon-loading exercise; VISA-P, Victorian Institute of Sports Assessment for Patellar Tendons.

Secondary outcomes

In the PTLE group, 21% (n=7) returned to the desired sports at preinjury level after 12 weeks and 43% (n=16) after 24 weeks. In the EET group, 7% (n=2) returned to the desired sports at preinjury level after 12 weeks and 27% (n=8) after 24 weeks. The dichotomised return to sports was not statistically different between both groups at 12 weeks (p=0.13) and 24 weeks (p=0.16). The return to sports rate after 12 weeks (p=0.12) and 24 weeks (p=0.25) was not influenced by the symptom duration prior to the interventions. After 12 weeks, 79% (n=26) of the patients were satisfied with the clinical outcome in the PTLE group and 63% (n=19) in the EET group. After 24 weeks, this was 81% (n=30) in the PTLE group and 83% (n=25) in the EET group. The dichotomised patient satisfaction was not statistically different between both groups at 12 weeks (p=0.18) and 24 weeks (p=0.81). The percentage of patients with an excellent satisfaction was significantly higher in the PTLE group (38%) than in the EET group (10%) (p=0.009). Subjective patient satisfaction after 12 weeks (p=0.58) and 24 weeks (p=0.14) was not influenced by the symptom duration prior to the interventions. Adherence to the tendon-specific exercises was not statistically different between the PTLE group and EET group after 12 weeks (p=0.54) and 24 weeks (p=0.33). Adherence to the exercises targeting risk factors was also not statistically different between the PTLE group and EET group after 12 weeks (p=0.91) and 24 weeks (p=0.97). The commonly used and advanced imaging outcomes are included in online supplemental appendix.

Adverse events

No serious adverse events occurred while performing the specific exercises of PTLE and EET during the trial. Two patients sustained ankle sprains while playing sports during the follow-up period. No patients reported using cointerventions during the study period.

Additional secondary outcomes

The additional secondary outcomes in the PTLE and EET groups are listed in online supplemental table S1. The VAS for pain (scale 0–10) related to tendon-specific exercises at 24 weeks was significantly lower in the PTLE group than in the EET group with an estimated mean of 2 vs 4 (adjusted mean between-group difference: 2 (95% CI 1 to 3); p=0.006). There were no significant between-group differences in any of the other additional secondary outcomes.

DISCUSSION

In this randomised controlled clinical trial of patients with PT, PTLE provided superior clinical outcomes compared with EET after 24 weeks follow-up.

The improved performance of PTLE is important and clinically relevant as EET is commonly used in clinical practice and currently the recommended therapy in some guidelines (eg, NICE guidelines).[9] Our findings also indicate that PTLE is still beneficial in patients who previously did not improve during prior treatment for PT. We, therefore, recommend a PTLE programme with additional exercises targeting risk factors, load management and patient education as the basis of treatment for physically active patients with PT.

Additional benefits of PTLE were that there was a trend towards a higher return to sports rate compared with EET (43% vs 27%) and that the exercises were significantly less painful to perform (VAS 2 vs 4). The percentage of patients with an excellent satisfaction was also significantly higher in the PTLE group (38% vs 10%). Both treatments involve performing rehabilitation exercises and in practice it would seem logical to opt for the most effective programme.

A suggested reason for the superiority of PTLE is the introduction of isometric exercises, which are considered to immediately reduce pain and facilitate muscle strengthening using isotonic exercises in the subsequent phase, due to an exercise-induced decrease in pain sensitivity.[26] Yet, recent well-designed studies did not detect this supposed effect.[27] In our study, the major between-group difference was found in the latter half of the exercise programme. This suggests that the phase of energy-storage loading is important to implement before starting the sport-specific exercises.

However, from a critical point of view, less than half of the patients returned to sports at preinjury level after performing PTLE for 24 weeks. Furthermore, despite the positive trend, the difference in return to sports rate with EET was not statistically significant. Also, the difference in patients achieving the predefined MCID after 12 weeks (49% vs 55%) and 24 weeks (87% vs 77%), was not statistically different between both groups. This implicates that there is room for improvement of the current unsupervised PTLE programme, for example, with guidance from a sports physiotherapist. Even with the substantial time investment for patients in both exercise groups, satisfaction after 24 weeks was fairly low. The possibility that a more rapid return to sports at preinjury level through a PTLE programme supervised by a physiotherapist should be investigated.

This is the largest clinical trial in patients with PT to date. Another strength is the comprehensive physical examination and ultrasound confirmation for the diagnosis of PT before enrolment. The outcome measures were extensive and included both clinically used and recently proposed advanced imaging methods.[28,29] The interventions were provided using a single consultation with web-based support, making the intervention feasible and generalisable for future implementation.

This study has several limitations. First, inherent in the interventions, blinding of the intervention was not possible for the study patients. However, blinding of the main investigator for the allocated treatment and blinding of the sports physician, radiologist and biostatistician for the clinical outcome was performed. Second, the finding of a better clinical outcome in patients performing PTLE no longer holds if the worst case scenario of the sensitivity analysis of missing data was correct. However, because this worst-case scenario is unlikely, we are confident the advantage of PTLE over EET will be maintained. Third, according to our predefined protocol, we adhered to stratifying patients with early PT vs longstanding PT. We expected a large number of patients with early (short duration) PT who did not yet start exercise therapy. Most patients, however, had longstanding symptoms and had been treated with exercise therapy for either a short period or longer than 12 months ago. Fourth, we observed a substantial spread of individual data points regarding the clinical outcome, indicating that the results of the proposed exercise programme may vary between subjects. This emphasises the importance of an individualised treatment approach. Fifth, the study population consisted of a mix of recreational and competitive athletes, and results could be more specific to either population if the study was more uniform. Finally, this study involved unsupervised exercise therapy, and results may be improved by using a supervised programme.

This study emphasises the importance of exercise therapy for the conservative treatment of patients with PT. Despite the chronicity of symptoms in the patients included in this trial, the large number of patients with bilateral symptoms from PT (42%) and the failure of conservative treatment prior to the time of study commencement (82%), patients in both treatment groups demonstrated improvement in pain, function and ability to play sports. A majority of the patients achieved the MCID or better after 24 weeks, even despite a limited adherence to the exercise programmes (40% for PTLE and 49% for EET).

CONCLUSION

In this trial among patients with mostly chronic PT, treatment with PTLE is superior to EET, despite presence of chronic symptoms and the previous conservative treatment in the majority of patients. These findings support the use of PTLE in the conservative treatment of PT.

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SUPPLEMENTARY APPENDIX

Information brochure for participants allocated to progressive tendon-loading exercises (PTLE) consisting of 4 stages.

Why exercise therapy?

Exercise therapy is an effective treatment for pain reduction and considered as the first treatment of choice for patellar tendinopathy. Conservative treatment approaches are directed at effecting changes in patellar tendon structure. Accordingly, the patellar tendon adapts to this specific loading. Inherent to the slow metabolic rate of tendons, the response to exercise therapy is usually slow, both in improving load capacity and in resolving pain.

Why progressive loading exercise therapy?

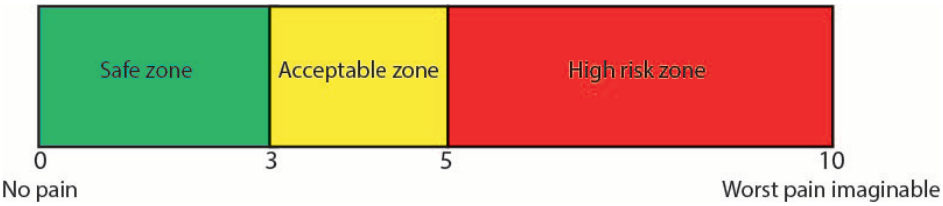
The rehabilitation process of patellar tendinopathy is designed in 4 subsequent stages – the isometric stage, isotonic stage, energy-storage stage and sport-specific exercises. These stages involve slowly progressive loading, in order to develop load tolerance of the patellar tendon before returning to sports. The duration of each stage is flexible, and determined by individual response to the isometric, isotonic or energy-storage exercises. The pain response is evaluated after 24 hours of exercise therapy using the single-leg squat pain provocation test.

Single-leg squat pain provocation test

The level of pain 24 hours after exercise is monitored using this pain provocation test. This test is administered daily, at the same time of the day, throughout the entire duration of the exercise therapy. The eccentric (downward) phase of the single-leg squat is performed by squatting down while keeping the elevated leg off the floor and a straight back. Then slowly flex the symptomatic knee to 90° or maximum angle allowed by pain. The concentric (upward) phase is performed by using both legs. The pain level that is considered acceptable is a pain rating of 3/10 or less (a score of 0 points is no pain and 10 points is the worst pain imaginable).

Pain during the exercise programme?

The exercises may induce muscle soreness, however, there should only be mild discomfort during the exercises. The level of pain that is accepted during exercise therapy and 24 hours after exercise is 3/10 or less. If the exercises provoke more pain and the symptoms persist after the performance of the exercises, the intensity of the exercises should be reduced by performing fewer repetitions and/or by reducing additional weight. If this does not resolve symptoms to the previous level, the specific exercises should be ceased temporarily. We advise continuing the exercises that can be performed without pain.



Training and competition during the exercise programme?

Modification of athletic activity (intensity, duration, frequency and type of load) will be necessary for activities that result in considerable patellar tendon pain throughout the 4 stages of the exercise programme. This means that sports activities with high patellar tendon loading or repetitive energy storage and release, such as jumping/landing, acceleration/deceleration and cutting should be significantly reduced or even avoided if this results in knee pain. These provoking sports activities should be stopped or adapted for at least 4 weeks.

Stages of the exercise programme and progression criteria

Participants will perform a 4-stage criteria-based exercise protocol within the limits of pain. This means that a maximum pain level (3/10 or less) will be maintained during all stages of the exercise programme. Each of the stages has specific goals, from reducing patellar tendon pain to increasing strength and introducing energy-storage loads. Individualized progression criteria will define the duration of each subsequent stage.

Stage 1 – Isometric stage

In the first stage, isometric loading of the patellar tendon will be applied with the aim to reduce and manage patellar tendon pain. In this stage, reduction of provoking athletic activity is advised and symptoms should resolve within 24 hours after exercise. Typically, this stage takes 1-2 weeks but may last longer in athletes with a high level of pain.

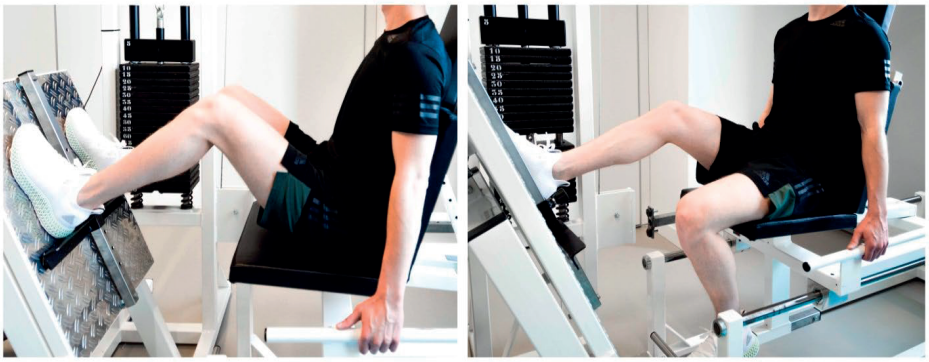
Exercises and dosage:

- Daily single-leg isometric exercises using a leg extension (preferentially) or leg press machine in mid-range knee flexion (around 60° of knee flexion), 5 repetitions of 45 seconds (with 2 minutes rest); progress to 70% maximum voluntary contraction (MVC).
- An alternative exercise that can be performed, only when no leg extension or leg press machine is available, is the isometric wall sit exercise (eventually increase the intensity of the exercise by adding external weights).
- Start with the exercises targeting risk factors for 3 times/week (Supplement 1c).

Progression criteria – Stage 2 can be initiated when:

- Stage 1 exercises can be performed within the acceptable levels of pain (3/10 or less) during 1 week
- The provocation test can be performed within the acceptable levels of pain (3/10 or less)

STAGE 1: ISOMETRIC LEG PRESS



Steps:

1. Start off sitting on a leg press machine or leg extension machine with both feet shoulder width apart against the footplate (or position both legs under the padded bar for the leg extension). Grasp the handle grips and keep your entire back firmly set against the seat for stability during the exercise.
2. Push the weight until your knees make a flexion angle of 60°. Then hold the weight for 45 seconds with only one leg, and leave the contralateral leg resting during the exercise.
3. After 45 seconds, place the contralateral leg on the footplate again and return back to the starting position using both legs.
4. Progress the weight in 5 repetitions of 45 seconds to 70% of the maximum voluntary contraction load (MVC) and rest for 2 minutes between the repetitions. Make sure to train both legs separately.

Tip: The 70% MVC load is approximately the maximum weight that can be held for 45 seconds. The MVC can be estimated using standard tables based on the maximum number of repetitions using a specific weight: https://krachttraining.info/1-rm-calculator/.

STAGE 1: ISOMETRIC WALL SIT

This exercise is an alternative for the isometric leg press or leg extension exercises.

Steps:

1. Start off sitting with your back flat against the wall. The feet are shoulder width apart and the knees are above the ankles.
2. Slide your back down the wall, until the knees are flexed in 90°.
3. Extend one leg and hold this position for 45 seconds, repeat this 5 times.
4. Rest standing upright for 2 minutes between the repetitions. Make sure to train both legs.

Tip: To increase the intensity of the exercise, you can hold a weight in different positions (guided by the maximum load that can be held for 45 seconds).

Stage 2 – Isotonic stage

In this second stage, isotonic loading will be applied to restore lower extremity strength through functional ranges of movement. Initially, isotonic exercises should be performed within 10-60° of knee flexion and can be progressed with increased loading and finally, towards 90° of knee flexion within the limits of pain.

Exercises and dosage:

- Every second day, single-leg isotonic exercises using a leg press (preferentially) or leg extension machine.

- Initiate with loading that can be performed in 4 sets of 15 repetitions (with 2 minutes rest) within 10-60° of knee flexion, and progress to heavier loading (6 repetition maximum; RM) if the exercises can be performed within the limits of pain.
- Then increase the range of motion towards 90° of flexion and fully extended leg (without locking or hyperextending the knee) as pain permits in 4 sets of 15 repetitions (15RM) and progress again to heavier loading (6RM).
- Alternative exercises that can be performed when no leg extension or leg press machine is available, are the walking lunge and step up exercises.
- Continue the exercises targeting risk factors for 3 times/week (Supplement 1c).

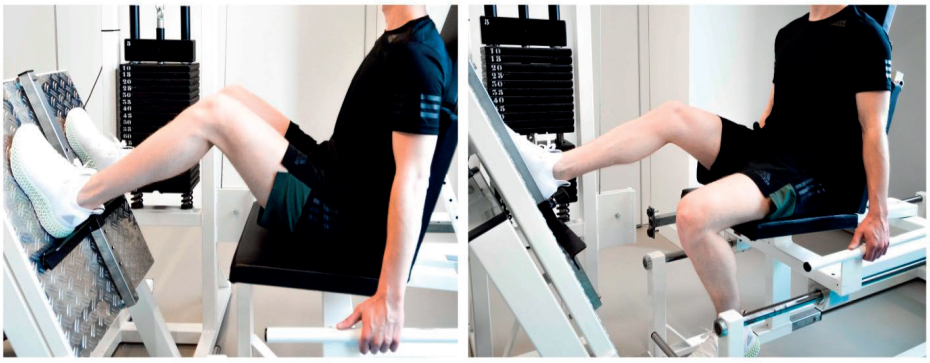
Maintenance exercises:

- Stage 1 exercises (isometric leg extension or leg press) are continued on the days when stage 2 exercises are not performed.

Progression criteria – Stage 3 can be initiated when:

- Stage 2 exercises can be performed within the acceptable levels of pain (3/10 or less) during 1 week
- The provocation test can be performed within the acceptable levels of pain (3/10 or less)
- The strength in both legs is similar, as measured by the weight that can be pushed away during the isotonic exercises. If there are bilateral symptoms, another guideline can help. In these cases. approximately 100-150% of the body weight can be accepted as sufficient external weight during the single-leg isotonic exercises. Multiply the body weight by 1.0 to 1.5 and set this weight on the leg press at the end of this stage. It should be possible to push this weight on the leg press machine in a series of 4x6 repetitions within the acceptable levels of pain (3/10 or less).

STAGE 2: ISOTONIC LEG PRESS



Steps:

1. Start off sitting on a leg press machine (or leg extension machine) with both feet shoulder width apart against the footplate (or position both legs under the padded bar for the leg extension). Grasp the handle grips on the machine and keep your entire back firmly set against the seat for stability during the exercise.
2. Push the weight with one leg to a flexion angle of 60°. Then briefly pause and slowly bring the weight back to the starting position, approximately 10° of knee flexion. Add enough weight that you can do maximum 15 repetitions (15RM). Leave the contralateral leg resting during the exercise.
3. Initiate with loading that can be performed in 4 sets of 15 repetitions. Progress the weight in 4 sets of 6 repetitions when the exercises can be performed within the acceptable limits of pain. Make sure to train both legs separately.
4. Increase the intensity of the exercise by first increasing the weight to 6RM. When heavy weights (similar to the asymptomatic leg or approximately the body weight) can be used within the limits of pain, lower the weights to the amount used with the 4 x 15 repetitions. Then increase the range of motion, by performing the exercise with a flexion angle of 90° to fully extended leg, without locking or hyperextending the knee.

Tip: First increase the load within 10-60° of knee flexion angles and then decrease the load again before starting exercises towards 90° of knee flexion and full knee extension within the limits of pain. Within this wide range, weights can be further progressed to values similar to the asymptomatic leg or to approximately the body weight.

STAGE 2: WALKING LUNGE & STEP UPS

These exercises are an alternative for the isotonic leg press or leg extension exercises.

WALKING LUNGE

Steps:

1. Start standing upright with your feet shoulder-width apart.
2. Step forward with one leg and lower down until the front knee is flexed to 90°.

3. Without moving the front leg, step forward with the contralateral leg and repeat the lunge.
4. Increase the intensity of the exercise by adding weight in a backpack or use dumbbells.

STEP UPS

Steps:

1. Approach the box and step up by placing one foot on the box.
2. Then stretch the standing leg on the box and lift the contralateral leg up in the air to a hip flexion angle of 90°.
3. Step off the box on the same side.
4. Increase the intensity of the exercise by increasing the box height (if possible) or by adding weight in a backpack or dumbbells.

Stage 3 – Energy-storage stage

In this third stage, energy-storage loads are introduced when lower extremity muscle strength is restored using the isotonic exercises. The goal is to further increase the load tolerance of the patellar tendon and to improve power. The type of energy-storage loading exercises will be individualized to the sports performed by the athlete. For example, basketball players and volleyball players will focus more on jumping and landing, whereas football players or field hockey players will focus more on acceleration/deceleration and cutting abilities. We advise to initiate with jump squats and split jump squats for all athletes.

Exercises and dosage:

- Every third day: jump squats, split jump squats, box jumps, interval runs or zig-zag runs.
- Initiate with loading that can be performed in 3 sets of 10 repetitions (with 2 minutes rest) and progress to landing on 1 instead of 2 legs for the jumping exercises and from interval runs to zig-zag runs.
- Then increase the loading by increasing the jump height for the jumping exercises and to higher speeds for the running exercises.
- Finally, increase the load by slowly progressing to 6 sets of 10 repetitions or remove the approach run for the running exercises so that the explosive running is initiated from a standstill.
- Continue exercises targeting risk factors for 3 times/week (Supplement 1c).

Maintenance exercises:

- Stage 1 exercises (isometric exercises) are continued on each first day after stage 3 exercises are performed.
- Stage 2 exercises (isotonic exercises) are continued on each second day after stage 3 exercises are performed.

Progression criteria – Stage 4 can be initiated when:

- Stage 3 exercises can be performed within the acceptable levels of pain (3/10 or less) during 1 week
- The provocation test can be performed within the acceptable levels of pain (3/10 or less)

STAGE 3: ENERGY-STORAGE EXERCISE

JUMP SQUAT

Steps:

1. Start standing upright with your feet shoulder-width apart.
2. Squat down while keeping your chest upright, and your head facing forward.
3. Initiate an explosive jump upwards and jump as high as you can.
4. Use your arms to add extra momentum into the jump (try to touch the ceiling!)
5. To increase the intensity of the exercise, adapt the exercise by first landing using only one leg and then increase your jump height.

Tip: Inhale as you descend into the squat and exhale as you jump.

Always keep your lower back straight and your hip in flexion during the landing phase!

SPLIT JUMP SQUAT

Steps:

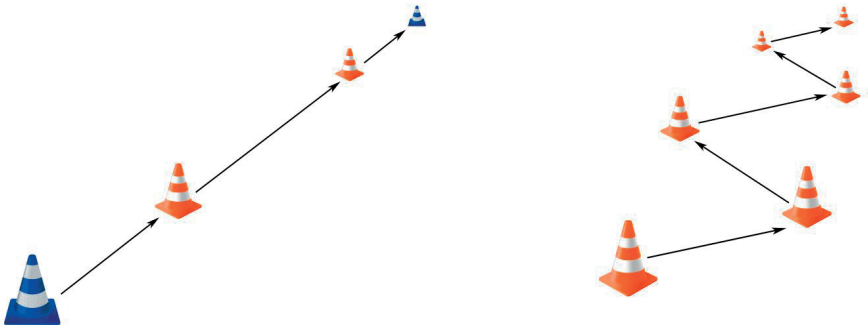
1. Start standing upright with your feet standing shoulder-width apart.
2. Initiate an explosive jump and land in a split squat position (as illustrated).
3. Without pausing, jump again and reverse the position of your legs.
4. To increase the intensity of the exercise, first increase the amount of sets performed from 3 to 6 and then increase your jump height.

BOX JUMPS

Steps:

1. Start standing upright with your feet standing shoulder-width apart, at a comfortable distance from the box.
2. Initiate an explosive jump and land softly on the box in a squat position (as illustrated).
3. The knee flexion angle should be minimal 60° (as illustrated) or greater (towards 90° knee flexion).
4. Without pausing, jump again and land in a squat position, in front of the box.
5. Use your arms to add extra momentum into the jump.
6. To increase the intensity of the exercise, first adapt the exercise by using only one leg and then increase the jump height.

Tip: Try to land softly on the box, don't let your feet make a lot of noise on landing.



RUNNING EXERCISES

INTERVAL RUNS

1. Approach the first cone (blue) and start jogging to the first orange cone (5 meters).
2. When approaching the orange cone, start to increase running speed until the second orange cone (30 meters). Begin with 60% of your maximum sprint speed.
3. Jog to the last (blue) cone and rest for 2 minutes before repeating the exercise.
4. Increase the intensity of the exercise by increasing your sprint speed gradually to 100%.

ZIG-ZAG RUNS

1. Approach the first cone and sprint from cone to cone.
2. Before approaching the first cone, start jogging for 5 meters as in exercise A).
3. Increase the intensity of the exercise by increasing your sprint speed and by removing the blue cones (start sprinting from a standstill).

Stage 4 – Sport-specific exercises

Athletes can gradually return to sport-specific training when all the relevant energy-storage exercises of stage 3 can be performed without provocation of knee symptoms during exercise and 24 hours after performing stage 1-2-3 exercises. The sport-specific exercises are ideally performed every 2-3 days, to allow for recovery from high tendon loading exercises. The type of sport-specific exercises will be individualized to the sports performed by the athlete. For example, basketball players could focus more on dribbling, jumping and cutting with the ball. Football players will focus more on shooting and passing exercises. If these individual exercises are not provoking pain, players could initiate group training (start 30 minutes of low intensity group training and gradually increase training time and intensity). When a minimum of 3 full group trainings can be done within the acceptable limits of pain, return to match play is allowed.

Return to competition:

- Returning to competition is only advised when the provocation test 24 hours after a minimum of 3 full group trainings can be performed within the acceptable levels of pain (3/10 or less);

Maintenance exercises:

- Continue to perform the stage 2 exercises (isotonic leg press) for at least 2x/week.
- Continue to perform the exercises targeting risk factors (Supplement 1c).

Information brochure for participants allocated to heavy-load eccentric exercise therapy (EET).

Why exercise therapy?

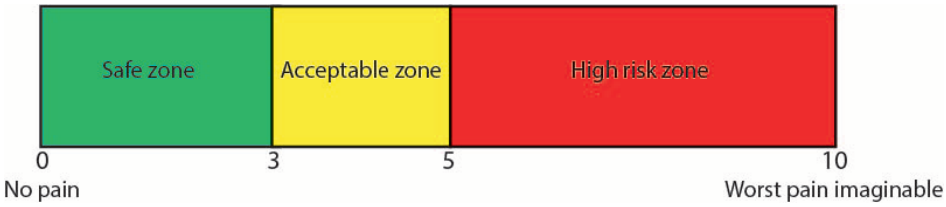
Exercise therapy is an effective treatment for pain reduction and considered as the first treatment of choice for patellar tendinopathy. Conservative treatment approaches are directed at effecting changes in patellar tendon structure. Accordingly, the patellar tendon adapts to this specific loading. Inherent to the slow metabolic rate of tendons, the response to exercise therapy is usually slow, both in improving load capacity and in resolving pain.

Why eccentric exercise therapy?

The single-leg decline squat exercise consists of a downward eccentric component performed on the symptomatic leg and an upward concentric component using mainly the contralateral leg. The exercise is typically performed on a 25° decline board to target the knee extensor mechanism more specifically than a regular squat. Studies using eccentric exercise protocols have shown positive effects. Therefore, these painful heavy-load exercises are currently considered as standard care.

Pain during the exercise programme?

The single-leg decline squat should be performed with pain. A pain scale can be used for this purpose, with a score of 0 points reflecting no pain and 10 points as the worst pain imaginable. The minimum pain score should be 5 out of 10 during the eccentric exercises in order to be effective. If the exercises provoke persisting symptoms for more than 24 hours after the performance of the exercises and problems with normal daily functioning, the intensity of the exercises should be reduced by performing fewer repetitions and/or by reducing additional weight.



Training and competition during the exercise programme?

Modification of athletic activity (intensity, duration, frequency and type of load) will be necessary for activities that result in considerable patellar tendon pain. This means that activities with high patellar tendon loading or repetitive energy storage and release, such as jumping/landing, acceleration/deceleration and cutting abilities should be significantly reduced or

even avoided if this results in knee pain. These provoking sports activities should be stopped or adapted for at least 4 weeks.

Stages of the exercise programme and progression criteria

Participants will perform a 2-stage criteria-based exercise protocol. In the first stage, heavy-load eccentric training will be applied for recovery from the knee pain. Then, sport-specific exercises will be applied in stage 2 before returning to sports.

Stage 1 – Eccentric exercises on a decline board

In this first stage, eccentric loading will be applied to restore the lower extremity strength through functional ranges of movement and with the aim to improve tendon structure. The eccentric exercises should be performed on a decline board and provoke pain during and shortly after performing the exercises.

Exercises and dosage:

- Twice-daily single-leg decline squat (around 90° of knee flexion), 3 sets of 15 repetitions per leg.
- Perform the exercises for at least 12 consecutive weeks.
- These exercises should be performed with pain (VAS ≥ 5/10). When the exercises are not painful to perform, increase the load by adding weights in a backpack or by using dumbbells.
- Start with the exercises targeting risk factors for 3 times/week (Supplement1c).

Progression criteria – Stage 2 can be initiated when:

- The eccentric exercise therapy has been performed conscientiously for least 3 consecutive weeks.
- The single-leg decline squat can be performed with a maximum pain score of 3 out of 10 over 1 week using external weights.

SINGLE-LEG DECLINE SQUAT

Steps:

1. Start upright with both feet standing on the 25° decline board.
2. Remove one leg from the decline board and perform a single leg squat in 3 seconds until 60° of knee flexion.
3. Then place the contralateral leg again on the decline board and use mainly the contralateral leg to come back to an upright position.
4. To increase the load of the exercise, add weight in a backpack or use dumbbells. Start with 5 kg external weight.

Tip: This exercise should be performed with discomfort (VAS ≥ 5/10).
No pain, no gain!

Stage 2 – Sport-specific exercises

Athletes can gradually return to sport-specific training when the single-leg decline squat exercises of stage 1 can be performed without provocation of knee symptoms during exercise and 24 hours after performing stage 1 exercises. The sport-specific exercises are ideally performed every 2-3 days to allow for recovery from high tendon loading exercises. The type of sport-specific exercises will be individualized to the sport performed by the athlete. For example, basketball players could focus more on dribbling, jumping and cutting with the ball. Football players will focus more on shooting and passing exercises. If these individual exercises do not provoke pain, players could initiate group training (start 30 minutes of low intensity group training and gradually increase training time and intensity). When a minimum

of 3 full group trainings can be done within the acceptable limits of pain, return to match play is allowed.

Return to competition:

- Returning to competition is only advised when the single-leg decline squat 24 hours after a minimum of 3 full group trainings can be performed within the acceptable level of pain (3/10 or less);

Maintenance exercises:

- Continue to perform the single-leg decline squat exercises for 2x/week.
- Continue to perform the risk factor exercises for 3x/week (Supplement 1c).

Information brochure for exercises targeting risk factors, applicable to both study arms.

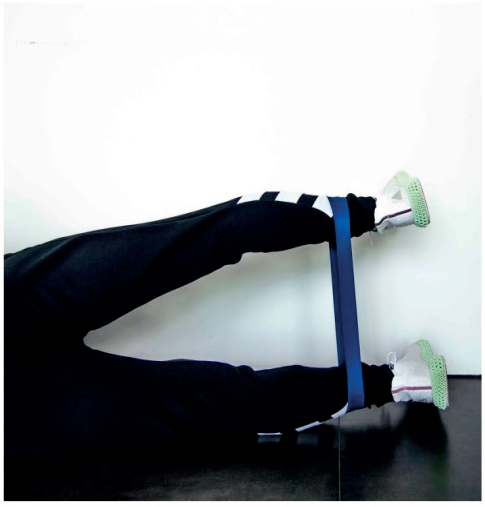
Exercises targeting risk factors

STRETCHING EXERCISES

Steps:

A) STANDING QUADRICEPS STRETCH EXERCISE – 3x/week, 3x 30 seconds
B) STANDING HAMSTRING STRETCH EXERCISE – 3x/week, 3x 30 seconds
C) CALF STRETCH (GASTROCNEMIUS) EXERCISE – 3x/week, 3x 30 seconds
D) CALF STRETCH (SOLEUS) EXERCISE – 3x/week, 3x 30 seconds

Tip: Don't forget to warm up for 10 minutes before stretching and only stretch to the point of mild discomfort.



RESISTANCE BAND EXERCISES

A) HIP ABDUCTOR STRENGTHENING EXERCISE – 3x/week, 3x 15 repetitions

B) HIP EXTENSOR STRENGTHENING EXERCISE– 3x/week, 3x 15 repetitions

Tip: Hold the outer range position for one second before slowly returning to the starting position in 3 seconds. When the exercises are easy to perform, increase the resistance by changing the resistance band to one with a heavier tension level.

SINGLE LEG BRIDGE

A) STATIC EXERCISE – 3x/week, 3x 30 seconds

B) DYNAMIC EXERCISE – 3x/week, 3x 15 repetitions

Tip: Hold the body in a straight line with the static exercise and outer range position of the dynamic exercise. When the exercises are easy to perform, increase the resistance by holding an external weight in front of the pelvis.

CALF STRENGTHENING EXERCISES

Steps:

A) STANDING CALF RAISE EXERCISE – 3x/week, 3x 15 repetitions

B) SEATED CALF RAISE EXERCISE – 3x/week, 3x 15 repetitions

Tip: Move through a complete range of motion of the ankle. When the exercises are easy to perform, increase the resistance by performing the exercises with single leg or add external weights.

ADDITIONAL SECONDARY OUTCOMES

Compliance

Compliance to the tendon-specific exercises and exercises targeting risk factors were registered using a weekly online questionnaire, in which the daily adherence to the tendon-specific exercises and exercises targeting risk factors of the preceding week was registered as a percentage. Accordingly, the average weekly compliance was analysed and presented for the first 12 weeks of the intervention period and for the total follow-up duration of 24 weeks. The questionnaire also included the reasons for not performing the tendon-specific exercises and exercises targeting risk factors (lack of time, pain, preferring sports activities, rest day and lack of motivation).

Registered training or match days

Patients were asked to register the number of training or match days in the same weekly online questionnaire. Also, the duration of the training or match (in minutes) and the intensity

of the training/match was registered using the rated perceived exertion (RPE) scale (range 1: very light to 10: maximum effort activity).

Pain scores

The visual analogue scale (VAS) was used for the assessment of pain related to the tendon-specific exercises, exercises targeting risk factors, most recent sport activity, activities of daily living, palpation of the patellar tendon, pain provocation test using the single-leg decline squat (Figure S1,e) and vertical jump test (Figure S1,h+i). The VAS score ranged from 0 to 10, with 0 indicating no pain and 10 indicating maximum pain. Palpation of the patellar tendon was performed manually by palpating its most tender locations.

Questionnaires

We used three questionnaires that were administered at baseline and after 24 weeks follow-up. First, the EuroQol 5 dimensions (EQ-5D) which is a frequently used questionnaire to measure health-related quality of life.[1] The score ranges from 0 (worst imaginable health state) to 100 (best imaginable health state). Second, the painDETECT questionnaire, which is a validated screening tool to aid in identifying neuropathic pain components. The score ranges from 0 to 38 and scores of ≥ 19 indicate a likelihood of more than 90% that a neuropathic pain component is present. Scores of ≤12 indicate that a neuropathic pain component is less likely than 15% to be present, and scores in between suggest an ambiguous result, however a neuropathic pain component could be present (e.g., in mixed pain).[2] Third, we used the Pain-Coping Inventory (PCI), which is a validated questionnaire to determine the levels of active (range, 0-100%) and passive coping mechanisms (range, 0-100%).[3] The subjects rated 33 questions on a 4-point Likert scale ranging from 1 (hardly ever) to 4 (very often) in order to calculate the level of active and passive coping.

Functional tests

The functional tests that we performed are illustrated in Figure S1.

Advanced imaging methods

Ultrasound was performed using a LOGIQ E9 (GE Healthcare) machine, equipped with shear-wave elastography (SWE). A linear 5-15 MHz transducer (ML6-15, GE Healthcare) was used for greyscale ultrasound and power Doppler ultrasound and a linear 3.1-10 MHz transducer (9L, GE Healthcare) for SWE. Maximum thickness of the proximal patellar tendon was measured in the transverse plane. Tendon vascularity was assessed using power Doppler, which was assessed using the modified-Öhberg score.[11] This is a 5-point grading scale to score neovascularization in various types of tendinopathy; 0 indicates the absence of Doppler flow, 1+ indicates 1-2 blood vessels mostly in the posterior portion of the tendon, 2 indicates 1-2 intratendinous blood vessels, 3 indicates 3-4 intratendinous blood vessels and 4 indicates a

network of intratendinous blood vessels. SWE was used as quantitative measure for patellar tendon stiffness in kilopascal (kPa). This is an ultrasound technique that measures tissue stiffness by measuring the velocity of directional propagating shear-waves that are generated by an acoustic radiation force.[12] The analysis of patellar tendon stiffness was performed using a previously described method, in which the stiffness of the proximal patellar tendon was quantified on elastograms.[13] These elastograms are color-coded maps overlying a normal greyscale ultrasound image, on which the quantitative analysis was performed by placing multiple regions-of-interest. Ultrasound gel (Sonogel Vertriebs GmbH) was used at room temperature (21°C).

Magnetic resonance imaging (MRI) was performed using a 3.0T clinical scanner (Discovery MR750, GE Healthcare). Quantitative T2* mapping was performed by using T2* relaxation times from an imaging sequence called 3D ultrashort echo time (UTE). This relatively new imaging sequence allows for detecting ultrashort T2* relaxation times from the patellar tendon, which can be used for voxel-wise quantification of patellar tendon hydration state.[14] This hydration state is influenced by the typical structural changes that are associated with patellar tendinopathy, and include increased proteoglycans and associated glycosaminoglycan side chains within the extracellular matrix of the patellar tendon.[15] Both have a strong potential for binding water and contribute to the increased hydration state.[16] The state in which water is present in the patellar tendon can be distinguished by investigating the specific T2* relaxation times, which reflect the macromolecular bound water compartment (short T2*) or loosely bound water (longer T2*).[17] The percentage of short T2* components was voxel-wisely calculated in three tissue compartments of the patellar tendon in tendinopathy: 1) collagen (mostly short T2*), 2) interface between collagen and degenerative tissue (mixed T2*) and 3) degenerative tissue (mostly long T2*). The full examination protocol was published elsewhere.

Outcomes

All additional secondary outcome measures performed are listed in Table S1. The single significant adjusted mean between-group difference after Bonferroni correction was VAS related to the tendon-specific exercises. The VAS related to tendon-specific exercises at 24 weeks was significantly lower in the PTLE group than in the EET group with an estimated mean of 1.8 vs 3.7 (adjusted mean between-group difference: 1.9 [95% CI, 0.7 to 3.0]; $P = .006$).

ADDITIONAL STATISTICAL METHODOLOGY

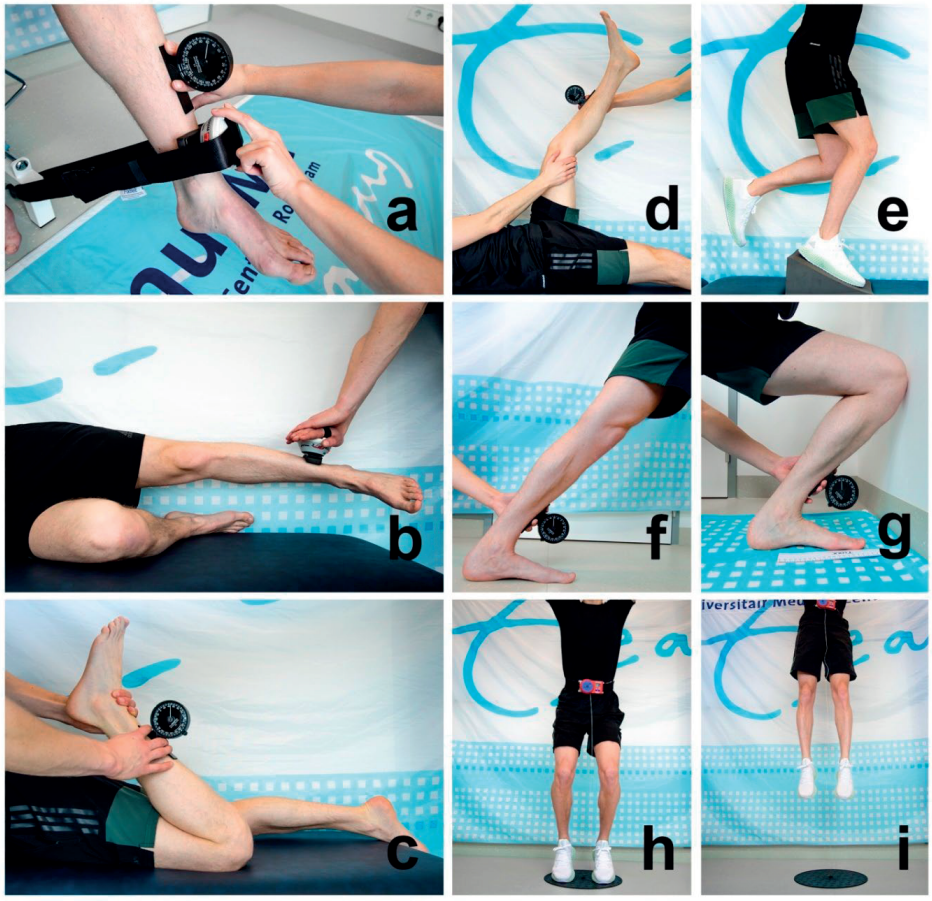
Post-hoc sensitivity analysis of missingness

Nine of the 76 included athletes (11.8%) were lost to follow-up for the primary outcome (VISA-P score). One was missing from the 4-stage progressive tendon-loading group and eight from the eccentric exercise group. To evaluate the impact of missingness on the primary outcome, sensitivity analysis was conducted using the following 3 approaches:

1. Worst case scenario for 4-stage progressive tendon-loading exercises: the single missing athlete from the progressive tendon-loading group was assigned the worst outcome of this treatment group (VISA-P 43 points and 49 points at 12 weeks and 24 weeks, respectively) while all missing patients from the eccentric exercise group were assigned the best outcome of their treatment group (VISA-P 91 points and 100 points at 12 weeks and 24 weeks, respectively).
2. Best case scenario for 4-stage progressive tendon-loading exercises: the single missing athlete from the progressive tendon-loading group was assigned the best outcome of this treatment group (VISA-P 100 points at 12 weeks and 24 weeks) while all missing athletes from the eccentric exercise group were assigned the worst outcome of this treatment group (VISA-P 32 points at both 12 weeks and 24 weeks).
3. Most likely scenario for both treatment groups: last observation carried forward (LOCF) approach, by imputing the last observed score of the VISA-P for all missing follow up measurements.

