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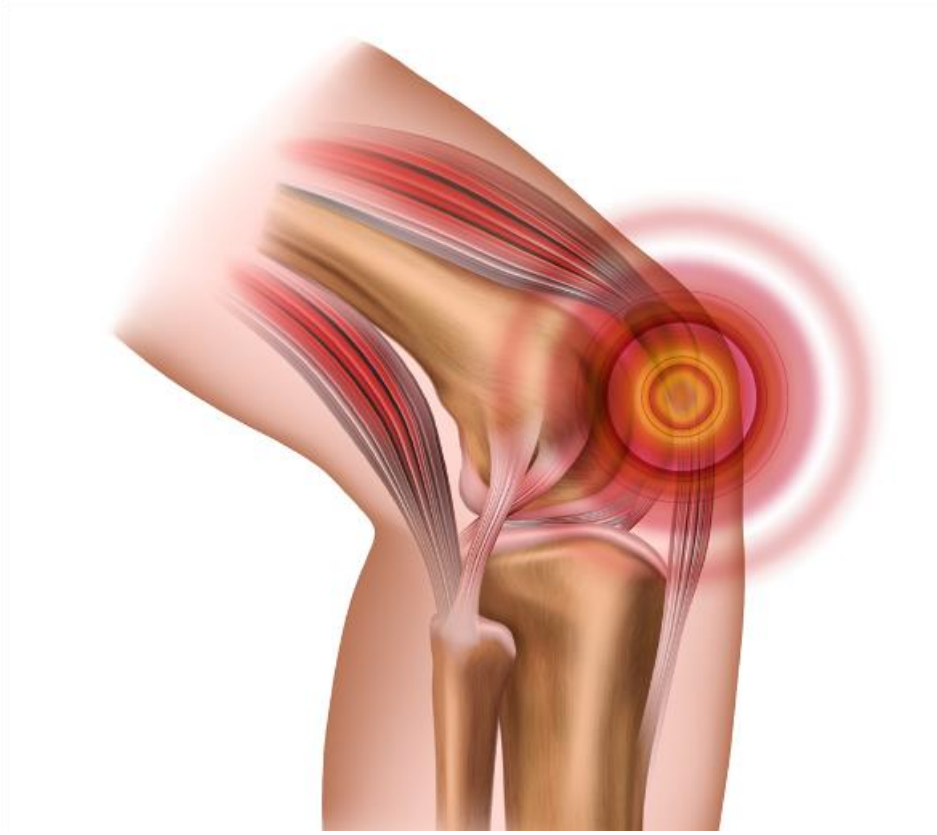

PhD Thesis

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Low-Load Blood Flow Restriction Training in the Rehabilitation of Patellar Tendinopathy

An Investigation of the Mechanisms and Efficacy

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This thesis has been submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen on 31st of October 2023

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1. PREFACE

This Ph.D. dissertation was accomplished at Bispebjerg-Frederiksberg Hospital and the University of Copenhagen. The thesis consists of two original studies and one ancillary analysis based on baseline data from two RCT studies. The studies were conducted between September 2020 and September 2023.

Study number I was funded by Team Danmark, The Danish Association of Physiotherapists, the Novo Nordisk Foundation, and University College Absalon. One supervisor was employed by the University College Absalon, but other funders did not partake in or influenced the study in any way.

List of studies included in the thesis

The current Ph.D. thesis is comprised by the following three papers:

Study I: Hjortshoej MH, Juneja H, Svensson R, Herzog R, Lundgaard-Nielsen M, Larsen FK, Wulff MW, Olsen AE, Nybing JD, Hansen P, Petersen J, Kjær M, Aagaard P, Magnusson SP, Couppé C. Low-Load Exercise with Blood-Flow Restriction Training Provides Similar Clinical Outcome Compared to Heavy-Slow Resistance Training in Elite and Recreational Male Athletes with Unilateral Patellar Tendinopathy: A Randomized clincial Trial. (Manuscript)

Study II: Hjortshoej MH, Aagaard P, Storgaard CD, Lundbye-Jensen J, Juneta H, Magnusson SP, Couppé C. Hormonal, Immune, and Oxidative Stress Responses to Blood Flow Restricted Exercise. Published in Acta Physiologica September 2023.

Study III: Hjortshoej MH, Agergaard A, Larsen FK, Thomsen LJP, Svensson R, Couppé C, Magnusson SP. Determination of differences in ultrasound parameters for patellar tendons in males with unilateral patellar tendinopathy – an Ancillary Analysis of data from two randomized clinical trials. (Manuscript)

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"Victoria Concordia crescit"

3. LIST OF ABBREVIATIONS

AI	Artificial Intelligence
AOP	Artery Occlusion Pressure
AP	Apex Patella
BMI	Body Mass Index
CI	Confidence Interval
CSA	Cross Sectional Area
ECM	Extra Cellular Matrix
ECR	Extensor Carpi Radialis
FFRE	Free-Flow Resistance exercise
GH	Growth Hormone
HL	Heavy-Load
HSRT	Heavy-Slow Resistance Training
ICC	Intraclass Correlation Coefficient
IGF-1	Insulin-like Growth Factor 1
iMVC	Isometric Maximal Voluntary Contraction
LL	Low-Load
LL-BFRT	Low-Load Blood Flow Restriction Training
MCID	Minimal Clinically Important Difference
MPA	Most Painful Area
MRI	Magnetic Resonance Imaging
NA	Noradrenaline
NPRS	Numeric Pain Rating Scale
PD	Power Doppler
PPT	Pain Pressure Threshold
PROM	Patient Reported Outcome Measure
RCT	Randomized Clinical Trial
ROB2	Risk Of Bias 2
ROBINS-I	Risk Of Bias In Non-randomized Studies – of Interventions
ROI	Region Of Interest
RM	Repetition Maximum
SD	Standard Deviation
SLDS	Single-Leg Decline Squat

SMD	Standardized Mean Difference
TA	Tibialis Anterior
TE	Typical Error
TESTEX	Tool for the assEssment of Study qualiTy and reporting in EXercise
US	Ultrasonography
VEGF	Vascular Endothelial Growth Factors
VISA-P	Victorian Institute of Sports Assessment-Patella Questionnaire

4. ENGLISH SUMMARY

Patellar tendinopathy is a debilitating overuse injury that has a high prevalence in explosive sports, such as basketball and volleyball. Patellar tendinopathy is characterized by pain exacerbation during physical activity, swelling of the tendon, and localized tenderness upon palpation. Furthermore, during ultrasonography examination, the tendon often displays increased thickness, neovascularization, and hypo echogenicity. Patellar tendinopathy is a considerable issue for the athlete, as many experience symptoms for a prolonged period (often months and years), a decrease in performance, and some may never return to their previous activity level or even end their sport career altogether. Currently, the preferred treatment of choice is heavy-slow resistance training (HSRT) in the rehabilitation of patellar tendinopathy. However, not all participants recover, and many may not tolerate the high peak loads. Blood-flow restriction with low loads (LL-BFRT) has demonstrated clinical effects in different patient populations, and recently, a pilot study demonstrated good effects on clinical and structural outcomes in the rehabilitation of patellar tendinopathy. Thus, understanding if and how LL-BFRT may optimize rehabilitation is important.