Table S2 shows the results of these 3 scenarios.

SUPPLEMENTAL FIGURES



[a]**Quadriceps strength measurement.** Maximal isometric voluntary contraction (MVC) of the quadriceps muscle was measured with a MicroFet 2 hand-held dynamometer (Hoggan Health Industries, USA), using an established method.[4] The quadriceps muscle strength was assessed in seated position of the participants, with a straight back and with both hands on their shoulders, so that holding on to the examination table was not possible. The flexion angle of the knee was fixed at 60° using a fixation belt (FixBelt) and a plurimeter (Dr. Rippstein, La Conversion, Switzerland). The participants were instructed to produce their maximal force in three seconds against the fixed dynamometer. Consequently, the isometric strength was tested (Newton). For each strength measurement, two maximal voluntary contraction trials were performed of which the highest score was used for analysis.

[b]**Hip abductor strength measurement.** Maximal isometric voluntary contraction (MVC) of the hip abductor muscles was measured with a MicroFet 2 hand-held dynamometer (Hoggan Health Industries, USA), using an established method.[5] The hip abductor muscle strength was assessed in side-lying position of the participants as a 'make test' (isometric contraction). The knee of the contralateral leg was in 90° flexion and the head of the patient was placed on his own hand with a flexed arm and the other hand was used for holding on to the examination table. The participants were instructed to produce their maximal force in three seconds against the resistance of the examiner. Consequently, the isometric strength was tested (Newton). For each strength measurement, two maximal voluntary contraction trials were performed of which the highest score was used for analysis.

[c]**Quadriceps flexibility measurement.** The passive flexibility of the quadriceps muscle was measured with the patient in prone position by measuring the maximum knee flexion angle after passive knee flexion. Eventual anterior pelvic tilt while performing the test was prevented by the investigator.[6] The fully extended leg defined the goniometric 0°.

[d]**Active knee extension test for hamstring flexibility.** The flexibility of the hamstrings was measured with the patient in supine position by measuring the maximum knee extension, dictated by the patient. The patients were instructed to hold their hands in the knee cavity and fixate the hip in 90° flexion (the goniometric 0°). The contralateral leg was fully extended. The maximum degree of knee extension was measured by placing a plurimeter (Dr. Rippstein, La Conversion, Switzerland) on the tibial shaft. This test has been shown to have an excellent reliability.[7]

[e]**Pain provocation test using the single-leg decline squat.** One single-leg squat was performed on a 25° decline board, in order to measure the provocation of pain in the patellar tendon.[8] The downward (eccentric) component was performed on the symptomatic leg and the upward (concentric) component using mainly the contralateral leg. Patients were asked to report the Visual Analogue Scale (VAS) for pain using the 0-10 scale.

[f+g]**Weight-bearing dorsiflexion lunge test.** The maximum ankle dorsiflexion range of motion was assessed using the weight-bearing dorsiflexion lunge test.[9] For this test, the patient was asked to lunge the knee towards the wall and where the foot was progressively moved away from the wall without lifting the heel. The angle of the tibial shaft was measured by placing a plurimeter (Dr. Rippstein, La Conversion, Switzerland) on the tibial shaft in the maximum range of ankle dorsiflexion by the investigator, which defined the soleus flexibility. The wall defined the goniometric 0°. Anterior pelvic tilt was avoided while performing the test. Subsequently, the patients were asked to move their foot as far from the wall as possible, while remaining the heel on the floor and the knee fully extended. The maximum range of ankle dorsiflexion was again tested which defined the gastrocnemius flexibility.

[h+i]**Vertical jump test.** The vertical jump test was performed by using a digital vertical jump meter (Takei 5406 Jump-MD, Takei Scientific Instruments Co., Japan). The rubber test mat was connected by a piece of rope to an adjustable belt which was fixated around the waist of the participant. After tightening the rope, the digital device was set to zero centimetres. Participants were asked to complete 3 maximal counter-movement jumps with arm swing on the jump mat (h).[10] The landing should be on the jump mat to qualify. The maximum jump height out of three attempts was registered. Patients were asked to report the VAS for the maximum pain during these vertical jumps using the 0-10 scale.

SUPPLEMENTAL TABLES

Table S1. Additional Secondary Outcome Measures in the Progressive Tendon-loading Exercise (PTLE) and Heavy-load Eccentric Exercise Therapy (EET) Groups

	PTLE group (n = 38)	EET group (n = 38)	Adjusted mean between-group difference
Additional Secondary Outcome Measures (GEE model)			
Compliance (%), tendon-specific exercises, estimated mean (95% CI)[1]			
0-12 weeks	47.0 (32.7 to 61.2)	53.1 (41.3 to 64.8)	-6.1 (-25.8 to 13.6)
0-24 weeks	40.2 (29.2 to 51.1)	48.6 (36.2 to 60.9)	-8.4 (-25.1 to 8.3)
Compliance (%), exercises targeting risk factors, estimated mean (95% CI)[1]			
0-12 weeks	27.5 (19.4 to 35.6)	28.2 (17.8 to 38.5)	-0.7 (-13.1 to 11.7)
0-24 weeks	21.4 (12.2 to 30.5)	21.6 (10.1 to 33.2)	-0.3 (-14.3 to 13.7)
Registered training or match days per week, estimated mean (95% CI)[1]			
0-12 weeks	1.5 (0.8 to 2.2)	1.3 (0.7 to 1.8)	0.2 (-0.6 to 1.0)
0-24 weeks	1.6 (1.0 to 2.2)	0.7 (0.2 to 1.2)	0.9 (0.2 to 1.6)
Duration of the training or match, minutes, estimated mean (95% CI) [1]			
0-12 weeks	80.7 (68.2 to 93.3)	67.3 (57.3 to 77.4)	13.4 (-1.1 to 27.9)
0-24 weeks	69.7 (56.9 to 82.6)	75.3 (52.1 to 98.4)	-5.6 (-33.8 to 22.7)
Rated Perceived Exertion (0-10 points), estimated mean (95% CI) [1]			
0-12 weeks	4.7 (3.9 to 5.5)	4.0 (3.2 to 4.8)	0.8 (-0.4 to 1.9)
0-24 weeks	3.9 (2.9 to 4.9)	4.8 (3.3 to 6.3)	-0.9 (-2.7 to 0.8)
VAS related to tendon-specific exercises, estimated mean (95% CI)[1]			
12 weeks	2.9 (2.0 to 3.8)	4.5 (3.8 to 5.3)	1.7 (0.4 to 2.9)
24 weeks	1.8 (1.1 to 2.6)	3.7 (2.9 to 4.5)	1.9 (0.7 to 3.0)*
VAS related to exercises targeting risk factors, estimated mean (95% CI)[1]			
12 weeks	2.7 (2.3 to 3.2)	3.3 (2.9 to 3.7)	0.6 (0.0 to 1.2)
24 weeks	3.0 (2.5 to 3.5)	3.0 (2.5 to 3.4)	0.0 (-0.6 to 0.7)
VAS related to most recent sport activity (0-10 points), estimated mean (95% CI)[1]			
Baseline	7.0 (6.5 to 7.5)	7.2 (6.6 to 7.7)	0.2 (-0.6 to 0.9)
12 weeks	4.2 (3.4 to 5.0)	5.2 (4.4 to 6.0)	1.1 (-0.1 to 2.2)
24 weeks	2.7 (2.1 to 3.3)	3.9 (3.0 to 4.8)	1.3 (0.2 to 2.3)
VAS related to activities of daily living (0-10 points), estimated mean (95% CI)[1]			
Baseline	4.3 (3.4 to 5.1)	4.8 (4.1 to 5.5)	0.5 (-0.5 to 1.6)

Table S1. Additional Secondary Outcome Measures in the Progressive Tendon-loading Exercise (PTLE) and Heavy-load Eccentric Exercise Therapy (EET) Groups (*continued*)

	PTLE group (n = 38)	EET group (n = 38)	Adjusted mean between-group difference
12 weeks	2.0 (1.2 to 2.8)	3.0 (2.2 to 3.8)	1.0 (-0.7 to 2.1)
24 weeks	1.3 (0.6 to 2.0)	1.7 (1.0 to 2.4)	0.4 (-0.5 to 1.2)
VAS related to palpation of the patellar tendon (0-10 points), estimated mean (95% CI)[1]			
Baseline	5.5 (4.5 to 6.4)	6.0 (4.9 to 7.1)	0.5 (-0.8 to 1.9)
12 weeks	2.8 (1.9 to 3.7)	3.6 (2.3 to 4.8)	0.8 (-0.6 to 2.1)
24 weeks	1.9 (1.2 to 2.7)	3.1 (2.0 to 4.3)	1.2 (-0.2 to 2.5)
VAS related to single-leg decline squat (0-10 points), estimated mean (95% CI)[1]			
Baseline	4.8 (4.1 to 5.5)	4.9 (4.2 to 5.7)	0.1 (-0.8 to 1.1)
12 weeks	2.6 (1.7 to 3.4)	3.4 (2.7 to 4.1)	0.8 (-0.3 to 1.9)
24 weeks	1.5 (0.9 to 2.2)	2.7 (1.8 to 3.5)	1.1 (0.1 to 2.1)
VAS related to vertical jump test (0-10 points), estimated mean (95% CI)[1]			
Baseline	2.9 (2.2 to 3.7)	2.5 (1.7 to 3.3)	-0.5 (-1.6 to 0.6)
12 weeks	1.4 (0.7 to 2.1)	1.4 (0.6 to 2.3)	0.0 (-1.0 to 1.0)
24 weeks	0.4 (-0.1 to 1.0)	1.4 (0.6 to 2.2)	1.0 (-0.0 to 2.0)
Vertical jump height, centimetres, estimated mean (95% CI)[1]			
Baseline	45.3 (42.7 to 48.0)	46.4 (44.0 to 48.8)	-1.1 (-4.4 to 2.2)
12 weeks	46.5 (44.0 to 49.1)	46.3 (43.9 to 48.7)	0.2 (-3.0 to 3.5)
24 weeks	46.5 (43.9 to 49.1)	46.2 (43.7 to 48.7)	0.3 (-3.0 to 3.6)
EQ-5D quality of life questionnaire (0-100 points), estimated mean (95% CI)[1]			
Baseline	81.8 (77.7 to 86.0)	81.3 (77.1 to 85.5)	0.6 (-5.2 to 6.3)
24 weeks	84.7 (80.0 to 89.4)	83.9 (80.0 to 87.8)	0.8 (-4.8 to 6.5)
painDETECT questionnaire (0-38 points), estimated mean (95% CI)[1]			
Baseline	8.7 (7.2 to 10.2)	9.8 (8.2 to 11.3)	1.1 (-1.0 to 3.1)
24 weeks	5.2 (3.9 to 6.5)	7.3 (5.8 to 8.8)	2.1 (0.3 to 4.0)
Pain coping inventory, % active coping (0-100%), estimated mean (95%) CI)[1]			
Baseline	35.0 (30.5 to 39.5)	31.8 (26.4 to 37.2)	4.2 (-3.6 to 12.1)
24 weeks	30.8 (25.1 to 36.5)	26.6 (20.5 to 32.8)	-5.2 (-10.9 to 0.5)
Pain coping inventory, % passive coping (0-100%), estimated mean (95%) CI)[1]			
Baseline	21.7 (17.8 to 25.6)	19.6 (15.5 to 23.7)	-4.3 (-10.6 to 2.0)
24 weeks	18.0 (13.9 to 22.1)	17.4 (12.0 to 22.8)	-0.6 (-7.0 to 5.8)

Table S1. Additional Secondary Outcome Measures in the Progressive Tendon-loading Exercise (PTLE) and Heavy-load Eccentric Exercise Therapy (EET) Groups (*continued*)

	PTLE group (n = 38)	EET group (n = 38)	Adjusted mean between-group difference
MVC strength hip abductors, Newton, estimated mean (95% CI)[1]			
Baseline	167 (156 to 178)	156 (145 to 167)	11 (-3 to 24)
12 weeks	177 (167 to 187)	171 (160 to 180)	7 (-6 to 20)
24 weeks	175 (165 to 185)	168 (159 to 178)	7 (-6 to 19)
MVC strength quadriceps, Newton, estimated mean (95% CI)[1]			
Baseline	357 (327 to 387)	351 (326 to 375)	6 (-30 to 42)
12 weeks	413 (389 to 436)	373 (349 to 396)	40 (8 to 72)
24 weeks	416 (392 to 440)	390 (366 to 412)	27 (-5 to 59)
Flexibility quadriceps, degrees, estimated mean (95% CI)[1]			
Baseline	147 (143 to 151)	144 (139 to 149)	3 (-1 to 7)
12 weeks	148 (144 to 152)	146 (142 to 151)	2 (-2 to 6)
24 weeks	148 (144 to 153)	145 (138 to 152)	4 (-2 to 9)
Flexibility hamstrings, degrees, estimated mean (95% CI)[1]			
Baseline	63 (57 to 69)	61 (54 to 68)	2 (-4 to 8)
12 weeks	67 (61 to 73)	64 (56 to 72)	3 (-4 to 11)
24 weeks	66 (59 to 72)	65 (59 to 72)	0 (-6 to 7)
Flexibility gastrocnemius, degrees, estimated mean (95% CI)[1]			
Baseline	39 (36 to 42)	38 (35 to 40)	1 (-2 to 4)
12 weeks	40 (38 to 43)	39 (37 to 41)	1 (-2 to 5)
24 weeks	40 (38 to 43)	41 (38 to 44)	-1 (-4 to 2)
Flexibility soleus, degrees, estimated mean (95% CI)[1]			
Baseline	41 (38 to 43)	41 (39 to 44)	-1 (-4 to 2)
12 weeks	42 (40 to 45)	42 (40 to 45)	0 (-3 to 3)
24 weeks	43 (40 to 45)	43 (41 to 46)	-1 (-4 to 3)
Ultrasound: patellar tendon thickness, mm, estimated mean (95% CI)[1]			
Baseline	7.4 (6.5 to 8.3)	7.9 (7.2 to 8.6)	0.5 (-0.5 to 1.6)
12 weeks	7.3 (6.4 to 8.2)	8.0 (7.3 to 8.8)	0.7 (-0.4 to 1.8)
24 weeks	7.0 (6.1 to 7.9)	7.7 (6.9 to 8.5)	0.7 (-0.4 to 1.8)
Ultrasound: degree of Doppler flow, Öhberg score, estimated mean (95% CI)[1]			
Baseline	2.7 (2.2 to 3.2)	3.3 (2.7 to 3.8)	0.6 (-0.0 to 1.1)

Table S1. Additional Secondary Outcome Measures in the Progressive Tendon-loading Exercise (PTLE) and Heavy-load Eccentric Exercise Therapy (EET) Groups (*continued*)

	PTLE group (n = 38)	EET group (n = 38)	Adjusted mean between-group difference
12 weeks	2.3 (1.9 to 2.8)	2.7 (2.2 to 3.3)	0.4 (-0.2 to 1.0)
24 weeks	2.0 (1.4 to 2.6)	2.7 (2.1 to 3.2)	0.6 (-0.0 to 1.3)
Ultrasound: patellar tendon stiffness, kilopascal, estimated mean (95% CI)[1]			
Baseline	73.7 (62.2 to 85.2)	63.2 (55.1 to 71.2)	-10.5 (-22.4 to 1.4)
12 weeks	57.4 (46.9 to 67.8)	64.5 (54.6 to 74.4)	7.1 (-4.5 to 18.7)
24 weeks	57.7 (48.6 to 66.7)	61.2 (51.3 to 71.2)	3.6 (-8.6 to 15.7)
MRI: percentage of short T2* components in voxels with mostly short T2*, percentage, estimated mean (95% CI)[1]			
Baseline	84.1 (82.3 to 85.8)	83.0 (80.3 to 85.7)	1.1 (-2.1 to 4.3)
12 weeks	84.6 (82.8 to 86.3)	84.1 (82.2 to 86.1)	0.5 (-1.7 to 2.6)
24 weeks	83.6 (81.7 to 85.6)	85.1 (83.0 to 87.1)	-1.4 (-4 to 1.2)
MRI: percentage of short T2* components in voxels with mixed T2*, percentage, estimated mean (95% CI)[1]			
Baseline	40.9 (37.3 to 44.4)	42.8 (38.3 to 47.4)	-2.0 (-7.1 to 3.1)
12 weeks	42.4 (38.7 to 46.1)	39.7 (36.4 to 43.1)	2.7 (-2.2 to 7.6)
24 weeks	44.3 (40.6 to 47.9)	45.1 (40.1 to 50.0)	-0.8 (-6.2 to 4.6)
MRI: percentage of short T2* components in voxels with mostly long T2*, percentage, estimated mean (95% CI)[1]			
Baseline	20.1 (19.2 to 21.0)	20.8 (19.5 to 22.0)	-0.7 (-2.1 to 0.8)
12 weeks	20.7 (19.6 to 21.9)	19.7 (18.3 to 21.0)	1.0 (-0.7 to 2.8)
24 weeks	22.5 (21.2 to 23.9)	20.9 (19.0 to 22.7)	1.6 (-0.6 to 3.9)
Additional Secondary Outcomes (Fisher exact test)			
Reasons for not performing tendon-specific exercises, n (%)[2]			
Lack of time	901 (37)	1072 (51)	
Pain	211 (9)	154 (7)	
Preferring sports activities	325 (13)	299 (14)	
Rest day	565 (23)	245 (12)	
Lack of motivation	417 (17)	339 (16)	
Reasons for not performing exercises targeting risk factors, n (%)[2]			
Lack of time	1097 (31)	1015 (33)	

Table S1. Additional Secondary Outcome Measures in the Progressive Tendon-loading Exercise (PTLE) and Heavy-load Eccentric Exercise Therapy (EET) Groups (*continued*)

	PTLE group (n = 38)	EET group (n = 38)	Adjusted mean between-group difference
Pain	149 (4)	105 (3)	
Preferring sports activities	521 (15)	253 (8)	
Rest day	1249 (35)	1284 (41)	
Lack of motivation	548 (15)	459 (15)	

Abbreviations: PTLE, progressive tendon-loading exercise therapy; EET, heavy-load eccentric exercise therapy; VAS, visual analogue scale; CI, confidence interval; MVC, maximum voluntary contraction; RPE, rated perceived exertion; SD, standard deviation.

[1]The mean estimated compliance to tendon-specific exercises, compliance to exercises targeting risk factors, number of registered training or match days per week, duration of the training or match, rated perceived exertion of the training or match, VAS related to tendon-specific exercises, VAS related to exercises targeting risk factors, VAS related to most recent sport activity, VAS related to activities of daily living, VAS related to palpation of the patellar tendon, VAS related to single-leg decline squat, VAS related to vertical jump test (3 maximal jumps), vertical jump height (maximum of 3 attempts), EQ-5D questionnaire, painDETECT questionnaire, pain coping inventory questionnaire (active/passive coping), MVC strength hip adductors, MVC strength quadriceps, flexibility quadriceps, flexibility hamstrings, flexibility gastrocnemius, flexibility soleus, ultrasound-based patellar tendon thickness, ultrasound-based Doppler flow, ultrasound-based patellar tendon stiffness (measured with shear-wave elastography), MRI-based percentage of short T2* in voxels with mostly short T2*, MRI-based percentage of short T2* in voxels with intermediate T2* and MRI-based percentage of short T2* in voxels with mostly long T2* are denoted for the PTLE and EET group. The estimated means and adjusted mean between-group differences were calculated using Generalized Estimating Equations (GEE) with adjustments for the following pre-defined baseline variables: age, sex, BMI, symptom duration and Cincinnati Sports Activity Scale. Positive adjusted mean between-group differences favour the PTLE-group.

The interaction term study arm*visit was significant for the following outcomes: VAS related to exercises targeting risk factors (P=.013), VAS related to vertical jump test (P=.039), MVC strength quadriceps (P=0.049) and ultrasound-based patellar tendon stiffness (P=.007). This means that the course of the VISA-P score over time was statistically different for the PTLE and EET group.

The interaction term study arm*visit was not statistically significant for the following outcomes: compliance to tendon-specific exercises (P=.84), compliance to exercises targeting risk factors (P=.94), number of registered training or match days per week (P=0.17), duration of the training or match (P=.22), rated perceived exertion (P=.11), VAS related to tendon-specific exercises (P=.68), VAS related to most recent sport activity (P=.23), VAS related to activities of daily living (P=.55), VAS related to palpation of the patellar tendon (P=.80), VAS related to single-leg decline squat (P=.21), vertical jump height (P=.35), EQ-5D questionnaire (P=.93), painDETECT questionnaire (P=.35), pain coping inventory questionnaire, active coping (P=.78) and passive coping (P=.66), MVC strength hip adductors (P=.73), flexibility quadriceps (P=.38), flexibility hamstrings (P=.35), flexibility gastrocnemius (P=.11), flexibility soleus (P=.60), ultrasound-based patellar tendon thickness (P=.63), ultrasound-based Doppler flow (P=.63), MRI-based percentage of short T2* in voxels with mostly short T2* (P=.37), MRI-based percentage of short T2* in voxels with intermediate T2* (P=.46) and MRI-based percentage of short T2* in voxels with mostly long T2* (P=.07). This means that the course of the VISA-P score over time did not differ between the PTLE and EET group for these outcome measures.

[2]The number and percentage of reasons registered for not performing the tendon-specific exercises are denoted for the PLTE and EET group. The reasons lack of time (P<.001), pain (P=0.045) and rest day (P<.001) were significantly different between the study arms and sports activities (P=.25) and lack of motivation (P=.16) were not.

The total number and percentage of reasons registered for not performing the exercises targeting risk-factors are denoted for the PLTE and EET group. The reasons pain (P=0.048), sports activities (P<.001) and rest day (P<.001) were significantly different between the study arms and lack of time (P=.06) and lack of motivation (P=.24) were not.

Table S2: Sensitivity Analysis of Missingness

Outcome Scenario	**Absolute mean between-group difference**		**Adjusted mean between-group difference (95% CI)**	
	12 weeks	**24 weeks**	**12 weeks**	**24 weeks**
1. Worst case	-4.5	2.7	-4.2 (-11.6 to 3.2)	3.0 (-4.7 to 10.7)
2. Best case	13.8	18.3	12.4 (4.6 to 20.1)*	16.7 (8.6 to 24.9)*
3. Most likely	1.8	10.8	1.7 (-5.1 to 8.6)	10.6 (3.4 to 17.8)*

*The mean between-group difference is significant at the .001 level.
Any positive mean difference indicates a favourable outcome for the progressive tendon-loading exercise (PTLE) group.

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3

The association between patellar tendon stiffness measured with shear-wave elastography and patellar tendinopathy-a case-control study.

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Eur Radiol. 2020 Nov;30(11):5942-5951.

ABSTRACT

Objectives: (1) To determine the association between patellar tendon stiffness and the presence of patellar tendinopathy (PT). (2) To evaluate the reliability of shear-wave elastography (SWE).

Methods: Participants were consecutively enrolled between January 2017 and June 2019. PT was diagnosed clinically and confirmed by either grayscale US or power Doppler US, or both. Controls had no history of anterior knee pain and no clinical signs of PT. Patellar tendon stiffness (kilopascal, kPa) was assessed using SWE. Logistic regression was used to estimate adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Reliability analyses included coefficients-of-variation (CV), coefficients-of-repeatability (CR), intraclass correlation coefficient (ICC) for intraobserver and interobserver reliability, and Bland-Altman analysis.

Results: In total, 76 participants with PT (58 men, mean age 24.4 ± 3.8 years) and 35 asymptomatic controls (16 men, mean age 21.5 ± 3.8 years) were included. Univariate analyses (OR 1.094, 95% CI 1.061-1.128, $p < .001$) and adjusted multivariate analyses (OR 1.294, 95% CI 1.044-1.605, $p = .018$) showed that athletes with PT had significantly increased patellar tendon stiffness. ICC for intraobserver reliability was 0.95 (95% CI 0.92-0.97), CR (CV) 12 kPa (10%) and 0.79 (95% CI 0.65-0.88), CR (CV) 18 kPa (21%) for interobserver reliability. Mean differences from Bland-Altman analysis were 5.6 kPa (95% CI 3.1-8.1, $p < .001$) for intraobserver reliability and 4.6 kPa (95% CI 1.9-7.2, $p < .001$) for interobserver reliability.

Conclusions: PT is associated with significantly higher patellar tendon stiffness. SWE measurements demonstrate excellent intraobserver reliability and good interobserver reliability. Therefore, SWE is a promising tool to implement in longitudinal studies and future studies should evaluate its prognostic value and utility as a monitoring tool in athletes with PT.

INTRODUCTION

Patellar tendinopathy (PT) is an overuse injury of the patellar tendon resulting in pain, decreased exercise tolerance, and impaired function.[1] PT is highly prevalent in jumping athletes, with reported rates of 45% for elite volleyball players and 32% for elite basketball players.[2] There is consensus that PT is a clinical diagnosis with focal load-related pain, established by medical history taking and clinical examination. Currently, the applicability of ultrasound (US) is limited to confirming the clinical diagnosis of PT by assessing morphological changes.[3] Tendinopathy-related abnormalities on US are tendon thickening with hypoechoic areas and/or increased Doppler flow.[4,5] These alterations are associated with tendinopathy; however, they have also been reported in up to 59% of asymptomatic athletes.[6] Therefore, changes in tendon structure on grayscale US (GSUS) are considered a risk factor for tendinopathy rather than indicative for PT or tendon pain.[7] Alternative imaging techniques that better reflect pain remain to be investigated as they could provide attractive novel biomarkers to assess therapy response.

Shear-wave elastography (SWE) is an ultrasound-based imaging technique which evaluates viscoelastic properties, depicted as color-coded images (elastogram).[8] Accordingly, SWE offers additional information to structural changes observed with GSUS. SWE assesses tendon stiffness both qualitatively and quantitatively by acquiring velocity measurements of directional propagating shear-waves generated by focused ultrasound pulses.[9] The assessment of patellar tendon stiffness using SWE could potentially correlate better with experienced pain in athletes with PT. Moreover, the superficial location of the patellar tendon facilitates implementation of SWE.

Musculoskeletal applications of SWE constitute a relatively new area which has emerged from well-established applications in breast, liver, thyroid, and prostate imaging.[10-13] Additionally, SWE has already shown potential to discriminate between athletes with unilateral PT and asymptomatic athletes.[14] However, recent studies reported conflicting SWE outcomes in PT.[15] Consequently, the association between patellar tendon stiffness measured with SWE and the presence of PT and the reliability of SWE are still largely unknown.

The primary aim of this study was, therefore, to determine the association between patellar tendon stiffness and the presence of PT in jumping athletes. The secondary aim was to evaluate the reliability of the patellar tendon stiffness assessment and image analysis using SWE.

MATERIALS AND METHODS

This case-control study in Erasmus MC University Medical Center Rotterdam, The Netherlands, was approved by the institutional review board. Participants provided written informed consent prior to inclusion. We performed cross-sectional analysis of baseline data from a prospective trial investigating two different exercise programs for PT (ClinicalTrials.gov, ID: NCT02938143).

Study participants

Participants were consecutively enrolled. National sports federations and regional healthcare providers facilitated recruitment. Athletes performing sports involving frequent jumping or cutting maneuvers were eligible. Potential subjects underwent initial online screening to assess the location of tenderness on a self-reported pain map.[16] The Victorian Institute of Sports Assessment questionnaire for patellar tendons. (VISA-P) was administered to measure symptoms, function, and ability to play sports.[17] A VISA-P < 80 was one of the inclusion criteria for PT.[18] All eligibility criteria are listed in Table 1.

Inclusion protocol

Jumping athletes with suspected PT and asymptomatic athletes were invited to our hospital to confirm eligibility. Clinical evaluation was performed by a sports physician (R.V.) with 10 years' experience, and athletes were regarded positive for PT if tenderness at the inferior patellar pole or patellar tendon could be reproduced on palpation and a single-leg squat.[19] Provocation tests of the patellofemoral joint were performed to exclude patellofemoral pain.[20] Subsequently, GSUS and power Doppler US (PDUS) were performed to verify the clinical diagnosis. US criteria for PT were presence of structural and/or hypoechoic changes and/or tendon thickening (anterior-posterior diameter > 6 mm) and/or the presence of intratendinous Doppler flow.[21] We defined our reference standard for having PT as a clinical diagnosis with affirmative findings on GSUS and/or PDUS. For athletes with bilateral PT, the individual selected the most painful side. Asymptomatic athletes who had a maximum VISA-P score (100/100) and no history of anterior knee pain or diagnosis of PT were used as controls (Table 1). GSUS and PDUS were acquired, but findings were not an eligibility criterion in this group. Weight and height measures were used to calculate body mass index (kg/m2). Activity level was assessed using the Cincinnati Sports Activity Scale (CSAS).[22]

Imaging methods

US was performed by one trained examiner (S.B.: radiologist-in-training with 5 years' experience) using an ultrasound machine equipped with SWE (LOGIQ E9, GE Healthcare). A linear 5–15-MHz transducer (ML6-15, GE Healthcare) was used for GSUS and PDUS and a linear 3.1–10-MHz transducer (9L, GE Healthcare) for SWE. Ultrasound gel (Sonogel Vertriebs GmbH) was used at room temperature (21 °C).

Table 1: Inclusion and Exclusion criteria

	Inclusion criteria	Exclusion criteria
Asymptomatic athletes	Age 18-35 years	Acute knee or patellar tendon injuries
	Playing patellar tendon-loading sports for at least 3 times a week	Prior knee surgery without full rehabilitation
	No history of anterior knee pain or diagnosis of PT	Known presence of inflammatory joint diseases or familial hypercholesterolemia
	VISA-P score 100/100 points	Daily use of drugs with a putative effect on the patellar tendon in the preceding 12 months (e.g. fluoroquinolones)
		Local injection therapy with corticosteroids in the preceding 12 months
		Previous patellar tendon rupture
Patellar tendinopathy	Age 18-35 years	Acute knee or patellar tendon injuries
	Playing patellar tendon-loading sports for at least 3 times a week	Prior knee surgery without full rehabilitation
	History of anterior knee pain located in the trajectory of the patellar tendon or its patellar or tibial insertion in association with training and competition	Known presence of inflammatory joint diseases or familial hypercholesterolemia
	Tenderness on palpation in the corresponding painful area	Daily use of drugs with a putative effect on the patellar tendon in the preceding 12 months (e.g. fluoroquinolones)
	Symptom duration of at least 2 weeks	Local injection therapy with corticosteroids in the preceding 12 months
	VISA-P score < 80/100 points	Previous patellar tendon rupture
	On ultrasound, presence of structural and/or hypoechoic changes of highly organized fiber bundles and/or tendon thickening (anterior-posterior diameter > 6mm) and/or the presence of Doppler flow detected with PDUS.	Daily exercise therapy with a minimum duration of 4 weeks in total in the preceding 12 months
		Contraindications for MRI

Abbreviations: PT, patellar tendinopathy. VISA-P, Victorian Institute of Sports Assessment questionnaire for patellar tendons. PDUS, Power Doppler Ultrasound.

Participants were examined in supine position with the back rest of the examination table upright in 60° for patient comfort and improved patellar tendon relaxation. GSUS was performed with both knees in 30° flexion, supported by a foam roll. PDUS and SWE were performed in passive extension of both knees. The standardized US acquisition protocol included longitudinal and transverse GSUS of the patellar tendon and transverse cine-loops for PDUS. The patellar tendon was designated as vascular if it demonstrated one or more blood vessels in the posterior portion of the patellar tendon or within the tendon. SWE was

performed with mild pressure, in the longitudinal plane with the inferior patellar pole just in the field-of-view. Elastograms were generated in dual-screen mode, displaying GSUS and the overlaying elastogram. Three elastograms were acquired, of which one was randomly selected for the first analysis directly after the image acquisition. A second analysis of all elastograms in PT athletes was performed by the same examiner (S.B.) after the recruitment of subjects had finished, blinded for the results of the first analysis. The second analysis consisted of stiffness measurements in all three elastograms acquired using the same method as the first analysis. Patellar tendon stiffness was averaged for the three elastograms and the relative variability of these measurements was calculated. The maximum thickness of subcutaneous tissue overlying the proximal patellar tendon was measured on a transverse GSUS image, at a standardized location within 1 cm below the inferior patellar border. A subset of controls was invited consecutively to be re-examined with SWE at the same time point by an independent examiner (A.V.) with 2 years' experience, who also performed the analyses of these collected images, blinded for the results of the first examiner. Quantitative analysis of patellar tendon stiffness was performed on the ultrasound machine, with maximum transparency of the elastograms to avoid subjective placements of regions-of-interests (ROIs). A reference ruler of 20 mm was set posterior to the patellar tendon, starting 5 mm distal to the inferior patellar pole. This guided placement of circular ROIs and avoided inclusion of artifacts from the patella (Fig. 2). ROIs were not fixed in size or number. Median tendon stiffness (kPa) was calculated for each ROI and overall median stiffness including all ROIs. The separate ROIs were labeled "ROI1-ROI4" from proximal to distal in the proximal patellar tendon.

Statistical analysis

SPSS software (version 25; IBM Corp.) was used. Normal distribution was tested using Shapiro-Wilk's test. Median and interquartile range (IQR) were obtained for non-normally distributed data. Between-group differences were assessed with Student's t test for normally distributed data and Mann-Whitney U test for non-normally distributed data. Analyses included the influence of tendon calcifications on patellar tendon stiffness in specific ROIs. In athletes with unilateral PT, we compared patellar tendon stiffness between the symptomatic and the asymptomatic patellar tendon. Logistic regression analysis was performed to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs). Univariate (unadjusted) and multivariate models adjusted for potential confounders, including age, sex, body mass index, and thickness of subcutaneous tissue, were applied. Determinants with p value $< .10$ were used in the multivariable model. Interaction terms for age*stiffness and sex*stiffness were added, based on findings in previous research.[23,24] Multicollinearity was tested using variance inflation factor (VIF), with an acceptable maximum of 2.5. The relative variability of the three SWE measurements was assessed using coefficient-of-variation (CV) and coefficient-of-repeatability (CR). The intraobserver reliability for the analyses of the different elastograms and interobserver reliability for independent SWE acquisitions and analyses were assessed using CV, CR,

intraclass correlation coefficient (ICC), and Bland-Altman analysis.[25-27] An ICC value reflected "poor" (less than 0.5), "moderate" (between 0.5 and 0.75), "good" (between 0.75 and 0.9), and "excellent" (greater than 0.90).[28] P values < .05 were considered statistically significant.

RESULTS

Study population

Participants were consecutively enrolled between January 2017 and June 2019. A total of 313 applications from potentially eligible PT athletes and asymptomatic controls were initially screened, of which 138 participants were invited to our hospital to verify or exclude the diagnosis of PT. Finally, 111 participants remained eligible for inclusion (Fig. 1).

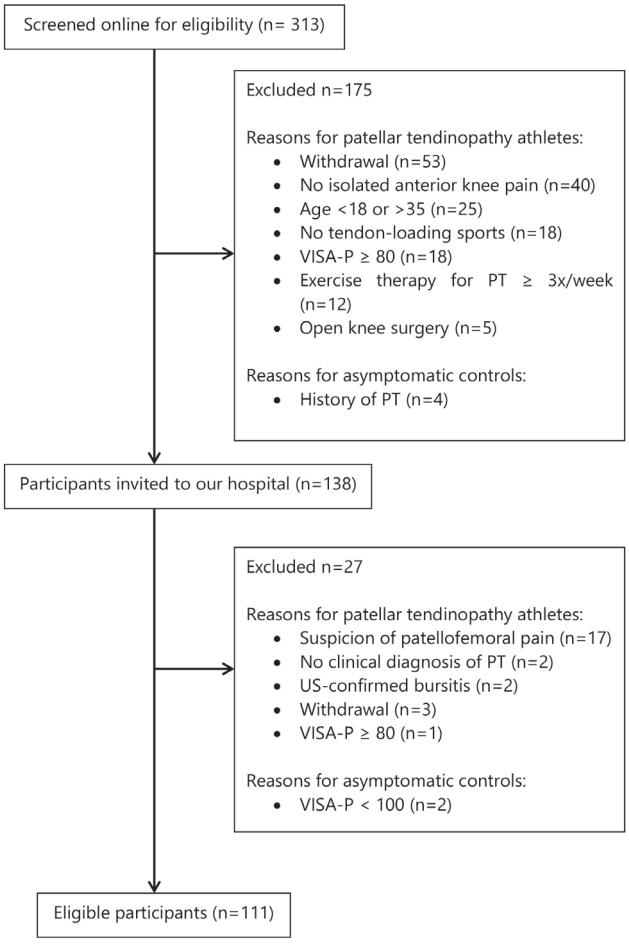

Figure 1: Recruitment flowchart of PT athletes and asymptomatic controls

Clinical and demographic characteristics of the study population are listed in Table 2. Participants with PT were significantly older, had higher BMI, and consisted of more men than asymptomatic controls. Athletes with PT (n = 76) participated in volleyball (n = 26), soccer (n = 17), basketball (n = 16), korfball (n = 8), track and field (n = 4), field hockey (n = 3), and handball (n = 2) as primary sports. Asymptomatic controls (n = 35) participated in basketball (n = 15), korfball (n = 10), volleyball (n = 9), and track and field (n = 1). No significant differences were found in activity levels between athletes with PT and asymptomatic controls. In PT athletes, the left patellar tendon was the primary site of symptoms in 41 participants (54%) and the right patellar tendon in 35 participants (46%). The diagnosis of PT was unilateral in 44 participants (58%), of which 26 were left-sided. Median duration of symptoms in PT athletes was 104 weeks (IQR, 43–208 weeks).

Table 2: Baseline Characteristics of Participants

Characteristic	**Asymptomatic athletes (*n* = 35)**	**Patellar tendinopathy (*n* = 76)**	***P* Value**
Mean age (y)	21.4 ± 3.8	24.4 ± 3.8	<.001
No. of men	18 (51)	58 (76)	.003
Mean height (cm)	180.1 ± 10.3	184.7 ± 9.3	.02
Mean weight (kg)	71.0 ± 9.5	81.8 ± 12.3	<.001
Mean BMI (kg/m^2)	21.9 ± 1.8	23.9 ± 2.9	<.001
Mean clinical score (VISA-P)	100 ± 0	55 ± 13	<.001
Sports activity scale (CSAS):			.10
Level I (4 to 7 days/week)			
100	8 (23)	17 (22)	
95	0 (0)	0 (0)	
90	0 (0)	0 (0)	
Level II (1 to 3 days/week)			
85	27 (77)	50 (66)	
80	0 (0)	9 (12)	

Data are means ± standard deviation except where they are numbers of participants and data in parentheses are percentages. BMI, body mass index. VISA-P, Victorian Institute of Sports Assessment questionnaire for patellar tendons. CSAS, Cincinnati Sports Activity Scale.