The aim of this thesis was to investigate a potential new treatment modality and the possible mechanisms behind LL-BFRT. Thus, we performed a randomized clinical trial to investigate the effect of LL-BFRT on clinical and structural outcomes in males with unilateral chronic patellar tendinopathy following a 12-week rehabilitation protocol. Our hypothesis was that LL-BFRT was superior to HSRT on the numerical pain rating scale (0 denoting no pain and 10 being the worst imaginable pain) during the single-leg decline squat at 12-week follow-up. Secondly, we aimed to investigate the hormone, immune, and oxidative stress responses at the initial (<10 min), intermediate (10-20 minutes), and late (30+ minutes) phases post-exercise, comparing LL-BFRT to heavy-load- (HL-FFRE) or low-load free flow resistance training (LL-FFRE). Lastly, the aim was to investigate power Doppler (PD) activity and tendon structure (tendon length, thickness, and echogenicity) in males with symptomatic unilateral patellar tendinopathy compared to their asymptomatic tendon. Secondly, we aimed to examine the intra-rater reliability of the measurement performed for PD activity and tendon structures.

There was no significant difference between LL-BFRT and HSRT on clinical and structural outcomes, as both groups seemed to improve equally following the 12-week rehabilitation protocol. In addition, when reviewing the current literature regarding hormone, immune, and oxidative stress responses, LL-BFRT and HL-FFRE demonstrated similar physiological responses at the initial, intermediate, and late phases post-exercise. However, LL-

BFRT demonstrated a significant increase in hormone, immune, and oxidative stress responses at the initial, intermediate, and late phases post-exercise compared to LL-FFRE. Lastly, in the ancillary study, there was significantly greater PD activity and tendon structure in the tendinopathic tendon compared to the asymptomatic contralateral tendon. Also, good-to-moderate intra-rater reliability was demonstrated for all measurements on the tendinopathic tendon.

In conclusion, LL-BFRT did not demonstrate superiority compared to HSRT in a 12-week intervention period. However, LL-BFRT demonstrated equal improvements in clinical and structural outcomes compared to HSRT. This indicates that LL-BFRT can be used as a treatment modality in the rehabilitation of patellar tendinopathy and LL-BFRT reduces peak loads in muscles, tendons, bones, and joints compared to HSRT. The potential mechanism for this could be that LL-BFRT demonstrates similar hormone, immune, and oxidative stress responses compared to HSRT; however, this should be further explored in future studies.

5. DANSK RESUMÈ

Patellar tendinopati, også kendt som springerknæ, er en invaliderende overbelastningsskade som ofte forekommer blandt atleter indenfor eksplosive sportsgrene såsom basketball og volleyball. Springerknæ er karakteriseret ved øgede smerter under fysisk aktivitet, hævelse af senen, og ømhed ved palpation af knæskalssenen. Man kan yderligere ved ultralydsskanning af senen ofte se forøget senetykkelse, øget blodgennemstrømning, og nedsat ekkogenicitet. Springerknæ kan udgøre et stort problem for atleten, da mange atleter oplever langvarige symptomer der kan vare måneder eller år, nedsat sportslig ydeevne, og nogle kommer aldrig tilbage til samme fysiske aktivitetsniveau eller må helt opgive deres sportskarriere. Tung, langsom styrketræning (TLS) er den foretrukne modalitet i genoptræningen af springerknæ, men ikke alle kommer sig fuldt og mange kan ikke tolerere de høje spidsbelastninger associeret ved TLS. Afklemmelse af blodtilførslen under udførelse af træning med lav belastning, også kaldet okklusionstræning (OT), har demonstreret kliniske effekter i andre patientpopulationer, og har for nyligt demonstreret gode kliniske effekter i et pilotstudie som undersøgte effekten OT i genoptræningen af springerknæ. Derfor er det vigtigt at undersøge om og potentielt hvordan OT kan optimere genoptræningen af patienter med springerknæ.

Det overordnede formål med denne Ph.D. afhandling var at undersøge en potentiel ny behandlingsmodalitet og de potentielle mekanismer bag OT. I studie I, undersøgte vi de kliniske og strukturelle effekter af et 12 ugers genoptræningsforløb bestående af enten OT eller TLS hos idrætsaktive mænd med ensidigt springerknæ et i randomiseret kontrolleret forsøg. I studie II, gennemgik vi den eksisterende litteratur, hvor vi undersøgte det hormonelle, immune, og oxidative stress respons i den initiale (<10 minutter), mellemliggende (10-20 minutter), og sene (30+ minutter) fase efter træning med OT sammenlignet med tung- og let styrketræning i et systematisk review og meta-analyse studie design. I studie III undersøgte vi blodgennemstrømningen og de strukturelle forskelle blandt mænd med ensidigt symptomatisk springerknæ og sammenlignede med deres modsatte asymptomatiske sene. Derudover, undersøgte vi også intra-rater reliabiliteten for opmåling af blodgennemstrømningen og sene strukturen.

I studie I var der ingen signifikante forskelle mellem OT og TLS på nogle kliniske eller strukturelle parametre, og begge grupper havde en klinisk forbedring efter det 12 ugers rehabiliteringsforløb. Efter at have gennemgået den eksisterende litteratur, fandt vi at OT og tung styrketræning giver det samme fysiologiske respons i den initiale, mellemliggende, og sene fase efter træning. Modsat fandt vi at OT øger det fysiologiske respons sammenlignet med lav

styrketræning i den initiale, mellemliggende, og sene fase efter træning. I studie III var der signifikant øget blodgennemstrømning og sene strukturelle ændringer i den symptomatiske sene sammenlignet med den asymptomatiske sene. Ligeledes, blev der demonstreret god til excellent intra-rater reliabilitet for alle parametre for den symptomatiske sene.

OT demonstrerede ikke bedre men sammenlignelige kliniske og strukturelle effekter med TLS efter et 12 uger rehabiliteringsforløb. Dette indikerer at OT kan være en anvendelig genoptræningsmodalitet i genoptræningen af springerknæ, og mindsker spidsbelastninger på muskler, sener, knogler, og led sammenlignet med TLS. Potentielle mekanisme kunne være at OT forårsager det samme hormonelle, immun, og oxidativ stress respons som TLS. Dette bør videre undersøges i fremtidige studier

6. INTRODUCTION

Patellar tendinopathy is an overuse injury that primarily impacts athletes in high-explosive sports, such as basketball and volleyball (1). Patellar tendinopathy can be a debilitating injury that can severely impact both work and social life (2). Loading-based rehabilitation modalities have in recent years been the preferred treatment of choice for tendinopathy (3). However, optimal treatment and rehabilitation protocols are still debated, as some patients do not seem to fully recover and continue to report pain and loss of function due to symptoms of patellar tendinopathy (4,5). Therefore, new rehabilitation protocols may unlock the enigma that is the treatment of patellar tendinopathy.

The purpose of this Ph.D. thesis was to investigate the clinical and structural effects of different rehabilitation protocols in the treatment of patellar tendinopathy. Hopefully, this thesis will provide new knowledge to the benefit of patients afflicted by patellar tendinopathy.

7. BACKGROUND

7.1 Tendon

7.1.1 Tendon structure

Tendon tissue acts as a spring that stores and releases mechanical strain energy, which optimizes functional operating conditions for muscles considering the force-length-velocity relationship (6). Tendon tissue can endure and transmit considerable force from contracting muscles to the skeletal system during locomotion (7). The patellar tendon is one of the largest tendons in the human body. It is fusiform in its course and originates from the apex of the patella before its insertion at the tibial tuberosity (8). The patellar tendon is 3-5 mm in thickness (9,10) and approximately 5 cm in length, but with large variations (11). The patellar tendon is part of the quadriceps extensor mechanism of the knee joint and can withstand forces of up to 4 kilonewtons during a single counter movement jump (7). The patellar tendon is comprised of an anterior and posterior layer. The anterior layer is a continuation of the quadriceps tendon, whereas the posterior layer is attached bone-to-bone (8). The collagen structure and fascicles are stronger at the anterior site compared to the posterior (12), indicating that the patellar tendon does not transfer force equally throughout the tendon and may operate in a more separate manner. Tendons possess passive, viscoelastic properties that are dependent on factors, such as sex and

anatomical location (13–16). The viscoelastic properties of the tendons are also dependent on physical activity levels (mechanical stimuli), as high intensity strength training can increase and immobilization can decrease viscoelastic properties, e.g., tendon stiffness (17–19). Likewise, mechanical stimuli are important to tendon healing and repair, whereas immobilization is detrimental to the healing process (20).

The tendon is a passive fibrous connective tissue structure that is relatively inelastic but has the capacity for high tensile strength (21). The tendon is organized in a hierarchical order and is a uniaxial structure that is aligned in the long axis of the tensile strength (22). The extracellular matrix (ECM) of the tendons consists primarily of collagen but also proteoglycans, glycoproteins, and glycosaminoglycans (23). The smallest component of the tendon is comprised of triple-helical type 1 collagen that is stabilized by covalent intermolecular crosslinks, which interconnect the collagen molecules, thus ensuring the integrity of the tendon fibrils (24). The fibrils are the primary force-transmitting structure of the tendon and are continuous throughout the whole length of the tendon (25). The tendon fibrils in turn comprise the tendon fibers, and the fibers in turn constitute the tendon fascicles, and multiple fascicles constitute the tendon unit (24). The endotenon encompasses the fascicles in order to stabilize the tendon and also contains blood vessels and nerves (21). The endotenon connects with the epitenon, which together with the paratenon forms a sheet encompassing the entire tendon to reduce friction with surrounding structures (22,24). Together, the epitenon and the paratenon, are also known as the peritenon, which is the outermost layer of the tendon proper. Throughout the tendon are scattered tenocytes, e.g., fibroblasts, that are interspersed in the fascicular and inter-fascicular matrix in the fibrillar orientation, albeit the tendon is characterized by its hypocellularity (21). Tenocytes facilitate tendon homeostasis by producing ECM components, such as collagen and proteoglycans (21,23). A hierarchical presentation of the tendon structure is illustrated in Figure 1.

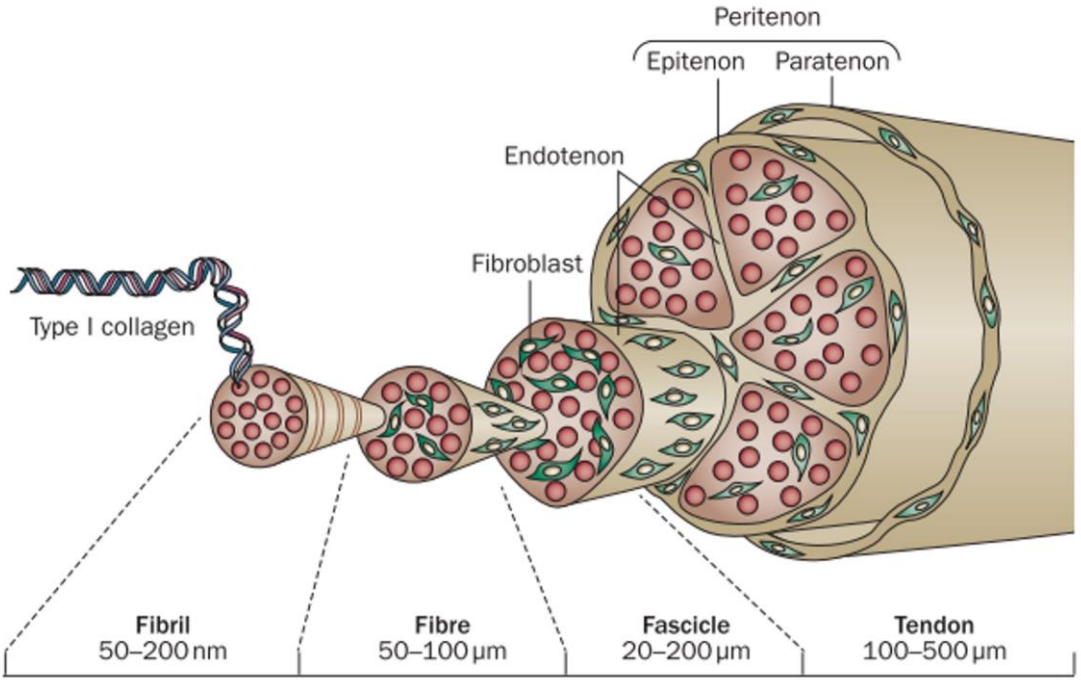


Figure 1: A hierarchical representation of the tendon structure. Modified from Nourissat et al. (24).

7.1.2 Tendon physiology

The ECM is a macromolecular network that contributes to both structural and regulatory functions while also controlling cell proliferation, migration, survival, and differentiation (26). The tendons ECM consists of more than 28 different types of collagens. Fibrillar collagen types I, II, III, V, and VI, where collagen type I is the most abundant, are primarily responsible for providing the tendons mechanical strength (27). As mentioned, collagen is the most abundant part of the tendon, and its dry weight constitutes 60-85% of the tendon, of which collagen type I constitutes 60-80%, type II collagen constitutes 0-10%, and the remaining part of the tendon is comprised of other collagens together with 2% elastin, and extracellular proteins (26,28). In addition, the normal tendon consists of 55-70% water, which is closely linked to the amount of proteoglycans, and these in combination have been suggested as a lubricant for the tendon (28). Besides proteoglycans, the tendon also consists of glycoproteins and glycosaminoacids, and all three contribute to the organization, development, and growth control of the tendon (28). The tendon is relatively avascular, where only ~1-2% of the ECM is occupied by blood vessels, which are primarily located in the epitenon (28). This relatively low blood supply and hypocellularity is possibly the explanation for the tendons poor healing and regenerative ability (29,30), which often leads to prolonged injury and/or incomplete homeostasis (31).

It may not only be due to the limited number of tenocytes and relatively low blood

supply that recovery seems difficult, but perhaps also to the structure of the tendon itself. As the tendon fibrils are continuous throughout the entire length of the tendon, it may be difficult to align, tension, and interweave new fibrils at the injured site, which could be the reason for poor clinical outcomes following tendon injuries (25). Unlike muscle tissue, tendon core tissue is not renewed continuously and remains stable from the early to mid-teenage years (32,33). All these factors combined most likely contribute to the poor regenerative capabilities of tendinous connective tissue.

7.2 Patellar tendinopathy – Prevalence, incidence, and societal and individual burden

Patellar tendinopathy has a relatively high prevalence, and the overall prevalence in elite and recreationally physically active adults has been reported to be 18.3% (34), whereas within explosive sports, e.g., volleyball and basketball, a study reported a prevalence of 45% and 35%, respectively (1).