GSUS and PDUS findings

The proximal patellar tendon was significantly thicker in PT athletes (mean 8.4 ± 2.4 mm) than in asymptomatic controls (mean 4.1 ± 0.9 mm) ($p < .001$). Hypoechoic changes were seen in 89% of PT athletes and 26% of asymptomatic controls. Tendon calcifications were observed in 27% of PT athletes and erosions of the inferior patellar border in 29%. Both were absent in asymptomatic controls. Intratendinous Doppler flow was present in 89% of PT athletes and 3% of asymptomatic controls.

SWE findings

Stiffness of the proximal patellar tendon was significantly higher in PT athletes (median 74.9 kPa, IQR [56.4–105.4]) than in asymptomatic athletes (median 35.6 kPa, IQR [29.9–43.0]) ($p < .001$) (Fig. 2). In PT athletes, no significant difference in patellar tendon stiffness was found between primary left-symptomatic athletes and primary right-symptomatic athletes ($p = .360$). Only in ROI 1, patellar tendon stiffness was significantly higher in PT with tendon calcifications than in PT without calcifications ($p = .017$). In PT athletes without tendon calcifications, symptomatic tendons were still significantly stiffer than asymptomatic tendons in ROI 1, both on the left ($p = .043$) and right ($p = .005$) side, but not in other ROIs. This increased stiffness in ROI 1 was not observed in the asymptomatic tendons (left $p = .679$ and right $p = .396$).

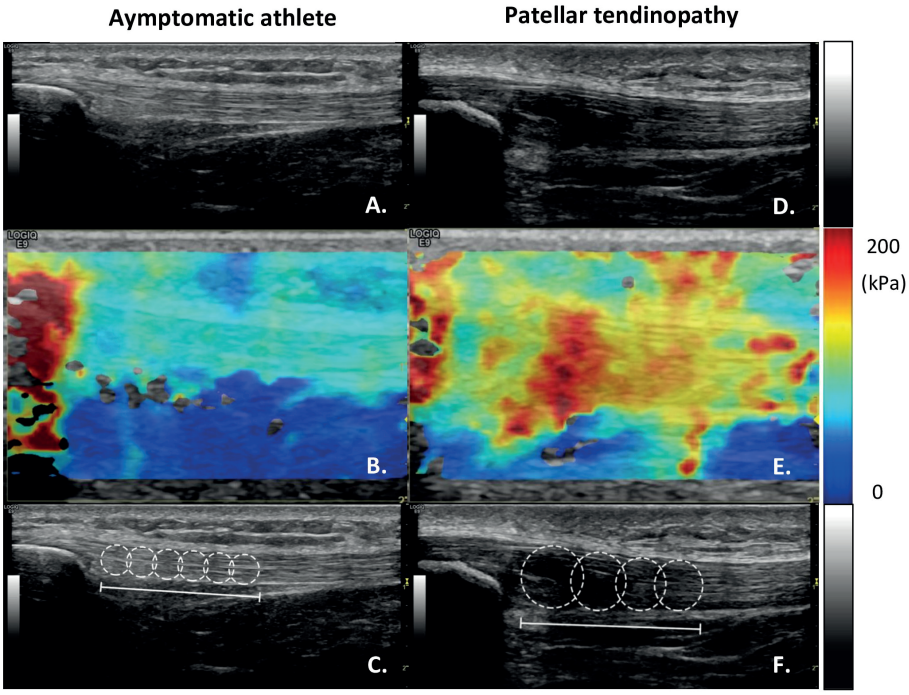

Figure 2: Grayscale US and Corresponding Shear-Wave Elastograms in an Asymptomatic Athlete and an Athlete With Patellar Tendinopathy. (a,d) Longitudinal grayscale ultrasound images of the proximal patellar tendon in an asymptomatic 19-year-old male basketball player (a) and in a 21-year-old male basketball player with patellar tendinopathy (d). (a) shows normal alignment of collagen bundles, whereas (d) shows disruption of the normal tendon architecture with hypoechoic areas separating collagen bundles. (b, e) Elastograms depicted as an overlay on grayscale images where user settings defined red as stiff tissues and blue as soft tissues. Pronounced red areas (indicating increased stiffness) were typically observed in the proximal patellar tendon of participants with patellar tendinopathy (e), compared to predominantly light blue areas (representing intermediate elasticity) in asymptomatic athletes (b). Dark blue areas posterior to the patellar tendon correspond to the relative soft Hoffa's fatpad. The small red area at the left border in both b and e corresponds to the inferior patellar border and was excluded for quantitative analysis. (c, f) Multiple partially overlapping circular regions of interest were placed for quantitative analysis of tendon stiffness, covering the proximal 20 mm of the patellar tendon (referred by reference ruler), starting 5 mm distal to the inferior patellar pole. The median stiffness (interquartile range) of the proximal patellar tendon in the asymptomatic athlete (c) was 30.6 kPa (29.3–32.2) and in the athlete with patellar tendinopathy (f) 117.4 kPa (112.3–133.8).

Variability of the SWE measurements in PT athletes

For the patellar tendon stiffness assessments in all ROIs, the CV was 5.3% (95% CI 4.0–6.3) and the CR was 6.6 kPa (IQR 3.6–12.1). For analysis in separate ROIs, the CV ranged from 10.8 to 11.8% and the CR ranged from 7.3 to 10.7 kPa.

Association between patellar tendon stiffness and PT

Patellar tendinopathy was associated with significantly higher patellar tendon stiffness, both in univariate analyses (OR 1.094, 95% CI 1.061–1.128, p < .001) and in adjusted multivariate regression analyses (OR 1.294, 95% CI 1.044–1.605, p = .018). The odds ratios for patellar tendon stiffness are estimated for each kilopascal (kPa). In univariate analysis, 7 determinants were associated with the presence of PT symptoms with a p value < 0.10, and therefore included in the multivariate model (Table 3). The variance inflation factors were well within the acceptable limit (range VIF, 1.25–1.56).

Table 3: The Association Between Patellar Tendon Stiffness and Patellar Tendinopathy

Determinant	**Univariable**	**Multivariable**[b]
Age at T0	**1.226 (1.114-1.350)**	1.407 (0.924-2.144)
Male sex	**3.412 (1.683-6.916)**	5.663 (0.090-355.276)
Index knee: left	1.111 (0.580-2.128)	
Body mass index at T0	**1.533 (1.268-1.853)**	**2.380 (1.554-3.642)**
Subcutaneous tissue (mm)	**0.545 (0.373-0.795)**	**0.365 (0.152-0.877)**
Cincinnati Sports Activity Scale	0.985 (0.937-1.035)	
Patellar tendon stiffness (kPa)	**1.094 (1.061-1.128)**	**1.294 (1.044-1.605)**[c]
Age*Stiffness	**1.004 (1.003-1.006)**	0.994 (0.986-1.003)
Sex*Stiffness	**1.034 (1.022-1.046)**	0.967 (0.890-1.049)

Data are presented as odds ratio (95% CI); data with P < .05 are bolded in univariable model.
[b]Determinants with P < .10 by univariable logistic regression were used in the multivariable model.
[c]Odds ratio for patellar tendon stiffness assessed with shear-wave elastography is estimated for each kilopascal (kPa).

Intraobserver reproducibility of SWE

The intraobserver reliability analysis (Table 4) revealed an intraclass correlation coefficient (ICC) of 0.95 (95% CI 0.92–0.97) for the median patellar tendon stiffness using all ROIs between analysis 1 (median stiffness 74.9 kPa [56.4–105.4]) and analysis 2 (median stiffness 69.9 kPa [54.7–100.3]). The coefficient-of-repeatability (CR) and coefficient-of-variation (CV) were 11.9 kPa [5.1–24.9] and 10.3% (95% CI 7.9–12.2), respectively. For the separate ROIs, the ICC ranged from 0.85 to 0.92 and CR (CV) from 13.3 to 20.2 kPa (15.1–19.2%). The mean difference from Bland-Altman analysis (Fig. 3) was 5.6 kPa (95% CI 3.1–8.1, p < .001) and limits of agreement were −15.8 kPa (lower limit) and 26.9 kPa (upper limit).

Table 4: Intraobserver Reliability Analysis of Patellar Tendon Stiffness in Seventy-Six Athletes with Patellar Tendinopathy (*N* = 76 tendons)

	Analysis 1 (SB)	Analysis 2 (SB)	Intraobserver reliability		
Location	**Stiffness (kPa) [IQR]**	**Stiffness (kPa) [IQR]**	**CV (%)[b] (95% CI)**	**CR (kPa)[c] [IQR]**	**ICC[d] (95%CI)**
All ROIs	74.9 [56.4-105.4]	69.9 [54.7-100.3]	10.3 (7.9-12.2)	11.9 [5.1-24.9]	0.95 (0.92-0.97)
ROI 1	78.3 [51.6-117.3]	78.4 [51.7-111.6]	15.8 (9.2-20.3)	14.8 [5.3-26.8]	0.92 (0.88-0.95)
ROI 2	85.4 [55.9-127.6]	72.4 [54.4-111.8]	15.1 (12.3-17.4)	16.2 [7.0-44.4]	0.89 (0.83-0.93)
ROI 3	69.7 [52.7-102.3]	63.8 [49.2-84.5]	19.2 (13.3-23.6)	20.2 [6.8-41.6]	0.85 (0.77-0.90)
ROI 4	59.9 [41.7-76.3]	48.9 [34.1-61.9]	18.9 (11.2-24.3)	13.3 [5.5-24.3]	0.92 (0.85-0.95)

Patellar tendon stiffness was assessed using Shear-wave Elastography (SWE), expressed as median [interquartile range] in kPa.

[b]CV: Coefficient of Variation (%), 95% confidence interval

[c]CR: Coefficient of Repeatability (kPa), also referred to as the Smallest Real Difference (SRD)

[d]ICC: Intraclass Correlation Coefficient (ICC), 95% confidence interval

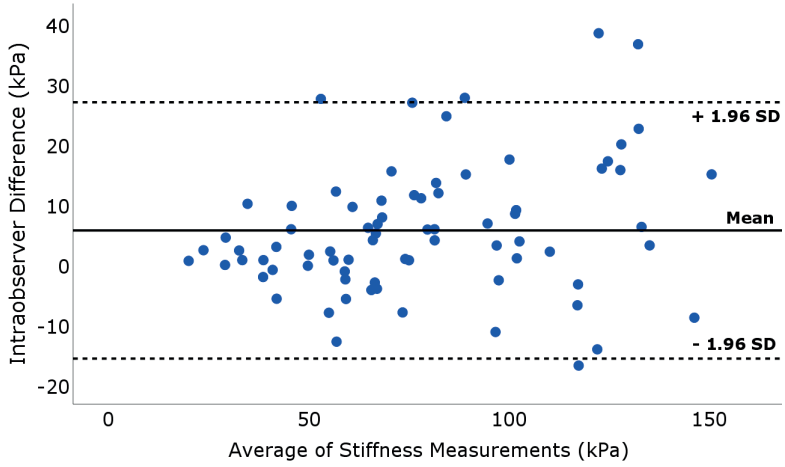

Figure 3: Intraobserver reliability of SWE in seventy-six athletes with patellar tendinopathy. Bland-Altman plot illustrating the intraobserver reliability for the patellar tendon stiffness assessment using SWE. The differences between each pair of the stiffness measurements plotted on the y-axis are shown against the mean of these measurements on the x-axis. The solid line represents the mean value and dashed lines represent the limits of agreement, defined as mean ± 1.96SD

Interobserver reproducibility of SWE

For the interobserver reproducibility, 56 paired measurements in 28 healthy athletes were used (Table 5). The ICC between examiner 1 (S.B.) and examiner 2 (A.V.) was 0.79 (95% CI 0.65–0.88) and CR (CV) was 18 kPa (21%). The mean difference from Bland-Altman analysis (Fig. 4) was 4.6 kPa (95% CI 1.9–7.2, $p < .001$) and the limits of agreement were −14.8 kPa (lower limit) and 24.0 kPa (upper limit).

Table 5: Interobserver Reliability Analysis of Patellar Tendon Stiffness in Twenty-Eight Healthy Athletes (*N* = 56 tendons)

	Examiner 1 (SB)	Examiner 2 (AV)	Interobserver reliability		
Location	Stiffness (kPa) [IQR]	Stiffness (kPa) [IQR]	CV (%)[b] (95% CI)	CR (kPa)[c] [IQR]	ICC[d] (95%CI)
All ROIs	35.7 [29.2-43.6]	30.4 [24.8-38.9]	21.0 (17.5-24.0)	18.0 [6.2-23.6]	0.79 (0.65-0.88)
ROI 1	31.4 [26.5-41.2]	28.3 [23.1-39.4]	30.2 (23.8-35.4)	19.9 [9.6-29.3]	0.64 (0.39-0.79)
ROI 2	36.2 [27.6-47.2]	49.4 [24.7-38.4]	29.7 (23.9-34.6)	14.3 [9.9-35.3]	0.74 (0.56-0.85)
ROI 3	35.3 [29.8-49.1]	31.1 [23.9-39.9]	33.4 (26.8-38.8)	14.9 [7.7-23.7]	0.66 (0.42-0.80)
ROI 4	37.1 [29.6-45.7]	30.9 [22.3-40.6]	41.8 (35.1-47.6)	16.2 [7.8-25.2]	0.51 (0.15-0.72)

Patellar tendon stiffness was assessed using Shear-wave Elastography (SWE), expressed as median [interquartile range] in kPa.
[b]CV: Coefficient of Variation (%), 95% confidence interval.
[c]CR: Coefficient of Repeatability (kPa), also referred to as the Smallest Real Difference (SRD).
[d]ICC: Intraclass Correlation Coefficient (ICC), 95% confidence interval.

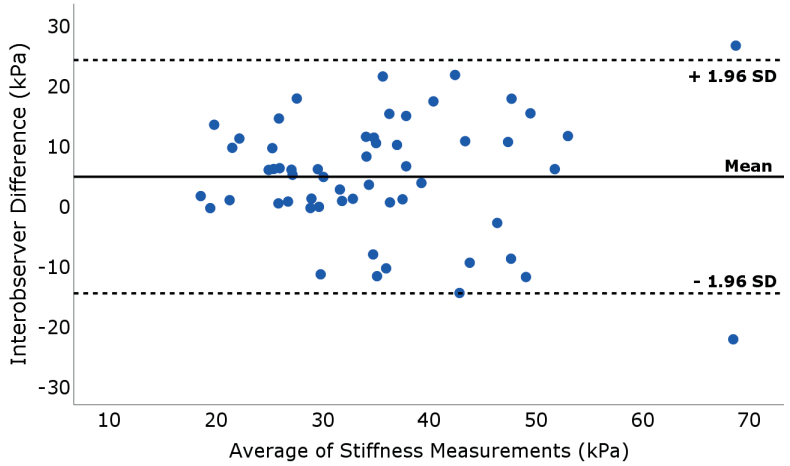

Figure 4: Interobserver reliability of bilateral SWE in twenty-eight healthy athletes. Bland-Altman plot illustrating the interobserver reliability for the patellar tendon stiffness assessment using SWE. The differences between each pair of the two examiners' stiffness measurements plotted on the y-axis are shown against the mean of these measurements on the x-axis. The solid line represents the mean value and dashed lines represent the limits of agreement, defined as mean ± 1.96SD

DISCUSSION

In this study on the implementation of SWE on the patellar tendon in jumping athletes with patellar tendinopathy and activity-matched controls, we found that patellar tendinopathy was associated with significantly higher patellar tendon stiffness, both in univariate analyses and in adjusted multivariate analyses. The intraobserver reliability of the SWE analysis was excellent and the interobserver reliability for independent SWE acquisitions and analyses was good. This finding of tendon stiffening in PT provides additional information to GSUS/

PDUS and could lead to improved understanding of the disease and eventually in altered therapeutic decision-making, for example, by staging the altered viscoelastic properties in PT and by monitoring the response to therapeutic interventions.

The trend of increased stiffness was in accordance with experiments on patellar tendon specimens that reproduced the increased state of tissue hydration in PT by using hypotonic solutions.[29] This effect may be explained by "hydraulic stiffening," which has previously been described in bones.[30] However, the findings of SWE implementations in PT by different authors are not only different, but even contradictory: both increased[14,31] and decreased stiffness[32,33] in PT have been reported.

Inconsistencies in those studies included methods of image analysis, different ultrasound equipment, and different positioning of the knee. These inconsistencies form potential explanations for the discordant SWE results.[15] First, the effect of knee positioning on SWE outcome has been studied by several authors in which the same trend of increased stiffening in more flexed positions of the knee was found.[34,35] In passive extension of the knee, we produced less physiological tensile stress on the patellar tendon which enabled to depict better contrasts in the acquired elastograms, whereas in 30 degrees of flexion, the tensile stress was much larger, which complicated the SWE acquisition. Therefore, standardized positioning of the knee is regarded as an important factor to enhance comparability of results.[36] Second, image analysis varied in other studies from a very small single ROI (1 mm diameter) in representative locations of the patellar tendon to a single ROI with flexible diameters centered in the hypoechoic region of the proximal patellar tendon.[14,33] We evaluated average stiffness over the proximal patellar tendon as we assumed that pathological intratendinous changes are diffuse, similar to histologic findings of tissue surrounding a tendinotic lesion in Achilles tendinopathy.[37,38] Moreover, our fixed region of interest facilitated the comparison of tendon stiffness with controls. Third, shear-wave velocities obtained with different US equipment can vary, even between different transducers and different acquisition depths.[39]

Other differences of our study compared with previous studies were [1] the extensive inclusion protocol to verify the eligibility of participants, including a comprehensive physical examination with ultrasonographic confirmation as the reference standard, and [2] the assessment of intraobserver and interobserver reproducibility of SWE, which has not been reported in studies with comparable sample size. Nevertheless, the intraobserver and interobserver reliability we found were comparable with other studies using smaller sample sizes.[34,40]

Strengths of our study are the relatively large sample size and homogeneity of the study population with respect to age and level of sports. Due to our stringent inclusion criteria, the study population represented the predefined target group consisting of athletes perform-

ing sports involving frequent jumping and cutting in which PT is most prevalent. We also excluded other causes for anterior knee pain than PT such as patellofemoral pain. Patellofemoral pain is difficult to distinguish from PT without focused physical examination[20] which has led to a substantial amount of exclusions after physical examination in our study (12% of athletes who were potentially eligible after online screening). Inadequate sampling methods for athletes with anterior knee pain can potentially affect results of tendon stiffness.

The main limitation of our study is the known clinical status of the athletes before the SWE acquisition was performed, because GSUS and PDUS were part of our initial eligibility assessment in PT athletes. A second limitation is the difference in baseline characteristics between PT athletes and controls, despite the relative small differences of age and anthropometric characteristics. Therefore, we interpreted the clinical relevance of these differences as minimal. Third, the intraobserver reliability was based on analysis of multiple elastograms from one acquisition in PT athletes and interobserver reliability was based on a subset of healthy controls, where both SWE acquisitions and image analyses were performed by independent examiners.

Future research directions would comprise implementation of SWE before any reference standard is performed using standardized acquisition protocols, assessment of the prognostic value of patellar tendon stiffness in longitudinal studies, and its role to monitor therapy response.

In conclusion, SWE is able to detect higher stiffness of the proximal patellar tendon in athletes with patellar tendinopathy with a good to excellent reliability, and could provide attractive novel biomarkers to assess therapy response.

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4

Decreasing patellar tendon stiffness during exercise therapy for patellar tendinopathy is associated with better outcome.

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J Sci Med Sport. 2022 May;25(5):372-378.

ABSTRACT

Objectives: To assess the associations between: 1) baseline patellar tendon stiffness and clinical outcome after exercise therapy in athletes with patellar tendinopathy and 2) the change in patellar tendon stiffness and clinical outcome during progressive tendon-loading exercise therapy and eccentric exercise therapy.

Design: Randomized controlled trial.

Methods: Athletes with patellar tendinopathy aged 18-35 years, playing tendon-loading sports at least 3 times per week were randomized in a 1:1 ratio between progressive tendon-loading exercise therapy and eccentric exercise therapy for 24 weeks. Patellar tendinopathy was diagnosed clinically, and confirmed by ultrasound. Patellar tendon stiffness (kilopascal, kPa) was assessed using shear-wave elastography. Clinical outcome was assessed using the validated Victorian Institute of Sports Assessment (VISA-P; range 0-100) questionnaire. Both were assessed at baseline, 12 and 24 week follow-up. Adjusted general linear, mixed-linear models and Generalized Estimating Equations were used.

Results: We included 76 athletes (58 men, mean age 24 ± 4 years). No association was found between baseline stiffness and VISA-P after 24 weeks ($p = 0.52$). Decreased stiffness (adjusted mean difference = 10 kPa (95% CI: 4-15) was significantly associated with improved clinical outcome at 12 weeks in all athletes ($p = 0.02$), and at both 12 and 24 weeks ($p = 0.01$) in athletes allocated to progressive tendon-loading exercise therapy.

Conclusions: Patellar tendon stiffness, assessed with shear-wave elastography, is unsuitable to use as a single predictive measurement for clinical outcome. Decreasing stiffness during the course of exercise therapy is associated with improved clinical outcome in athletes recovering from patellar tendinopathy.

INTRODUCTION

Patellar tendinopathy (PT) is an overuse injury of the patellar tendon, which commonly occurs in athletes performing sports that involve repetitive jumping and landing (e.g. basketball, volleyball).[1] PT results in load-related anterior knee pain and often affects sports participation and performance.[2] Additionally, participation in physically demanding work is reduced in 58% of the patients with PT.[3] Recently, the concerns, frustrations, impact on quality of life and daily functioning in individuals with tendinopathy have been well described.[4]

The diagnosis of PT is based on load-related pain localized at the inferior patellar pole.[5] The role of imaging, mostly ultrasound, is to confirm the clinical diagnosis by assessing alterations in tendon morphology.[6] The treatment of PT consists of strengthening exercises and aims to improve tendon symptoms, function and structure.[7] Heavy-load eccentric exercise therapy (EET) is regarded as preferential treatment.[8] However, the role of EET is controversial because EET is painful to perform and studies have found that EET is ineffective when applied in the competitive season.[9] A novel approach is progressive tendon-loading exercise therapy (PTLE) that is performed within the limits of pain.[2]

The monitoring of clinical outcome in PT is typically performed using the validated Victorian Institute of Sports Assessment questionnaire for patellar tendons (VISA-P).[10] From a clinical perspective, parameters associated with clinical outcome or structural tendon changes would facilitate defining patient subgroups and assessment of therapeutic response. However, there is strong evidence to support that there is no adaptation of patellar tendon structure on ultrasound, MRI or CT in response to eccentric exercise therapy.[11] Hence, suitable prognostic imaging biomarkers for PT are currently lacking.

Shear-wave elastography (SWE) is an ultrasound-based technique that is able to assess tendon stiffness quantitatively and can be implemented to estimate structural tendon properties.[12] Using SWE, a higher patellar tendon stiffness was found in athletes with patellar tendinopathy than in healthy athletes.[13] In relatively small longitudinal trials, altered tendon stiffness measured with SWE was associated with improved tendinopathy symptoms.[14,15] However, the direction of change was contradictory in those studies, where both increased tendon stiffness[14] and decreased tendon stiffness[15] have been associated with improved clinical outcome after conservative treatment. We hypothesized that temporal changes in patellar tendon stiffness can be detected using shear-wave elastography and are associated with clinical outcome in athletes with patellar tendinopathy performing exercise therapy.

Our first aim was to investigate whether baseline patellar tendon stiffness, as measured with SWE, is associated with clinical outcome after exercise therapy in athletes with PT. The second

aim was to evaluate the association between longitudinal changes in patellar tendon stiffness and changes in symptom severity during PTLE and EET.

METHODS

Participants included in the JUMPER-study, a randomized-controlled trial investigating progressive tendon-loading exercise therapy (PTLE) versus eccentric exercise therapy (EET) in patients with PT were studied.[16] The trial protocol was registered on ClinicalTrials.gov (ID: NCT02938143) before recruitment. Ethical approval was obtained by the institutional review board and all participants provided written informed consent.

Inclusion criteria were: age 18–35 years old; history of knee pain localized in the region of the patellar tendon in association with training and competition; performing sports at least 3 times a week; tenderness on palpation of the corresponding area on the proximal patellar tendon; structural tendon changes on grayscale ultrasound and/or increased tendon vascularity on power Doppler; Victorian Institute of Sports Assessment (VISA-P) score < 80 out of 100 points.[10] Exclusion criteria are presented in the trial register.

Eligibility of applicants was initially assessed with medical history taking and comprehensive physical examination, including tests for assessing presence of patellofemoral pain.[17] Activity level was evaluated using the Cincinnati Sports Activity Scale (CSAS).[18] Clinical evaluation was performed by an experienced sports physician (R-JdV) with 10 years experience.

Grayscale ultrasound (GSUS) and power Doppler US (PDUS) were performed to confirm the clinical diagnosis, using a GE Logiq E9 ultrasound machine (GE Healthcare) and a linear 5–15 MHz transducer (ML6-15, GE Healthcare). Ultrasound gel (Sonogel Vertriebs GmbH) was used at room temperature (21 °C). Ultrasound was performed by one investigator with 5 years experience (SJB), and regarded conclusive for PT when structural changes to normal parallel ordered collagen fibers and/or hypoechoic changes and/or tendon thickening (anterior-posterior diameter >6 mm) were confirmed and/or presence of intratendinous Doppler flow was detected on PDUS.[19]

Shear-wave elastography (SWE) was performed on the same machine with a linear 3.1–10 MHz transducer (9L, GE Healthcare). Patellar tendon stiffness was quantified in the proximal patellar tendon using a standardized protocol described previously.[13] The shear wave speed acquired was directly converted to Young's Modulus on the ultrasound system. SWE was performed with patients in supine position and passive extension of both knees to remove tensile stress from the patellar tendon.

Patients were randomized to progressive tendon-loading exercise therapy (PTLE) or eccentric exercise therapy (EET) for 24 weeks. PTLE (interventional treatment) was performed within limits of acceptable pain and consisted of four consecutive stages (isometric, isotonic, plyometric and sport-specific exercises).[2] The EET-group (control treatment) performed painful usual care single-leg squats on a decline board.8. Details regarding the trial interventions are published elsewhere.[16]

Clinical and imaging outcomes were collected at baseline, 12 and 24 weeks by the main investigator (SJB) who was blinded for allocated treatment during the entire follow-up period.

Clinical outcome was assessed using the self-administered validated Victorian Institute of Sports Assessment questionnaire for patellar tendons (VISA-P). This questionnaire incorporates pain, function and ability to play sports (range 0–100), on which 100 represents no pain, maximum function and unrestricted ability to play sports.[10] Clinical outcome was assessed before the imaging outcomes were obtained. The main investigator was blinded for the VISA-P scores at the time of image acquisition and analysis.

Quantitative analyses of the elastograms for assessment of tendon stiffness in the proximal patellar tendon were performed by the same investigator, directly after acquisition. ROIs were placed on GSUS-images with fully transparent elastograms overlaying GSUS, covering the proximal 2 cm of the patellar tendon, starting 5 mm distally from the inferior patellar border. This image analysis procedure was published elsewhere and demonstrated excellent intraobserver and good interobserver reliability.[13]

Normality of data was assessed using Shapiro–Wilk's test. The association between baseline patellar tendon stiffness and clinical outcome was analyzed using an adjusted general linear model. Longitudinal changes in stiffness and clinical outcome were assessed using adjusted Generalized Estimating Equation (GEE) models, to estimate population-averaged effects. Whole group analyses were performed and between-group differences in relation to the time course of the dependent variables were evaluated using an interaction term 'study arm ∗ visit' in the GEE model, where the visit variable defined baseline, 12 weeks or 24 weeks. Bonferroni corrections were applied for results of the GEE-models to minimize type-I errors. Associations with clinical outcome were evaluated using adjusted mixed linear models. All models were adjusted for pre-defined potential confounding factors, including age, sex, BMI, CSAS and symptom duration. Baseline stiffness was additionally added as an adjustment factor. All analyses were performed following an intention-to-treat principle. Imputation of missing data was not performed, because missing data was assumed to occur not at random. Instead, posthoc sensitivity analysis using the last observation carried forward (LOCF) approach was performed when the amount of missing data exceeded 5% of the total number

of observations.[20] Statistical analysis was performed using IBM SPSS software version 25 (IBM Corp.). Statistical significance was defined as a p-value <0.05.

RESULTS

In total, 272 athletes were screened for eligibility and 76 athletes with clinically diagnosed and ultrasound-confirmed PT were consecutively included between January 2017 and June 2019. Athletes participated in volleyball (n = 26), soccer (n = 17), basketball (n = 16), korfball (n = 8), track and field (n = 4), field hockey (n = 3), and handball (n = 2) as primary sports. Of these, 38 were randomized to PTLE and 38 to EET (Fig. 1). Most patients (82%) underwent prior treatment for PT but failed to recover fully. Nine athletes (12%) were lost to follow-up. Demographic characteristics of the study population are listed in Supplementary Table 1.

Among all athletes, the estimated mean VISA-P score improved significantly from 57 (95% CI: 53–61) at baseline to 72 (95% CI: 67–76; p < 0.001) at 12 week and 80 (95% CI: 76–84; p < 0.001) at 24 week follow-up (Table 1). The estimated mean VISA-P score improved from 56 (95% CI: 52–61) at baseline to 84 (95% CI: 79–89; p < 0.001) at 24 weeks in the PTLE-group and from 57 (95% CI: 53–62) to 75 (95% CI: 69–82; p < 0.001) in the EET-group. The adjusted mean between-group difference of the VISA-P score at 24 weeks was 9 (95% CI: 1–16; p = 0.02), in favor of the PTLE-group.[16]

Table 1. Main Outcome Measures at 12 and 24 Weeks in the Progressive Tendon-loading Exercise (PTLE) and Eccentric Exercise Therapy (EET) Groups

VISA-P score, estimated mean (95% CI)	**Whole group analysis (N=76)**	**PTLE group (n = 38)**	**EET group (n = 38)**	**Adjusted mean between-group difference[a]**
Baseline	56.8 (53.1 to 60.5)	56.2 (51.6 to 60.8)	57.4 (52.5 to 62.3)	-1.2 (-7.1 to 4.7)
12 weeks	71.5 (67.3 to 75.7)	72.1 (67.0 to 77.2)	70.7 (65.0 to 76.3)	1.4 (-5.5 to 8.3)
24 weeks	80.0 (75.8 to 84.3)	84.0 (79.3 to 88.6)	75.2 (69.0 to 81.5)	**8.7 (1.2 to 16.2)**
VISA-P score, unadjusted mean (±SD)	**Whole group analysis (N=76)**	**PTLE group (n = 38)**	**EET group (n = 38)**	**Unadjusted mean between-group difference**
Baseline	55.3 ± 13.1	55.0 ± 13.1	55.6 ± 13.2	-0.6
12 weeks	69.5 ± 14.6	71.2 ± 13.8	67.7 ± 15.4	3.5
24 weeks	78.8 ± 15.7	82.8 ± 13.1	73.7 ± 17.3	9.1

[a]The mean estimated patellar tendon stiffness (95% CI) is denoted. These scores and the adjusted between-group differences were calculated using Generalized Estimating Equations (GEEs) with adjustments for the following pre-defined baseline variables: age, sex, BMI, symptom duration and Cincinnati Sports Activity Scale. Adjusted between-group differences that were significant at 0.05 level after Bonferroni correction are bolded.

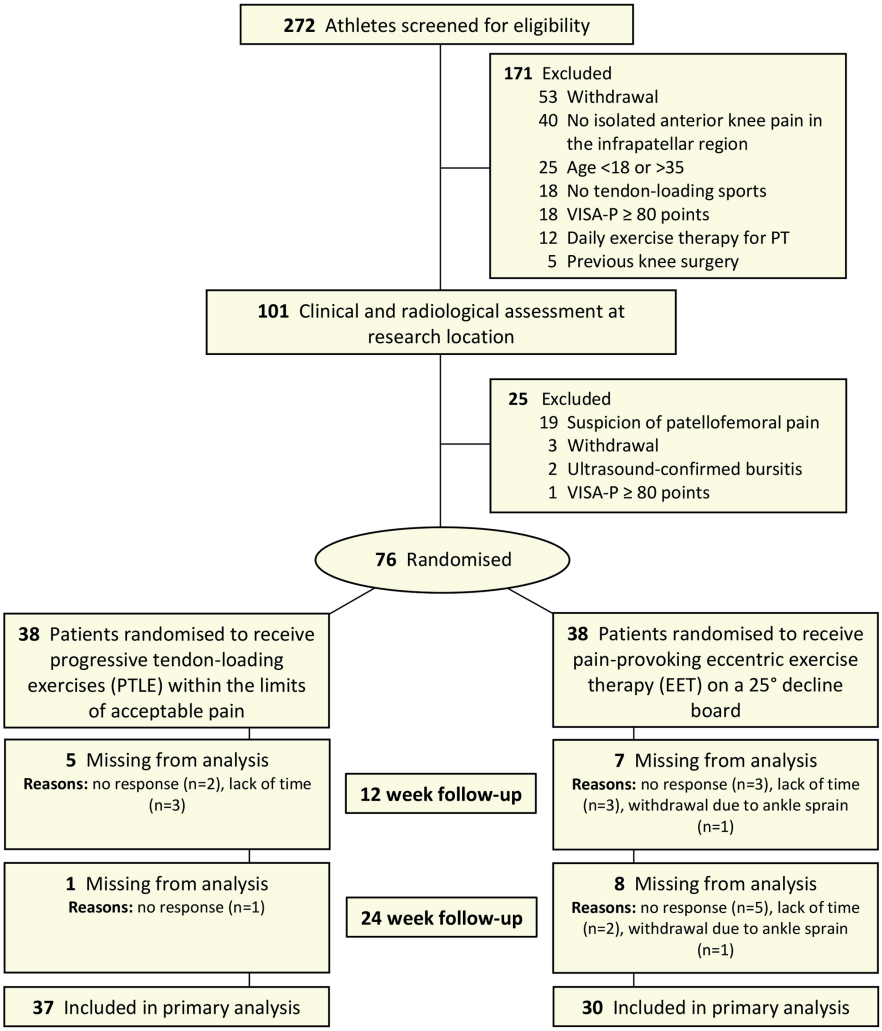

Figure 1: The CONSORT flow diagram. CONSORT: Consolidated Standards of Reporting Trials.

Median [IQR] baseline stiffness of the proximal patellar tendon among all athletes was 75 kPa [56–105]. At baseline, athletes allocated to PTLE had higher median stiffness (86 kPa [58–115]) than athletes allocated to EET (70 kPa [51–97]) ($p = 0.08$). There was no association between patellar tendon stiffness at baseline and VISA-P scores at 12 week ($\beta = -0.27$ [95% CI: −0.84 to 0.30]; $p = 0.34$) and 24 week follow-up ($\beta = -0.18$ [95% CI: −0.71 to 0.37]; $p = 0.52$). Likewise, no association was found between baseline stiffness and clinical outcome at 12 and 24 week follow-up, both for athletes allocated to PTLE (12 weeks $\beta = -0.70$ [95% CI: −1.72 to 0.32]; $p = 0.17$ and 24 weeks $\beta = -0.76$ [95% CI: −1.75 to 0.24]; $p = 0.13$) and to EET (12 weeks $\beta = -0.12$ [95% CI: −1.01 to 0.78]; $p = 0.79$ and 24 weeks $\beta = -0.18$ [95% CI: −1.07 to 0.71]; $p = 0.67$).

Among all athletes, median [IQR] patellar tendon stiffness decreased significantly from 75 kPa [56–105] to 70 kPa [50–92] at 12 weeks (adjusted mean difference (95% CI) = 8 kPa (2–14), p = 0.03) and 68 kPa [49–94] at 24 weeks (adjusted mean difference (95% CI) = 10 kPa (4–15), p = 0.005). The difference between 12 and 24 weeks (1 kPa [95% CI: −5 to 8]; p = 1) was not statistically significant.

In the PTLE-group, median [IQR] stiffness decreased significantly from 86 kPa [58–115] at baseline to 69 kPa [50–91] at 12 weeks (adjusted mean difference (95% CI) = 16 kPa (7–26), p = 0.005) and 66 kPa [49–98] at 24 weeks (adjusted mean difference (95% CI) = 16 kPa (9–23), p < 0.001). The mean difference between 12 and 24 weeks (0.3 kPa [95% CI: −9 to 9]; p = 1) was not statistically significant.

In the EET group, there was no significant change in median [IQR] patellar tendon stiffness from baseline (70 kPa [51–97]) to 12 weeks (72 kPa [52–99]) and 24 weeks (69 kPa [47–93]). Adjusted mean differences (95% CI) were − 1 kPa (−8 to 6) and 2 kPa (−7 to 11), respectively (p = 1).

Adjusted and unadjusted longitudinal changes in patellar tendon stiffness are listed in Table 2 and illustrated in Supplementary Fig. 1. An example of the longitudinal assessment of patellar tendon stiffness is illustrated in Supplementary Fig. 2.

The parameter estimate for the 'study arm ∗ visit' interaction using GEE was statistically significant (p = 0.006), indicating a different course of patellar tendon stiffness over time between both study arms. Adjusted mean between-group differences were not statistically significant in the original analyses at 12 weeks (7 kPa [95% CI: −5 to 19]; p = 1) and at 24 weeks (4 kPa [95% CI: −9 to 16]; p = 1). Additional analyses including baseline stiffness as the adjustment factor showed that the between-group difference was statistically significant at 12 weeks (14 kPa [95% CI: −25 to −4]; p = 0.04), but not at 24 weeks (11 kPa [95% CI: −21 to −1]; p = 0.22).

The relation between changes in patellar tendon stiffness and VISA-P score is illustrated in Supplementary Fig. 3. Among all athletes, no significant relationship between change in patellar tendon stiffness over time and change in VISA-P score during 24 weeks of exercise therapy was found (β = −0.03 [95% CI: −0.11 to 0.04]; p = 0.36). However, a significant association was found between decreased patellar tendon stiffness after 12 weeks and improved clinical outcome after 12 weeks (β = −0.12 [95% CI: −0.21 to −0.02]; p = 0.02).

Among athletes allocated to PTLE, we found a significant association between decrease in patellar tendon stiffness over time and improved VISA-P score after both 12 weeks (β = −0.22

[95% CI: −0.34 to −0.10]; p = 0.001) and 24 weeks (β = −0.12 [95% CI: −0.20 to −0.03]; p = 0.01). No relationship was found in athletes allocated to EET (β = 0.13 [95% CI: 0.0 to 0.3]; p = 0.05).

Table 2. Adjusted and unadjusted comparisons of the change in patellar tendon stiffness from baseline to 12 and 24 weeks

Whole group analysis (N=76)	**Patellar tendon stiffness (kPa), [IQR] (raw data)**	**Unadjusted change from baseline to 24 weeks [IQR]**	**Estimated mean (95% CI)[a]**	**Adjusted within-group difference (from baseline)**
Baseline	74.9 [56.4 to 105.4]		68.4 (60.2 to 76.6)	
12 weeks	69.7 [50.2 to 91.8]	-2.4 [-12.9 to 10.1]	60.2 (51.5 to 69.0)	**-8.1** **(-14.5 to -1.9)**
24 weeks	68.0 [48.7 to 94.1]	-11.0 [-28.7 to 8.3]	58.9 (51.4 to 66.3)	**-9.5** **(-15.2 to -3.8)**
PTLE-group (N=38)	**Patellar tendon stiffness (kPa), [IQR] (raw data)**	**Unadjusted change from baseline to 24 weeks [IQR]**	**Estimated mean (95% CI)[a]**	**Adjusted within-group difference (from baseline)**
Baseline	86.4 [57.9 to 115.1]		73.7 (62.2 to 85.2)	
12 weeks	69.2 [50.0 to 91.0]	-3.7 [-42.8 to 6.3]	57.4 (46.9 to 67.8)	**-16.3** **(-25.8 to -6.8)**
24 weeks	66.3 [48.8 to 97.5]	-15.7 [-30.5 to 0.7]	57.7 (48.6 to 66.7)	**-16.0** **(-23.0 to -9.1)**
EET-group (N=38)	**Patellar tendon stiffness (kPa), [IQR] (raw data)**	**Unadjusted change from baseline to 24 weeks [IQR]**	**Estimated mean (95% CI)[a]**	**Adjusted within-group difference (from baseline)**
Baseline	70.0 [50.9 to 96.7]		63.2 (55.1 to 71.2)	
12 weeks	72.4 [52.3 to 98.7]	2.0 [-7.4 to 14.6]	64.5 (54.6 to 74.4)	1.3 (-5.6 to 8.2)
24 weeks	69.1 [46.9 to 92.7]	-1.9 [-13.5 to 12.3]	61.2 (51.3 to 71.2)	-1.9 (-10.8 to 6.9)

[a]The mean estimated patellar tendon stiffness (95% CI) is denoted. These scores and the adjusted within-group differences were calculated using Generalized Estimating Equations (GEEs) with adjustments for the following pre-defined baseline variables: age, sex, BMI, symptom duration and Cincinnati Sports Activity Scale. Adjusted within-group differences that were significant at 0.05 level after Bonferroni correction are bolded.