There is a great societal and individual burden of patellar tendinopathy, as 1.1/1000 patients in a Danish general practice present with patellar tendinopathy which indicates that patellar tendinopathy costs a significant amount of resources in the general health care system (35). Likewise, the individual burden of patellar tendinopathy is also substantial, as 16% report that their work ability is negatively impacted, and 36% report a decrease in work productivity due to symptoms from patellar tendinopathy (2). And in adults performing demanding work, 23-30% experienced decreased work ability, and 17-58% reported a decrease in work productivity (2,36). Reduced work ability has been demonstrated to predict long-term sickness absence, decreased work performance, more health care use, and a decrease in health-related quality of life (37,38), while a loss in work productivity may have individual economic costs. Lastly, upwards of approximately 33% of athletes with patellar tendinopathy were unable to return to sports participation within 6 months (39), and a study reported that approximately 50% of athletes with patellar tendinopathy were forced to retire from sports, albeit in a relatively small sample (40).

7.3 Patellar tendinopathy – Pathology, symptoms and diagnosis

7.3.1 Patellar tendinopathy pathology

The pathogenesis of patellar tendinopathy is still not fully understood but seems to be multifactorial and complex. Several theories have been proposed as to the etiology of patellar tendinopathy, but there is still no consensus (41). Several intrinsic and extrinsic risk factors might play a role in the origin of patellar tendinopathy. Among the intrinsic factors, systemic diseases (e.g., diabetes mellitus and hyperlipidemia), obesity, genetic factors, age, and muscle weakness seem to play a part, whereas overuse, rapid increase in physical activity, initiation of new activities, especially with highly repetitive motions, a lack of recovery, and some medications (e.g., fluoroquinolones and hormone replacement therapy) seem to be some of the important extrinsic factors for developing tendinopathy (41–44).

Dysregulation of the ECM in response to overloading has been suggested to play an important role in the development of tendinopathy (30,45). It seems that in tendinopathic tendons, protein degradation exceeds protein synthesis following physical activity. As previously described, there is very little collagen turnover in normal tendons, and there is no collagen turnover in the tendon core after the early to late teenage years (32). However, this has been found to be different in tendinopathic tendons, where a study found an increase in collagen turnover to the extent that they estimated that 50% of the collagen in the tendinopathic tendons had undergone slow but continuous turnover for years prior to being symptomatic (33). This suggests that symptomatic tendinopathic tendons may be years in the making or that abnormally high turn-over rates are a risk factor for developing tendinopathy.

The pathological process seems to be initiated by continuous overloading of the tendon, initiating structural injury and disruption of the collagen fibrils (as mentioned above), which is in contrast to macroscopic tearing of the tendon associated with partially or fully ruptured tendons (41,45). Several different and distinct histologic characteristics are associated with a tendinopathic tendon that is in sharp contrast to a healthy tendon. The collagen fibrils seem disorganized, with an increased amount of proteoglycan, i.e. aggrecan and versican, and glycosaminoglycan leading to increased water content (46) that may increase the intratendinous pressure (47), increase in collagen type III and non-collagenous ECM (41,48), nerve ingrowth (49), hypercellularity with more rounded fibroblasts (23), and neovascularization (50,51) (see Figure 2). To what extent inflammation is involved in tendinopathy is still debated, and it seems that inflammation is part of early tendinopathy where different indicators have been found, whereas in the chronic tendinopathic tendon, inflammation does not seem to be present (45,52).

However, it is important to note that our current understanding of the etiology of patellar tendinopathy is limited to after the onset of pain, as tendinopathy seemingly has a slow onset. Therefore, with our current knowledge, it is impossible to establish if these changes are the cause or result of tendinopathy (41).

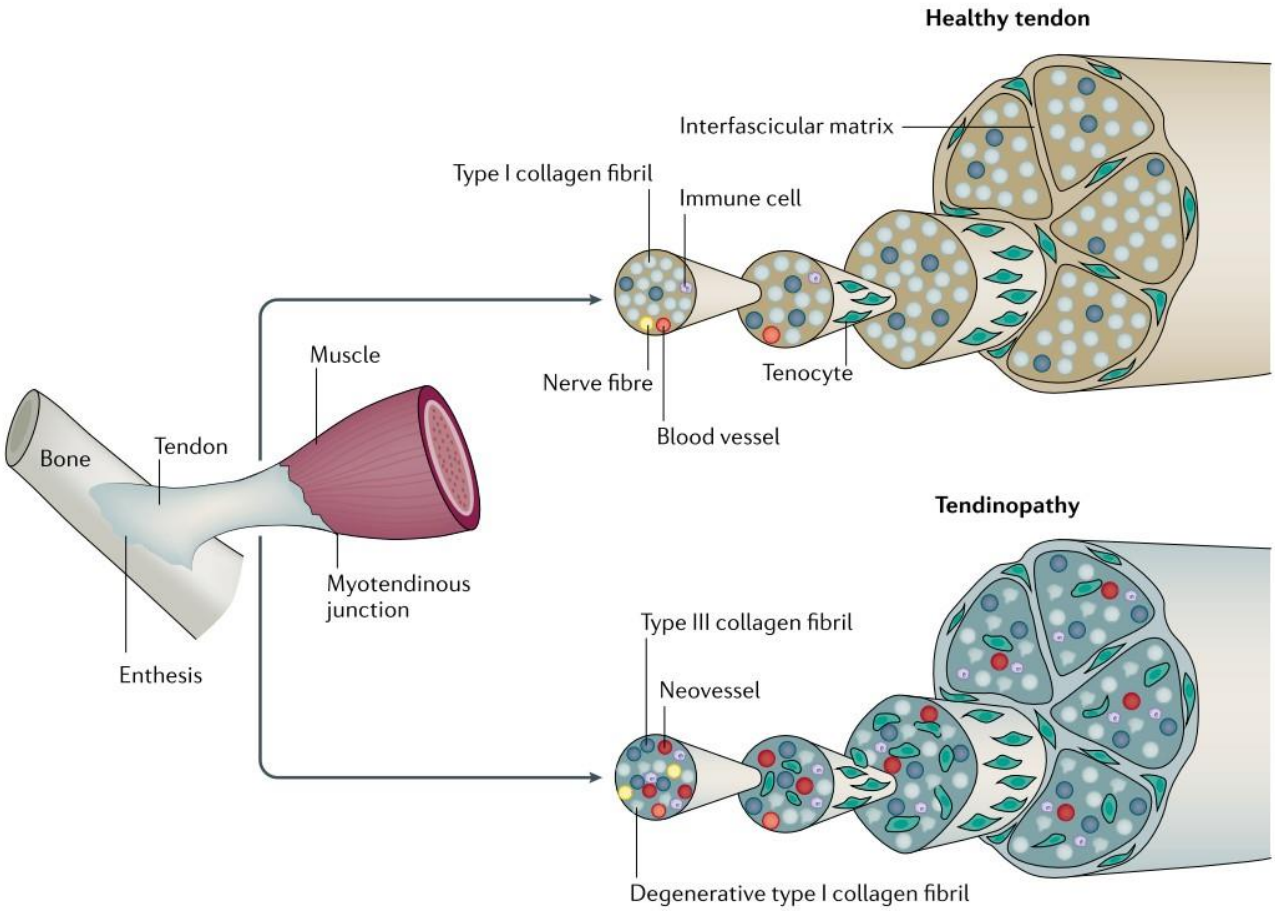


Figure 2: A illustration of the healthy tendon and tendinopathic tendon from Millar et al. (41)

7.3.2 Patellar tendinopathy symptoms and diagnosis

Patellar tendinopathy is characterized by localized pain at the apex patellar during palpation, and the symptoms are exacerbated during or following physical activity (51). In addition, many report pain during prolonged sitting and experience a decrease in sports performance (2). Patellar tendinopathy can be sub-categorized into three subgroups based on symptom duration: the acute stage, defined as symptoms between 0-4 weeks; the sub-acute stage, defined as symptoms between 5-12 weeks; and the chronic stage, defined as symptoms for more than 12 weeks (48).