Twenty-two of the 228 SWE-acquisitions (10%) were missing. Sensitivity analyses to assess the influence of missing data showed that the estimated mean VISA-P score improved significantly from 56 points (95% CI, 53–60) at baseline to 69 points (95% CI, 65–73; p < 0.001) at 12 week and 78 points (95% CI, 74–82; p < 0.001) at 24 week follow-up among all athletes. After 24 weeks, the adjusted mean between-group difference was 11 (95% CI, 3–18; p = 0.004). For patellar tendon stiffness, the adjusted mean difference (95% CI) was 14 kPa (5–23; p = 0.01) for the PTLE-group and 1 kPa (−5 to 6; P = 1) for the EET-group at 12 weeks.

At 24 weeks, the adjusted mean difference (95% CI) was 16 kPa (9–22; $p < 0.001$) for the PTLE-group and 2 kPa (–5 to 10; $p = 1$) for the EET-group. In the additional analyses including baseline patellar tendon stiffness as the adjustment factor, the association of patellar tendon stiffness with clinical outcome was significant at both 12 week follow-up ($\beta = -0.13$ [95% CI: –0.22 to –0.03]; $p = 0.009$) and 24 week follow-up ($\beta = -0.08$ [95% CI: –0.16 to –0.00]; $p = 0.04$).

DISCUSSION

We found no predictive value of patellar tendon stiffness at baseline for clinical outcome after 24 weeks in athletes with patellar tendinopathy (PT). Stiffness of the patellar tendon decreased significantly during exercise therapy in athletes that performed progressive tendon-loading exercise therapy (PTLE), but not in athletes performing usual care eccentric exercise therapy (EET). Decreased stiffness was significantly associated with improved clinical outcome at 12 weeks in all athletes, and at both 12 and 24 weeks in PTLE-allocated athletes.

Clinical outcome after 24 weeks improved significantly both in athletes allocated to PTLE (intervention group) and athletes allocated to EET (control group), but PTLE provided superior clinical outcomes compared with EET. Patellar tendon stiffness decreased significantly in the PTLE-group and this group had a favorable clinical outcome. The athletes allocated to EET had less clinical improvement and patellar tendon stiffness did not change in this group. The observation that patellar tendon stiffness decreased significantly in only PLTE-allocated athletes but not in EET-allocated athletes despite improved clinical outcome in both groups after 24 weeks indicates that there is no one-to-one relationship between stiffness and clinical outcome. This difference could be related to the superior clinical outcome in PTLE-allocated athletes (adjusted mean between-group difference of 9 points on the VISA-P scale), but could also be related to the different mechanisms of the therapeutic interventions. There is lacking pathophysiologic explanation for the decrease in patellar tendon stiffness in response to PTLE but not to EET. Our study adds to the evidence that supports an adaptation process of the patellar tendon in response to exercise therapy, a finding that had currently been based on studies that implemented more complex methods for assessment of structural patellar tendon properties.[21-23]

Decreasing patellar tendon stiffness in patients performing eccentric exercises and more progressive tendon-loading exercises (such as heavy slow resistance training) was also found in studies performed by Lee et al. (EET) and Kongsgaard et al. (HSR).[22,23] Lee et al. implemented 12 weeks of eccentric exercises (with and without extracorporeal shock-wave therapy) among 34 in-season athletes with patellar tendinopathy.[22] The eccentric exercise protocol used in

that study was comparable to EET performed in our study. Patients in both studies were instructed to apply additional load in a backpack to increase the intensity of the exercises if no or only minimal pain was experienced when performing the exercises.[16,22] The association of a greater reduction in tendon stiffness with better clinical outcomes was in accordance to our findings. However, our findings also partly differed from the study by Lee et al. because we observed the decreasing trend in patellar tendon stiffness in response to exercise therapy only in patients allocated to PTLE and not in patients allocated to EET. Another difference is the quantification of patellar tendon stiffness. We applied shear-wave elastography (SWE) to quantify patellar tendon stiffness and Lee et al. performed measurements of tendon deformation during muscle contraction with conventional ultrasound and EMG-measurements. In the study by Kongsgaard et al., eight patients with PT performed 12 weeks of heavy slow resistance training with increasing loads.[23] Similar to the study performed by Lee et al., the authors used force–deformation curves from patellar tendon elongation measurements obtained from ultrasound to calculate patellar tendon stiffness. Kongsgaard et al. also found decreasing patellar tendon stiffness after HSR training.

The major differences with the studies described above were the measurements of patellar tendon stiffness, the sample size and the follow-up duration. We used SWE to measure patellar tendon stiffness, which is less dependent on custom made experimental set-ups, the need for EMG measurements and potential confounding by antagonist coactivation during the graded knee extension efforts that could lead to an underestimation of tendon stress.[24] Moreover, SWE is not dependent on the inability of the ultrasound transducer to cover the entire area of the patellar tendon from the inferior patellar border to the tibial tuberosity. The sample size in our study was considerably larger (76 patients vs. 34 and 8 patients) and the follow-up duration was twice as long than in the other two trials. This might be an explanation for the observed differences between our results and the above-mentioned studies.

A possible explanation for the decrease in patellar tendon stiffness in the PTLE-group but not in the EET-group is that the elastic properties of the patellar tendon change differently in response to the different loading types in the exercise groups. Whereas athletes in the PTLE-group performed exercises that progressively increased loads to the patellar tendon, athletes in the EET-group performed repetitive exercises with continuously high strains.[16] Previous work showed that EET results in an immediate increase in patellar tendon stiffness, but normalized stiffness after 48 h.[25] It might be that EET only has acute effects on pain and stiffness, but no long-lasting effects. Our observation that decreasing stiffness in athletes undergoing PTLE also had a better clinical outcome than athletes allocated to EET, provides an additional argument to opt for PTLE over the current usual care (EET) in the rehabilitation of PT.[8,16]

Results in other studies that assessed SWE longitudinally were contradictory regarding the relationship between patellar tendon stiffness and clinical outcome. An increased stiffness was associated with improved symptoms in a study that included Achilles, patellar and humeral-epicondylar tendons treated with stretching exercises, temporary sports cessation and local polidocanol administration.[14] This study population was less homogenous than our study population and assumed that the direction of the change in tendon stiffness was similar for all different tendons studied. Other authors have found that athletes with Achilles and patellar tendinopathy displayed lower Achilles tendon stiffness and higher patellar tendon stiffness, respectively, compared to controls.[26] Decreased stiffness was associated with improved symptoms in a small study of 31 athletes that were treated with extracorporeal shockwave therapy.[15] The association with VISA-P was demonstrated using correlation analysis only, without correction for potential confounders using advanced statistical methods. In both studies, different SWE equipment vendors and different methods for analyzing the elastograms were used and information regarding reproducibility was lacking.

Strengths of our study were the standardized protocol for image acquisition and analysis, that both were performed by one trained examiner who was blinded to the severity of symptoms. Our method for quantification of patellar tendon stiffness demonstrated excellent intra-observer reliability and good interobserver reliability.[13] We considered the face validity (does SWE appear to measure what it aims to measure?) of SWE as good, because we found a significant difference in patellar tendon stiffness between healthy athletes and patients with PT in our previous study.[13] This was in accordance with findings in other studies investigating the difference in patellar tendon stiffness between patients and healthy athletes.[26,27] Another strength is the specific study population that was identified by both clinical examination and ultrasound confirmation, to rule out any other causes for anterior knee pain than PT, such as patellofemoral pain.[28] The VISA-P questionnaire used for assessing pain, function and ability to play sports was validated and specifically developed for scoring symptoms from patellar tendinopathy.[10] The VISA-P score was administered before image acquisition on every visit of the trial and, therefore, imaging findings could not have influenced the participants' scoring.

Limitations of our study were mainly related to the validity of SWE as an imaging biomarker. Despite the fact that SWE was able to detect higher stiffness of the proximal patellar tendon in athletes with patellar tendinopathy than in healthy athletes with a good to excellent reliability, the technical validity of SWE is not yet supported by gold standard tests, such as direct measurements on muscle-tendon units in rats during stimulated contractions.[29]

From the data presented in Table 2, one could conclude that there is a baseline difference in patellar tendon stiffness between the PTLE-group and EET-group. Inherent to the study design of our randomized controlled trial, eligible athletes were randomly assigned to the

PTLE-group or EET-group. Therefore, the observed difference in baseline tendon stiffness has occurred most likely by chance. By adjusting for the difference in baseline stiffness, we increased the internal validity of the effect estimates. In the additional analyses that also included baseline stiffness as the adjustment factor, we observed that there was a significant between-group difference in the course of the patellar tendon stiffness over time at 12 weeks. This finding indicates that the patellar tendon stiffness tends to decrease during PTLE-exercises, regardless of the difference in baseline stiffness. This indicates that the patellar tendon structure is able to change as a result of PTLE-exercises.

CONCLUSION

In patients with patellar tendinopathy undergoing exercise therapy, SWE is able to identify changes in patellar tendon stiffness during therapy indicating favorable clinical outcome after 24 weeks, while it is unsuitable as a single predictive measurement at baseline for clinical outcome.

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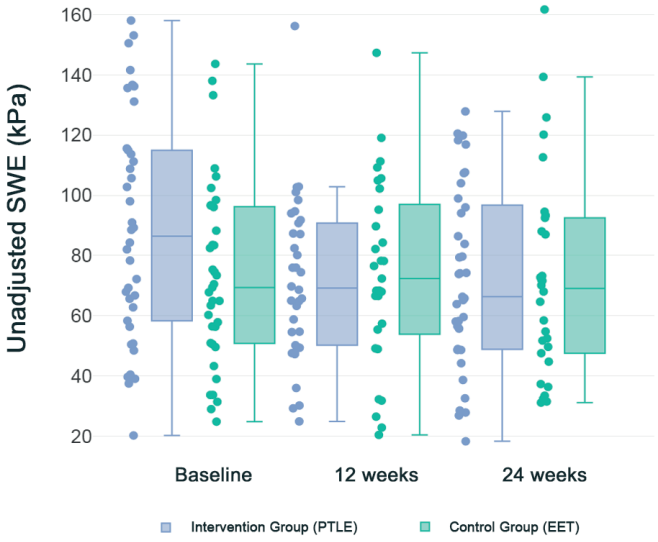
SUPPLEMENTARY MATERIAL

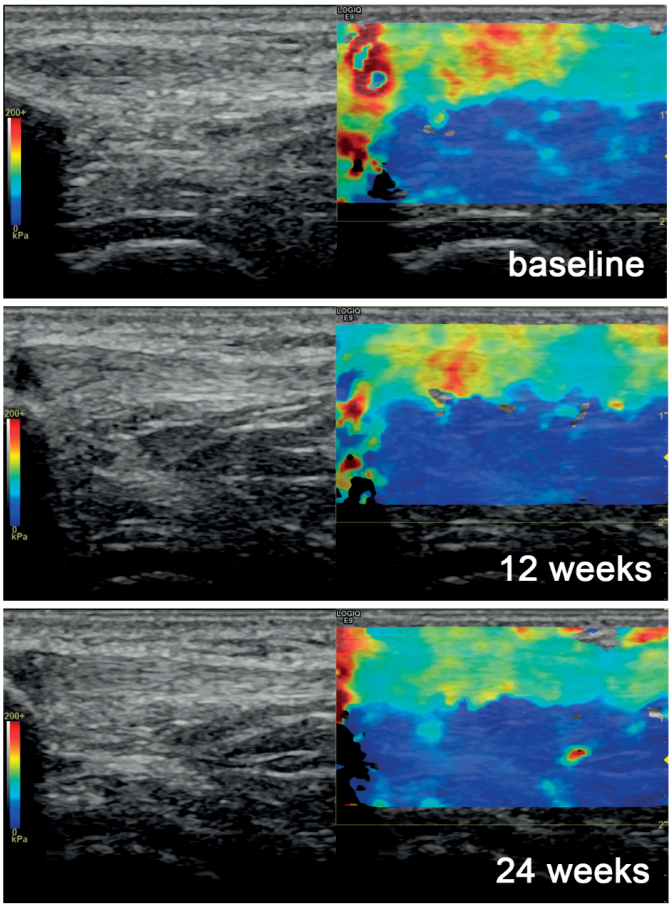
Supplementary Table 1: Baseline Characteristics

Characteristics	**Whole group (n=76)**	**PTLE Group (n = 38)**	**EET Group (n = 38)**
Age, mean (SD), years	24 (3.8)	24 (3.5)	24 (4.2)
Sex, male	58 (76)	31 (82)	27 (71)
BMI, mean (SD)	23.9 (2.9)	23.8 (2.5)	24.1 (3.2)
Symptom duration, median [IQR], weeks	104 [43-208]	119 [64-273]	78 [40-169]
VISA-P score, mean (SD)	55 (13.1)	55 (13.1)	56 (13.2)
Sports Activity Scale (CSAS) prior to onset of PT			
Level I (4 to 7 days/week)			
100	17 (22)	10 (26)	7 (18)
95	0 (0)	0 (0)	0 (0)
90	0 (0)	0 (0)	0 (0)
Level II (1 to 3 days/week)			
85	50 (66)	23 (61)	27 (71)
80	9 (12)	5 (13)	4 (11)
Sports participation in desired sport at the time of study commencement, n (%)			
Equal	19 (25)	10 (26)	9 (24)
Reduced	29 (38)	14 (37)	15 (40)
Ceased	28 (37)	14 (37)	14 (37)
Affected side			
Unilateral, left/right, n (%)	26 (59) / 18 (41)	10 (53) / 9 (47)	16 (64) / 9 (36)
Bilateral, n (%)	32 (42)	19 (50)	13 (34)
US-assessment			
AP thickness, mm ± SD	8.4 ± 2.3	8.2 ± 2.7	8.6 ± 2.0
Hypoechoic regions, n (%)	76 (100)	38 (100)	38 (100)
Tendon calcifications, n (%)	20 (26)	9 (24)	11 (29)
Patellar erosions, n (%)	24 (32)	17 (45)	7 (18)
Power Doppler			
0: absence of Doppler flow	7 (9)	5 (13)	2 (5)
1: Doppler flow posterior to tendon	0 (0)	0 (0)	0 (0)
2: 1-2 intratendinous blood vessels	18 (24)	12 (32)	6 (16)
3: 3-4 intratendinous blood vessels	7 (9)	3 (8)	4 (11)
4: network of blood vessels	44 (58)	18 (47)	4 (68)

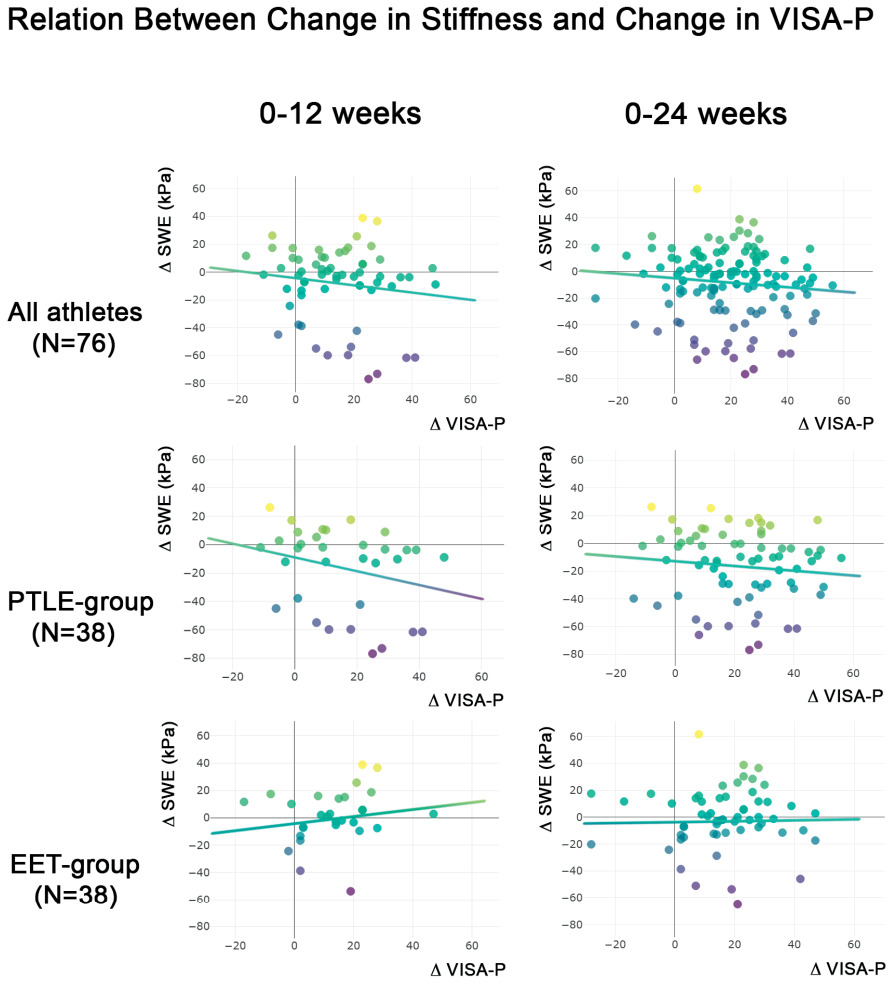
Data are presented as No. (%) unless otherwise specified.



Supplementary Figure 1: Longitudinal changes in patellar tendon stiffness.
Box plot and scatter diagram of longitudinal unadjusted measurements of patellar tendon stiffness.



Supplementary Figure 2: Illustration of longitudinal SWE-acquisitions. Longitudinal shear-wave elastography acquisitions of the proximal patellar tendon in an 21 year old female elite volleyball player, allocated to progressive tendon-loading exercises. At baseline, pronounced red areas were observed in the proximal patellar tendon, indicating increased stiffness. Qualitatively, a gradual decrease of the red areas were observed. The mean patellar tendon stiffness of the proximal patellar tendon was calculated at 78 kPa (baseline), 69 kPa (12 weeks) and 49 kPa (24 weeks). The VISA-P score (0-100) increased from 65 at baseline to 87 after 12 weeks and 92 after 24 weeks.



Supplementary Figure 3: Association between (change in) patellar tendon stiffness and (change in) VISA-P score. Scatter plot of unadjusted changes in patellar tendon stiffness (Δ SWE) values versus unadjusted changes in symptom severity as scored with the validated VISA-P questionnaire for patellar tendinopathy (Δ VISA-P). A decreased patellar tendon stiffness was associated with an improved clinical outcome after 12 weeks in the whole-group analysis (all athletes) and at both follow-ups in the progressive tendon-loading exercises (PTLE) group. There was no relationship between patellar tendon stiffness and clinical outcome in the eccentric exercise therapy (EET) group.

5

Tissue-Specific T2* Biomarkers in Patellar Tendinopathy by Subregional Quantification Using 3D Ultrashort Echo Time MRI.

Breda SJ, Poot DHJ, Papp D, de Vries BA, Kotek G, Krestin GP, Hernández-Tamames JA, de Vos RJ, Oei EHG.

J Magn Reson Imaging. 2020 Aug;52(2):420-430.

ABSTRACT

Background: Quantitative MRI of patellar tendinopathy (PT) can be challenging due to spatial variation of T_2* relaxation times.

Purpose: 1) To compare T_2* quantification using a standard approach with analysis in specific tissue compartments of the patellar tendon. 2) To evaluate test-retest reliability of different methods for fitting ultrashort echo time (UTE)-relaxometry data.

Study type: Prospective.

Subjects: Sixty-five athletes with PT.

Field strength/sequence: 3D UTE scans covering the patellar tendon were acquired using a 3.0T scanner and a 16-channel surface coil.

Assessment: Voxelwise median T_2* was quantified with monoexponential, fractional-order, and biexponential fitting. We applied two methods for T_2* analysis: first, a standard approach by analyzing all voxels covering the proximal patellar tendon. Second, within subregions of the patellar tendon, by using thresholds on biexponential fitting parameter percentage short T_2* (0-30% for mostly long T_2*, 30-60% for mixed T_2*, and 60-100% for mostly short T_2*).

Statistical tests: Average test-retest reliability was assessed in three athletes using coefficients-of-variation (CV) and coefficients-of-repeatability (CR).

Results: With standard image analysis, we found a median [interquartile range, IQR] monoexponential T_2* of 6.43 msec [4.32-8.55] and fractional order T_2* 4.39 msec [3.06-5.78]. The percentage of short T_2* components was 52.9% [35.5-69.6]. Subregional monoexponential T_2* was 13.78 msec [12.11-16.46], 7.65 msec [6.49-8.61], and 3.05 msec [2.52-3.60] and fractional order T_2* 11.82 msec [10.09-14.44], 5.14 msec [4.25-5.96], and 2.19 msec [1.82-2.64] for 0-30%, 30-60%, and 60-100% short T_2*, respectively. Biexponential component short T_2* was 1.693 msec [1.417-2.003] for tissue with mostly short T_2* and long T_2* of 15.79 msec [13.47-18.61] for mostly long T_2*. The average CR (CV) was 2 msec (15%), 2 msec (19%) and 10% (22%) for monoexponential, fractional order and percentage short T_2*, respectively.

Data conclusion: Patellar tendinopathy is characterized by regional variability in binding states of water. Quantitative multicompartment T_2* analysis in PT can be facilitated using a voxel selection method based on using biexponential fitting parameters.

INTRODUCTION

Patellar tendinopathy (PT) is an overuse tendon injury that is typically observed in athletes performing repetitive jumping activities, such as volleyball and basketball.[1] PT results in load-related anterior knee pain at the site of the patellar tendon attachment to the patella.[2] Pain in PT is often chronic, resulting in decreased activity levels and in more than half of the patients in decreased work participation.[3,4]

On histopathological analysis, PT is associated with degenerative tissue changes that are typically located at the posterior aspect of the proximal patellar tendon.[5] Histopathological features of tendinopathy include collagen disorganization and fiber separation with increased proteoglycans and associated glycosaminoglycan (GAG) side chains within the extracellular matrix.[6] This accumulation of GAGs in the proximal patellar tendon leads to an increased water content within the extracellular matrix, because of the highly negative charge of GAGs with a strong potential for binding water.[7] A simplified model to characterize the different water pools within the patellar tendon is the bicomponent model.[8] Water in voxels that contain highly organized collagen is primarily in a "bound" state, thereby restricting the motion of water molecules by stronger spin–spin interactions, thus resulting in shorter T2* relaxation times (reflecting the macromolecular bound water compartment). Loosely bound water or even "free" water pools result in a longer T2*.[9] The different water pools reflect specific tissue compartments within the patellar tendon.[10] Quantifying these different water pools may be clinically relevant, as a previous histological study in patients undergoing surgery demonstrated an association between levels of GAGs and severity of PT symptoms.[11]

Currently, imaging in PT with morphologic magnetic resonance imaging (MRI) techniques is of limited value, because the diagnosis of PT is primarily made clinically.[12] These MR techniques are sensitive for detecting increased signal in the proximal patellar tendon, representing an elevated water content.[13] However, conventional MRI of tendons is typically limited for the assessment of different water pools in the patellar tendon due to the fast free induction decay of collagen.[12] The short T2*-components in tendons will consequently appear dark using conventional sequences. Ultrashort echo time (UTE) sequences are sensitive to different water pools in the patellar tendon.[14] Quantitative T2* mapping is performed by multiple-spin-echo decay analysis using voxelwise fitting methods.[15] Monoexponential, or single-component fitting is a robust method to describe signal decay in which the MR signal in each voxel is assumed to result from only a single component. However, residual signal is observed using this method, indicating that the signal from each voxel consists of different components.[9] In order to gain insight in this subpixel composition, the biexponential model has been introduced to reveal both short and long water components in each voxel.[16] Fractional order fitting has also been proposed as an alternative mathematical model to describe

relaxation in complex heterogeneous tissues and is derived from a nonlinear generalization of the Bloch equations.[17]

The primary aim of this study, therefore, was to quantify T2* in specific tissue compartments by optimizing the image analysis approach in which voxels containing comparable water pools are automatically selected. Moreover, we compared different methods for fitting T2* relaxometry data and evaluated test–retest reliability of the T2* quantification.

MATERIALS AND METHODS

This single-center prospective observational study was approved by the local Institutional Review Board (decision number: NL58512.078.16). Participants provided written informed consent prior to inclusion. We performed cross-sectional analysis of baseline data from a prospective trial investigating the effectiveness of two different exercise programs for PT.

Study Population

Participants were consecutively recruited. To be eligible for inclusion, athletes aged 18–35 years must have a clinical diagnosis of patellar tendinopathy that was confirmed by ultrasound and had to perform sports involving frequent jumping or cutting maneuvers for at least 3 times per week. The activity level was assessed using the Cincinnati Sports Activity Scale (CSAS), which incorporates both frequency of sports participation and the general types of forces experienced by the lower extremity during the sport.[18] The Victorian Institute of Sports Assessment questionnaire for patellar tendons (VISA-P) was administered to measure symptoms, function, and ability to play sports.[19] Criteria for the clinical diagnosis were: 1) a history of localized pain at the inferior pole of the patella, 2) recognizable pain on palpation over the patellar tendon, and 3) injury pain on the single leg squat. Clinical evaluation was performed by a sports physician (R.V.) with 10 years of experience in athlete care. The clinical evaluation was followed by an ultrasound examination (LOGIQ E9, GE Healthcare, Chicago, IL) of the patellar tendon performed by one trained examiner (S.B.: radiologist-in-training with 5 years' experience), and was regarded positive for PT when there was the presence of structural and/or hypoechoic changes and/or tendon thickening (anterior–posterior diameter >6 mm) and/or the presence of intratendinous power Doppler flow.[20] Other eligibility criteria are mentioned in the preregistered trial protocol, ClinicalTrials.gov (ID: NCT02938143).

MR Examination

MRI was performed with a 3.0T clinical scanner (Discovery MR750, GE Healthcare, Waukesha, WI) using a 16-channel small flexible coil (NeoCoil, Pewaukee, WI). For stabilization of the knee, a support device was used in combination with a plastic cylindrical tube and foam

padding to keep the knee flexed at 30° (Fig. 1). The center-spot of the coil was aligned with the inferior patellar border. Acquisition was initiated with a sagittal 3D proton-density (PD) fast spin echo sequence of the knee, which was subsequently used to create precise localizer images to plan further acquisitions aligned with the direction of the collagen fibers of the patellar tendon. The patellar tendon was scanned in the axial plane using 3D-UTE-Cones (GE Healthcare), which is a gradient-echo-based acquisition using radial readout of the k-space. A total of 16 echoes were acquired in four separate multiecho sequences containing four echoes in interleaved order. For each multiecho acquisition, the same repetition time (TR) was used. Total acquisition time was 65 minutes. The full protocol for sequence parameters in this study is listed in Table 1. The MR examination was repeated in three athletes with patellar tendinopathy, who returned the next day for the purpose of measuring reproducibility.

Figure 1: Standardized positioning of the knee during MRI. Illustrated is the positioning of the 16-channel flexible coil in combination with the support device that was used for knee stabilization and standardization of the knee flexion angle.

Table 1. Imaging protocol

Sequence	3D PD Cube	3D PD Cube FS	3D ME-UTE
Matrix	384 x 384	384 x 384	252 x 252
Scan plane	Sagittal	Sagittal	Axial oblique
Fat saturation	-	Fat	2 excitations per FS
FOV (cm)	15.0	15.0	15.0
Resolution (mm)	0.4 x 0.4 x 1.0	0.4 x 0.4 x 1.0	0.6 x 0.6 x 1.5
Slice Thickness (mm)	1.0	1.0	1.5
Number of Slices	120	120	60
TE (ms)	30.0	30.0	0.032/4.87/12.67/20.47 0.49/6.82/14.62/22.42 0.97/8.77/16.57/24.37 2.92/10.72/18.52/26.32
Number of Echoes	1	1	16
TR (ms)	1200.0	1200.0	83.4
Flip Angle (°)			17
Bandwidth (± kHz)	83.33	83.33	125
NEX	0.5	0.5	1.0
Scan Time (mm:ss)	03:17	03:18	13:15

PD: proton density. ME: multi-echo. UTE: ultra-short echo time. FOV: field-of-view. FS: fat saturation. TE: echo time. TR: repetition time. NEX: number of excitations.

Image Preparation

Image registration was performed in order to perform a spatial one-to-one mapping from voxels between the different UTE acquisitions with in-house-developed registration tools (Elastix v. 4.8, Rotterdam, The Netherlands)[21, 22] and MatLab software (R2015b; MathWorks, Natick, MA). Initially, a rigid registration to correct for rotation and translation was performed on the entire knee to compensate for motion in between multiecho scans and separate visits (for the test–retest subjects). Second, a groupwise nonlinear refinement registration was performed inside a volume of interest covering the patellar tendon.[22] The volume of interest was constructed from regions of interest drawn on three orthogonal views.

Fitting Methods

Fitting of the UTE-T2* maps was performed using different models, namely, monoexponential, fractional order, and biexponential fitting. The T2* relaxation time was calculated using three different analysis algorithms, written in MatLab (R2015b; MathWorks).
Mono-exponential T2* was fitted using the model:[23]

$$\boldsymbol{M_m}(TE) = \boldsymbol{a_0} \cdot \boldsymbol{e}^{-\frac{TE}{T_2^*}} \quad \textbf{(1)}$$

Where a_0 is the signal intensity at TE=0.

For bi-exponential T2* analysis, short T2* (T_{2S}*) and long T2* (T_{2L}*) components were fitted with the model:[23]

$$\boldsymbol{M_b}(TE) = \boldsymbol{b_0} \cdot \boldsymbol{e}^{-\frac{TE}{T_{2S}^*}} + \boldsymbol{b_1} \cdot \boldsymbol{e}^{-\frac{TE}{T_{2L}^*}} \quad \textbf{(2)}$$

Where b_0 and b_1 are the magnetization of the short T2* and long T2* components, respectively.

The fractional order T2* relaxation model is given by:[17]

$$\boldsymbol{M_f}(TE) = \boldsymbol{c_0} \cdot \boldsymbol{E_\alpha}\left[-\left(\frac{TE}{T_2}\right)^{\alpha}\right] \quad \textbf{(3)}$$

Where c_0 is the signal intensity at TE=0 and E_a is the stretched Mittag-Leffler (M-L) function.[24] Note that for $a = 1$, the M-L function is equivalent to the mono-exponential function.

Fractional order fitting results in a stretched exponential T2* and a parameter "α" ($0 < \alpha < 1$) of the differential equation, which represents tissue heterogeneity.[25] In a voxel where $\alpha = 1$, the signal decay is best described as monoexponential and likely resulted from a single

component. We used maximum likelihood estimation incorporating the Rician noise model for fitting the parameters of all methods.[26] This corrects for the noise-dependent bias in magnitude images.[27]

Image Analysis

For calculation of median T2* relaxation times for the monoexponential, fractional order and biexponential fitting parameters in all subjects, we selected individual voxel data on 10 consecutive slices covering the proximal patellar tendon and for each separate slice of the proximal patellar tendon (Fig. 2). On each slice, we drew a mask that covered the outer margins of the patellar tendon, in order to analyze all voxels. The first region of interest (ROI) was drawn on the second slice distal from the patellar apex, to avoid partial volume effects of patellar bone. The subregional analysis in different tissue compartments was performed using thresholds on the percentage short T2* components, a parameter resulting from biexponential fitting. The thresholds resulted in an automatic selection of voxels within the mask of the patellar tendon, indicating the different tissue compartments. Based on the frequency distribution of the percentage short T2* components in a histogram, we defined 0–30% short T2* components for the highly hydrated degenerative tissue, which mainly contains long T2* components, 30–60% short T2* as the intermediate zone, and 60–100% for the ultrashort T2* components, such as the macromolecular bound water pools associated with aligned collagen. For quantitative analysis, only voxels within the initial mask covering the patellar tendon were selected.

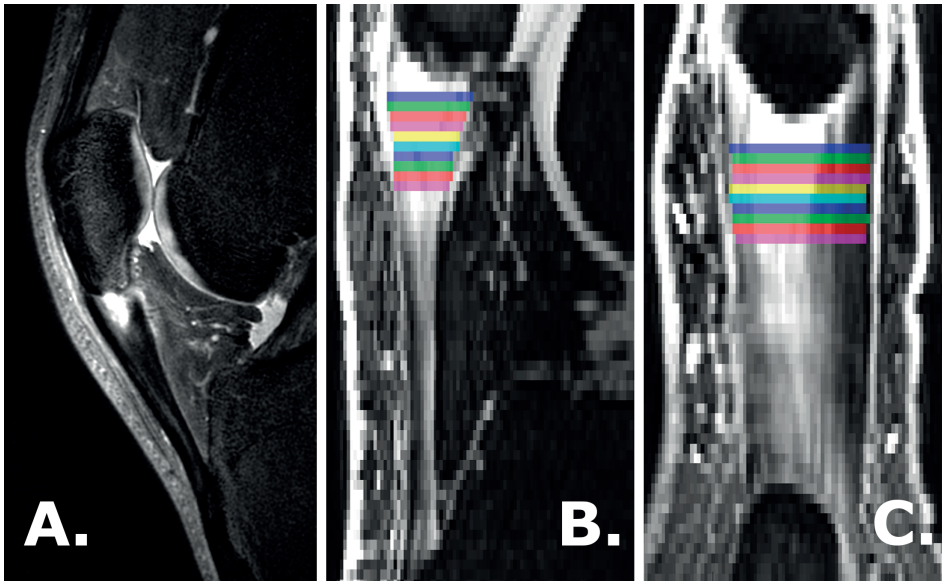


Figure 2: Locations for T2* quantification in patellar tendinopathy. (a) Sagittal PD Cube scan in an athlete with patellar tendinopathy and corresponding sagittal (b) and coronal (c) 3D-UTE scans (TE 4.87 msec). Color bars in the proximal patellar tendon represent the locations of the manually drawn masks in 10 slices for T2* quantification.

Statistical Analysis

Statistical analysis was performed using IBM SPSS software v. 25 (Armonk, NY). Coefficients-of-variation (CV) were calculated using the root-mean-square method to assess test–retest reliability in each voxel. In this method, the CV is calculated voxelwise as the square root of the squared summed percentage differences in each voxel between the test and retest scans divided by the total number of voxels.[28] Within-subject variances were calculated as half the square of the differences between two scans.[29] Test–retest repeatability was assessed using coefficient-of-repeatability (CR), also referred to as smallest real difference (SRD), calculated by multiplying the median within-subject standard deviation by 2.77 ($\sqrt{2}$ times 1.96).[30] Overall CV and CR were calculated as a mean over the three subjects. Normality of data was tested using the Shapiro–Wilk's test. One-way analysis of variance (ANOVA) was used to determine whether there were statistically significant differences between the means of the subselected voxel groups. Differences between monoexponential fitting and fractional order fitting were assessed with Student's t-test for normally distributed data and the Mann–Whitney U-test for nonnormally distributed data. Statistical significance was defined as $P < 0.05$.

RESULTS

Study Population

In total, 76 athletes with clinically diagnosed and ultrasonographically confirmed PT were consecutively enrolled between January 2017 and June 2019. After exclusion of 11 subjects due to a change in our MR acquisition protocol during the study period, 65 athletes remained eligible for inclusion. Demographic characteristics of the study population are listed in Table 2.

Table 2. Baseline characteristics

Characteristic	N=65
Mean age (years) ± SD	24.5 ± 3.8
No. of men (%)	50 (77)
Mean BMI (kg/m^2) ± SD	24.0 ± 2.9
Mean waist circumference (cm) ± SD	85.7 ± 9.4
Mean clinical score (VISA-P, 0-100) ± SD	55 ± 13
Median symptom duration (weeks) [IQR]	104 [40-182]
Sports activity scale (CSAS, 0-100)	N (%)
Level I (4 to 7 days/week):	15 (23)
100	0 (0)
95	0 (0)
90	
Level II (1 to 3 days/week):	44 (68)
85	6 (9)
80	

SD: standard deviation. IQR: interquartile range. BMI: body mass index. VISA-P: Victorian Institute of Sports Assessment questionnaire for patellar tendons. CSAS: Cincinnati Sports Activity Scale.

Acquired 3D UTE-Cones Images

Figure 3a shows axial images of the knee in an athlete with patellar tendinopathy at all 16 echoes of the 3D UTE-Cones acquisitions, illustrating the fast signal decay occurring at the shortest echo times. Figure 3b–d shows signal intensity curves in the different tissue compartments of the patellar tendon (mostly long T2*, mixed T2*, and mostly short T2*), fitted using monoexponential, biexponential, and fractional order models.

Image Analysis Using All Voxels

When using all voxels in all slices covering the proximal patellar tendon, we found a median [interquartile range, IQR] monoexponential T2* of 6.43 msec [4.32–8.55] and fractional order T2* 4.39 msec [3.06–5.78]. The overall percentage of short T2* components was 52.9% [35.5–69.6]. Table 3 illustrates that the longest T2* was found in the slice closest to the inferior patellar border (slice 1) and gradually decreased in the distal direction. Fractional order T2* revealed a similar gradual decrease; however, fractional order T2* was systematically lower than monoexponential T2*. In addition, the percentage of short T2* components was lowest in the slice closest to the inferior patellar border and gradually increased in the distal direction along the patellar tendon. The difference in median T2* between the monoexponential and fractional order fitting in all voxels was statistically significant ($P < 0.001$).

Subregional Image Analysis Approach

In Fig. 4, a representative axial slice of an athlete with patellar tendinopathy is illustrated with the corresponding monoexponential, biexponential, and fractional-order T2* maps. Voxels were selected with a percentage of short T2* between 0–30%, 30–60%, and 60–100% based on histogram analysis (Fig. 5), and visually corresponded to degenerative tissue, transitional area between degenerative tissue and aligned collagen, and aligned collagen in the patellar tendon, respectively. There were statistically significant differences in monoexponential and fractional order T2* between all three different tissue compartments ($P < 0.001$). Table 4 illustrates that the longest T2* was found in degenerative tissue (median monoexponential T2* 13.78 msec, IQR [12.11–16.46], and fractional order T2* 11.82 msec, IQR [10.09–14.44]) and the shortest T2* in the voxels representing aligned collagen (median monoexponential T2* 3.05 msec, IQR [2.52–3.60], and fractional order T2* 2.19 msec [1.82–2.64]).