The diagnosis of patellar tendinopathy is based on patient history and clinical examination (51). Patients often report that symptoms increase at the initiation of physical

activity, followed by a “warm-up effect”, where symptoms decrease, followed by an increase in pain after cessation of physical activity (51). Likewise, palpation tenderness of the patellar tendon is a frequent sign of patellar tendinopathy; however, palpation tenderness demonstrates low specificity, thus its use in clinical diagnostics has been questioned (53). Further, paraclinical tools, such as ultrasonography (US) and magnetic resonance imaging (MRI), can be a helpful tool in the diagnosis of patellar tendinopathy (51), although an ICON consensus statement from 2019 stated that “imaging is not always necessary for the diagnosis of tendinopathy” (54); however, a study from Fredberg et al. (55) demonstrated a high degree of misdiagnosis without the use of US examination.

7.4 Patellar tendinopathy and imaging

US is the most widely used paraclinical tool and is a valuable tool in the diagnosis, treatment, and prognosis of patellar tendinopathy (51,55,56). US is often used due to its non-invasive nature, low cost, and it is less time consuming compared to other paraclinical tools (57). Another paraclinical tool, used primarily for research purposes, is MRI. However, due to its high cost and inaccessibility for most clinical practices, MRI is often not used in the diagnosis of patellar tendinopathy (50).

7.4.1 Ultrasonography examination in tendinopathy

US can be used to diagnose patellar tendinopathy not only in the chronic stage but also in the acute and sub-acute stages (58). During US examination, patellar tendinopathy often presents with local proximal anterior-posterior thickening, hypo-echogenicity, and increased neovascularization visualized by Power Doppler (9,51,55,59,60). Asymptomatic tendons can also present with structural changes, such as increased neovascularity and echogenicity. In contrast, healthy tendons are approximately 3-5 mm in thickness and display an organized fibrillar alignment with a high echogenicity (10,61). However, most comparisons between healthy and tendinopathic tendons have been performed using healthy controls, thus, not accounting for individual variances. Likewise, direct comparison between studies may be difficult, as several studies have evaluated tendon thickness at different sites from the apex of the patella (5,9,10,62).

US has demonstrated a high degree of intra-rater, inter-rater, and test-retest reliability in healthy and tendinopathic tendons (56). Also, US findings of structural changes in

asymptomatic tendons have shown good prognostic value for the future development of patellar tendinopathy (63). This indicates that US is a good paraclinical tool to assess tendon structure in healthy and tendinopathic tendons; however, US is highly operator dependent, which may influence the results (64,65).

7.4.2 MRI in patellar tendinopathy

MRI can be used to diagnose and evaluate patellar tendinopathy. On MRI, the healthy patellar tendon displays homogenous tendon thickness throughout the whole length of the tendon and demonstrates low intensity, whereas the tendinopathic patellar tendon appears thicker and wider, has an increased CSA, and is also present with a heterogenous increase in signal intensity (66). However, MRI of tendons will appear black due to water and collagen molecules alignment, which substantially shortens the dipole interactions (67), thus limiting the information of structural alterations achieved from MRI. A new technique, isotropic 3D T1 weighted sequence, has led to increased clinical and research applications due to its advantages, including the ability to acquire high-resolution isotropic images with relatively short acquisition time and a reduction in partial volume averaging artifacts while also being suited for volumetric measurement (68). Another benefit of MRI is that other pathologies can be excluded, and that MRI provides a global assessment of the region (50).

Patellar thickness has been obtained by US imaging and MRI in healthy patellar tendons and has demonstrated good reliability (69). The US imaging and MRI of the patellar tendon reported good-to-excellent reliability between the measurements, suggesting that both paraclinical tools can be used reliably to assess the patellar tendon (70,71). A study reported that US was more accurate in confirming the clinical diagnosis of patellar tendinopathy than MRI (72). However, a more recent study demonstrated similar specificity and sensitivity between US and MRI (62). Likewise, US may also provide higher image resolution compared to MRI, making measurement of tendon thickness more accurate (73).

7.5 Patellar tendinopathy - Current treatment modalities

7.5.1 Current treatment modalities

Symptoms of patellar tendinopathy may be long-lasting (1) and recovery may be difficult to achieve in both the short and long-term (4,5,74–76). Further, a wait-and-see approach does not seem to have an impact on symptom relief (77). Possibly because of this, many treatment

modalities are currently available and utilized in the treatment and pursuit of proliferation for patellar tendinopathy. Currently available treatments include corticosteroid injections, platelet-rich plasma injections, hyaluronic acid injections, percutaneous needle electrolysis, dry needling, ultrasound therapy, focal and radial extracorporeal shock-wave therapy, and loading-based therapy, such as eccentric and isometric training, moderate slow resistance training, and heavy-slow resistance training (HSRT) (78).

7.5.2 Passive treatment modalities

As mentioned, several passive treatment modalities are available for the treatment of patellar tendinopathy, and including, but not limited to, surgery, injection therapy, shockwave therapy, laser therapy, and therapeutic ultrasound.

Surgery has been investigated in several retrospective and prospective studies, however, only two RCT studies have investigated surgery compared to exercise or sclerosing injections (79,80) with a Cochrane review from 2019 rating the level of evidence from very low to low (81).

Injection therapy such as platelet-rich plasma, corticosteroid, and high-volume injections have also been proposed as a modality in the treatment of patellar tendinopathy (82). In a recent systematic review investigating different injection therapies in PT, the authors concluded that injection therapy demonstrated promising results; however, the number of studies was too few to make any firm conclusions (83).

Shockwave therapy has been another modality proposed in the treatment of patellar tendinopathy. In a recent meta-analysis, shockwave therapy did not demonstrate superiority compared to placebo shockwave therapy, and similarly, it did not demonstrate superiority as a supplement therapy to eccentric exercise compared to placebo shockwave therapy and eccentric exercise. In addition, shockwave therapy was also compared to conservative treatment and demonstrated a significant and large effect. However, the authors rated the level of evidence from very low to moderate (84).

Laser therapy has been investigated in two studies investigating low-level laser therapy compared to placebo and eccentric exercise in the treatment of patellar tendinopathy (85,86). Low-level laser therapy demonstrated superior effect compared to placebo (85); however, compared to eccentric exercise, both groups demonstrated significant improvements but no between-group differences (86).

Low-intensity pulsed therapeutic ultrasound has been investigated in one study

where they compared active low-intensity pulsed therapeutic ultrasound to placebo low-intensity pulsed therapeutic ultrasound (87). In this study, they found a significant improvement for both groups with no between-group differences.

Based on the presented evidence for the different passive treatment modalities, there is generally low level of evidence with few studies, thus making any conclusion on their effect in the treatment of patellar tendinopathy difficult.