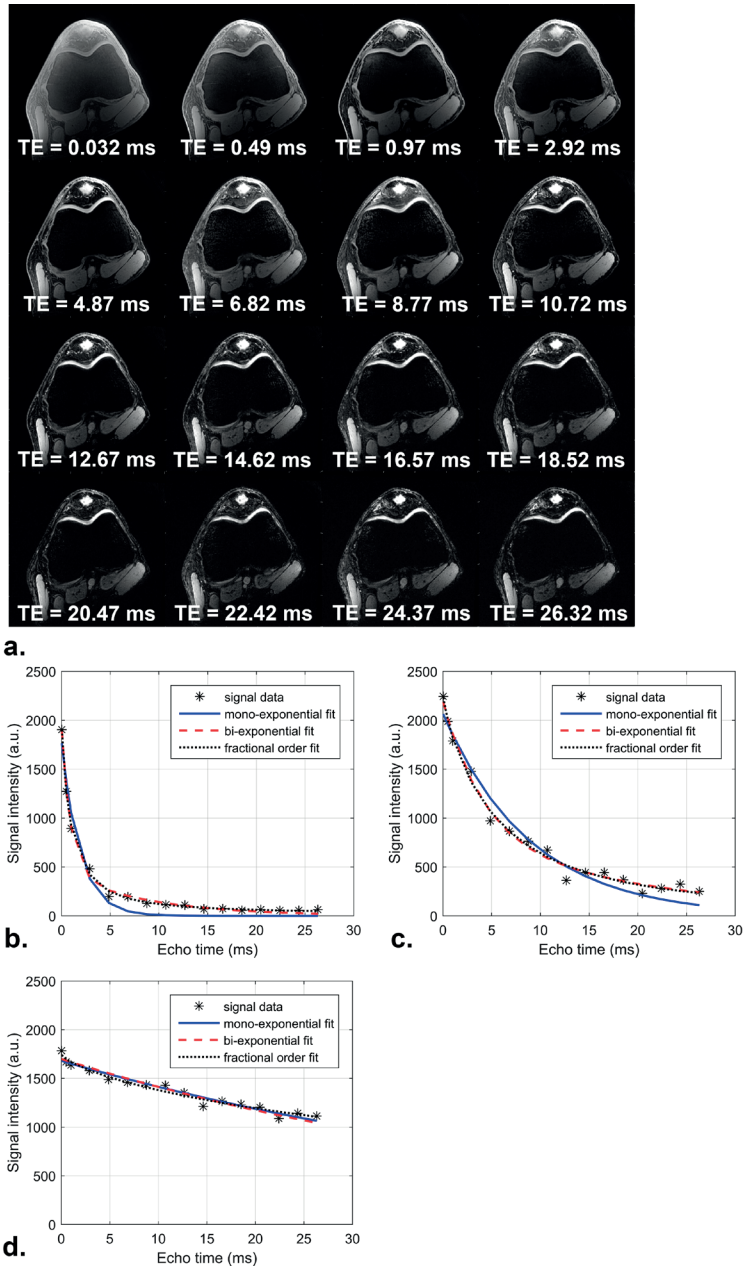


Figure 3: Axial 3D UTE-Cones images of the knee and corresponding T2* relaxation curves. (a) Axial images of the knee in a 21-year-old male basketball player with patellar tendinopathy at all 16 echoes acquired using the 3D UTE-Cones acquisitions. Note that the signal in the voxels corresponding to aligned collagen in the patellar tendon rapidly decays, and is not visible anymore on images with TEs of 4.87 msec and longer. (b) Signal intensity curves for an ROI in voxels containing mostly short T2* components (aligned collagen). Note that there is significant residual signal that is not fitted by the monoexponential model and that there is visibly improved curve fit of the signal data when using the biexponential or fractional order model. (c) Signal intensity curves for an ROI in voxels containing intermediate T2* components (interface between aligned collagen and degenerative tissue). (d) Signal intensity curves for an ROI in voxels containing mostly long T2* components (degenerative tissue).

Table 3. Measurements resulting from mono-exponential, bi-exponential and fractional order fitting of UTE images of the proximal patellar tendon, by using voxel-wise T2* relaxation data for all slices and for each individual slice combined for 65 subjects (20.000-250.000 voxels).

	Mono-exponential	Bi-exponential			Fractional order	
	T_2^*	T_{2S}^*	T_{2L}^*	$\%T_{2S}^*$	T_{2F}^*	α
All slices	6.43 [4.32-8.55]	1.160 [0.909-1.325]	15.10 [13.73-16.96]	52.9 [35.5-69.6]	4.39 [3.06-5.78]	0.829 [0.809-0.845]
Slice 1	10.39 [7.71-12.38]	0.947 [0.710-1.112]	17.64 [15.10-21.15]	32.5 [25.4-49.2]	7.69 [4.78-9.49]	0.816 [0.797-0.839]
Slice 2	9.58 [6.65-11.49]	0.906 [0.734-1.109]	17.29 [14.83-20.54]	37.1 [26.8-54.0]	6.62 [4.09-8.68]	0.811 [0.790-0.836]
Slice 3	8.51 [5.65-10.15]	0.938 [0.731-1.114]	15.94 [14.51-19.34]	36.4 [30.2-60.8]	5.84 [3.36-7.42]	0.821 [0.793-0.838]
Slice 4	7.28 [4.50-9.74]	1.010 [0.778-1.197]	15.17 [13.51-18.07]	41.6 [31.5-62.4]	5.00 [3.19-7.02]	0.824 [0.796-0.840]
Slice 5	6.50 [4.18-9.13]	1.072 [0.771-1.352]	14.80 [12.85-16.95]	45.4 [36.0-67.0]	4.48 [3.01-6.30]	0.831 [0.807-0.847]
Slice 6	5.96 [4.11-7.71]	1.177 [0.883-1.418]	14.23 [12.46-16.01]	53.1 [35.9-69.4]	4.25 [2.89-5.79]	0.832 [0.811-0.852]
Slice 7	5.58 [3.81-7.19]	1.259 [0.943-1.511]	13.91 [12.45-16.28]	59.5 [36.6-75.8]	3.79 [2.57-5.14]	0.837 [0.815-0.852]
Slice 8	5.16 [3.54-6.49]	1.332 [0.947-1.538]	13.78 [12.33-16.43]	63.6 [42.5-80.5]	3.47 [2.35-4.84]	0.839 [0.820-0.856]
Slice 9	4.81 [3.32-6.02]	1.416 [1.039-1.678]	13.81 [12.28-16.75]	69.1 [47.6-81.7]	3.38 [2.26-4.47]	0.838 [0.821-0.858]
Slice 10	4.55 [3.26-5.63]	1.503 [1.203-1.734]	14.27 [12.12-17.34]	71.3 [53.9-82.8]	3.08 [2.24-4.07]	0.838 [0.818-0.857]

T_2* relaxation times are expressed as median ± interquartile range in milliseconds (ms)
T_{2S}*: short T2* relaxation time.
T_{2L}*: long T2* relaxation time.
$\%T_{2S}$*: percentage of short T2* components.
T_{2F}*: fractional order T2* relaxation time.
α: fractional order exponent.

Table 4. Measurements resulting from mono-exponential, bi-exponential and fractional order fitting, separated for different subregions of the patellar tendon based thresholds (0-30%, 30-60% and 60-100%) on bi-exponential fitting parameter percentage short T2*.

	Mono-exponential	Bi-exponential			Fractional order	
	T_2^*	T_{2S}^*	T_{2L}^*	$\%T_{2S}^*$	T_{2F}^*	α
0-30%	13.78 [12.11-16.46]	0.441 [0.388-0.523]	15.79 [13.47-18.61]	20.1 [18.6-21.8]	11.82 [10.09-14.44]	0.856 [0.835-0.873]
30-60%	7.65 [6.49-8.61]	1.042 [0.751-1.507]	11.76 [10.68-13.72]	40.3 [33.6-46.8]	5.14 [4.25-5.96]	0.814 [0.789-0.828]
60-100%	3.05 [2.52-3.60]	1.693 [1.417-2.003]	17.29 [14.90-19.22]	83.2 [80.2-86.9]	2.19 [1.82-2.64]	0.828 [0.804-0.852]

T2* relaxation times are expressed as median ± interquartile range in milliseconds (ms)
T_{2S}*: short T2* relaxation time.
T_{2L}*: long T2* relaxation time.
$\%T_{2S}$*: percentage of short T2* components.
T_{2F}*: fractional order T2* relaxation time.
α: fractional order exponent.

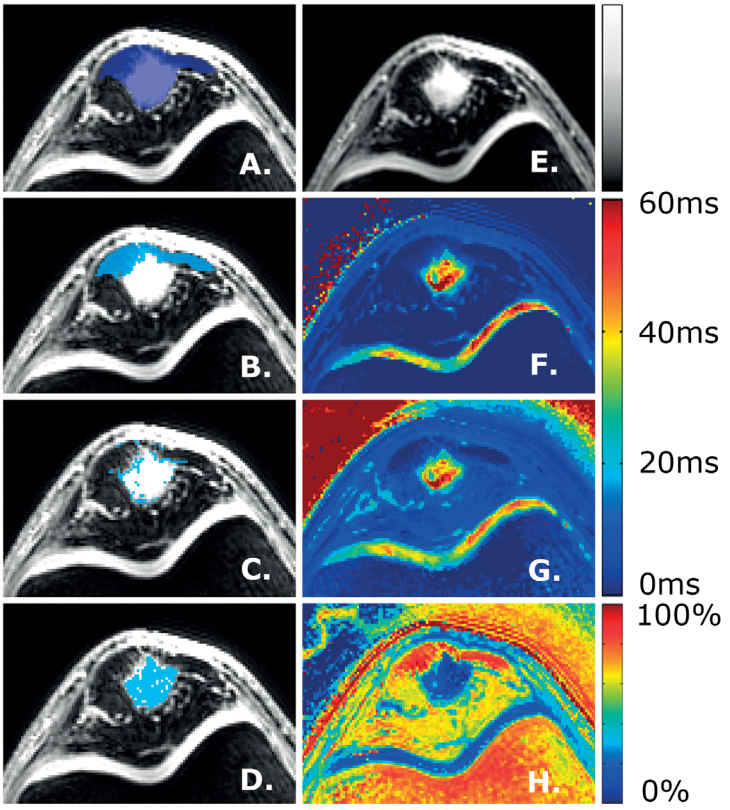


Figure 4: Representative axial MR images in an athlete with patellar tendinopathy. (a) Mask (blue) covering all voxels within the outer margins of the patellar tendon. (b) Subselected voxels with 60–100% short T2* components, corresponding to aligned collagen in the patellar tendon. (c) Subselected voxels with 30–60% short T2* components, corresponding to the interface between aligned collagen and degenerative tissue. (d) Subselected voxels with 0–30% short components, corresponding to degenerative tissue. (e) Original UTE image (TE 4.82 msec) revealing the regional variations of T2* in patellar tendinopathy, with hypointense aligned collagen and hyperintense degenerative tissue. (f) Quantitative T2* map from fractional order fitting, depicting short T2* in dark blue (0.032–10 msec) and longer T2* on a scale from light blue/green (10–30 msec) to orange/red (30–60 msec). (g) Quantitative T2* map from monoexponential fitting, on the same scale as (f). (h) Quantitative T2* map from biexponential fitting, depicting the percentage of short T2* components on a scale from dark blue (0% short T2* components) to red (100% short T2* components).

Test–Retest Reliability

Intravoxel test–retest CV and CR are listed in Table 5. Comparable reliability was found for monoexponential and fractional order fitting; we found an average CV of 15% and CR of 2 msec and an average CV of 19% and CR of 2 msec, respectively. The percentage short T2* (biexponential fitting) had an average CV of 22% and CR of 10%. Average repeatability (CV) of biexponential T2* quantification improved by using the subregional image analysis approach from 45% to 30% for short T2* and from 25% to 11% for long T2* in the subselected voxels with 60–100% short T2* components and in the subselected voxels with 0–30% short T2* components, respectively.

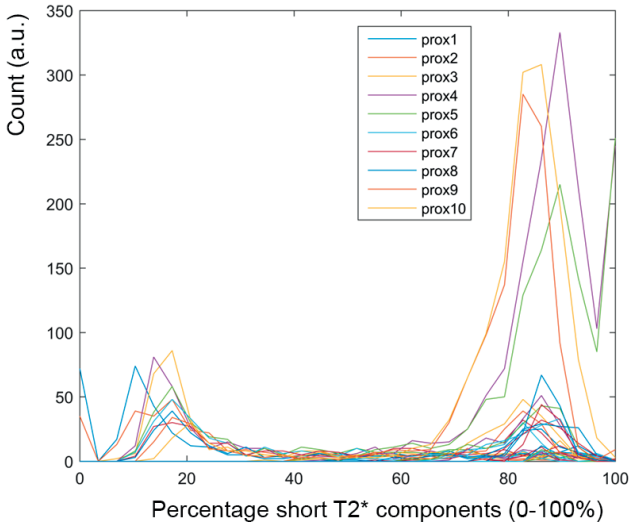


Figure 5: Frequency distribution of the percentage of short T2* components. Exemplary histogram of the frequency distribution of the percentage of short T2* components in the proximal patellar tendon. The different lines correspond to the manually drawn masks in 10 slices ("prox1-prox10") for T2* quantification. Note that there are two main peaks in the histogram, namely, the component with mostly long T2* (left peak) and the component with mostly short T2* (right peak). Based on this frequency distribution, we opted to set thresholds at 30% and 60% short T2* components to distinguish between three different water pools; "mostly short T2* (60-100% short T2*)," "intermediate T2* (30-60% short T2*)," and "mostly long T2* (0-30% short T2*)." Based on these thresholds on the percentage short T2* components, the corresponding voxels were automatically selected within each mask for analysis.

Table 5. Reliability of T2* quantification in three athletes with patellar tendinopathy

	Athlete 1		**Athlete 2**		**Athlete 3**	
	CV (%)	**CR (ms)**	**CV (%)**	**CR (ms)**	**CV (%)**	**CR (ms)**
T2*	17.9 (17.5-18.4)	2.4 [1.4-3.9]	20.9 (20.5-21.4)	1.7 [1.0-2.9]	7.4 (7.1-7.6)	1.6 [0.9-2.5]
$T2^{S}$*	43.2 (41.6-44.7)	0.7 [0.3-1.3]	54.2 (27.9-55.6)	1.8 [0.9-3.3]	37.9 (36.2-39.4)	0.3 [0.1-0.5]
$T2^{L}$*	22.5 (21.6-23.4)	4.8 [2.5-9.7]	45.4 (44.1-46.6)	14.8 [6.1-33.1]	6.6 (6.3-6.8)	1.6 [0.7-2.7]
% T2S*	24.0 (22.8-25.2)	11% [5-20]	26.2 (25.0-27.3)	16% [6-35]	14.4 (13.4-15.4)	4% [2-8]
$T2^{F}$*	20.2 (19.8-20.5)	2.2 [1.2-4.4]	26.4 (25.9-26.9)	1.7 [1.0-3.1]	9.8 (9.5-10.1)	1.9 [1.1-2.9]
α	4.1 (3.9-4.2)	0.05 [0.02-0.09]	5.9 (5.7-6.2)	0.08 [0.04-0.14]	3.5 (3.3-3.8)	0.04 [0.02-0.08]

CV: coefficient of variation in percentages (95% confidence interval).
CR: coefficient of repeatability in milliseconds (ms) [interquartile range], except for "% T2S*" where they are percentages.
T_{2S}*: short T2* relaxation time.
T_{2L}*: long T2* relaxation time.
$\%T_{2S}$*: percentage of short T_2* components.
T_{2F}*: fractional order T_2* relaxation time.
α: fractional order exponent.

DISCUSSION

We found that parameters resulting from biexponential fitting of UTE relaxometry data successfully led to the identification and quantification of specific tissue compartments within the patellar tendon in athletes with patellar tendinopathy and that repeatability of biexponential T2* quantification improved using this subregional analysis compared to the standard image analysis approach. The observed T2* distribution in patellar tendinopathy was not homogeneous, but revealed regional variations in binding states of water, in which aligned collagen was characterized by ultrashort T2* and degenerative tissue generally by long T2* components. Conventional analysis with an ROI delineating the outer margins of the patellar tendon averages the spatial differences in T2* relaxation time in these different compartments. Accordingly, in such analyses the regional T2* variability complicates the detection of changes over time.

Spatial Variability in T2* Relaxation

To overcome the issues of spatial T2* variation in the patellar tendon, we introduced an alternative approach to quantify T2* in specific tissue compartments. This is important for identifying UTE-based biomarkers that better reflect tendon structure, other than just analyzing the average over all voxels containing different components resulting from different binding states of water. Moreover, not only spatial variability in T2* relaxation in the patellar tendon, but also the different components in each voxel can be quantified using biexponential fitting of UTE relaxometry data. We hypothesized that these specific biomarkers have more potential to correlate with clinical findings and hopefully better reflect the pathological changes observed in tendinopathy. Conceivably, these specific biomarkers are surrogate markers for the increased levels of glycosaminoglycans (GAGs) in patellar tendinopathy, which have already been associated with worse clinical status.[11]

Previous Studies

Previous studies have shown potential of bicomponent analysis to discriminate between athletes with patellar tendinopathy and healthy controls[31] and to quantify different water pools in heterogeneous tissues.[9,32] Also, regional T2* variations have been observed for the Achilles tendon[32] and segmentation of the entire patellar tendon volume was performed to calculate mean T2*.[33] Those studies performing T2* quantification implemented sagittal scan planes and relatively large ROIs, probably due to time restrictions.[31,34] We acquired UTE relaxation data in an axial oblique scan plane with a high in-plane resolution, thereby facilitating the introduced subregional quantification.

Strengths

The strengths of our study are the relatively large sample size and the homogeneity of the study population with respect to age and level of sports. We applied strict eligibility criteria by including only athletes with clinically and ultrasound-confirmed PT, and thereby ruling out other causes for anterior knee pain. Another strength is that the UTE MRI relaxation data were acquired by a single examiner using a standardized protocol, regarding both patient positioning and acquisition. Moreover, the postprocessing and analysis of the data were performed by the same investigator.

Limitations

First, the biexponential model that we used for defining the thresholds for selection of voxels with comparable water pools might be a simplified method. In fact, the MR signal in each voxel can consist of more than two (short and long) components.[8] However, we found that the percentage of short T2* components was able to clearly discriminate between the different tissue compartments in the patellar tendon. Moreover, biexponential fitting has been stated to be better than monoexponential fitting, because of the systematic residual signal that is seen with monoexponential fitting.[9] Second, the reliability of the biexponential model is relatively poor compared to the more robust monoexponential and fractional order model in the small number of subjects included for reliability measurements. However, the reliability of biexponential fitting parameters increased in specific tissue compartments compared to the conventional image analysis approach. Third, despite the noninvasiveness of MRI, the time-consuming acquisition protocol and postprocessing pipeline used in this study would both not be applicable in daily clinical practice. However, the total acquisition time of our comprehensive 3D UTE-Cones T2* mapping protocol can be shortened considerably by reducing the number of echoes and number of slices acquired, without compromising the T2* mapping results.

Further Implications

Further research projects could strengthen the need for T2*-quantification in specific tissue compartments in patellar tendinopathy if longitudinal data depicted changes in T2* relaxation over time. Subsequently, the effectiveness of different therapeutic interventions for patellar tendinopathy could be evaluated. Ultimately, imaging biomarkers would serve as surrogate markers for the increase in GAGs, thereby strongly facilitating the assessment of the severity of patellar tendinopathy at a microstructural level. Accordingly, the therapeutic response could be quantified without the need of histological samples.

CONCLUSION

Our study showed that quantitative multicompartment T2* analysis in heterogeneous tissues such as the patellar tendon can be facilitated using a voxel selection method based on biexponential fitting parameters that differentiate between tissue compartments with comparable water pools, and that monoexponential and fractional order fitting methods have equal reliability to quantify UTE relaxometry data. Subregional quantitative analysis using 3D UTE MRI leads to the identification of tissue-specific T2* biomarkers with high repeatability, which can facilitate the detection of changes in the tendon hydration state over time, for example, as a result of therapeutic interventions.

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6

Fractional order vs. exponential fitting in UTE MR imaging of the patellar tendon.

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Magn Reson Imaging. 2020 Jul;70:91-97.

ABSTRACT

Purpose: Quantification of the T_2^* relaxation time constant is relevant in various magnetic resonance imaging applications. Mono- or bi-exponential models are typically used to determine these parameters. However, in case of complex, heterogeneous tissues these models could lead to inaccurate results. We compared a model, provided by the fractional-order extension of the Bloch equation with the conventional models.

Methods: Axial 3D ultra-short echo time (UTE) scans were acquired using a 3.0 T MRI and a 16-channel surface coil. After image registration, voxel-wise T_2^* was quantified with mono-exponential, bi-exponential and fractional-order fitting. We evaluated all three models repeatability and the bias of their derived parameters by fitting at various noise levels. To investigate the effect of the SNR for the different models, a Monte-Carlo experiment with 1000 repeats was performed for different noise levels for one subject. For a cross-sectional investigation, we used the mean fitted values of the ROIs in five volunteers.

Results: Comparing the mono-exponential and the fractional order T_2^* maps, the fractional order fitting method yielded enhanced contrast and an improved delineation of the different tissues. In the case of the bi-exponential method, the long T_2^* component map demonstrated the anatomy clearly with high contrast. Simulations showed a nonzero bias of the parameters for all three mathematical models. ROI based fitting showed that the T_2^* values were different depending on the applied method, and they differed most for the patellar tendon in all subjects.

Conclusions: In high SNR cases, the fractional order and bi-exponential models are both performing well with low bias. However, in all observed cases, one of the bi-exponential components has high standard deviation in T_2^*. The bi-exponential model is suitable for T_2^* mapping, but we recommend using the fractional order model for cases of low SNR.

INTRODUCTION

Tissues with low water content such as tendons, ligaments, menisci, or cortical bone have extremely short T2* decays.[1] The MR signal of these tissues rapidly decreases with longer echo times. Therefore, in most of the routinely used MR sequences[2-5] they exhibit very low signal intensity. With short echo times, fast spin echo (FSE) sequences provide more opportunities to visualize these tissues, but due to T2 blurring and the lack of the efficiency of the acquisition, fine-scale structures are still not well depicted.[6] However, if the echo time (TE) is drastically reduced, the signal from these tissues can be detected as well. The TE reduction gives the opportunity to characterize the tissues and to manipulate the visibility.[7] Currently there is an increasing interest in MR pulse sequences which provide extremely short echo time, such as ultrashort TE (UTE) sequence[8], zero TE (ZTE) technique[9], single point imaging technique[10], and hybrid techniques (e.g. PETRA[11] and AWSOS[12]). In order to quantify relaxation times, proper mathematical models and post-processing algorithms are as important as the acquisition strategy. Due to relatively new developments in MRI, quantification of multiple T2 and T2* components has become available.[13] These components can be used as markers for different pathophysiological conditions. For example T2* has been proposed as a marker for subclinical changes in menisci.[15] In general, the assumption is that two types of water exist in connective tissues, free and bound water. In the bound water compartment the molecules are assumed as bound to collagen fibers or proteoglycan molecules. In case of two-component T2* analysis, the shorter component (assumed as bound water) is usually only detectable with ultrashort/zero echo times sequences.[30] The problem with the multiple component analysis is the high sensitivity to noise.[14,19]

In case of complex, heterogeneous or porous tissues the simple mono-exponential or sum of exponential solution of the Bloch equation cannot perfectly describe the dynamics of the relaxation. In such complex materials we observe stretched-exponential or power law behavior.[20,21,26,27] Fractional order generalization of the Bloch equation provides an alternative mathematical model to describe the observed signal in such tissues. It offers a description of the relationship between relaxation processes and internal material structure. In this study we tested the previously introduced fractional order model for patellar tendon T2* quantification. We investigated three different models using UTE acquisitions: mono-exponential, bi-exponential and fractional order models and assessed their repeatability.

METHODS

In this study we compared three different mathematical models and evaluated their repeatability and the bias of their derived parameters by fitting at various noise levels. The math-

ematical models of signal intensity as a function of echo time were the mono-exponential, bi-exponential and fractional order models.

2.1. Mathematical models

Fractional calculus defines real or complex number powers of the differentiation operator as well as of the integration operator and develops a calculus for these operators that generalizes the classical operators.[22,23] We used a generalization of Bloch equations with convolution kernels from Magin et al.[21] The exact forms of these kernels are unknown, and power law kernels with fading memory have been introduced. The fractional order relaxations are the following for T1 relaxation:

$$\boldsymbol{M_z}(t) = \boldsymbol{M_z}(0) + [\boldsymbol{M_0} - \boldsymbol{M_z}(0)]\left[\mathbf{1} - \boldsymbol{E_\beta}\left[-\left(\frac{t}{T_1}\right)^{\beta}\right]\right] \quad \textbf{(1)}$$

Where $M_z(t)$ is the longitudinal magnetization, M_0 is the steady state magnetization, and E_β is the stretched Mittag-Leffler (M-L) function: $E_\beta(z) = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(\beta k + 1)}$. Note that for $\beta = 1$, the M-L function is equivalent to the simple exponential function.

The fractional order T2* relaxation model is given by:

$$\boldsymbol{M_{FO}}(TE) = \boldsymbol{M_{xy}}(0)\boldsymbol{E_\alpha}\left[-\left(\frac{TE}{T_2}\right)^{\alpha}\right] + \boldsymbol{M_{xy}}(\infty) \quad \textbf{(2)}$$

Where $M_{xy}(0)$ is the transversal magnetization at TE=0, and $M_{xy}(\infty)$ is the transversal magnetization at the steady state. The $M_{xy}(0)$ is related to the proton density, and α can be interpreted as the memory of the spin system.

The mono-exponential T2* relaxation model is given by:

$$\boldsymbol{M_m}(TE) = \boldsymbol{a_0}\cdot\boldsymbol{e}^{-\frac{\boldsymbol{TE}}{\boldsymbol{T_2^*}}} + \boldsymbol{a_1} \quad \textbf{(3)}$$

Where a_0 is the signal intensity at TE=0, and a_1 is the baseline.[29]

The bi-exponential T2* relaxation model is given by:

$$\boldsymbol{M_b}(TE) = \boldsymbol{b_0}\cdot\boldsymbol{e}^{-\frac{\boldsymbol{TE}}{\boldsymbol{T_{2,s}^*}}} + \boldsymbol{b_1}\cdot\boldsymbol{e}^{-\frac{\boldsymbol{TE}}{\boldsymbol{T_{2,l}^*}}} + \boldsymbol{b_2} \quad \textbf{(4)}$$

where b_0 *and* b_1 are the component sizes, $T_{2,s}^*$ is the short T_2^* component, $T_{2,l}^*$ is the long T_2^* component, and b_2 is the baseline.

The tissue-related parameters are the corresponding T2* values. In case of the fractional order method parameter α is also regarded as an intrinsic parameter.

2.2. Volunteers

In order to compare the performance of the different methods, we have randomly chosen 5 volunteers from a clinical study on patellar tendinopathy (PT). We have considered PT suitable to evaluate the different fitting models on a disease condition.[31]

The single-center prospective observational study was approved by the local institutional review board. The volunteers were consecutively recruited between January 2016 and January 2019. To be eligible for inclusion, volunteers had to be aged 18–35 years, had to perform sports involving frequent jumping or cutting maneuvers for at least 3 times per week, and have a clinical diagnosis of patellar tendinopathy which was confirmed by ultrasound.

PT is a sports-related overuse injury of the patellar tendon occurring in tendon-loading sports, such as basketball, volleyball and soccer.[16] PT is associated with morphologic changes in tendon microstructure, with mucoid degeneration, increased levels of hydrophilic (water-attracting) glycosaminoglycans and water content as a result.[17,18]

2.3. MR acquisition

MRI of the symptomatic knee was performed using a 3T MR system (Discovery 750, General Electric, Boston, Massachusetts, USA) using a flexible 3.0 T 16-channel surface coil (NeoCoil, Pewaukee, Wisconsin, USA). The volunteers were scanned feet-first in supine position with the knee flexed in 30 degrees. The knee was fixed by a support base for knee stabilization (NeoCoil, Pewaukee, Wisconsin, USA). The center of the surface coil was aligned with the patellar apex. Prior to scanning high-resolution images and 3D-UTE sequences[32,33], we acquired 3D variable flip angle FSE sequences with and without fat saturation in order to provide an overview of the entire knee and to use these images as localizer to prepare the UTE-scans. Regarding 3D-UTE-MRI, a total of 16 echoes were acquired at TEs of 0.032, 0.49, 0.97, 2.92, 4.87, 6.82, 8.77, 10.72, 13.6, 12.67, 16.57, 18.52, 18.7, 20.47, 22.42, 24.37, 26.32 ms, where TE was defined as the start of the cones readout. The 16 echoes were acquired in 4 separate multi-echo sequences containing 4 echoes in interleaved order. For each multi-echo acquisition, the same TR was used. The full MR acquisition protocol of the patellar tendinopathy study is listed in Table 1.

Table 1. Imaging protocol for patellar tendon imaging.

Sequence	3D PD Cube	3D PD Cube FS	3D ME-UTE
Matrix	384 x 384	384 x 384	252 x 252
Scan plane	Sagittal	Sagittal	Axial oblique
Fat saturation	-	Fat	2 excitations per FS
FOV (cm)	15.0	15.0	15.0
Resolution (mm)	0.4 x 0.4 x 1.0	0.4 x 0.4 x 1.0	0.6 x 0.6 x 1.5
Slice Thickness (mm)	1.0	1.0	1.5
Number of Slices	120	120	60
TE (ms)	30.0	30.0	0.032/4.87/12.67/20.47 0.49/6.82/14.62/22.42 0.97/8.77/16.57/24.37 2.92/10.72/18.52/26.32
Number of Echoes	1	1	16
TR (ms)	1200.0	1200.0	83.4
Flip Angle (°)			17
Bandwidth (± kHz)	83.33	83.33	125
NEX	0.5	0.5	1.0
Scan Time (mm:ss)	03:17	03:18	13:15

2.4. MR imaging analysis

The post-processing of the 3D-UTE images was performed with an in-house developed script using Matlab software (R2015b; TheMathWorks). All three models where fitted to all echoes of the dataset. The relaxation time per voxel was estimated using the FIT routine, and mean relaxation time and the standard deviation inside different regions of interest (ROI) were calculated. The Mittag Leffler function (Eα) uses the implementation of Garrappa.[24] ROI's were manually drawn inside tendon (patellar tendon), bone marrow (femur) and muscle (sartorius muscle), and each ROI contained approximately 50 voxels (Fig. 1). The voxel based fitting was used to compare the resulting maps from the different models by visual inspection. ROI based fitting (fit on mean over ROI) was used for quantitative measurements, and to test the effect of the signal-to-noise ratio (SNR). Additionally the mean T2* value is given for the different models. For a cross sectional investigation we used the mean fitted values of the ROIs of five volunteers.

2.5. Effect of signal to noise ratio

To investigate the effect of the SNR for the different models, we performed a Monte-Carlo experiment with 1000 repeats for different noise levels in case of one volunteer. To obtain Rice distributed data with lower SNR we computed the magnitude after adding zero mean complex Gaussian noise with standard deviation σ to the original ROI means.

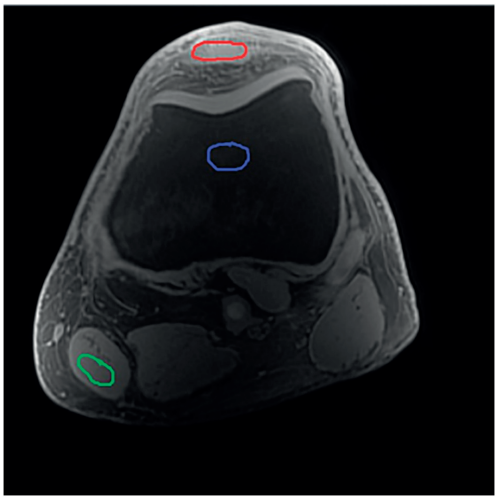

Figure 1: ROIs for the quantitative measurements. Red - patellar tendon, blue - bone marrow (femur), and green - muscle (sartorius muscle). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

We selected 12 σ from 1% to 35% of the mean inside the ROI of the TE = 0.032 ms image. All three models were fitted to the realizations. The mean and the standard deviation of the resulting parameters were taken. Two datasets were used, extracted from the ROI of the patellar tendon and the muscle. The resulting bias from the original parameters and the standard deviation were investigated. The more bias appears, the less robust is the method, and the higher the standard deviation is, the less repeatable the fitting is. The difference between the fitting results of an original derived parameter (po), and the mean of that derived parameter over the 1000 Monte-Carlo simulations ($\overline{p_n}$) is what we refer to as the bias (B):

$$\mathbf{B} = \frac{|p_o - \overline{p_n}|}{p_o} \cdot \mathbf{100} \tag{5}$$

This bias is shown as function of the noise percentage (N), defined as:

$$\mathbf{N} = \frac{\mathbf{1}}{\mathbf{SNR}} \cdot \mathbf{100}, \tag{6}$$

where

$$\mathbf{SNR} = \frac{\mathbf{mean\ signal(inside\ the\ tissue)}}{\sigma(\mathbf{noise})}, \tag{7}$$

where mean signal (inside the tissue at TE = 0.032 ms) is the mean signal value of the chosen ROI, and σ(noise) is the standard deviation of the signal value in this ROI.

RESULTS

The bias and the repeatability of the T2∗ parameter estimation using three different fitting models at different noise levels were the main interest in our investigation. Simulations showed (see in Fig. 2, Fig. 3) a nonzero bias for all three mathematical models. Our main interest was the patellar tendon, where the original SNR was 39. For the muscle this value was 26. In case of the patellar tendon the resulting highest bias (≥200%) appeared for only 10% of extra added noise for the short bi-exponential component. In contrast, the highest values for the bias for the other 2 fitting models and for the other bi-exponential component were below 80% after 35% of extra added noise. The mono-exponential and the fractional order model showed similar behavior, but the bias of the mono-exponential model's in the patellar tendon was a few percent lower. For the muscle the bias of the long bi-exponential component exceeded 1000% after 15% of extra added noise. The short bi-exponential component had a lower but still ≥100% bias after 20% of extra added noise. The bias of the other two models (mono-exponential and fractional order) was below 50%. None of the component sizes of the bi-exponential model were negligible (Table 2 b_s, b_l) so the bias was not the result of the small component size.

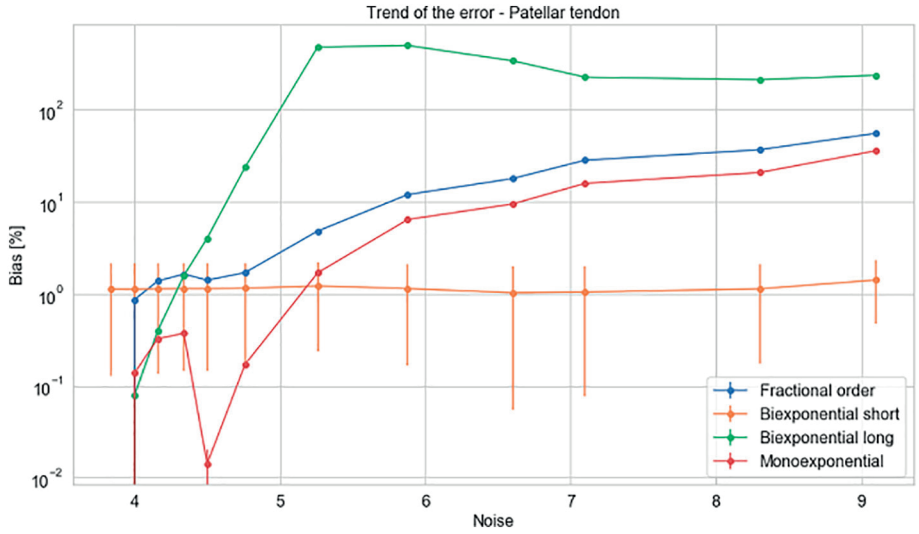

Figure 2: Bias of T2* in the patellar tendon as given by Eq. (5). $B = \frac{|p_0 - \overline{p_n}|}{p_0} \cdot 100$ as function of the noise level N. With extra added noise we assessed the robustness of the different fitting methods. Extra added noise is equivalent to the decreasing SNR. The level of the extra added noise ranged from 1% to 35% of the mean signal inside the tissue Eq. (6). The original SNR was 39. The standard deviation over the 1000 different fits in the Monte-Carlo experiment is shown as error bars. The horizontal axis shows

Noise= $\frac{\sigma(\text{noise})}{\text{mean signal(inside the tissue)}} \cdot 100$ (Eq. (6).).

Table 2. Comparison of the different fitting methods in different tissues for one volunteer.

	Bi-exponential				Mono-exponential	Fractional order	
	$T_{2,s}$* [ms]	$T_{2,l}$* [ms]	b_s	b_l	T_2* [ms]	T_2* [ms]	α
Patellar tendon	4.56 ± 0.68	7.25±9.05	1412.4±247.68	448.41±102.05	1.4±7.41	5.05±0.97	0.79±0.02
Muscle	1.10±3.16	22.71±5.49	103.53±44.24	428.29±71.24	24.84±1.68	24.08±1.93	0.79±0.06
Bone marrow	0.34±0.36	10.31±12.79	327.59±108.16	112.41±105.52	0.96±0.82	0.51±0.15	0.5±0.15

The indicated values are the mean ± the standard deviation of the T2∗-s in [ms] and the α parameter. The chosen tissues were the patellar tendon, muscle (sartorius muscle) and the bone marrow (of the femur). The results are from the ROIs ≥50 voxels.

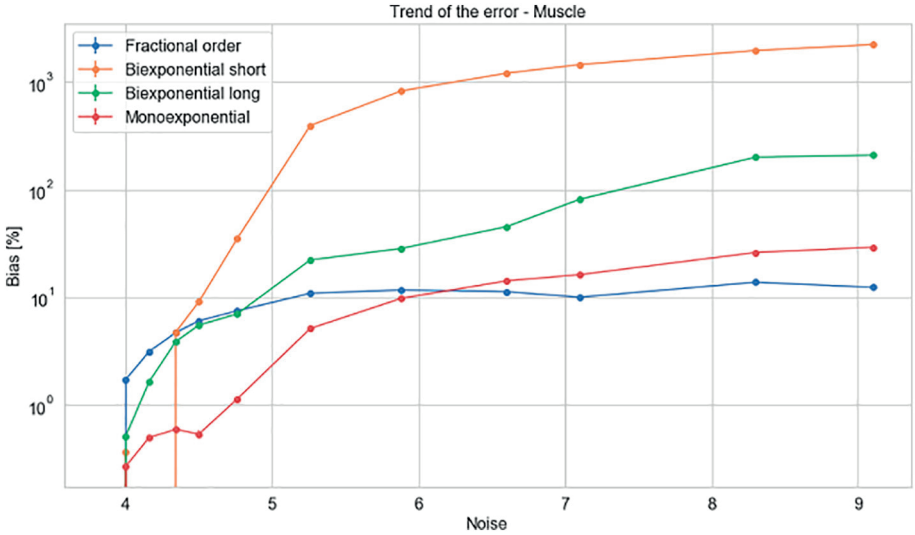

Figure 3: Bias of T2* inside the muscle. The method is the same as for the patellar tendon. The original SNR of the muscle was 26.

In the patellar tendon the T2, l∗ had the highest coefficient of variation (≥50%). The T2∗ and α values from the fractional order, the mono-exponential and the short bi-exponential models had a coefficient of variation below 15%. In case of the fitting in the muscle the coefficient of variation was below 15% for all of the three models.

Fig. 4 shows representative axial T2∗ and α maps for all three models. On visual inspection, the fractional order maps showed the anatomy clearly, the contrast between tissues was higher than for the mono-exponential map, and the parameter maps were homogenous within the tissues. Clearly, when comparing the mono-exponential and the fractional order maps, the fractional order fitting method yielded enhanced contrast, an improved delineation of the different tissues, and a higher homogeneity inside a given tissue. In case of the bi-exponential method the long component map demonstrated the anatomy clearly with high contrast. Nevertheless, the short component map exhibited poor contrast.