7.5.2 Loading-based therapy

Currently, loading-based rehabilitation is the preferred treatment for patellar tendinopathy (78); however, it still remains unclear which type of contraction (isometric, eccentric, or concentric), how much load, how many sets and repetitions, frequency, and duration of training periods are required in the rehabilitation of patellar tendinopathy. The eccentric exercise protocol was the first clinically examined rehabilitation modality in Achilles tendinopathy (88) and is currently the recommended rehabilitation modality in both Achilles and patellar tendinopathy (78). However, no evidence supports the superiority of an eccentric-based rehabilitation protocol, as in recent years, studies have not been able to demonstrate any clinically significant differences between eccentric exercise protocols and other loading-based protocols (4,89). Likewise, tendons are a mechanically passive structure that lengthens when force is applied and shortens when force is reduced (90). In addition, similar collagen expression and tendon hypertrophy have been demonstrated between eccentric exercise and HSRT (91,92), thereby questioning the importance of contraction type.

7.5.2 Heavy-slow resistance training

HSRT was first proposed as a rehabilitation modality for patellar tendinopathy by Kongsgaard et al. in 2009 (4). Since then, several studies have demonstrated significant clinical effect of a HSRT protocol in the rehabilitation of tendinopathy in the patellar and Achilles tendon (5,76,89,93,94).

The theory for the application of HSRT is that exercise is followed by an increase in both the synthesis and degradation of collagen (23). Within 24-36 hours post-exercise, there is a higher degradation than synthesis, thus resulting in a net loss of collagen, whereas an increase in net synthesis occurs 36-72 hours post-exercise, as represented in Figure 3. HSRT protocols utilize a 48-hour restitution period between training sessions, which may ensure sufficient restitution time compared to daily eccentric exercises (95). HSRT has shown increased

mechanical and morphological adaptational responses to high cyclic strain compared to moderate cyclic strain in healthy human Achilles tendons (96,97), but this has been questioned in a study in patients with patellar tendinopathy, which did not find a significant increase in the mechanical adaptations for the HSRT compared to moderate slow resistance training (5). In addition, time under tension also seems to be of importance. Two studies examined the mechanical and morphological adaptational responses to high cyclic strain compared to moderate cyclic strain in healthy human Achilles tendons, but with different contraction times (1 second concentric/1 second eccentric vs. 3 seconds concentric/3 seconds eccentric) (96,97). Both studies found a significant increase in mechanical adaptations, but only the study utilizing a slow contraction time demonstrated significant morphological adaptations (96). Thus, it seems that time under tension may also be an important aspect of HSRT. In addition, morphological tendon changes have been demonstrated following an intervention consisting of HSRT. A study by Kongsgaard et al. (98) found a 70% significant increase in fibril density, a 26% decrease in mean fibril area, and significant increases in fibril diameter distribution. This supports the notion that HSRT induces ECM normalization of the tendinopathic tendon.

Another important aspect is patient satisfaction, where a study reported higher patient satisfaction in favor of HSRT compared to eccentric training (70% versus 22%) (4); thus, patient preference also seems to support the use of HSRT.

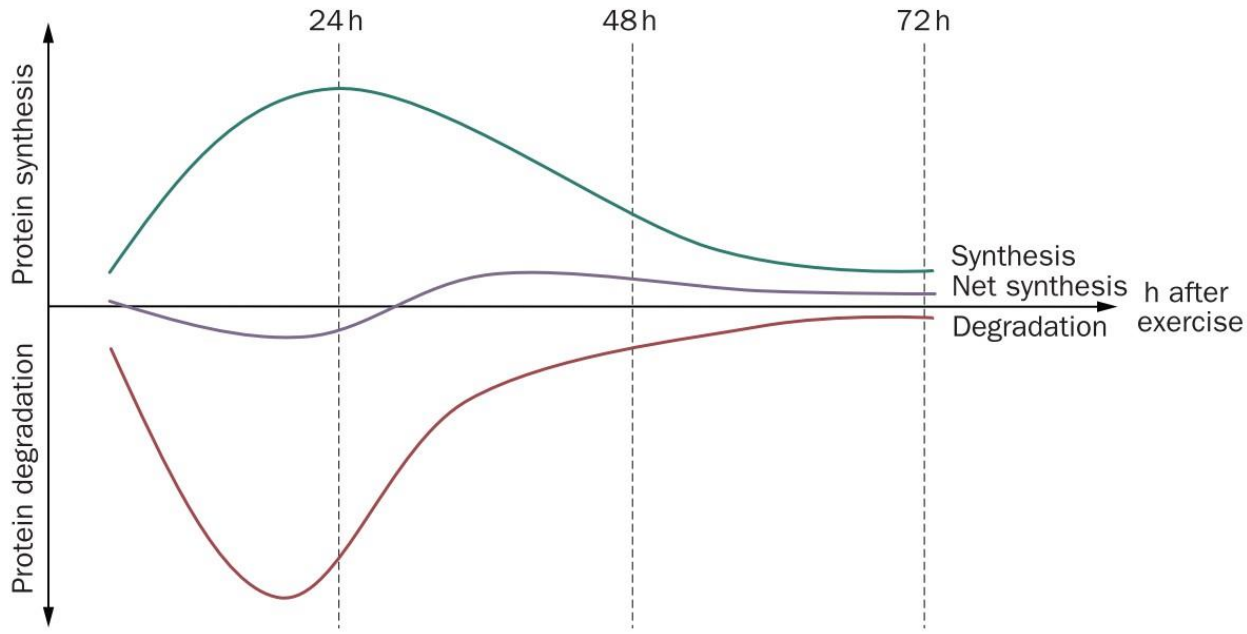


Figure 3: A representation of protein degradation/protein synthases and the tendons adaptation to mechanical stress from Magnusson et al. (23).

7.6 Blood Flow Restricted Training

7.6.1 Blood flow restriction training

Low-load blood flow restriction training (LL-BFRT) is also known as “Kaatsu training” or “Occlusion training” but is commonly referred to its abbreviation BFR training. LL-BFRT can be applied in multiple different settings, and can be applied during voluntary muscle contractions, during aerobic training, or as a passive treatment modality without exercise (99). LL-BFRT has gained increasing popularity in clinical practice as well as within research in the past few years (100). LL-BFRT has been demonstrated to induce a similar muscular hypertrophy response compared to heavy resistance training in two systematic reviews and meta-analyses (101,102); however, they demonstrated conflicting evidence regarding strength gains, where Lixandrao et al. (101) reported increased strength gains in favor of heavy resistance training and Grønfeldt et al. (102) reported no difference in strength gains between LL-BFRT and heavy resistance training. Additionally, LL-BFRT has also demonstrated significant clinical rehabilitative benefits in different musculoskeletal populations, e.g., anterior cruciate ligament reconstruction and knee or hip arthroscopy (103,104).

BRFT is a training modality using relatively low external loads where the arterial inflow is partially or fully restricted and the venous outflow is fully restricted in contracting muscles by using a (pneumatic) tourniquet cuff that exerts external forces at the most proximal region of the upper and/or lower limb, thus reducing inflow and outflow of blood (99,105). The reduction in adequate arterial blood inflow to the contracting muscles results in insufficient oxygen provision, which leads to a hypoxic environment within the restricted limb, while the fully restricted venous outflow results in a stacked blood pool within the capillaries (99).

In the literature, the amount of pressure applied using the (pneumatic) tourniquet cuff has been determined using either absolute or individualized relative external pressure. However, within recent years, there has been a shift towards using individualized relative external pressure (99). The reason is that many different factors can influence the amount of pressure needed to restrict arterial inflow and venous outflow. These factors can include extrinsic factors, such as the tourniquet cuff width, material, and positioning (seated vs. supine) and intrinsic factors, such as the size of the limb, blood pressure, and anatomical variances; thus, individualized relative pressure has been recommended (99,105). The amount of pressure required to completely cease blood flow to a limp is referred to as the total arterial occlusion pressure (AOP) (99). The pressure required for total AOP is then applied by using a percentage

during exercise. The current recommendation is to use a percentage of 40-80% of AOP, as some studies suggest that greater pressures may augment the cardiovascular response while also increasing the discomfort for the participants (106).

The external training load differs between studies, and some have used no external force when BFR has been used as a passive treatment modality (107,108). It is recommended that a relative training load of 20-40% of an individual's 1 repetition maximum (1-RM) is applied (109); however, some studies have utilized heavy loads (60-80% of 1-RM) (110,111). The range between 20-40% of 1-RM has been suggested as it likely optimizes muscle growth and strength; however, lower external loads are suggested to complement higher external pressures, and conversely, higher external loads are suggested to complement lower external pressures, but this is no absolute recommendation (99).

The most common and frequently applied protocol is a total of 75 repetitions spread out across four sets, where the first set is comprised of 30 repetitions and the following three sets are each 15 repetitions (99). However, in the literature, many have also applied a protocol of 3-5 sets to volitional failure (112,113). Usually, inter-set rest periods are between 30-60 seconds (109), and normally the tourniquet cuffs are inflated in a continuous fashion, but an intermittent fashioned rest period can also be applied (99). LL-BFRT is usually performed at a frequency of 2-4 times per week, similar to normal strength training, with progressive overload in order to induce strength increases and muscular hypertrophy (109). A higher frequency has also been applied, with training sessions twice daily (114,115). Lower frequencies are often applied throughout longer training periods (>3 weeks), whereas the higher frequency is used for shorter training periods (1-3 weeks) (99).

7.6.2 Blood flow restriction and tendinous tissue

It is hypothesized that LL-BFRT generates an ischemic and hypoxic milieu, which leads to high levels of metabolic stress that, together with the mechanical stress of exercise, lead to synergetic effects on the muscular and tendinous tissue (99,109). LL-BFRT has been theorized to activate other mechanisms for the induction of tissue growth, such as systemic hormone production, while the hypoxic milieu also improves the cross-linking and mechanical properties of collagen-rich tissues (116,117). This has recently been demonstrated in a systematic review and meta-analysis, where LL-BFRT was found to increase hormone levels, such as growth hormone (GH), when compared to conventional low-load exercise, and induce similar hormone responses compared to conventional heavy-load exercise (118). In turn, elevated blood levels of lactate and

GH may promote collagen production (119,120), while also stimulating the mechanical properties and morphology of the tendon (121). LL-BFRT may also alter the nitric oxide response to loading (122), which has been linked to tendon healing (123,124), possibly by attenuating the inflammatory response to facilitate extracellular matrix collagen synthesis (125,126). However, the exact mechanism is still not fully understood.

Studies investigating the effect of LL-BFRT on healthy tendons found that LL-BFRT and heavy resistance training induce comparable increases in both Achilles tendon and patellar tendon CSA (127–129). Likewise, the studies also found comparable mechanical increases in tendon mechanical properties, i.e., tendon stiffness (127,128). In tendinopathic tendons, only case studies have investigated a rehabilitation protocol consisting of LL-BFRT (130–132). In the case studies, they all found improvements of the clinical condition. In Sata et al. (132), there was a clinical improvement, and MRI T2 signal intensity was considerably reduced using a LL-BFRT protocol of 30% of 1-RM for 3 weeks. In Cuddeford et al. (131), there were improvements on the VISA-P, pain during sport, and the participants returned to sport in an in-season rehabilitation protocol. Similarly, Skovlund et al. (130) investigated LL-BFRT training in 7 patients with chronic unilateral patellar tendinopathy and also demonstrated clinical improvements and reduced resting PD activity after 3 weeks of intervention, comparable to the clinical response usually seen after 12 weeks of HSRT (4,5,76). Further, a recent scoping review stated that “preliminary evidence for beneficial effects of LL-BFRT on tendons and clinical outcomes is encouraging” and also encouraged future studies to investigate the clinical effects of LL-BFRT on tendon injuries (133).

8. AIM AND HYPOTHESES OF THE THESIS

8.1 Aims of the thesis

The overall aim of this thesis was to examine the rehabilitative effect of LL-BFRT vs. HSRT in elite and recreationally physically active males with chronic unilateral patellar tendinopathy on clinical and structural outcomes. In addition, this thesis also examined the current literature for hormone, immune, and oxidative stress responses following LL-BFRT compared to free flow resistance training to examine a theoretical framework for the application of LL-BFRT. Lastly, ultrasonography images of patellar tendons with unilateral patellar tendinopathy were compared

to their contralateral healthy tendons to examine the intra-rater reliability and structural differences between tendinopathic and healthy tendons.

Specific aim Study I

To examine a 12-week rehabilitation program of LL-BFRT vs. HSRT effects on clinical and structural outcomes at the short-term (3 and 6 weeks), mid-term (12 weeks; primary endpoint), and long-term (52 weeks) in elite and recreational male athletes with chronic unilateral patellar tendinopathy. Data from long-term follow-up are not included in this Ph.D. thesis, as it is still being analyzed at the deadline of submission. (Paper I)

Specific aim Study II

To evaluate the initial (<10 min post-exercise), intermediate (10-20 minutes post-exercise), and late (30+ minutes post-exercise) hormonal, immune, and oxidative stress responses following acute bouts of LL-BFRT compared to conventional heavy-load (HL) and low-load (LL) free-flow resistance exercise (FFRE) in healthy human adults. (Paper II)

Specific aim Study III

To investigate PD activity and tendon structure (tendon length and thickness) in males with symptomatic unilateral patellar tendinopathy compared to their asymptomatic tendon. Secondly, we aimed to examine the intra-rater reliability of the measurement performed for PD activity and tendon structures. Lastly, an exploratory quantification of the hypoechoic area in the whole tendon and at the apex of the patella was performed. (Paper III)

8.2 Hypotheses of the thesis

Study I

In study I, it was hypothesized that LL-BFRT would significantly reduce pain on the numerical pain rating scale (NPRS) during the single-leg decline squat (SLDS) test (primary outcome) compared to HSRT at 12-week (primary endpoint). In addition, it was hypothesized that LL-BFRT would demonstrate favorable clinical and structural outcomes compared to HSRT at short-term (3 and 6 weeks), mid-term (12 weeks), and long-term (52 weeks) follow-up.

Study III

In study III, it was hypothesized that the symptomatic tendon would be thicker at the proximal and mid part of the tendon but not the distal part of the tendon compared to the asymptomatic tendon. It was also hypothesized that all intra-rater reliability measurements would demonstrate a good-to-excellent reliability score.

9. MATERIAL AND METHODS

All data included in the three papers were collected at Bispebjerg-Frederiksberg Hospital between September 2020 and September 2023, except for some of the data in the ancillary study (Study III) that was collected between April 2017 and July 2018. An overview of the studies is presented in the flow chart (Figure 4).

In this section, the methodological considerations, and the application of these are discussed in the relevant sections. A more in-depth description of the methodological approaches can be found in the materials and methods section of each individual paper.