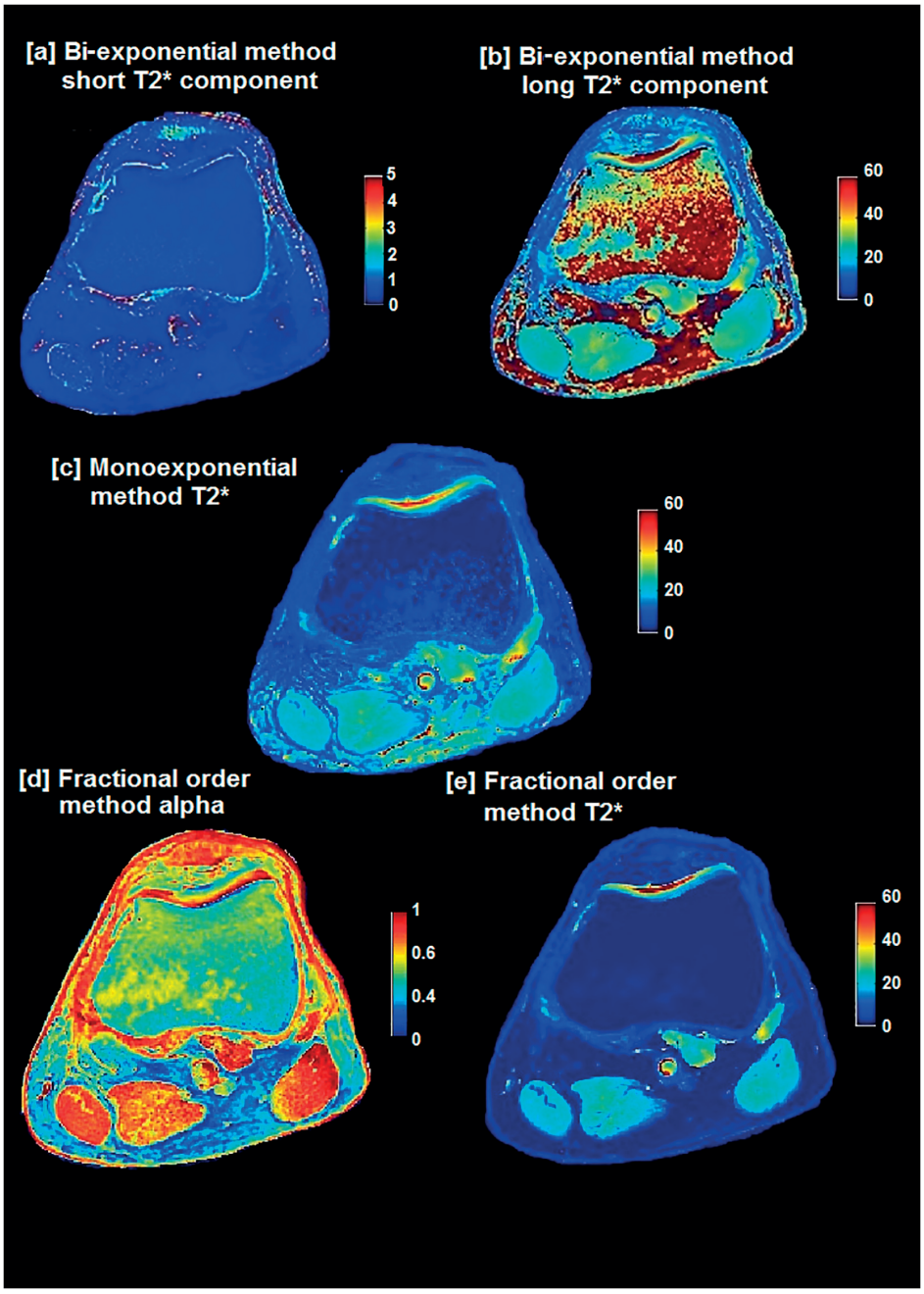

Figure 4. [a] Bi-exponential method T2, s∗, [b] bi-exponential method T2, l∗, [c] mono-exponential method T2∗, [d] fractional order α, [e] fractional order T2∗. T2∗ maps for all three different fitting models. The fitting was not performed in the background, shown black in the images. The α parameter is dimensionless, the T2∗ values are in ms.

Table 2 shows the mean quantitative parameters (Xi, where i stands for the different fitting parameters) and the standard deviation over the ROI's (σi) for one volunteer for each of the fitting methods. The T2∗ values were different depending on the applied method, and they differed most for the patellar tendon. In case of the muscle the derived T2∗ values were within the standard deviation for all of the three different models. For the bi-exponential model the component sizes were included, and this showed that none of the compartments were negligible (std < mean value). The T2∗ values in the bi-exponential model showed the largest standard deviation among the models. In all tissues, the T2∗ of one of the components had a larger standard deviation than the average value. In the patellar tendon the mono-exponential model showed similar behavior to the bi-exponential one, while the T2∗ of the fractional order model had a lower standard deviation.

For ROI based fitting we made a comparison for the five subjects. Table 3 shows the mean $\bar{X}$, and the standard deviation (σX) of the quantitative parameters over the five volunteers and the mean of the standard deviations within the ROIs; the pooled standard deviations $\bar{\sigma}$. σX shows the variability over their individual anatomies, contains more information by describing how much the parameters differs inside the given ROI for all volunteers. The bi-exponential model short T2∗ value shows the largest standard deviation for the for all three tissues. The fractional order model's highest variance is 14% for the same value, while the mono-exponential's is 15%.

Table 3. Comparison of the different fitting methods in different tissues in case of five volunteers. The indicated values are the mean of the five volunteers: $\bar{X}$, the standard deviation over the five volunteers σX, and the pooled standard deviations: $\bar{\sigma}$. The T2∗-s are in [ms] and the α parameter is dimensionless. The chosen tissues were the patellar tendon, muscle (sartorius muscle) and the bone marrow (of the femur). The results are from the ROIs ≥50 voxels.

		Bi-exponential				Mono-exponential	Fractional order	
		$T_2^*{}_S$ [ms]	$T_2^*{}_L$ [ms]	b_s	b_l	T_2^* [ms]	α	$T_2^*{}_S$ [ms]
Patellar tendon	$\bar{X}$	4.01	15.46	1477.56	457.81	7.17	5.36	0.77
	σX	0.44	8.08	359.67	94.19	4.29	0.55	0.55
	$\bar{\sigma}$	4.98	5.18	52.60	51.59	0.18	0.46	0.02
Muscle	$\bar{X}$	0.49	9.78	63.19	332.40	0.62	0.69	0.46
	σX	0.02	3.08	23.30	31.58	0.06	0.02	0.04
	$\bar{\sigma}$	3.38	3.14	43.67	45.03	0.03	0.10	0.03
Bone marrow	$\bar{X}$	0.28	24.09	376.78	86.18	14.42	22.53	0.74
	σX	0.05	2.74	58.74	5.64	1.84	2.82	0.04
	$\bar{\sigma}$	0.16	2.63	24.46	7.20	0.93	0.71	0.02

DISCUSSION

Our simulations show that the results of parameter fitting vary with signal to noise ratio. One component of the bi-exponential method (depending on the type of tissue) has extremely

large (≥100%) bias from the original value at a given noise level after 10% of extra added noise. In the patellar tendon, the component with the larger bias is the one with the larger component value (76%) and, in the case of the muscle, the long component (80% component value) has the largest bias. While the bias curve is flat, the ROI based standard deviation is the highest in the case of the bi-exponential long component, so the repeatability of the values is low. The bias curve for the mono-exponential and the fractional order models are close to each other in both the patellar tendon and the muscle. However, due to the tissue characteristics, it is known that the T2* decay curves are not simply mono-exponential. We may expect mono-exponential behavior inside the muscle, but a previous study[28] and the α parameter as well as the bi-exponential component sizes show that the muscle tissue is heterogeneous.

Our results clearly demonstrate that, in the case of lower SNR, the bi-exponential model has low repeatability. None of the components simultaneously has small bias and low standard deviation. In this study, the focus was on different regions of the knee, however, the acquisition was optimized for the patellar tendon, and a surface coil (NeoCoil, Pewaukee, Wisconsin, USA) was used to maximize SNR. This experimental setup resulted in sufficiently high SNR at the tendon, but that is not feasible for all the tissues. The difference in bias between the mono-exponential and the fractional order model is only a few percent (≤10%), and in the case of lower SNR the fractional order model has the smallest standard deviation. The heterogeneity of the tissues also indicates that the fractional order or the bi-exponential models are the most appropriate models for fitting.

The parametric maps of the different methods demonstrated differences in contrast and tissue homogeneity. Comparing the mono-exponential map to the long T2∗ bi-exponential map, we observed a similar trend as both of them give more contrast, and the tissue outlines are more visible. The short T2* bi-exponential map did not distinguish the different tissues clearly, and the contrast to noise level was low. The α map offers the best anatomical visualization along with a high tissue contrast, and it gave different values for the different tissue types. On the fractional order model T2* map, a given tissue is homogenous. The reason why we observed even a heterogeneous tissue as homogeneous (e.g. Fig. 4 fractional order T2* map, bone marrow), is because apparently the α value of the fractional order model captures the heterogeneity. This corresponds to the observation that, for bone marrow, the standard deviation of the fractional order model T2* is lower than that of the other two models.

Although the ROIs were chosen in the middle of the tissues - as it is shown in Fig. 1 - size and positioning could lead to some variability due to the different anatomies of the volunteers, σX shows this difference. For the patellar tendon, the volunteers had different levels of patellar tendinopathy, which leads to higher variance as well. However $\bar{\sigma}$ shows the pooled

standard deviations; the difference inside the given ROIs. We found that this reaches >100% of X^-in case of the patellar tendon, and the muscle for the bi-exponential method, while in case of the other two methods it is maximum 15% of X^- for the T2* parameters. As σT2* is much smaller than the difference among the T2*. The main reason behind the different T2* values is the chosen fitting method as in most cases $\sigma T2^{*-}$ is greater than σT2*.

In conclusion, when SNR is high, a fractional order and bi-exponential model are both performing well with low bias. However, in all observed cases, one of the bi-exponential components has high standard deviation in T2* (≥50%). The bi-exponential model is suitable for T2* mapping, but we recommend to use the fractional order model in the case of low SNR.

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7

Association Between T2* Relaxation Times Derived From Ultrashort Echo Time MRI and Symptoms During Exercise Therapy for Patellar Tendinopathy: A Large Prospective Study.

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J Magn Reson Imaging. 2021 Nov;54(5):1596-1605.

ABSTRACT

Background: Exercise therapy is considered preferential treatment for patellar tendinopathy (PT). However, there is conflicting evidence for structural patellar tendon adaptation in response to exercise therapy and its association with symptoms is weak.

Purpose: To assess the association between 1) T_2^* relaxation times and symptom severity; 2) baseline T_2^* and clinical outcome; and 3) longitudinal T_2^* changes and clinical outcome in athletes with PT performing exercise therapy.

Study type: Randomized controlled clinical trial.

Subjects: Seventy-six athletes (18-35 years) with clinically diagnosed and ultrasound-confirmed PT.

Field strength/sequence: 3D gradient echo sequence (3.0 T).

Assessment: Patients were enrolled in a randomized trial of progressive tendon-loading exercises (PTLE) versus eccentric exercise therapy (EET). Symptoms were assessed using the Victorian Institute of Sports Assessment (VISA-P) questionnaire. 3D-Ultrashort echo time (UTE)-MRI was acquired at baseline, 12 and 24 weeks. Voxel-wise T_2^* relaxation times were quantified using mono-exponential and bi-exponential models. T_2^* analysis was performed in three patellar tendon tissue compartments representing: aligned collagen, degenerative tissue, and interface.

Statistical tests: Adjusted general linear, mixed-linear models, and generalized estimating equations.

Results: We included 76 patients with PT (58 men, mean age 24 ± 4 years); 38 in the PTLE-group and 38 in the EET-group, of which 57 subjects remained eligible for analysis. T_2^* relaxation times were significantly associated with VISA-P in degenerative and interface tissues of the patellar tendon. No association was found between baseline T_2^* and VISA-P after 24 weeks ($P > 0.29$). The estimated mean T_2^* in degenerative tissue decreased from 14 msec (95%CI: 12-16) at baseline to 13 msec (95%CI: 11-15) at 12 weeks and to 13 msec (95%CI: 10-15) at 24 weeks. The significant decrease in T_2^* from baseline to 24 weeks was associated with improved clinical outcome.

Data conclusion: Tissue-specific T_2^* relaxation times, identified with 3D-UTE-MRI, decreased significantly in athletes with patellar tendinopathy performing exercise therapy and this decrease was associated with improved clinical outcome.

INTRODUCTION

Patellar tendinopathy (PT) is a common disorder due to tendon overuse injury in athletes.[1] PT is diagnosed, based on localized pain at the attachment of the patellar tendon to the patellar bone.[2] Symptoms occur with tendon loading, such as jumping, landing, and cutting in sports activities and activities of daily living, or physically demanding work.[3, 4] Symptoms from PT can be assessed using the validated Victorian Institute of Sports Assessment (VISA-P) questionnaire, with an outcome ranging from 0 to 100 points. A score of 100 indicates no pain, maximum function and unrestricted ability to play sports.[5] Conservative treatment of PT consists of exercise therapy and is focused on increasing the tendon's capacity to tolerate load.[6]

The pathophysiology of PT is largely unknown but involves characteristic degenerative changes at the latter stages.[7] The hierarchical architecture of the patellar tendon normally consists of parallel ordered collagen fibers and ground substance.[8] Proteoglycans are composed of multiple glycosaminoglycan chains that are attached to a protein core and are found in the extracellular matrix of tendons.[9] Highly negatively charged proteoglycans attract water and contribute to compressive resistance within the tissue.[10] In tendinopathy, there is an increase in cellularity and ground substance volume.[11] Exercise therapy is assumed to reverse this degenerative cascade.[12] However, there is conflicting evidence that exercise therapy results in structural adaptation measured with clinically available imaging modalities (eg, ultrasound and MRI).[13] Although the correlation between imaging outcomes and clinical outcomes remains unclear, the glycosaminoglycan content from tendon biopsies correlates well with tendon pain.[13, 14]

Imaging of tendons using MRI with conventional pulse sequences is typically limited by the fast free induction decay of collagen, commonly only visualizing increased signal intensity in the proximal patellar tendon, which may reflect increased water content.[15] Strong spin–spin interactions usually lead to undetectable signal from short T2* relaxation components, such as collagen.[16]

Ultrashort echo time (UTE) MRI facilitates the detection of signal from short T2* tissues such as tendons, which can be used to infer tendon hydration state by voxel-wise T2* quantification.[17] T2* analysis reflects signal from protons in different water pools within the patellar tendon, consisting of collagen-bound water pools (shorter T2* relaxation times) and free water pools (longer T2* relaxation times).[18] While mono-exponential T2* fitting models have shown the best reliability, bi-exponential models allow differentiating voxels in highly organized collagen compartments from degenerative tissue compartments within the patellar tendon.[19, 20]

Previous studies on UTE in tendinopathy have consistently shown increased T2* relaxation times.[21, 22] However, quantification of T2* changes in PT within specific tissue compartments has not been performed. Moreover, associations with symptoms have not been studied. We hypothesized that temporal changes in T2* can be detected using UTE-MRI and might be associated with clinical outcome in athletes with patellar tendinopathy performing exercise therapy.

The first aim of this study was to investigate the association between T2* relaxation times within different tissue compartments of the patellar tendon and symptom severity. The second aim was to investigate the association between baseline T2* and clinical outcome after exercise therapy. The third aim was to evaluate the association between longitudinal T2* changes and changes in severity of symptoms in athletes with PT.

MATERIALS AND METHODS

Study Participants

Ethical approval was obtained by the institutional review board and all participants provided written informed consent. Participants enrolled in the JUMPER-study, a randomized controlled trial investigating the effect of progressive tendon-loading exercises (PTLE) vs. eccentric exercise therapy (EET) for PT (ClinicalTrials.gov ID: NCT02938143). Inclusion criteria were age 18–35 years; history of knee pain in the patellar tendon region associated with training and competition; playing sports ≥3 times a week before injury onset; tenderness on palpation of the proximal patellar tendon; structural tendon changes on grayscale ultrasound and/or increased tendon vascularity on power Doppler; Victorian Institute of Sports Assessment (VISA-P) score < 80/100. Exclusion criteria are presented in the trial register. Activity level was measured using the Cincinnati Sports Activity Scale (CSAS).[23]

Inclusion Protocol

After an initial screening of online applications from study advertisements, potentially eligible athletes were invited to our hospital for medical history taking and physical examination performed by one sports physician (R.V.) with 10 years' experience. Subsequently, grayscale ultrasound (including anteroposterior tendon thickness and the presence of hypoechoic regions, tendon calcifications and erosions of the inferior patellar border) and power Doppler ultrasound (PDUS) were performed by the main investigator, a radiologist-in-training with 5 years' experience (S.B.) under supervision of a senior musculoskeletal radiologist with 16 years' experience (E.O.) to confirm the clinical diagnosis PT. Ultrasound was regarded conclusive for PT when structural changes to normal parallel ordered collagen fibers and/or hypoechoic changes and/or tendon thickening (anterior–posterior diameter > 6 mm) were confirmed and/or presence of intratendinous Doppler flow was detected on PDUS.[24]

Interventions

The intervention group performed progressive tendon-loading exercises (PTLE) within limits of acceptable pain, consisting of four consecutive stages (isometric, isotonic, plyometric, and sport-specific exercises).[3] The control group performed usual care eccentric exercise therapy (EET), which typically provokes substantial pain.[25] Centralized computer-based randomization was performed in a 1:1 ratio to PTLE or EET, using computer-generated block randomization with a variable block size ranging from 4 to 10. Patients in both study arms were also instructed to perform exercises targeting risk factors for PT. All patients received detailed advice and education on tendon care. Modification of pain-provoking athletic activities was advised for at least 4 weeks and we advised to perform (sports) activities within the limits of acceptable pain (pain score ≤ 3 points on a scale 0–10). Details regarding these therapeutic interventions are published elsewhere.[26] The main investigator (S.B.) was blinded for the allocated treatment during the entire period of data collection.

Outcomes

Clinical and imaging outcomes were collected at baseline, 12 and 24 weeks by the main investigator (S.B.). Patients were included in the primary analysis when there was at least one follow-up measurement available.

Clinical Outcome

Symptom severity was assessed using the validated Victorian Institute of Sports Assessment (VISA-P) questionnaire prior to image acquisition at every visit.[5] The main investigator was blinded for VISA-P scores at the time of image acquisition and analysis.

Image Acquisition

Imaging was performed at 3.0T (Discovery MR750, GE Healthcare, Waukesha, WI, USA) using a 16-channel flexible coil (NeoCoil, Pewaukee, WI, USA) and a fixation device. The knee was positioned in 30° flexion, using a cylindrical tube and foam padding.[19]

Using a research prototype 3D-UTE-Cones sequence (GE Healthcare), 16 echoes (0.032, 0.49, 0.97, 2.92, 4.87, 6.82, 8.77, 10.72, 12.67, 14.62, 16.57, 18.52, 20.47, 22.42, 24.37, 26.32 msec) were acquired using four multi-echo sequences with a constant repetition time of 83.4 msec.27 The axial 3D-UTE-Cones sequence parameters were acquisition time = 13:15 minutes per multiecho sequence, field-of-view (FOV) = 15 cm, matrix size = 252 × 252, voxel size 0.6 × 0.6 × 1.5 mm^3, number of slices = 60, number of excitations (NEX) = 1, bandwidth 125 kHz, flip angle = 17°, and two excitations per fat saturation. Echoes were scanned in interleaved order using four fat saturated multiecho UTE-acquisitions with a total scan time of 53 minutes. The full acquisition protocol is described elsewhere.[19] This final protocol was implemented after changing our previously designed image protocol that consisted of seven single echo ac-

quisitions and one multiecho acquisition in the coronal oblique plane without fat saturation (data not included), in order to increase SNR for T2* quantification.

Image Preparation

Image registration was performed to facilitate spatial one-to-one mapping of voxels across longitudinal UTE-acquisitions, using in-house developed tools (Elastix v.4.8, Rotterdam, The Netherlands) and Matlab software (R2015b; TheMathWorks, Natick, MA, USA).[28] First, rigid registration was performed on the entire knee volume, which corrected for rotation and translation between multiecho acquisitions and examinations from baseline and follow-up visits. Second, groupwise nonlinear refinement registration was performed on a volume of interest drawn on three orthogonal views, including only the anterior knee part including the patellar tendon.[29]

Image Analysis

Image analysis was performed by the main investigator, a radiologist-in-training with 5 years' experience (S.B.) under supervision of a postdoctoral researcher specialized in image analysis with 14 years' experience (D.P.) using an in-house developed Matlab script. For quantitative T2* analysis, mono-exponential and bi-exponential models were fitted to registered UTE-images, using maximum likelihood estimation incorporating the Rician noise model.[20,30] The initial step after fitting the data was to manually segment the outer margins of the patellar tendon on 10 consecutive slices covering the proximal patellar tendon, as described elsewhere.[19]

Second, the T2* data within this mask were categorized into three groups, by selecting voxels based on the average over visits of the percentage of short T2* components from the bi-exponential model (0%–30%, 30%–60%, and 60%–100% short T2*).[19] These three subregions that together spanned the manually drawn mask represented: 1) mostly short T2* (60%–100% short), 2) mostly long T2* (0%–30% short), and 3) an interface that separated the two (30%–60% short). The subregions were considered to represent aligned collagen, degenerative tissue, and an interface, respectively and were based on histogram analysis of the T2* frequency distribution in previous work.[19] Finally, the corresponding mono-exponential T2* relaxation times were used, in these selected voxel groups that were constant over visits, to calculate T2* relaxation times for each voxel group (patellar tendon subregion) accordingly. Thus, the selected voxel groups that delineated the regions of interest used for analysis were defined on the baseline scans and propagated to follow-up scans to assess temporal changes in T2* on subsequent scans (after 12 weeks and 24 weeks). The mono-exponential T2* relaxation times were fitted voxel-wisely in the entire registered scan volume from three separate visits.

Statistical Analysis

Normality of data was assessed using the Shapiro–Wilk test and homogeneity of variances was tested using the Levene test. Associations between T2* relaxation times and VISA-P score were assessed using multiple linear regression analyses. Adjusted general linear models were used to assess associations between baseline T2* and clinical outcome after 24 weeks. Longitudinal data were analyzed using adjusted generalized estimating equations (GEE) models, to estimate population-averaged effects. Whole group analyses were performed and between-group differences in relation to the time course of the dependent variables were evaluated using an interaction term "study arm*visit" in the GEE model, where the visit defined baseline, 12 weeks or 24 weeks. Bonferroni corrections were applied in the GEE-models for the following comparisons: 1) baseline vs. 12 weeks, 2) 12 weeks vs. 24 weeks, and 3) baseline vs. 24 weeks. Associations with clinical outcome were evaluated using adjusted mixed linear models. All models were adjusted for predefined potential confounding factors, including age, sex, BMI, CSAS, and symptom duration. All analyses were performed following an intention-to-treat principle. Imputation of missing data was not performed. Instead, posthoc sensitivity analyses using the last observation carried forward (LOCF) approach were performed when the amount of missing data exceeded 5% of the total number of observations.[31] Statistical analysis was performed using IBM SPSS software version 25 (IBM Corp., Armonk, NY, USA). Statistical significance was defined as a P-value < 0.05.

RESULTS

Study Population

Athletes were consecutively enrolled between January 2017 and June 2019. A total of 76 included athletes (58 men, mean age 24 ± 4 years) with clinically diagnosed and ultrasound-confirmed PT were included of which 38 were randomized to PTLE and 38 to EET (Fig. 1). Due to a change in the MR acquisition protocol during the study period, 11 subjects were missing for T2* analysis. Furthermore, eight subjects could not be included in the primary analysis due to missing data. Demographic characteristics of the study population are listed in Table 1.

Clinical Outcome

Among all athletes, the estimated mean VISA-P score improved significantly from 57 (95% CI: 53–61) at baseline to 72 (95% CI: 67–76) at 12 weeks and 80 (95% CI: 76–84) at 24 weeks follow-up. In the PTLE group, the estimated mean VISA-P score improved significantly from 56 (95% CI: 52–61) at baseline to 84 (95% CI: 79–89) at 24 weeks and in the EET-group it improved significantly from 57 (95% CI: 53–62) to 75 (95% CI: 69–82). The parameter estimate for the "study arm*visit" interaction using GEE was statistically significant. The homogeneity

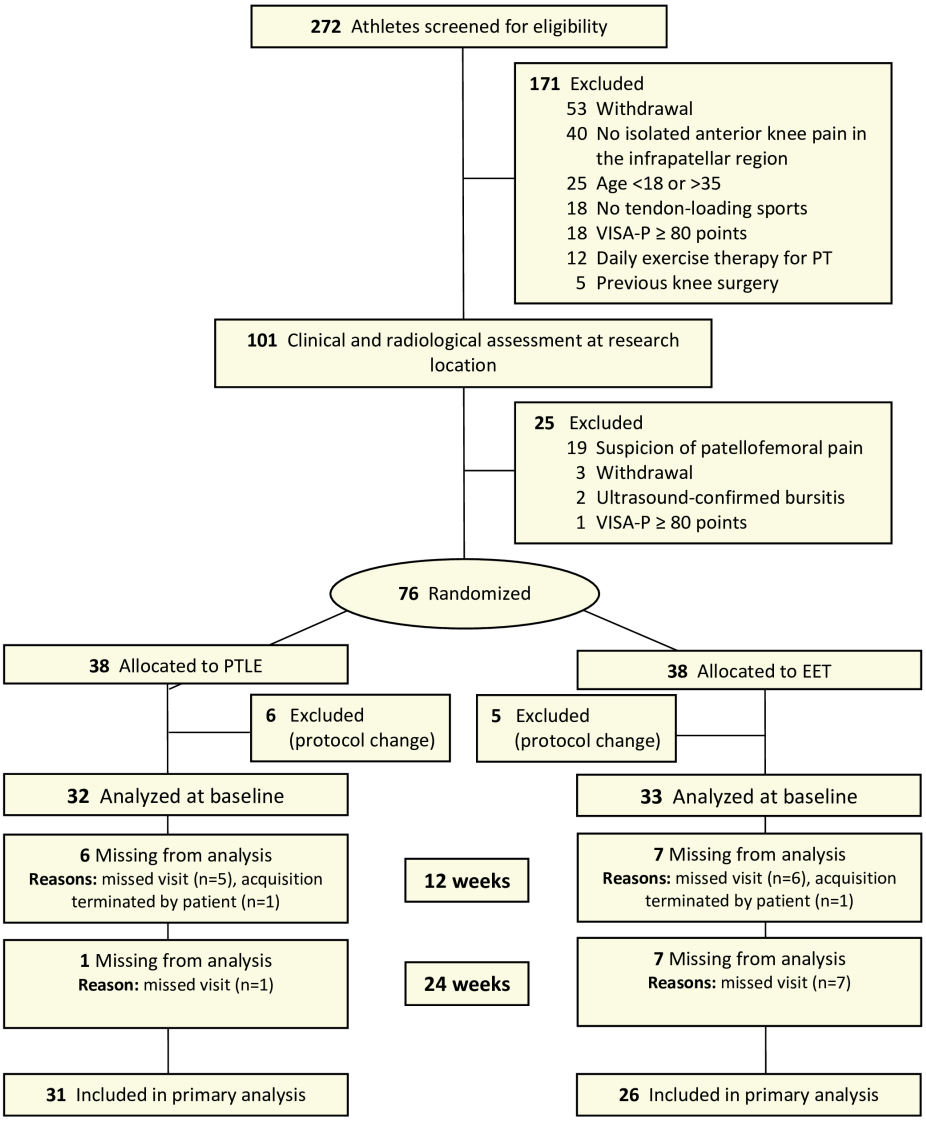

Figure 1: The consort flow diagram. PT = patellar tendinopathy; VISA-P = Victorian Institute of Sports Assessment questionnaire for patellar tendons.

of variance assumption was not violated (P = 0.59). The significant adjusted mean between-group difference of the VISA-P score at 24 weeks was 9 points (95% CI: 1–16), in favor of the PTLE group, indicating an improved clinical outcome in athletes performing progressive tendon-loading exercises (PTLE).[26]

Table 1. Baseline Characteristics

Characteristics	**Whole group (n=76)**	**PTLE Group (n = 38)**	**EET Group (n = 38)**
Age, mean (SD), years	24 (3.8)	24 (3.5)	24 (4.2)
Sex, male	58 (76)	31 (82)	27 (71)
BMI, mean (SD)	23.9 (2.9)	23.8 (2.5)	24.1 (3.2)
Symptom duration, median [IQR], weeks	104 [43-208]	119 [64-273]	78 [40-169]
VISA-P score, mean (SD)	55 (13.1)	55 (13.1)	56 (13.2)
Sports Activity Scale (CSAS) prior to onset of PT			
Level I (4 to 7 days/week)			
100	17 (22)	10 (26)	7 (18)
95	0 (0)	0 (0)	0 (0)
90	0 (0)	0 (0)	0 (0)
Level II (1 to 3 days/week)			
85	50 (66)	23 (61)	27 (71)
80	9 (12)	5 (13)	4 (11)
Sports participation in desired sport at the time of study commencement, n (%)			
Equal	19 (25)	10 (26)	9 (24)
Reduced	29 (38)	14 (37)	15 (40)
Ceased	28 (37)	14 (37)	14 (37)
Affected side			
Unilateral, left/right, n (%)	26 (59) / 18 (41)	10 (53) / 9 (47)	16 (64) / 9 (36)
Bilateral, n (%)	32 (42)	19 (50)	13 (34)
US-assessment			
AP thickness, mm ± SD	8.4 ± 2.3	8.2 ± 2.7	8.6 ± 2.0
Hypoechoic regions, n (%)	76 (100)	38 (100)	38 (100)
Tendon calcifications, n (%)	20 (26)	9 (24)	11 (29)
Patellar erosions, n (%)	24 (32)	17 (45)	7 (18)
Power Doppler			
0: absence of Doppler flow	7 (9)	5 (13)	2 (5)
1: Doppler flow posterior to tendon	0 (0)	0 (0)	0 (0)
2: 1-2 intratendinous blood vessels	18 (24)	12 (32)	6 (16)
3: 3-4 intratendinous blood vessels	7 (9)	3 (8)	4 (11)
4: network of blood vessels	44 (58)	18 (47)	4 (68)

PTLE = progressive tendon-loading exercise therapy; EET = heavy-load eccentric exercise therapy; SD = standard deviation; BMI = body mass index; IQR = interquartile range; VISA-P = Victorian Institute of Sports Assessment Questionnaire for patellar tendons; CSAS = Cincinnati Sports Activity Scale; PT = patellar tendinopathy; n = number; US = ultrasound; AP = anterior–posterior. Data are presented as No. (%) unless otherwise specified.

Association between T2* in Different Tissue Compartments and Symptom Severity

Adjusted linear regression analysis demonstrated a statistically significant linear association between VISA-P score and T2* relaxation times in both degenerative tissue and in the interface between aligned collagen and degenerative tissue (Table 2). Scatter plots of individual associations between mono-exponential T2* in specific tissue-compartments and VISA-P score are illustrated in Fig. 2.

Table 2: Association between VISA-P and T2* (multiple linear regression analysis)

Factor	**Degenerative tissue (0-30% short T2*)**			**Interface (30-60% short T2*)**			**Aligned collagen (60-100% short T2*)**		
	β	**95% CI**	***P* value**	**β**	**95% CI**	***P* value**	**β**	**95% CI**	***P* value**
Age	.008	-.125 to .141	.908	.023	-.040 to .085	.472	.043	.011 to .076	.010
Sex	1.460	.300 to 2.620	.014	.422	-.121 to .965	.127	.049	-.234 to .332	.732
BMI	.015	-.175 to .205	.876	.026	-.063 to .115	.561	.052	.006 to .098	.028
Duration	<.001	-.004 to .004	.989	.001	-.001 to .002	.482	.001	.000 to .002	.046
CSAS	-.044	-.119 to .031	.252	.010	-.025 to -.006	.565	.006	-.012 to .025	.506
VISA-P	**-.046**	**-.075 to -.018**	**.002**	**-.019**	**-.033 to -.006**	**.005**	-.003	-.010 to .004	.461

CI = confidence interval; BMI = body mass index; CSAS = Cincinnati Sports Activity Scale; VISA-P = Victorian Institute of Sports Assessment Questionnaire for patellar tendons.
Adjusted mean differences that were significant at 0.05 level after Bonferroni correction are in bold.

Association between Baseline T2* and Change in Symptom Severity

Baseline T2* values for all tissue compartments are listed in Table 3. There was no significant association of baseline T2* with clinical outcome after 24 weeks of exercise therapy for all of the tissue compartments of the patellar tendon (degenerative tissue [$R^2 = 0.17$, P = 0.29], aligned collagen [$R^2 = 0.17$, P = 0.95], and the interface compartment [$R^2 = 0.15$, P = 0.55]).

Table 3: Unadjusted and adjusted change in T2* over time

T2* subregion	Unadjusted T2* (ms) ± SD (raw data)		Adjusted mean difference (95% CI), from baseline[a]		
	Baseline	**12 weeks**	**Baseline**	**12 weeks**	**24 weeks**
Degenerative tissue (0-30% short T2*)	14.2 ± 3.2	13.5 ± 3.4	12.8 ± 3.5	-0.7 (-1.3 to -0.1)	-1.3 (-2.0 to -0.6)
Interface (30-60% T2*)	7.5 ± 1.6	7.3 ± 1.5	6.9 ± 1.5	-0.3 (-0.7 to 0.2)	-0.6 (-1.1 to -0.1)
Aligned collagen (60-100% T2*)	3.1 ± 0.9	3.2 ± 0.6	3.1 ± 0.9	0.1 (-0.2 to 0.3)	-0.0 (-0.2 to 0.2)

[a] The adjusted mean differences were calculated using Generalized Estimating Equations (GEE) with adjustments for the following pre-defined baseline variables: age, sex, BMI, symptom duration and Cincinnati Sports Activity Scale.
Adjusted mean differences that were significant at .05 level after Bonferroni correction are bolded.

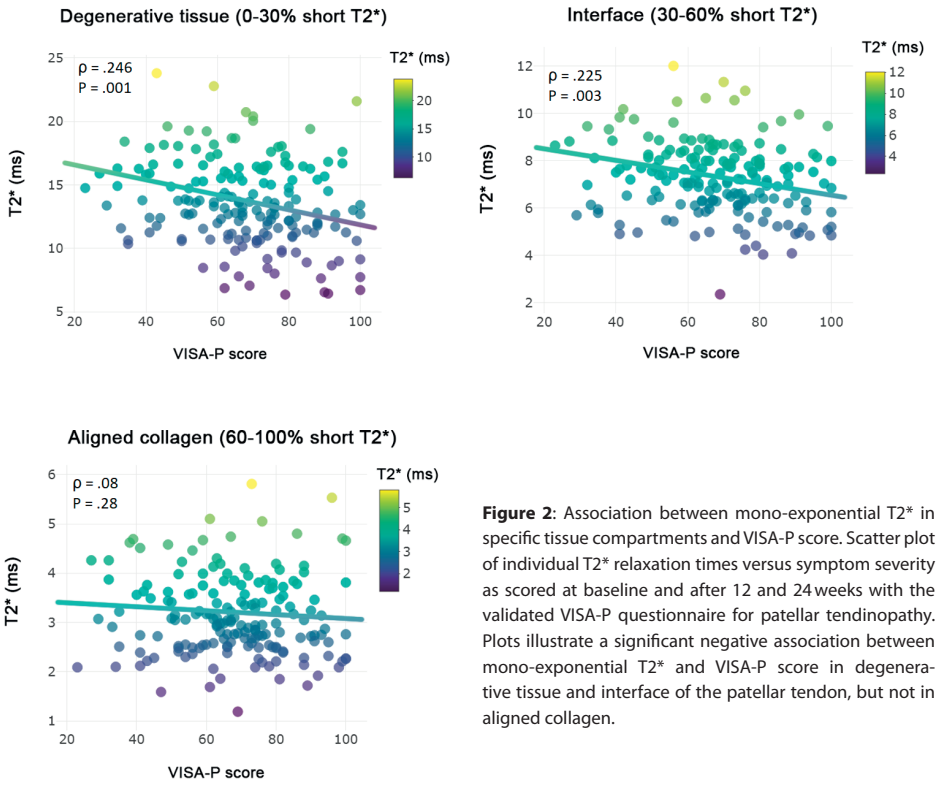

Figure 2: Association between mono-exponential T2* in specific tissue compartments and VISA-P score. Scatter plot of individual T2* relaxation times versus symptom severity as scored at baseline and after 12 and 24 weeks with the validated VISA-P questionnaire for patellar tendinopathy. Plots illustrate a significant negative association between mono-exponential T2* and VISA-P score in degenerative tissue and interface of the patellar tendon, but not in aligned collagen.

Longitudinal UTE-MRI Data and Relation with Clinical Outcome

Among all athletes, a significant decrease in T2* was found in the voxels that represented the degenerative tissue of the patellar tendon, from 14 ± 3 msec at baseline to 13 ± 4 msec at 24 weeks (adjusted mean difference [95% CI] = 1 msec [1–2]). The change in T2* was not significant at 12 weeks (adjusted mean difference [95% CI] = 1 msec [0–1], P = 0.09). For voxels that represented aligned collagen and voxels that represented the interface between aligned collagen and degenerative tissue, the adjusted mean differences were not statistically significant (Table 3). The interaction term "study arm*visit" was not statistically significant for any of the tissue compartments (aligned collagen, P = 0.42; interface, P = 0.49; degenerative tissue, P = 0.54) (Fig. 3). The homogeneity of variance assumption was not violated for all tissue compartments (aligned collagen, P = 0.59; interface, P = 0.17; degenerative tissue P = 0.23). An example of the longitudinal T2* change is illustrated in Fig. 4.

The significant T2* decrease in the degenerative tissue compartment was significantly associated with the improvement in severity of symptoms as measured with the VISA-P score (main effect, −1.2 [95% CI: −2.0 to −0.4]), Fig. 5. There was no association with clinical outcome for the aligned collagen (P = 0.77) and interface (P = 0.06) tissue compartments.

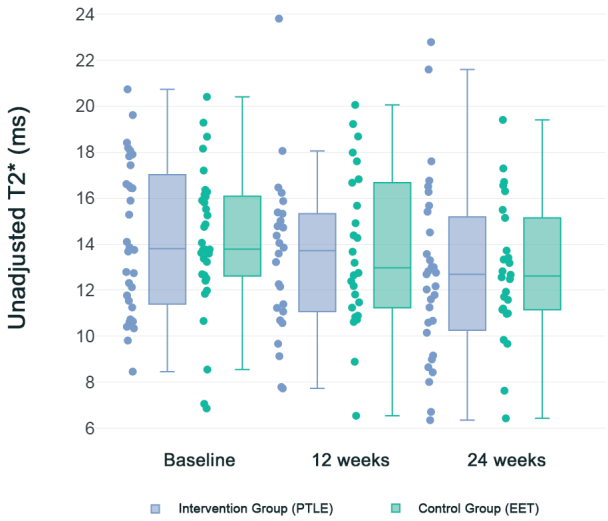

Figure 3: Longitudinal T2* changes in degeneratie tissue. Box plot and scatter diagram of longitudinal T2* measurements in the degenerative tissue of the patellar tendon. Results are divided by study arm (progressive tendon-loading exercises [PTLE] and eccentric exercise therapy [EET]). The midline of the boxplot represents the median of the data, with the upper and lower limits of the box being the 25th and 75th percentile. The whiskers extend up to 1.5 times the interquartile range.

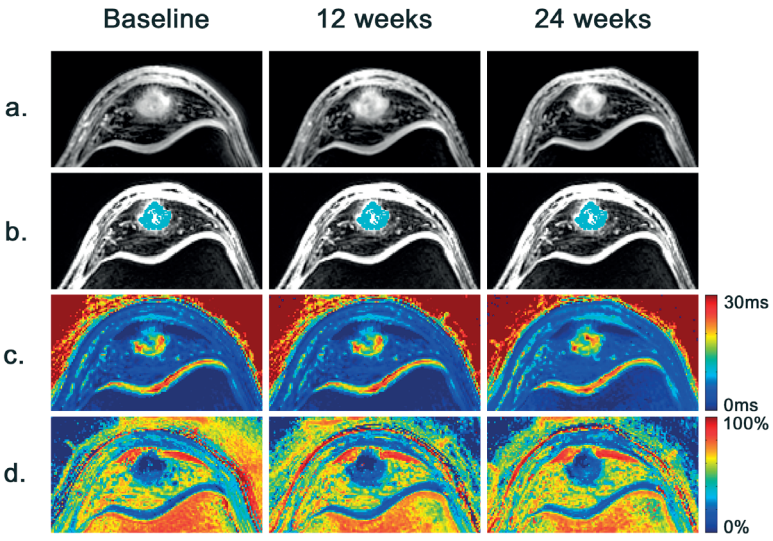

Figure 4: Illustration of longitudinal T2* analysis. (a) Transverse 3D-UTE images (TE = 4.82 msec) of the proximal patellar tendon in a 19-year-old male volleyball player with clinically diagnosed and ultrasound-confirmed patellar tendinopathy. (b) Automatically selected voxels (cyan colored) for tissue-specific T2* analysis in the degenerative tissue of the patellar tendon, based on the bi-exponential fitting threshold indicating 0%–30% short T2* components. In this patient, mean T2* decreased from 19.9 ± 7.3 msec (baseline) to 17.2 ± 5.8 msec (12 weeks) to 16.8 ± 4.9 msec (24 weeks). (c) Mono-exponential T2* maps, on a scale from dark blue (short T2* relaxation times) to red (long T2* relaxation times). (d) Bi-exponential fitting maps, displaying the percentage of short T2* components on a scale from dark blue (0% short T2* components) to red (100% short T2* components).

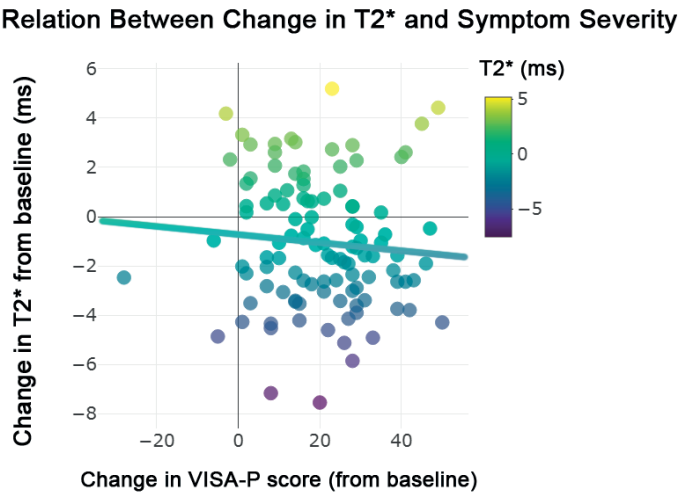

Figure 5: Relation between change in T2* and symptom severity. There was a significant association between a decrease in mono-exponential T2* within the degenerative tissue and clinical improvement (P = 0.005). There was no association with clinical outcome for the aligned collagen (P = 0.77) and interface (P = 0.06) tissue compartments.

Post hoc Sensitivity Analysis of Missing Data

Twenty one of the 195 UTE-MRI acquisitions (11%) were missing (Fig. 1). Sensitivity analyses to assess the influence of missing data showed that the estimated mean VISA-P score improved significantly from 56 points (95% CI: 53–60) at baseline to 69 points (95% CI: 65–73) at 12 weeks and 78 points (95% CI: 74–82) at 24 weeks follow-up among all athletes. After 24 weeks, a significant adjusted mean between-group difference of 11 points (95% CI: 3–18) was found. The T2* decrease in degenerative tissue between baseline and 24 weeks follow up remained significant (mean difference, 1 [95% CI: 1–2]). The association with clinical outcome was significant (main effect, −1.1 [95% CI: −1.9 to −0.3]) when the most recent preceding T2* value was carried forward to substitute all missing values. There were no significant T2* changes in voxels that represented aligned collagen (main effect, 0.7 [95% CI: −2.1 to 3.4]; P = 0.64) and the voxels that represented the interface (main effect, −1.3 [95% CI: −2.7 to 0.1]; P = 0.07) between aligned collagen and degenerative tissue.

DISCUSSION

We found that T2* relaxation times within the degenerative tissue of the patellar tendon were associated with symptom severity in athletes with patellar tendinopathy. There was no predictive value of T2* at baseline for the clinical outcome after 24 weeks. Decreasing T2* relaxation times were related to a better clinical outcome after 24 weeks using tissue-specific T2* analyses.

This randomized controlled trial demonstrated longitudinal changes in T2* in patellar tendinopathy using a tissue-specific analysis method based on bi-exponential fitting parameters.[19] The capability of UTE-MRI to detect longitudinal changes had already been demonstrated by others, specifically in healing tendon grafts following anterior cruciate ligament reconstruction, in human cadaveric tendons that were subjected to tensile static loading, and in Achilles tendons of long distance runners.[32-34]

The small, but significant, decrease in T2* relaxation times within the degenerative tissue may demonstrate the patellar tendon's ability to change structurally in response to exercise therapy. Conservative treatment options focus on structural adaptation of the patellar tendon to progressive loading of the tendon.[35] However, the current evidence is conflicting regarding the effect of exercise therapy on structural adaptation measured with clinically available imaging modalities.[6,13] The significant association between decreased T2* relaxation times and improved clinical outcome in our study further emphasizes the benefit of strengthening exercises in the treatment of tendinopathy.[3] The hydration state of the degenerative tissue as quantified with T2* mapping that was significantly associated with symptom severity was in accordance with a previous study that found an association of glycosaminoglycan content from tendon biopsies with VISA-P score.[14] Subregional T2* quantification, facilitating the monitoring of tendon hydration state that is associated with pain when quantified in specific tissue compartments without the need of invasive tendon biopsies, is of great value for future research focusing on clinical outcome after therapeutic interventions.[36]

The mechanism behind the ultrastructural changes that resulted in a T2* decrease in the degenerative tissue of the patellar tendon remains unclear. Theoretically, the decrease of long T2* components could result from changes in the macromolecular binding state of water, due to an increase or change of the proteoglycan and glycosaminoglycan content within the degenerative tissue.[37] Another possible explanation is that within the degenerative tissue, the voxels contained an increasing proportion of (ultra)short T2* components over time, for example, due to newly formed collagen fibers as a response to exercise therapy.

A strength of this study is that we performed a large clinical trial that implemented longitudinal UTE-MRI acquisitions to evaluate T2* changes in patients with PT. Other strengths are the advanced methods for image preparation and postprocessing of the UTE-images, including in-house developed linear and nonlinear registration tools for a spatial one-to-one mapping of voxels that were constant over visits from different UTE-acquisitions and the analysis of T2* in specific tissue compartments of the patellar tendon. We believe that these methods strongly facilitated the analysis of longitudinal data. After performing sensitivity analyses, our findings were consistent with those from the primary analysis and would lead to similar

conclusions about the association between decreased T2* in the degenerative tissue of the patellar tendon and improved clinical outcome.

Limitations

We proposed a method to quantify T2* in different tissue compartments of the patellar tendon, represented by thresholding the percentage of short T2* components voxel-wisely into 0%–30%, 30%–60%, and 60%–100% short T2* components. Despite the observation that these subcategories of voxels with similar T2* characteristics visually corresponded well to degenerative tissue, interface and aligned collagen, respectively, there is uncertainty if these subcategories really represent these tissues. This primarily affects the construct validity of this method of T2* analysis, and is difficult to overcome without direct histologic confirmation of this subcategorization. The chosen thresholds were based on histogram analysis of the frequency distribution of the percentage short T2* components in each voxel, which categorized the T2* data in three groups, irrespective of what the absolute values were for the short and long components within each voxel.[19] Second, the reliability of the T2* quantification is most likely insufficient to detect a clinically relevant difference. From previously published data, we know that the coefficient of repeatability was estimated at 2 msec; however, the change in T2* after 24 weeks in all athletes was only 1.3 msec (0.6–2.0).[19] Third, the long acquisition time of our current protocol impedes application in clinical practice. The protocol as implemented was designed to provide an integral sampling of echo times and to provide a high spatial resolution. For this project, this scanning protocol was acceptable, because we did not intend to develop an image protocol that could be used in clinical imaging. For clinical applications, we recommend an abbreviated protocol, for example, as implemented by Fukuda et al.[32] With only six echo times in the short TE range, they managed to observe a decreased T2* in a remodeling anterior cruciate ligament graft 6 months post-surgery. Forth, a change in the MR acquisition protocol during the trial was required to optimize SNR for better fitting of T2* data, which unfortunately lead to exclusion of 11 patients in the final analyses. Moreover, the unbalanced loss of follow-up between the exercise groups (one in the PTLE group and seven in the EET group), could suggest that the eccentric exercises were less easy to sustain, which seems logical due to the fact that these exercises should be performed with pain.[38] This may also be reflected by the previously reported lower subjective patient satisfaction reported in the control group.[26] Finally, despite the fact that the significant decrease in T2* after 24 weeks was associated with clinical improvement in our study participants, it is important to note that the validity of the T2* parameters in tendinopathy (with tissue histopathology as reference standard) is currently unknown.

Conclusion

Tissue-specific T2* relaxation times identified with 3D-UTE-MRI are associated with symptom severity in athletes with patellar tendinopathy. Decreasing T2* relaxation times in the

degenerative tissue of the patellar tendon are associated with improved clinical outcome after exercise therapy for patellar tendinopathy, while it is unsuitable as a single predictive measurement at baseline for clinical outcome. While the change in T2* was small and the technique has limitations to use in clinical practice, our findings indicate that the hydration state of the patellar tendon is able to change in response to conservative exercise therapy.

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General Discussion

Patellar tendinopathy (PT) is a common tendon injury in athletes that often results in prolonged sport absence.[1] The disease burden of PT is significant; it leads to retirement from sports participation in more than half of the athletes.[2] Invasive treatment options such as injection therapies are discouraged because they have been proven insufficient to manage PT. They are sometimes even associated with deterioration of the patellar tendon, such as patellar tendon rupture following corticosteroid injections.[3] Therefore, exercise therapy has become the cornerstone treatment in order to improve symptoms and reverse the degenerative cascade that is typically seen in tendinopathy.[4]

The primary aim of this thesis was to compare eccentric exercise therapy (EET) with progressive tendon-loading exercises (PTLE) based on clinical outcome after 24 weeks. Secondary aims were to investigate the use of shear-wave elastography (SWE) and ultrashort echo time (UTE) MRI-based T2* mapping as advanced imaging methods in the longitudinal assessment of structural changes in association with symptoms that are associated with PT.

Exercise therapy for patellar tendinopathy

Despite the increased knowledge regarding the aetiology and pathogenesis of PT, no consensus on optimal management of tendinopathy has been established.[5,6] The recognition of tendinopathy as a degenerative disorder, rather than a primarily inflammatory disorder, has led to a scientific catch-up with trials focusing on exercise therapy instead of injection therapies that used to focus on tendon inflammation.[7]

In the JUMPER-study, the largest trial in PT to date, we assigned 76 athletes with clinically diagnosed and ultrasound-confirmed PT to two different exercise therapy groups. The JUMPER-study is a stratified, investigator-blinded, block-randomised trial.[8] The intervention group consisted of progressive tendon-loading exercises (PTLE) within the limits of acceptable pain and the control group was assigned to eccentric exercise therapy (EET). EET was regarded to have strong evidence of effectiveness for PT and is considered standard clinical care and is also supported in guidelines by the National Institute for Health and Care Excellence (NICE).[9,10] The need for an alternative treatment is because EET is painful to perform and because the therapeutic effects have been debated when applied in the competitive season.[11,12]

We found that, after 24 weeks, PTLE was superior to EET in reducing pain and in increasing function and ability to play sports.[8] Despite the fact that the difference of 9 points between PTLE and EET did not reach the previously reported minimum clinically important difference (MCID) of 13 points or better for the VISA-P scale, we feel safe to conclude that the statistically significant difference was also clinically relevant.[13] There are several reasons that substantiate the clinical relevance and significance of the superiority of PTLE. First, both treatments

involve performing rehabilitation exercises and in practice it would seem logical to opt for the most effective programme. Second, there are no additional costs or risks associated with performing PTLE over EET. We even think that the between-group difference of 9 points is fairly high considering the fact that athletes in the JUMPER-study had long-lasting symptoms with a median symptom duration of more than 2 years in the PTLE-group and 74% of those athletes already performed physical therapy for PT but remained symptomatic. More than a third of athletes allocated to PTLE had an excellent patient satisfaction, which was significantly higher than in the EET group (10%). Moreover, the prescribed exercises in the PTLE group were also significantly less painful to perform (mean VAS score 2 vs 4).

PTLE differs from EET in several ways. First, the exercises are performed within the limits of acceptable pain, whereas athletes allocated to EET were instructed to perform the exercises with pain (VAS score ≥5 points on a scale 0–10 during the exercises).[11,14] Second, PTLE exercises are slowly progressive in tendon loads and are performed in four subsequent stages: isometric, isotonic, plyometric and sport-specific stages. This is in contrast to the monophasic EET exercises which do not have progressive loading. Third, the program is more individualised, using progression criteria to proceed to the next stage. The instructions for the EET exercises are more universal and have no criteria that allow for individualisation. Based on our results, we would advise patients with PT to perform this 4-stage criteria-based exercise protocol.[15] We recommend to perform this protocol in the pre-season, in order to gradually prepare the patellar tendon to increasing loads. However, PTLE has also been found effective in athletes of the JUMPER-study that were outside of the pre-season and continued sports activities in the second half of the exercise protocol. We recommend all athletes to modify or even cease all athletic activities that are associated with increased pain in the patellar tendon region. These include jumping/landing, acceleration/deceleration and cutting manoeuvres which should optimally be ceased for at least 4 weeks in order to gain optimal focus on the exercise therapy. Exercise therapy is too often rushed because the training load of the regular training sessions and competitions is often already high. A short break from this load pattern and shifting the focus to recovery, despite not meeting the social desire to continue training and playing competitions, can be very beneficial to the athlete. All details regarding the PTLE (and EET) exercises is available in the online supplemental appendix of the BJSM publication.[16]

Isometric (static) exercises

Fairly different from EET is the introduction of isometric exercises in the PTLE protocol.[17] Isometric exercises are performed within the limits of acceptable pain (VAS pain score ≤3 points on a scale 0-10).[14] Using a leg press or leg extension machine, high isometric loading of the patellar tendon can be easily administered. Isometric exercises have been proposed for acute pain relief in a study by Rio et al.[17] Therefore, this type of contraction has been con-

sidered as ideal first stage of an exercise protocol with progressive loading within the limits of acceptable pain.[15] With the goal to reduce pain levels from PT and a parallel reduction in cortical inhibition, athletes were thought to be better prepared for subsequent isotonic exercises.[17] Other benefits of reducing pain in the beginning of an exercise programme have been well elaborated on in a systematic review and include removing fear of exercise and an improved awareness to be able to influence pain and hereby gain sense of control.[18–20] We hypothesised that this first stage of PTLE is a possible reason for the superiority of PTLE over EET and could explain the higher patient satisfaction in the PTLE group. However, because the largest group-difference in VISA-P scores was observed in the second half of the study (12-24 weeks), there are presumably other reasons that are responsible for the superiority of PTLE over EET. Moreover, the analgesic effect was only clear in the first study by Rio et al.,[17] while results on acute effects of isometric exercise on pain in patients with PT were less clear in a second trial conducted by the same authors.[21] A replication study using the same methods and outcomes as the study conducted by Rio and a systematic review that also included this replication study found no statistically or clinically relevant benefits of isometric exercises over isotonic exercises for pain relief.[6,22] Therefore, the type of contraction may not be the most important factor in the acute analgesic effect. Also, the exact effect of pain perception during exercise therapy has not yet been fully clarified. Performing exercises using an individualised treatment approach within the limits of acceptable pain might already explain the superiority of PTLE over EET.[23]

Isotonic (dynamic) exercises

Isotonic contractions consisted of a concentric phase immediately followed by an eccentric phase and, therefore, its contraction load partially overlaps with EET. This second stage of PTLE was initiated when stage 1 exercises (and a single leg decline squat as pain provocation test) could be performed single-legged with additional external weights and with minimal pain (3/10 or less). The time frame for achieving this progression criterion was not fixed, but determined by the individual athlete. This is an important difference with EET which involved the same type of exercise during the entire follow-up period and lacked individualised progression criteria that determined progression in loading. The isometric exercises were also performed on a leg extension or leg press machine. The rationale behind stage 2 exercises was to restore muscle strength through functional ranges of movement. These exercises were also easily modifiable within this stage to suit the athletes' load capacity by adjusting the degrees of knee flexion during the exercises (from 10-60 degrees to 0-90 degrees) and to progress to heavier loading using external weights (and less repetitions) as tolerated. The aim in this stage was to reach the desired functional capacity of the patellar tendon within the acceptable limits of pain.

Energy-storage (explosive) exercises

The introduction of plyometric (or explosive) exercises to the exercise program was initiated when stage 2 exercises could be performed within the limits of acceptable pain. The pain from a highly irritable tendon has diminished from isometric and isotonic exercises and the strength and load tolerance of the tendon has been largely restored to be able to withstand exercises with high energy-storage and release loads, such as in jumping or cutting manoeuvres. The introduction of explosive exercises is also gradual, to ensure a progressive increase in tendon loading in all stages of the exercise program. From the clinical outcome data, we observed the largest difference in VISA-P score increase in the second half of the exercise program.[8] At that stage most athletes were focussing on stage 3 exercises (at 12 weeks follow-up, almost 50% reached stage 3 or 4 of the PTLE program). The re-introduction of energy-storage loads provided a gradual progression to sport-specific exercises.

Sport-specific exercises

The last step providing a gradual return to sports is the addition of sport-specific exercises to the exercise protocol, depending on the demands of the individual's sport. These exercises may thus vary greatly between a volleyball player who mainly adds vertical jumps after abrupt stops as sport specific exercises and a soccer player who mainly adds cutting manoeuvres and sprints as exercises that simulate the loads that reflect the demands of those types of sports.

We believe that the slowly progressive approach in the PTLE protocol and the use of individualised pain-guided activity modification during treatment for PT are key factors that explain its superiority over EET. The isometric and isotonic exercises can reduce pain from PT through an increased loadbearing capacity for athletes in-season. This provides athletes an active tool to be in control of patellar tendon pain and it further strengthens their belief in the therapeutic effect of the exercise therapy. This is psychologically very different from EET exercises, that are painful to perform and have to be performed with more repetitions.[11] However, it would be incorrect to conclude that performing these exercises with pain is not effective, as clinical improvement was also seen in the EET group (+18 points on the VISA-P scale after 24 weeks vs +28 for PTLE). Performing exercises with pain did not influence subjective patient satisfaction (81% vs 83%) and exercise adherence (40% vs 49%) significantly, for PTLE and EET respectively. Although the data does not show a clear difference between these variables that would support choosing a certain type of contraction with or without pain, in practice it is most obvious to choose the most effective program.

There are some potential improvements that could be made to the PTLE protocol which also might further improve the disappointing patient adherence in the JUMPER-study (only 40% performed all prescribed exercises). We think that a supervised program or mobile application might help to motivate athletes and to guide them through the exercise therapy during

the entire follow-up duration of 24 weeks. Despite the therapy was instructed carefully at baseline and aided through instructional videos, the duration of the exercise protocol might be too long for this information strategy to be sufficient to the needs of the athlete. We also believe that the effects on clinical outcome might be even better when the adherence is higher than the adherence to the allocated exercises in the JUMPER-study.

Ultrasound-based assessment of patellar tendinopathy

Morphologic changes that can be visualised using clinically available ultrasound (US) systems are thickening of the patellar tendon, hypoechoic changes within the patellar tendon and disorganisation in tendon structure.[24] With Doppler US increased vascularity in the patellar tendon can be imaged, which can be graded using the Modified-Öhberg score.[25] Both the hypoechoic changes and increased vascularity of the patellar tendon are associated with pain.[26] However, their relationship and clinical relevance in patients with PT has been extensively debated.[27] In both basketball and volleyball players with no past history of knee pain, patellar tendons examined were found to have abnormal tendon morphology on US (incidence ranging from 32% to 54%).[28–30] Hypoechoic changes did not predict prognosis or was only weakly predictive for the development of future disabling tendon symptoms in studies where US was implemented longitudinally.[31–34] This is one of the reasons to investigate the additional value of shear-wave elastography (SWE) for prognostic and monitoring purposes.

SWE is a relatively new ultrasound-based technique that is not routinely used in clinical patient care, which is able to estimate viscoelastic properties of tissues.[35] Stiffness measurements are obtained using an acoustic radiation force (ARF) by the ultrasound transducer, which deforms tissue (e.g., patellar tendon) and hereby generates shear-waves which travel in the patellar tendon in the direction perpendicular to the ARF. The ultrasound transducer also measures the speed of the shear-waves which can be transferred to stiffness as outcome measure using Young's modulus.[36]

Since the application of SWE in the field of PT was relatively new at the start of the trial, we experimented a lot with the technique in the run-up to the first inclusions. We did this on the one hand to get a feel for the acquisition, but also to design a protocol for the acquisition that was as reproducible as possible. We practiced a lot with this, talked to an application expert and optimised the parameters together and hired a technical student for a project to test all variables, such as the influence of the knee flexion angle during acquisition but also the most comfortable position on the examination table. We then also performed reproducibility measurements by involving a fellow tendon researcher. In the end, we had built up so much experience that both acquisition and image processing were familiar. These experiences also allowed us to quickly recognise artifacts in the acquisition, such as the inadvertent contraction of the quadriceps muscles during acquisition, resulting in unreliably high SWE values.

SWE was able to discriminate well between PT and patellar tendons from age-related and activity-matched controls.[37] Patellar tendons in tendinopathy were stiffer than asymptomatic tendons, with areas of increased stiffness mainly located in the proximal third of the patellar tendon. When SWE was assessed longitudinally in athletes performing exercise therapy, SWE was able to detect a significant decrease in patellar tendon stiffness in athletes allocated to PTLE, but not to EET.[8] While the intra-observer reproducibility of SWE was excellent, inter-observer reproducibility was inferior but still could be classified as good.[37]

Previous studies investigating the changes in patellar tendon stiffness in PT found conflicting results. Both increased and decreased patellar tendon stiffness were found in patients with PT when compared to asymptomatic individuals.[38–41] The two studies that both used an Aixplorer ultrasound unit (Supersonic Imaging) and implemented similar acquisition protocols, found similar trends in patellar tendon stiffness (higher patellar tendon elastic modulus in PT).[38,39] However, a study that used the same ultrasound system but examined the knee in a relaxed extended position (instead of 30 degrees flexion) and implemented a gel cushion delay block found an opposite trend in patellar tendon stiffness (lower patellar tendon stiffness in PT).[41] Also, the size of the region of interest for quantification of tendon stiffness was sometimes standardised to 1 mm[41] or determined by the width of the tendon.[38] Therefore, we assume that differences between studies are likely explained by lacking standardisation of SWE examination protocols.

Another explanation for these discrepant results regarding tendon stiffness could be the level of hyaline degeneration in the patellar tendon.[42,43] Hyaline degeneration is characterised by hardness of the tendon rather than softness seen in mucoid degeneration.[44] The occurrence of hyaline degeneration in patients with long-standing symptoms could be the explanation for the increased patellar tendon stiffness observed with SWE and should be further investigated to better understand the discrepancies of stiffness changes reported in the literature. Only one article reported findings on the level of hyaline degeneration in relation to the duration of symptoms. They found that patients with more long-standing symptoms tended to have a higher concentration of hyaline degeneration, although quantification was not possible in this study because surgical debridement degraded a considerable amount of tissue.[42] Due to the fact that a classic tissue-based diagnosis paradigm has been increasingly abandoned, new insights in the field of histopathological research will probably be seriously hampered in the future by the fact that the treatment of PT is largely conservative.[45]

To this date, we believe that the use of SWE lacks additional value for assessment of prognosis in PT or for monitoring treatment response in routine patient care. This because SWE has demonstrated only limited evidence in a very controlled clinical research setting as the JUMPER study. To date, SWE results are moderately generalisable to clinical practice, on the one hand

due to the use of different ultrasound systems and the lack of a standardised protocol for the acquisition of SWE data and on the other hand due to insufficient, consistent, data confirming the direction of changes in tendon stiffness in different populations. However, the clinical application of conventional US is also limited to confirming the clinical diagnosis of PT, since morphological abnormalities seen on ultrasound are not specific for PT and have no clear prognostic value. Moreover, structural changes typically persist after symptom resolution. Therefore, there is no clear relationship between clinical improvement and normalisation of the patellar tendon structure.[46,47] In the development of new exercise programmes, US techniques might help in improved understanding of the structural changes that may occur after exercise therapy.

MRI-based assessment of patellar tendinopathy

Magnetic resonance imaging (MRI) is not frequently used for confirming the diagnosis of PT.[27] In clinical practice, athletes are sometimes referred for an MRI scan to rule out intra-articular problems, such as osteochondral defects, meniscal injury, injury to cruciate or collateral ligaments or trochlear dysplasia.[48] For the diagnosis of PT, US performs better in terms of detecting morphologic changes to patellar tendon structure and increased vascularity but also in terms of spatial resolution. Moreover, MRI is a less available imaging method, with often long waiting lists and contra-indications for patients with pacemakers, metal implants or claustrophobia.

Changes that are visible on MRI scans that are performed in clinical care are often limited to the detection of an increased antero-posterior thickness of the proximal patellar tendon and an increase in signal intensity within the proximal patellar tendon that indicates an increase of water within the tendon.[49] Typically, tendons appear hypo-intense on all clinically available MRI-sequences, due to the fast free induction decay of collagen.[50] This means that the relaxation time (and thus available signal) of the patellar tendon is so low, that echo times used in clinical practice are too long to capture any signal from the patellar tendon. This phenomenon is due to the fact that tendons are composed of collagen, which is a molecule that is highly organised in a hierarchical matrix of collagen bundles and collagen fibres and is tightly bound to water molecules which results in ultrashort relaxation times.[51]

New MRI sequences that are able to capture these ultrashort relaxation times are called UTE-MRI sequences. These sequences enable to scan with ultrashort echo times (as low as 0.032 milliseconds).[52] The advantage of using these UTE sequences is that signals can be captured from the patellar tendon, which in turn enables quantitative measurements.

By far the most time in the preparations for the JUMPER study has gone into developing the UTE MRI sequence and analysing these images. Since UTE was a prototype sequence, we had

to test and optimise all possible variables that could affect the final images ourselves. These numerous variables consisted, for example, of choosing echo times, whether or not to apply fat saturation and investigating the influence of fat saturation on the measured T2* value, choosing between separate single echo sequences or multiple echo times in a multi-echo sequence. We also spent a lot of time optimising the SNR, by scanning many phantoms and even inventoried the coil elements in the knee coil by making an X-ray of the coil and relating it to the measured signal on water phantoms. Not only did we spend hours scanning of volunteers, but also pineapples and even pig's trotters via the local butcher. Once we had the sequence working and the results seemed to be sufficient, we didn't stop experimenting and we tried to make the sequence even better than it already was. This meant that we had to make a switch from the MRI acquisition protocol at the start of the study, where we switched from multiple single echo acquisitions to four multi echo sequences. We noticed that the SNR had to be as high as possible to obtain enough signal for our future analyses. Once the patient enrolment was running, we spent more than a year writing a MatLab script for the image analysis, where the image registration methods were also extensively tested to see which one yielded the best results. Once the image analysis protocol was up and running, it took approximately two full days per patient to run all the analyses and process the results. We are proud of the collaborations in the hospital between clinical radiology, sports medicine and MRI physicists who have made this very intensive development possible. In addition, we've had many conference calls with GE's sequence developers to discuss the results mid-term, and we've gone to conferences to talk to people about our findings.

The structural complexity of heterogeneous tissue like the patellar tendon and the interaction of water protons with glycoproteins (proteoglycans and glycosaminoglycans) result in different components of T2* relaxation within the tendon.[53] This implicates a more complex transverse signal decay in the patellar tendon than that described by a mono-exponential model. We used the bi-exponential model to provide T2*s of two different water fractions, namely bound and free water. The bound fraction is regarded as water protons that are influenced by the macromolecules in the tendon, such as collagen and proteoglycans. In the JUMPER-study, T2* relaxometry data from the three visits was fitted to registered UTE images using both mono-exponential and bi-exponential models. The method, as described in Chapter 5 of this thesis, was designed to overcome the high spatial anisotropy of T2* in tendinopathy.[54] The fraction of short-T2* components, a parameter resulting from bi-exponential fitting, was used to define three subregions for this reason. The first subregion was identified by selecting voxels with mostly short-T2*s (60-100% short-T2* components) and was considered to represent normally aligned collagen. The second subregion was identified by selecting the voxels with mostly long-T2*s (0-30% short-T2* components) and was thought to represent degenerative tissue. The last subregion (30-60% short-T2* components) was the interface that separated the two subregions mentioned above. Using this method,

we found a significant decrease in T2* in the voxels that represented the degenerative tissue of the patellar tendon after 24 weeks of exercise therapy. The T2* decrease in the tissue compartment that corresponded with degenerative tissue was also significantly associated with an improvement in the severity of symptoms as measured with the VISA-P score. UTE MRI seems less suitable for the purpose of describing the prognosis of PT. We found no association between baseline T2* and clinical outcome after 24 weeks. This despite the fact that the absolute T2* relaxation time values correlated with symptom severity in degenerative tissue of the patellar tendon as scored at baseline and after 12 and 24 weeks.[55] The application of UTE MRI techniques is currently limited to scientific research, as the mechanisms underlying the ultrastructural changes that result in a reduction of T2* are not yet sufficiently known for clinical use. In addition, the reliability of the T2* quantification technique is also insufficient to demonstrate a clinically relevant difference. For example, the margin of error (coefficient of repeatability) has been estimated at 2 msec, while the change in T2* at group level was only 1.3 msec (0.6-2.0).[54] Thus, at an individual level, small differences will not have much clinical relevance. Moreover, the time-consuming acquisition protocols and post processing that are presently involved in UTE MRI preclude its large scale application in routine clinical practice.

Future perspectives

A new treatment approach for PT and quantitative imaging in the longitudinal assessment of PT has been extensively discussed in this thesis, yet some questions remain unanswered and new questions arose. We recommend further research projects should focus on the following topics.

General recommendations

We recommend for any study that aims to evaluate the effectiveness of a therapeutic intervention to implement strict inclusion and exclusion criteria, in order to create a study group that is as homogeneous as possible. During the inclusion phase of the randomised controlled trial, we found out that as many as 171 patients had to be excluded from 272 athletes that were screened online for eligibility. Another 25% of the patients who were potentially eligible after this online screening and were invited for clinical and radiological assessment (N=101) had to be excluded (N=25). These athletes met all criteria at the initial screening and their complaints indeed seemed to match PT, but only after an extensive inclusion protocol it was found that symptoms could be completely or partly explained by patellofemoral pain. However, we would like to emphasise that we consider this strict inclusion necessary for any scientific study investigating a particular sports injury, despite the fact that this type of inclusion will inherently lead to a lower inclusion rate. We would like to highlight the need for specific tests that help distinguishing between different overuse injuries, otherwise the study population will be less homogeneous and study results will be biased. We encourage the use of provocation tests according to the patellofemoral pain consensus statement, and for PT

the recommended single leg decline squat (SLDS) which is a test that has demonstrated the best ability to assess patellar tendon pain.[56] Due to large heterogeneity in pain presentation of athletes that self-report PT, diagnosing PT remains challenging, as there is no widely accepted gold standard for the clinical diagnosis.[57] Consensus statements and findings from many studies have led to increased understanding of the pathophysiological mechanisms that occur in PT, leading to a paradigm shift from the classical tissue-based diagnosis. This significantly boosted studies investigating exercise therapy for PT in recent years. However, there are still many knowledge gaps that make new studies essential to better understand how best to treat PT. Due to the lack of the possibility to examine structural changes using histological examination, imaging techniques will be crucial to gain some insight into the morphological changes resulting from exercise therapy.

Treatment

Regarding the exercise interventions, we advise to investigate the additional effect of a supervised training scheme on clinical outcome and adherence. It is plausible that supervised sessions in the PTLE-group would have promoted better progression than in the unsupervised program of our study (because the athlete might be fearful of overload and thus too conservative).[18] In our trial, participants were carefully instructed about the allocated treatment arm at baseline, but were not routinely supervised in performing the exercises. Instead, instructional videos on a dedicated website were provided to guide the athletes through their treatment scheme. For future trials, we would be interested in a randomised trial that compares the effect of supervised PTLE with an unsupervised program where the instructions are provided in a mobile application or as instructional videos as in our trial.

We agree that PT requires an individualised approach to management, as tendinopathy is a difficult problem to manage clinically and no consensus on optimal management of tendinopathy has been established.[18] The criteria that can be used best for this individualisation of the load and progression criteria were unfortunately lacking, since the common use of pain-based criteria are not supported by strong evidence, as found in a systematic review by Escriche-Escuder.[23] However, we found that the criteria-based PTLE protocol within the limits of acceptable pain using individual single-leg squats to assess pain leads to an improved clinical outcome with a strong level of evidence. Because the slowly progressive exercises are specific to PTLE, it would be difficult to compare the PTLE exercise program to the same exercises without individual progression criteria. However, it is very likely that not the type of contractions but the slowly progressive nature of the PTLE exercises performed within the limits of acceptable pain explains the better clinical outcome than the EET program that does not apply this individualisation.

For the evaluation of the effectiveness of exercise therapy, we used the previously reported MCID of 13 points on the VISA-P scale. There is only one study that investigated the MCID of 13 points for PT to date, and individuals included in that study had a significantly shorter symptom duration than athletes included in the JUMPER-study.[13] We emphasise the need for new studies that investigate MCID in athletes with long lasting symptoms from PT who failed to manage pain after multiple conservative treatments in order to re-evaluate the currently used MCID.

While only one participant fulfilled the previously defined criterion of having symptoms less than 6 months, we investigated only therapeutic effectiveness of exercise therapy in chronic PT. The question remains what the effect is of exercise therapy in short-living (reactive) PT and we advise to investigate this as a separate research question in future studies.

The role of imaging in patellar tendinopathy

In the author's opinion, ultrasound is the most valuable imaging technique for PT in the clinical setting. Firstly, because ultrasound is much more accessible than MRI, both the waiting lists for ultrasound are shorter in clinical practice and the examination is also cheaper. In addition, it is possible to collaborate more easily with the sports medicine physician or orthopaedic surgeon, by referring patients from his or her clinic directly for an ultrasound scan of the patellar tendon. In this way, the examination is more accessible than MRI and can provide confirmation of the diagnosis that is needed at that moment, so that the athlete quickly gains clarity and can work on his recovery. Secondly, ultrasound has a higher spatial resolution than MRI, which in combination with the fact that the patellar tendon is very easy to examine with ultrasound due to its favourable anatomical position, makes US the imaging modality of choice. The examination is also dynamic, whereby the athlete can indicate exactly which parts of the patellar tendon are painful, so that targeted examination can be done. The clinical application of ultrasound is limited to confirming morphological changes in tendon structure within an adequate clinical setting where there is a strong suspicion of PT. When these structural changes are confirmed, this supports the diagnosis of PT. However, if no ultrasound abnormalities are found, this gives reason to reconsider this diagnosis and possibly additional diagnostics to exclude intra-articular pathology. However, US has no clinical value in the follow-up of PT.

With regard to quantitative parameters such as tendon stiffness and T2* mapping, these techniques are particularly interesting to investigate in the context of scientific research. Although we have conducted the largest trial in the field of PT, future studies are certainly needed to confirm or refute the definitive value of these quantitative parameters. Interestingly, SWE was able to demonstrate a decreasing trend in tendon stiffness, despite the technique appearing unsuitable for use as a prognostic biomarker. As far as T2* mapping is concerned, this tech-

nique is still in its infancy stage. Further refinement of the imaging protocol is certainly useful to investigate the ultimate value of the technique. In the first place, by considerably shortening the acquisition time, which was very long in the JUMPER study. At the same time, there are opportunities to shorten this acquisition, such as reducing the number of echo times that are scanned. Although T2* mapping may still be a long way from being applied in clinical practice, it is a promising technique to gain insight into some of the molecular changes in the patellar tendon (hydration state) that are the result of exercise therapy, without the need for biopsies. In this way, new forms of exercise therapy can be better compared with each other and the results do not have to be based solely on pain scores. On the one hand, quantitative imaging biomarkers may provide additional information about the improvement of PT on a scale that is more accurate than is typically used in patient reported outcome measurements. Furthermore, imaging biomarkers that have a strong association with pain can provide better insight into the disease process or the response to certain treatments. This allows the care for the individual athlete to be optimised, because subgroups with different response to treatment can be made transparent.

Furthermore, it is possible that new imaging techniques will be introduced in sports medicine in the future, primarily for research, but perhaps also for specific clinical indications. A robust imaging biomarker could be of great importance for comparing exercise therapy or monitoring treatment response. An example from nuclear radiology is the use of 18F-FDG PET MRI or 68Ga-FAPI PET MRI to measure standardised uptake values (SUV) that could potentially be used for monitoring therapy. Positron emission tomography (PET) is superb at absolute quantification as well as visualisation of specific processes at the molecular level, such as metabolism or inflammation. A systematic review found a diversity of data and conclusions in regard to inflammation as part of the pathogenesis of tendinopathy, ranging from ongoing or chronic inflammation to non-inflammatory degeneration and chronic infection.[58] Fluorine-18 (18F) labelled [18F] fluoro-2-deoxy-2-D-glucose (FDG), an analogue of glucose, is the most widely used PET radiotracer in clinical practice.[59] Integrated PET-MRI could be a very valuable imaging tool to monitor therapy response in PT.[60] Because fibroblast activation protein (FAP) is highly expressed during tissue repairing, this tracer could be of high interest in PT where inflammatory mediators produced by tendon fibroblasts in response to repetitive mechanical loading may be starting point for using this technique.[61] FDG is less specific for tendon inflammation but has shown increased metabolic activity in the Achilles tendinopathy using PET scans.[62] These techniques combine functional information of MRI, with molecular data provided by PET technology and could positively impact on the management of PT.[63] PET has also potential to detect changes in metabolic activity that precedes structural and even biochemical changes.

CONCLUSION

The purpose of this thesis was to compare eccentric exercise therapy (EET) with progressive tendon-loading exercises (PTLE) based on clinical outcome after 24 weeks. We found that PTLE is superior to EET, despite presence of chronic symptoms and the previous conservative treatment in the majority of patients. These findings support the use of PTLE in the conservative treatment of PT.

Secondary aims were to investigate advanced ultrasound and MRI-based imaging methods in the longitudinal assessment of structural changes that are associated with PT.

We found that PT is associated with significantly higher patellar tendon stiffness, but is unsuitable to use as a single predictive measurement for clinical outcome. Although a small decrease in patellar tendon stiffness was found in athletes allocated to PTLE and this decrease was also associated with improved clinical outcome, we don't recommend the use of SWE in standard clinical care. The technique is lacking a standardised acquisition protocol and the direction of change in patellar tendon stiffness in different stages of PT remain unclear due to conflicting results in literature.

Although it has been shown that T2* mapping of the tendon with UTE MRI has the potential to detect degenerative changes and possibly even subtle changes in T2* over time, the limitations of the technique, many of which cannot easily be overcome, likely preclude the application of the technique in routine clinical practice. However, the technique currently has potential to investigate microstructural tissue properties in a non-invasive manner in clinical research and therefore can contribute to deeper understanding of the structural changes that occur in healthy tendon due to ageing, tendon overload in athletes and response to therapy in tendinopathy. Although we don't recommend the use of the new quantitative image measures that we investigated, we feel that our research has significantly contributed to understanding changes in patellar tendon structure as a result of exercise therapy. We are proud to be the first research group to investigate these new quantitative biomarkers in a trial of this scale.

The impact of our findings is evident by the fact that they have changed the Dutch guideline for the treatment of anterior knee pain that has been adopted for several years and we are looking forward to see the change of international guidelines promoting PTLE and, ultimately, lead to enhanced patient care.

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A

Appendices

Summary

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SUMMARY

Patellar tendinopathy (PT) is a clinical diagnosis, characterised by pain localised to the patellar tendon and load-related pain that increases with physical activity. The overuse injury is common in athletes participating in sports involving repetitive jumping or cutting manoeuvres, such as basketball, volleyball and football. The prevalence of PT is up to 45% in elite athletes and disease burden is significant due to its chronicity leading to prolonged sports absence and even retirement from sports participation and decreased work productivity. In clinical practice, the role of imaging in tendinopathy is to assist in differential diagnosis as a complementary examination and to confirm the presence of characteristic findings that support the clinical diagnosis. Novel ultrasound (US) and magnetic resonance imaging (MRI) based imaging techniques are developing and their current role in diagnosis and estimating prognosis have not yet been identified. Exercise therapy is the cornerstone treatment in order to improve symptoms and potentially reverse the degenerative cascade that is typically seen in tendinopathy. While eccentric exercise therapy is recommended by clinical guidelines, there is a low level of evidence supporting one specific exercise program over another. The major aims of this thesis were to (1) assess the therapeutic effects of current and new exercise interventions and (2) evaluate novel biomarkers identified using advances imaging modalities that enable tissue quantification.

In **Chapter 2**, we investigated the effectiveness of newly proposed progressive tendon-loading exercises (PTLE) versus eccentric exercise therapy (EET) as the current standard of clinical care in athletes with PT. In the JUMPER study, the largest trial in PT to date, we included 76 athletes with clinically diagnosed and ultrasound-confirmed PT and randomised them to receive either PTLE or EET. The primary end point was symptom severity after 24 weeks, as assessed with the validated Victorian Institute of Sports Assessment for patellar tendons (VISA-P) questionnaire measuring pain, function and ability to play sports. Secondary outcomes included the return to sports rate, subjective patient satisfaction and exercise adherence. The improvement in VISA-P score was significantly better for PTLE than for EET after 24 weeks (28 vs 18 points, adjusted mean between-group difference, 9 points (95% CI 1 to 16); p=0.023). No significant between-group difference was found for return to sports rate (43% vs 27%, p=0.16), subjective patient satisfaction (81% vs 83%, p=0.54) and exercise adherence between the PTLE group and EET group after 24 weeks (40% vs 49%, p=0.33). We concluded that PTLE are superior to EET and are therefore recommended as initial conservative treatment for PT.

In **Chapter 3**, we investigated shear-wave elastography (SWE) as advanced imaging technique that is able to estimate stiffness of the patellar tendon. We determined the association between patellar tendon stiffness and the presence of PT and evaluated the reliability of SWE.

We assessed patellar tendon stiffness in all 76 athletes of the JUMPER-study and compared these results with 35 asymptomatic controls who were matched with the symptomatic individuals based on physical activity level. We found that PT was associated with significantly higher patellar tendon stiffness. The intraobserver reliability of SWE was excellent and the interobserver reliability for independent SWE acquisitions and analyses was good. SWE hereby provided improved understanding of pathophysiological changes that occur in PT and could potentially be an interesting biomarker in patients with PT for monitoring the response to therapeutic interventions.

In **Chapter 4**, we used SWE to assess the association between baseline patellar tendon stiffness and clinical outcome after exercise therapy. We also evaluated the association between the change in patellar tendon stiffness and clinical outcome after performing PTLE and EET. The 76 athletes of the JUMPER study were assessed at baseline, and after 12 and 24 weeks follow-up. No association was found between baseline stiffness and VISA-P after 24 weeks (p=0.52). Decreased stiffness (adjusted mean difference = 10 kPa (95% CI: 4-15) was significantly associated with improved clinical outcome at 12 weeks in all athletes (p=0.02), and at both 12 and 24 weeks (p= 0.01) in athletes allocated to PTLE. Therefore, patellar tendon stiffness, assessed with SWE, is unsuitable to use as a single predictive measurement for clinical outcome. Decreasing stiffness during the course of exercise therapy is associated with improved clinical outcome in athletes recovering from patellar tendinopathy. This means that treatments aimed at adjusting the stiffness of the tendon may have added value in the future.

In **Chapter 5**, we implemented a new MRI technique with ultrashort echo time (UTE) sequences in 65 athletes included in the JUMPER-study. UTE sequences have been developed to encode signal from tissues with extremely rapid signal decays, such as tendons. This enables quantitative analysis of tendons (T2* mapping), and have the potential to detect structural abnormalities earlier than conventional morphological sequences. PT is characterised by regional variability in binding states of water. Quantifying different water pools within the tendon using UTE MRI (which reflect specific tissue compartments within the patellar tendon) may be clinically relevant, as a previous histological study in patients undergoing surgery demonstrated an association between levels of water-attracting glycosaminoglycans and severity of PT symptoms.

T2* relaxation times can be calculated from UTE MRI using mono-exponential or bi-exponential decay models. In **Chapter 5** we proposed a method that allowed separate analysis of changes in different regions of the patellar tendon. This method was designed to overcome the high spatial anisotropy of T2* in tendinopathy. The fraction of short-T2* components, a parameter resulting from bi-exponential fitting, was used to define three subregions. The first subregion was identified by selecting voxels with mostly short-T2*s (60-100% short-T2* com-

ponents) and was considered to represent normal aligned collagen. The second subregion was identified by selecting the voxels with mostly long-T2*s (0-30% short-T2* components) and was thought to represent degenerate tissue. The last subregion (30-60% short-T2* components) was the interface that separated the two subregions mentioned above. Voxels were automatically selected, based on thresholding the percentage of short-T2* components within a manual region of interest covering the outer margins of the proximal patellar tendon on 10 consecutive slices. Using this method, we found an average coefficient-of-repeatability (coefficient-of-variation) of 2 msec (15%), 2 msec (19%) and 10% (22%) for monoexponential, fractional order and percentage short T2*, respectively.

In **Chapter 6**, we investigated the fractional order fitting as an alternative mathematical model that can be used for quantification of T2* relaxation times using UTE MRI. This alternative model had been proposed for T2* quantification in heterogeneous tissues (such as the patellar tendon in PT). The quantification of the multiple T2* components resulting from this tissue heterogeneity can be highly sensitive to noise. In the JUMPER study, both fractional order and bi-exponential models were both found to perform well with low bias. This was mainly due to the optimised acquisition in the study, by using a surface coil to maximise signal to noise ratios (SNR). However, in cases with lower SNR, the proposed fractional order fitting method could perform better.

In **Chapter 7**, the UTE MRI technique was sequentially performed in all athletes included in the JUMPER study. The aim of this study was to evaluate the association between T2* changes and clinical outcomes. We also assessed its use as predictive measurement at baseline for clinical outcome. MRI was performed at baseline, after 12 weeks and after 24 weeks follow-up in athletes performing exercise therapy for PT. Decreasing T2* relaxation times in the degenerative tissue of the patellar tendon were associated with improved clinical outcome after exercise therapy for PT. However, T2* relaxation times were unsuitable as a single predictive measurement at baseline for clinical outcome. While the change in T2* was small and the technique has limitations to use in clinical practice, our findings indicate that the hydration state of the patellar tendon is able to change in response to conservative exercise therapy.

Finally, **Chapter 8** discusses the main findings and limitations of this thesis. The outcomes of the JUMPER-study are interpreted within a broader context and opportunities for future research are provided.

SAMENVATTING

Patella tendinopathie (PT) is een blessure van de patellapees die vaak voorkomt bij sporters met een hoge sprongbelasting, zoals basketbal en volleybal spelers. De diagnose PT wordt klinisch gesteld en geeft als typische klachten pijn ter plaatse van de aanhechting van de patellapees aan de onderrand van de patella. De klachten dienen gerelateerd te zijn aan belasting van de patellapees en nemen vaak toe met toenemende belasting tijdens trainingen en wedstrijden. PT komt vaak voor, met een prevalentie tot 45% bij topvolleybalspelers. Door chronische klachten leidt PT tot onvermogen om deel te kunnen nemen aan trainingen en wedstrijden en ook bij een substantieel deel van de patiënten tot een verminderde werkproductiviteit. Soms stoppen sporters zelfs volledig met sporten die de klachten in de patellapees verergeren. De rol van beeldvorming is in de klinische praktijk vaak beperkt tot het bevestigen van de klinische diagnose en om andere differentiaaldiagnosen voor anterieure knieklachten meer of minder waarschijnlijk te maken. De rol van nieuwe beeldvormingstechnieken op het gebied van zowel echografie als MRI bij het stellen van de diagnose en het kunnen inschatten van prognose is nog niet goed bekend. De behandeling van PT bestaat uit oefentherapie, met als doel de pijnklachten te verminderen en mogelijk ook om de cyclus van degeneratieve structurele veranderingen om te keren. Hoewel excentrische oefentherapie wordt aanbevolen in klinische richtlijnen, is er weinig bewijs dat het ene oefenprogramma beter is dan het andere ondersteund. De belangrijkste doelstellingen van dit proefschrift waren (1) het beoordelen van de therapeutische effecten van huidige en nieuwe oefentherapieën voor PT en (2) het evalueren van nieuwe biomarkers die zijn geïdentificeerd met behulp van geavanceerde beeldvormingsmodaliteiten die weefselkwantificering mogelijk maken.

In **Hoofdstuk 2** onderzochten we de effectiviteit van nieuw voorgestelde opbouwende peesbelastende oefeningen (PTLE) versus excentrische oefentherapie (EET) als de huidige standaard van klinische zorg bij sporters met PT. In de JUMPER studie, de grootste studie in het wetenschappelijke werkveld van PT tot nu toe, hebben we 76 sporters met klinisch gediagnosticeerde en echografisch bevestigde PT gerandomiseerd om PTLE of EET geïnstrueerd te krijgen. De primaire uitkomstmaat was de ernst van de klachten na 24 weken, zoals gescoord met de gevalideerde Victorian Institute of Sports Assessment (VISA-P) vragenlijst die pijn, functie en vermogen om te sporten kwantificeert. Secundaire uitkomstmaten waren onder andere het percentage terugkeer naar sport, subjectieve patiënttevredenheid en therapietrouw. De verbetering van de VISA-P score was significant beter voor PTLE dan voor EET na 24 weken (28 versus 18 punten, gecorrigeerd gemiddeld verschil tussen groepen, 9 punten (95% CI 1 tot 16); p=0.023). Er werd geen significant verschil tussen de groepen gevonden voor terugkeer naar sport (43% versus 27%, p=0.16), subjectieve patiënttevredenheid (81% versus 83%, p=0.54) en therapietrouw tussen de PTLE-groep en de EET-groep na 24 weken

(40% versus 49%, p=0.33). We concludeerden dat PTLE beter is dan EET en daarom wordt aanbevolen als initiële conservatieve behandeling voor PT.

In **Hoofdstuk 3** hebben we shear-wave elastografie (SWE) onderzocht als geavanceerde beeldvormingstechniek die stijfheid van de patellapees kan kwantificeren. We onderzochten het verband tussen stijfheid van de patellapees en de aanwezigheid van PT en evalueerden de betrouwbaarheid van SWE. We hebben hiervoor de stijfheid van de patellapees bij alle 76 sporters van de JUMPER studie gemeten en vergeleken deze resultaten met 35 asymptomatische sporters met een vergelijkbaar niveau van fysieke activiteiten. We vonden dat PT geassocieerd was met een significant hogere stijfheid van de patellapees. De intraobserver-betrouwbaarheid van SWE was uitstekend en de interobserver-betrouwbaarheid voor onafhankelijke SWE-acquisities en -analyses was goed. De resultaten van dit onderzoek zorgden voor een beter begrip van de pathofysiologische veranderingen die optreden bij PT. Peesstijfheid zou op basis van deze resultaten een interessante biomarker kunnen zijn in PT voor het monitoren van de respons op therapeutische interventies, zoals oefentherapie.

In **Hoofdstuk 4** hebben we SWE toegepast om de associatie tussen stijfheid van de patellapees voorafgaande aan de start van behandeling en klinische uitkomst na oefentherapie te onderzoeken. Ook onderzochten we de associatie tussen verandering in patellapees stijfheid en klinische uitkomst na PTLE en EET. De 76 sporters van de JUMPER studie werden beoordeeld bij aanvang van het onderzoek, na 12 en 24 weken follow-up. Er werd geen verband gevonden tussen baseline-stijfheid van de patellapees en VISA-P na 24 weken (p=0.52). Verminderde stijfheid (gecorrigeerd gemiddeld verschil = 10 kPa (95% CI: 4-15) was significant geassocieerd met een verbeterde klinische uitkomst na 12 weken bij alle sporters (p=0.02), en na zowel 12 als 24 weken (p= 0.01) bij sporters die gerandomiseerd waren in de PTLE groep. Daarom is patellapees stijfheid, beoordeeld met SWE, niet geschikt om de prognose in te schatten van het klachtenbeloop bij sporters die starten met een oefenprogramma. Afname in patellapees stijfheid tijdens oefentherapie wordt in verband gebracht met verbeterde klinische uitkomst bij sporters die herstellen van patella tendinopathie. Dit betekent dat behandelingen gericht op het aanpassen van de stijfheid van de pees in de toekomst mogelijk meerwaarde hebben.

In **Hoofdstuk 5** hebben we een nieuwe MRI-techniek met ultrakorte echotijd (UTE)-sequenties toegepast bij 65 sporters die deelnamen aan de JUMPER-studie. UTE-sequenties zijn ontwikkeld om signalen te coderen van weefsels met extreem snel signaalverval, zoals pezen. Dit maakt kwantitatieve analyse van pezen mogelijk (zogenaamde T2* mapping) en heeft potentieel om structurele afwijkingen eerder te detecteren dan met conventionele MRI-sequenties die in de klinische praktijk worden gebruikt. PT wordt gekenmerkt door regionale variabiliteit in bindingstoestanden van water. Het kwantificeren van verschillende hydratietoestanden in

de patellapees met behulp van UTE MRI (die specifieke weefselcompartimenten in de patellapees weerspiegelen) kan klinisch relevant zijn, aangezien eerder histologisch onderzoek bij patiënten met PT die een operatie ondergingen een verband aantoonde tussen de niveaus van wateraantrekkende glycosaminoglycanen en de ernst van de klachten.

T2* relaxatietijden kunnen worden berekend met behulp van mono-exponentiële of bi-exponentiële vervalmodellen. In Hoofdstuk 5 stelden we een methode voor die afzonderlijke analyse van veranderingen in verschillende weefselcompartimenten van de patellapees mogelijk maakte. Deze methode is ontworpen om de nadelen van sterke regionale variabiliteit van T2* bij tendinopathie te overwinnen. De fractie van korte T2*-componenten, een parameter afkomstig van bi-exponentiële fitting, werd gebruikt om drie subregio's te definiëren. De eerste subregio werd bepaald door voxels te selecteren met voornamelijk korte T2* componenten (60-100% korte T2*-componenten) en werd geacht normaal gerangschikt collageen te vertegenwoordigen. De tweede subregio werd geïdentificeerd door de voxels te selecteren met overwegend lange-T2*s (0-30% korte T2*-componenten) en werd verondersteld degeneratief weefsel te vertegenwoordigen. De laatste subregio (30-60% korte T2*-componenten) was de interface die de twee bovengenoemde subregio's scheidde. Voxels werden automatisch geselecteerd op basis van het percentage korte T2*-componenten binnen een handmatig ingesteld gebied van interesse van de proximale patellapees op tien opeenvolgende coupes. Met behulp van deze methode vonden we een gemiddelde coefficient-of-repeatability (coefficient-of-variation) van respectievelijk 2 msec (15%), 2 msec (19%) en 10% (22%) voor mono-exponentiële, fractional order fitting en percentage short T2*.

In **Hoofdstuk 6** hebben we een alternatief vervalmodel voor de T2* relaxatietijden onderzocht, de zogenaamde fractional order fitting. Deze kan net als mono-exponentiele en bi-exponentiele fitting ook worden gebruikt voor het kwantificeren van T2* relaxatietijden met behulp van UTE MRI. Dit alternatieve model is voorgesteld voor T2*-kwantificering in heterogene weefsels (zoals de patellapees die aangedaan is door PT). De kwantificering van de meerdere T2*-componenten die het gevolg zijn van deze weefselheterogeniteit kan zeer gevoelig zijn voor ruis. In de JUMPER studie bleken zowel fractional order fitting als bi-exponentiële fitting beiden goed te presteren met een lage bias. Dit was voornamelijk te danken aan de geoptimaliseerde acquisitie, door een oppervlaktespoel te gebruiken om de signaal-ruisverhouding (SNR) te maximaliseren. In gevallen met een lagere SNR zou de voorgestelde methode van fractional order fitting echter beter kunnen presteren.

In **Hoofdstuk 7** werd de UTE MRI-techniek longitudinaal toegepast om de associatie tussen T2*-veranderingen en klinische uitkomsten te beoordelen. We hebben ook de prognostische waarde voor klinische uitkomst onderzocht. MRI werd uitgevoerd op baseline, na 12 weken

en na 24 weken follow-up bij de 76 sporters die deelnamen aan de JUMPER-studie en oefentherapie uitvoerden. Afnemende T2*-relaxatietijden in het degeneratieve weefsel van de patellapees waren geassocieerd met een verbeterd klinisch resultaat na oefentherapie voor PT. De mate van T2*-relaxatietijden voorafgaande aan de oefentherapie was echter ongeschikt als voorspellende biomarker voor het klinisch resultaat na de oefentherapie. Hoewel de verandering in T2* klein was en de techniek beperkingen heeft voor gebruik in de klinische praktijk, geven onze bevindingen aan dat de hydratatietoestand van de patellapees kan veranderen als reactie op oefentherapie.

Ten slotte zijn in **Hoofdstuk 8** de voornaamste bevindingen en beperkingen van dit proefschrift bediscussieerd. De uitkomsten van de JUMPER-studie zijn daarbij in een bredere context geplaatst met aanbevelingen voor toekomstig onderzoek.

PHD PORTFOLIO

Erasmus University Rotterdam

	Description	Organizer	EC
Required	Radiologendagen (2016)	NVvR	1.00
	MRI safety and scanning course (2016)	Erasmus MC	2.00
	The Radiological Society of North America's 102th Scientific Assembly and Annual Meeting (2016)	RSNA	3.00
	GE gebruikersdag echografie (GE Healthcare) (2017)	GE Healthcare	0.30
	Symposium of Sports Medicine (2017)	Erasmus MC	0.20
	Erasmus MC - BROK® (Basic course Rules and Organisation for Clinical researchers) (2017)	Erasmus MC	1.50
	Imaging Research on the Move meeting (2017)	Erasmus MC	0.30
	Erasmus MC - Scientific Integrity (2017)	Erasmus MC	0.30
	Erasmus MC - ESP01 Principles of Research in Medicine and Epidemiology (2017)	NIHES	0.70
	Imaging Research on the Move meeting (2017)	Erasmus MC	0.30
	European Congress of Radiology (2018)	ESR	2.00
	Symposium of Sports Medicine (2018)	Erasmus MC	0.20
	5th International Scientific Tendinopathy Symposium (2018)	UMCG	2.00
	Imaging Research on the Move meeting (2018)	Erasmus MC	0.30
	Erasmus MC - CC02 Biostatistical Methods I: Basic Principles (2018)	NIHES	5.70
	The Radiological Society of North America's 104th Scientific Assembly and Annual Meeting (2018)	RSNA	3.00
	Upgrade cursus Stralingsbescherming (2019)	Erasmus MC	0.30
	Erasmus MC - Personal Leadership & Communication (2019)	Erasmus MC	1.00
	Conference of Sport injury epidemiology and injury prevention (2019)	Erasmus MC	0.50
	Imaging Research on the Move meeting (2019)	Erasmus MC	0.30
	ESMRMB 36th Annual Scientific Meeting (2019)	ESMRMB	2.00
	Biomedical English Writing and Communication (2019)	Erasmus MC	3.00
	SportsKongres Copenhagen, Denmark (2020)		2.00
	ISMRM 2020 Virtual Conference (2020)	ISMRM	3.00
	Research meetings ADMIRE-group (2020)	Erasmus MC	3.00
	ISMRM 2021 Virtual Conference (2021)	ISMRM	3.00
	Sportmedisch Wetenschappelijk Jaarcongres (2021)	Erasmus MC	3.00
	VSG Wetenschappelijke avond (2021)	Erasmus MC	1.00
	Teaching tasks: Junior Med School (2016)	Erasmus MC	0.30
	Basic course in applied MR techniques (2016)	ESMRMB	2.00
Optional	Teaching tasks: Hands-on ultrasound workshop IFMSA Get Practical (2017)	IFMSA	0.20
	Teaching tasks: Imaging of Sports Injuries (minor Sports Medicine) (2017)	Erasmus MC	0.20

	Teaching tasks: Junior Med School (2017)	Erasmus MC	0.30
	Teaching tasks: Supervising Medical Technology trainee (24 weeks) (2018)	Erasmus MC	3.00
	Teaching tasks: Hands-on ultrasound workshop IFMSA Get Practical (2018)	IFMSA	0.20
	Teaching tasks: Imaging of Sports Injuries (minor Sports Medicine) (2018)	Erasmus MC	0.20
	Teaching tasks: Junior Med School (2018)	Erasmus MC	0.30
	Teaching tasks: Hands-on ultrasound workshop MFVR Ouderdag (2019)	MFVR	0.40
	Teaching tasks: Hands-on ultrasound workshop IFMSA Get Practical (2019)	IFMSA	0.20
	Intelligence. Innovation. Imaging. - The Perfect Vision of AI (2019)	ESR	1.00
	Teaching tasks: Imaging of Sports Injuries (minor Sports Medicine) (2019)	Erasmus MC	0.20
	Teaching tasks: Junior Med School (2019)	Erasmus MC	0.30
	Teaching tasks: Coaching Bachelor Students Medicine (n=12) (2020)	Erasmus MC	5.00
	Workgroup communication (2020)	Erasmus MC	3.00

Total EC **61.70**

LIST OF PUBLICATIONS

Decreasing patellar tendon stiffness during exercise therapy for patellar tendinopathy is associated with better outcome.
Breda SJ, de Vos RJ, Krestin GP, Oei EHG. *J Sci Med Sport. 2022 May;25(5):372-378.*
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Association Between T_2^* Relaxation Times Derived From Ultrashort Echo Time MRI and Symptoms During Exercise Therapy for Patellar Tendinopathy: A Large Prospective Study.
Breda SJ, de Vos RJ, Poot DHJ, Krestin GP, Hernandez-Tamames JA, Oei EHG. *J Magn Reson Imaging. 2021 Nov;54(5):1596-1605.*
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Breda SJ, Oei EHG, Zwerver J, Visser E, Waarsing E, Krestin GP, de Vos RJ. *Br J Sports Med. 2021 May;55(9):501-509.*
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doi: 10.1186/s13075-021-02436-8. PMID: 33581741.

Diagnostic accuracy of grayscale, power Doppler and contrast-enhanced ultrasound compared with contrast-enhanced MRI in the visualization of synovitis in knee osteoarthritis.
de Vries BA, **Breda SJ**, Meuffels DE, Hanff DF, Hunink MGM, Krestin GP, Oei EHG. *Eur J Radiol. 2020 Dec;133:109392.*
doi: 10.1016/j.ejrad.2020.109392. PMID: 33157371.

The association between patellar tendon stiffness measured with shear-wave elastography and patellar tendinopathy-a case-control study.
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Oei L, Koromani F, **Breda SJ**, Schousboe JT, Clark EM, van Meurs JB, Ikram MA, Waarsing JH, van Rooij FJ, Zillikens MC, Krestin GP, Oei EH, Rivadeneira F. *J Bone Miner Res. 2018 Apr;33(4):560-568.*
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Osteoporotische wervelfracturen of ziekte van Scheuermann? [Osteoporotic vertebral fractures or Scheuermann's disease?].
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Oei L, Rivadeneira F, Ly F, **Breda SJ**, Zillikens MC, Hofman A, Uitterlinden AG, Krestin GP, Oei EH. *Eur Radiol. 2013 Feb;23(2):476-86.*
doi: 10.1007/s00330-012-2622-z. PMID: 22892721.

CONFERENCE ABSTRACTS

- Sportmedisch Wetenschappelijk Jaarcongres, Sportgeneeskunde Nederland 2021
- International Society for Magnetic Resonance in Medicine (ISMRM): 2018, 2019, 2020, 2021
- SportsKongres Copenhagen, Denmark: 2020
- European Society for Magnetic Resonance in Medicine and Biology (ESMRMB): 2017, 2019
- European Congress of Radiology (ECR): 2019
- Radiological Society of North America (RSNA): 2018, 2019, 2020
- International Scientific Tendinopathy Symposium: 2018

AWARDS

- 1st price star paper session (Sportmedisch Wetenschappelijk Jaarcongres 2021) for oral presentation: Effectiveness of progressive tendon-loading exercise therapy in patients with patellar tendinopathy: a randomised clinical trial.
- Student Travel Award RSNA 2018 for abstract SSJ16-02: Shear Wave Elastography Demonstrates Reduced Patellar Tendon Elasticity in Jumping Athletes with Patellar Tendinopathy Compared to Activity-Matched Healthy Jumping Athletes"

DANKWOORD

Op de eerste plaats wil ik graag alle **76 deelnemers** van de JUMPER-studie heel hartelijk bedanken voor jullie deelname. Uit 272 aanmeldingen was het geen gemakkelijke klus om jullie te vinden! Ondanks jullie drukke schema's met trainingen, studie en werk lukte het jullie alsnog bijna allemaal om voor de controle bezoeken naar het Erasmus MC te komen. En zoals jullie weten waren dat geen korte bezoekjes! Zelfs tot in de avonduren moest ik jullie lastigvallen met vragenlijsten, krachtmetingen en niet te vergeten die MRI scan waar jullie wel meer dan een uur per bezoek in moesten liggen! Ondanks wij hopelijk met onze aanpak van oefentherapie en de motiverende woorden van sportarts Robert-Jan de Vos jullie iets konden bieden in het herstel van jullie blessure, hebben jullie mij en vooral de wetenschappelijke kennis over de jumper's knee ook enorm veel gebracht. Zonder jullie was het echt niet gelukt om de JUMPER-studie tot zo'n groot succes te maken. En wat ben ik trots dat ik na zoveel van jullie gevraagd te hebben nu eindelijk dit proefschrift kan geven!

Edwin Oei, ik leerde jou en je vrouw al in 2010 kennen toen ik als research assistent aan de slag mocht met de data van de ERGO Rotterdam bevolkingsstudie. De allereerste kennismaking met röntgenfoto's heb ik door jou opgedaan in het archiefhok waar alle analoge röntgenfoto's ingescand moesten worden, en dat waren er nogal wat! Omdat we in korte tijd zoveel mogelijk werk moesten verzetten werd ik in eerste instantie aangenomen voor de tijdsstippen 06:00-08:00 uur 's ochtends. Maar al snel had je door dat ik de smaak te pakken had en meer wilde werken. Zodoende werd ik ook betrokken bij de analyse van de röntgenfoto's met SpineAnalyzer en later de ABQ-methode. Wat vond ik het heerlijk om hiermee aan de slag te gaan, en ik leerde in korte tijd ook veel over de verschillende wervelafwijkingen. Later kon ik ook mijn keuzeonderzoek van mijn studie Geneeskunde bij jou doen. Zo mocht ik meeschrijven aan artikelen en zelf een stuk schrijven voor het NTvG. We waren een goed team! Nadat ik ook mijn coschappen op de afdeling Radiologie had gelopen wist ik zeker dat ik jou, als mijn grote voorbeeld, achterna wilde gaan en solliciteerde voor de opleiding Radiologie. Direct na mijn Geneeskunde studie kon ik aan de slag en had het al meteen enorm naar mijn zin! Toen ik bijna 2 jaar van mijn specialisatie erop had zitten spraken we elkaar in de bespreekruimte van de mammoradiologie in het destijdse Daniel den Hoed. Je had een aantal leuke onderzoeken op de rol staan, een met het segmenteren van gewrichten en een andere studie waar je tot dan toe nog niet veel over kwijt kon maar waar we misschien wel een enorme onderzoeksbeurs voor zouden winnen. Samen met Robert-Jan de Vos had je namelijk gereageerd op de oproep van de NBA en GE Healthcare. Ik werd van deze tweede optie al snel enorm enthousiast en zei dat als we hem zouden winnen, ik geen seconde meer hoefde na te denken. Een aantal weken later mocht ik mijn opleider Winnifred van Lankeren gaan vertellen dat jullie de beurs van $300.000 hadden gewonnen en dat ik heel graag mijn opleiding enkele jaren zou willen onderbreken voor deze prachtige kans! Ik ben nog steeds

dankbaar dat ze me deze kans heeft gegeven want wat waren het 4 fantastische jaren! Ik herinner me nog zo goed dat we samen werden uitgenodigd op de RSNA voor de basketbalwedstrijd tussen de Chicago Bulls en LA Lakers! Eigenlijk is dit dankwoord te kort om je te bedanken voor alle leermomenten, goede gesprekken en vooral ook iemand waarmee ik mijn enthousiasme kon delen!

Robert-Jan de Vos, ik leerde jou pas kennen toen ik ja had gezegd op het fantastische avontuur dat nog komen ging. Maar vanaf dag 1 realiseerde ik me eigenlijk meteen dat Edwin en ik ons enorm gelukkig mochten prijzen met zo'n bevlogen en betrokken partner! En dat gevoel heb ik tot op de dag van vandaag. Ik bewonder jou manier van werken en je bevlogenheid als geen ander, een tweede Robert-Jan bestaat in mijn ogen gewoon niet. Ondanks je drukke poli's en andere onderzoekstaken was je altijd in de gelegenheid om mee te sparren of een van mijn artikelen door te lezen. Die voorzag je dan ook gretig met feedback en commentaar! Maar wat was het vooral leuk en gezellig om de inclusies van de deelnemers samen met jou te doen! Ik keek daar altijd erg naar uit, want de manier hoe jij met patiënten omgaat is zowel inspirerend als ook heel motiverend. En dat geluid hoorde ik dan ook van veel deelnemers terug, je bent erg betrokken en kan je heel goed verplaatsen in de specifieke behoefte van een individu. En dat maakt je erg bijzonder en eigenlijk gewoon de beste sportarts van Nederland. Waar je me in hebt verrast zijn je Super Mario skills, want ook al hadden we een druk congresprogramma achter de boeg in Kopenhagen, was je altijd te porren voor een potje Mario Kart op de hotelkamer samen met Iris en Arco. Maar ook op de weg ben je lastig bij te houden! Na met een kleine voorsprong uit Bilthoven vertrokken te zijn met aardig gas op de plank wist je me vlak voor Rotterdam alsnog weer in te halen. Bedankt voor alles wat ik van je heb mogen leren, je inspiratie en enthousiasme!

Winnifred van Lankeren, ik ken je al meer dan 10 jaar en je bent vanaf dag 1 niet alleen mijn opleider maar ook mijn belangrijkste coach. Jou gave om voor alle AIOS die je onder je hoede hebt een rode draad te spannen is echt uitzonderlijk. Zonder jou had ik zowel mijn opleiding als promotie echt niet zo goed kunnen doorlopen. Je inspirerende gesprekken en adviezen heb ik altijd erg ter harte genomen en enorm gewaardeerd. Maar ik heb ook enorm genoten van je gezelligheid tijdens de AIOS BBQ's in Wassenaar. Woorden schieten me echt tekort om je te bedanken voor alles wat je me hebt gebracht, maar volgens mij weet je wel dat ik je eeuwig dankbaar ben.

Mamma, ik hield je lekker even in spanning na zoveel woorden maar de enige plek waar jij eigenlijk in dit proefschrift zou horen is op de kaft (al viel dat niet helemaal binnen het thema, dus heb ik nu dit maar gekozen). Ik weet eigenlijk niet eens waar ik moet beginnen om jou te bedanken, je steun is altijd zo onvoorwaardelijk en ondanks de vele keuzes die ik heb moeten maken weet je me altijd het juiste te laten kiezen. Dit proefschrift zie ik als een bekroning van

jouw steun en toeverlaat! Ik weet dat je echt super trots bent dat het na zoveel jaren zwoegen nu eindelijk is gelukt! En daarom voel ik me ook enorm vereerd om jou het eerste exemplaar te mogen geven!

Paranimfen, **Bas de Vries** en **Karsten Veldhuizen**, het is niet voor niks dat ik jullie heb gevraagd als paranimf. Jullie zijn echt enorm belangrijke mensen in mijn leven en ik voel me vereerd dat jullie me mogen bijstaan tijdens mijn promotie. We gaan deze dag nog heel lang vieren en lekker nagenieten van alle mooie verhalen! Ik ben echt vereerd dat ik jou paranimf mocht zijn Bas!

Melanie Verdoorn, jij bent de enige kaakchirurg waarvoor ik niet bang ben maar boven alles een gigantische steun en toeverlaat. Op de dagen dat je geen harde deadlines voor me stelt weet je me wel de meest fantastische verrassingen te bezorgen, zoals een spontaan dagje Londen. Niet alleen dat maar je vriendschap en steun zal ik echt nooit vergeten en hoop nog veel leuke tripjes met je te maken. Maar dan mag je de deadlines stellen voor het uitzoeken van een leuke bestemming!

Carlo Peeters, vriend, wat kijk ik toch enorm naar je op! Wat jij zegt of adviseert neem ik direct voor waar aan. Je kent me echt als geen ander en hebt aan een half woord al genoeg (je vader trouwens ook aan de telefoon, haha). Wat heb jij me toch een enorme dosis inspiratie gegeven! Ik kan echt enorm met je lachen, maar ook heel serieus praten over onze carrière! Ik ben zo trots op je man dat jij straks ook gepromoveerd bent, en hoe jij dat hebt gecombineerd met je specialisatie tot orthopedisch chirurg, je prachtige kind, je kinderboeken en al je andere neventaken! Iets wat ik je echt met veel bewondering heb zien doen (net als het koeien melken trouwens). Een ding weet ik zeker, je wordt de beste chirurg die ik ken.

Bernard van Rossum en **Janneke Dirks**, ik prijs me enorm gelukkig dat ik al jaren zo'n mooie vriendschap met jullie heb opgebouwd en wat fijn dat Otis daar nu ook deel van uit maakt! Ik kom echt helemaal tot rust als ik met jullie lekker pizza's kan bakken of met Otis door de woonkamer kan scheuren. We kennen elkaar eigenlijk zo goed dat we bijna niet meer hoeven te vragen hoe het gaat want dat weten we gewoon. En wat is dat fijn geweest tijdens die drukke tijd als AIOS en PhD-student!

Kars Compagne, **Desiree de Vreede**, **Iris Lagas** en **Arco van der Vlist**, zonder jullie was PhD-life echt een stuk minder leuk geweest! We hebben zoveel met elkaar kunnen delen en elkaar op weg kunnen helpen als we het even nodig hadden. De koffiemomentjes waren in dat opzicht bijna therapeutisch en een ideale brainstormsessie! Maar ook een potje Mario Kart op de hotelkamer en het vangen van Pokémon in de congreszaal deden het goed! En

Arco, het liefst slaap ik met een gezellig armpje erbij! Echt supergaaf dat we samen twee artikelen hebben kunnen publiceren!

Mariëlle Olsthoorn, Tessa Brabander, **Laura Graven** en **Pinar Yilmaz** (of moet ik zeggen "sexy banana's"), jullie zijn niet alleen fantastische collega's maar ook geweldige vrienden! We hebben de traditie om poepsjiek te gaan uiteten en mooie verhalen te vertellen. Maar ook door een lekker fikkie te stoken of te rijden met de graafmachine voel ik me weer helemaal kind. En dat heeft me altijd enorm geholpen om de soms zware tijden van het PhD leven te doorstaan!

Susanne Eijgenraam, **Loes Schiphouwer**, **Madelon Tieleman** en **Ivo Wagensveld**, niet alleen in flamingo-outfit shinen wij op z'n best maar wat zijn jullie toch ook lieve vrienden en fantastische collega's! Heel erg bedankt voor jullie steun en vooral veel gezelligheid!

Collega stafleden van het Erasmus MC en ETZ, ik heb met jullie veel interessante gesprekken gehad over mijn PhD project en ik heb veel aan jullie input gehad! Dank voor jullie steun en toeverlaat en vooral jullie begrip voor mijn onderzoekstaken naast mijn specialisatie!

Collega AIOS, ik heb tussen 2014 en 2023 fantastische groepen AIOS voorbij zien komen en soms dacht ik door het onderzoek eeuwig AIOS te zijn, maar er is nu eindelijk een eind in zicht! Gelukkig heb ik zowel in het Erasmus MC als het ETZ zo'n leuke AIOS meegemaakt dat het soms zelfs niet eens als werken voelde!

Collega laboranten, jullie zijn allemaal zo betrokken! Op de wandelgangen hebben we soms de meest interessante gesprekken! Het liefste zou ik jullie hier nu allemaal persoonlijk willen bedanken, maar dan wordt het proefschrift zo dik! Wel licht ik **Sylvia Bruininks** er nog graag even uit, want wat was ik verbaasd dat je voor mij speciaal koffiebonen uit Costa Rica had meegenomen! Ik vreesde al dat het de lekkerste koffie zou zijn die ik sinds lange tijd gedronken had, en jammer dat je geen pallets vol kon meenemen! Maar los daarvan heel erg bedankt voor het meedenken met de MRI-protocollen en het onderzoek! Ook wil ik alle andere MRI-laboranten speciaal even bedanken voor hun begrip dat ik altijd alle kussentjes uit de kamers stal om de JUMPER-patiënten maar zo goed mogelijk in de scanner te laten liggen.

Andere collega's van het secretariaat Radiologie & Nucleaire Geneeskunde, Trialbureau ook heel erg bedankt voor jullie hulp, het meedenken en de gezelligheid!

BIGR-group and **MRI physics-group**, my great gratitude cannot be expressed well in words, but is better expressed in voxels. I have illustrated this for you on the cover of the thesis,

where a basketball falls apart in voxels. I am super proud of the final product that I completed with you after hours of work optimizing the UTE sequence and analyzing this data.


NBA

ABOUT THE AUTHOR

Stephan Jonathan Breda was born on March 27th, 1989 in Eindhoven, The Netherlands. In 2008 he started his bachelor's degree in medicine at the Erasmus University in Rotterdam and completed the medical studies in 2011. During his study, he was active as research assistant in the ERGO (Erasmus Rotterdam Gezondheid Onderzoek) Rotterdam Study and responsible for scoring osteoporotic vertebral fractures using different scoring methods. During his internships he visited Liverpool for an internship in Radiology at the Royal Liverpool and Broadgreen University Hospital NHS Trust. After obtaining his medical degree, he started his radiology residency at the Erasmus MC in 2014. When he was approached during his second year for a PhD project, he interrupted his radiology training for 4 years to perform a full-time research project (supervised by prof.dr. Edwin Oei and dr. Robert-Jan de Vos). The PhD project was a joint venture between the Department of Radiology & Nuclear Medicine and Department of Orthopaedics and Sports Medicine. He simply couldn't refuse the offer since we had received a research grant from a NBA and GE sports collaboration. The PhD project in which he was the main investigator, was called JUMPER study and aimed to compare the effectiveness of two different exercise therapies in the largest randomised controlled trial in patellar tendinopathy to date. Novel quantitative imaging techniques were used to evaluate structural changes in the patellar tendon as a result of exercise therapy. He coordinated the clinical trial and guided patients during their rehabilitation. He also invested considerable time in developing the Ultrashort Echo Time (UTE) MRI sequence and analysed all data after extensively testing image registration options and image analysis methods. Moreover, he proposed an image analysis approach for analysing tissues with high spatial heterogeneity which was published and shortly after recommended in an editorial. Subsequently he was asked to write a book chapter for the book series "MRI of Short T2 Tissues: Making the Invisible Visible". For an ultrasound-based quantitative image biomarker, called shear-wave elastography (SWE), he designed a protocol for the acquisition that was as reproducible as possible together with a student Healthcare Technology from the Hogeschool Rotterdam whom he supervised during his graduation project. During the PhD project, he built valuable relationships with colleagues from the Departments of Orthopaedics and Sports medicine, BIGR image analysis group, application specialists and MRI sequence developers from GE Healthcare. In 2020 he resumed his radiology training at Erasmus MC and exchanged a year at the Elisabeth TweeSteden Ziekenhuis (ETZ) in Tilburg for his peripheral internship. He expects to finish his radiology training by the end of 2023.