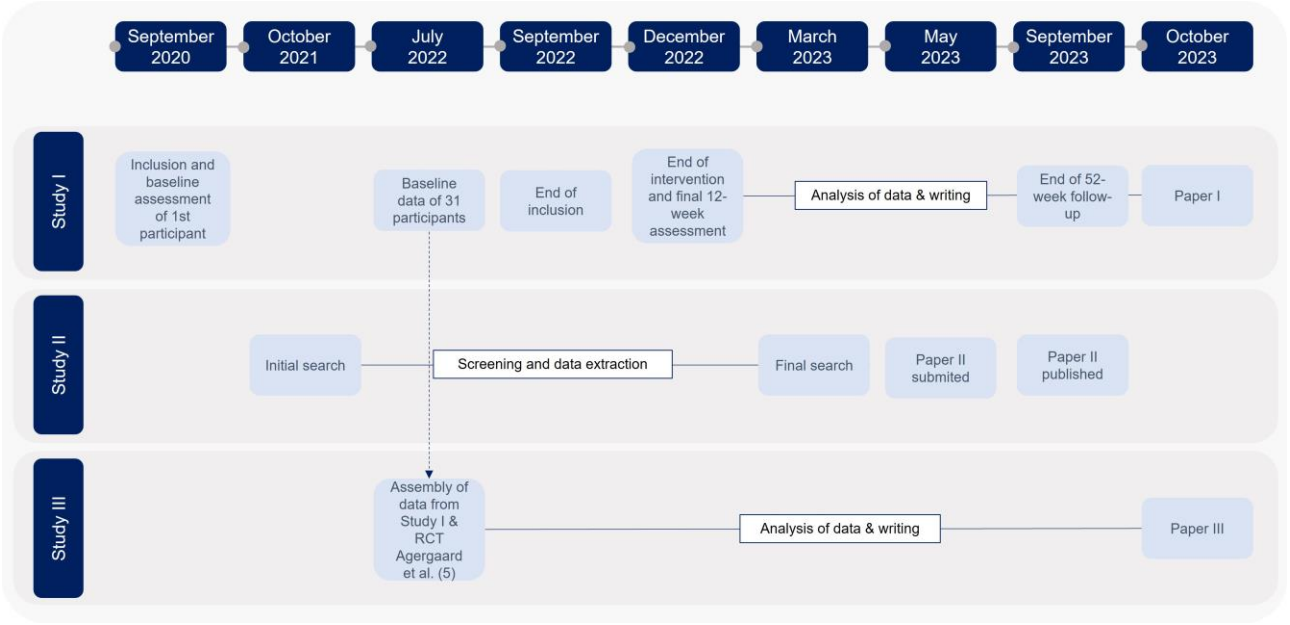


Figure 4: Flowchart demonstrating the timeline and overview of the three studies comprising this Ph.D. thesis.

9.1 Study design

9.1.1 Study I

The first study was designed as a prospective randomized clinical trial (RCT), where the outcome assessor was blinded to intervention allocation. The RCT was designed as a superiority trial with two parallel groups, where LL-BFRT was hypothesized to be superior to HSRT. The study was pre-registered at clinicaltrials.gov under the identifier: NCT04550013. Likewise, this study was reported to the Regional Ethics Committee for Medical Research (No. H-19039320) and the Danish Data Protection Agency (P-2019-551). We pre-registered our study at clinicaltrials.gov to increase the transparency of the study. Likewise, we also used the CONSORT reporting guidelines to increase the level of structure and transparency in reporting. To increase transparency further, we could have published our study protocol.

The primary endpoint was assessed 3-5 days following the 12-week rehabilitation protocol. We chose the 12-week endpoint to be able to compare our results with the current literature; however, tendons have a relatively low turnover rate, as mentioned previously (32). Thus, it could be discussed if a 12-week rehabilitation protocol is sufficient to induce structural adaptations in the patellar tendon. However, clinically relevant outcomes have been reported following a 12-week rehabilitation protocol. In addition, we included a 3-week test to compare results from the current RCT study to those from a previously conducted pilot study (130). Lastly, to provide insights into the long-term effects of the rehabilitation protocol, we included the final assessment at 52 weeks. Due to time restraints and logistical complications (allocation of equipment and physiotherapists to supervision, participant behavior, and adherence), we did not choose a longer lasting rehabilitation protocol.

9.1.2 Study II

The second study was designed as a systematic review and meta-analysis and utilized original research from randomized controlled trials, randomized crossover trials, non-randomized controlled trials, and non-randomized crossover trials. We chose to include all the abovementioned study types to provide an exhaustive synthesis of the current available data. Also, as the included data was objectively measured (blood and saliva samples), the study design may have little influence on the results. A sensitivity analysis was also performed based on study design to ensure the exclusion of the abovementioned factors. In the sensitivity analysis, synthesized data from only randomized controlled trials and randomized crossover trials were analyzed, and the sensitivity analysis did not change any of the results from the analysis. The

study was registered at PROSPERO (CRD42021276798) and followed the PRISMA guidelines to increase transparency and optimize reporting standards.

9.1.3 Study III

The third study was designed as an ancillary study based on US images from two RCT studies, where one has previously been published (5) and the other is data from study I. In this study, we included baseline demographic and US data from participants with symptomatic unilateral patellar tendinopathy. The two RCT studies were designed in a similar manner and utilized the same US settings and protocol. No ethical approval or data management approval was obtained for this study, as the original studies had obtained all relevant approvals.

The US settings and protocol were identical in the two studies, with the only variable changing being the operators. Both operators have experience with US examination of the lower limb and tendinopathic tendons, and studies have found good-to-excellent inter-rater reliability (56,134). This indicates that operator variances may be limited and further validates the pooling of data from the two studies.

9.2 Study population

9.2.1 Study I

Participants were included between September 2020 and September 2022 and were recruited from the outpatient clinic at the Institute of Sports Medicine Copenhagen and through advertisements on the internet and social media, such as Facebook and Instagram. We included a total of 36 participants with chronic unilateral patellar tendinopathy in the study. There was one dropout prior to the 6-week assessment. The participants were randomly allocated to either LL-BFRT or HSRT. We used a random procedure and stratified according to symptom duration (<12 months/≥ 12 months) and age (<35 years/≥ 35 years). This was done to ensure that groups were similar for these two variables. The sample size calculation was performed based on previous data (5) and using NPRS during the SLDS test to detect a 2-point minimal clinically important difference (MCID) between groups (135). In addition, we used an $\alpha = 0.05$ and a $\beta = 0.20$. Based on the sample size calculation, we estimated that we needed 16 participants in each group to detect a MCID between-group difference of 2 NPRS. We then accounted for a dropout rate of 10% and estimated that a total of 36 participants needed to be included in the study. Inclusion and exclusion criteria for Study I are presented in Table 1.

In Study I, we included male athletes with chronic (symptom duration ≥ 3 months) unilateral patellar tendinopathy. We decided only to include male participants due to different reasons: i) Previous studies have demonstrated that male and female tendons respond differently to training loads (14), which could confound our results when we had a relatively small pool of participants; ii) within recent years, the safety of LL-BFRT has been discussed within clinical practice and research, where some studies have discussed the possibility of increased risk of thrombosis (136,137). And as many females use some sort of contraception (e.g., oral contraception), which also increases the risk of thrombosis (138), we decided to exclude females. However, LL-BFRT has recently been deemed as safe to perform as normal strength training (139). Further, we chose to only include participants with unilateral patellar tendinopathy due to practical and scientific reasons. The practical reasons were that each participant was given one tourniquet cuff, and if each limb was to be exercised, it would have taken more time for the participants and the physiotherapist to complete and supervise the training sessions, and the physiotherapists would also use more time to assess individual AOP for each leg. In addition, we wanted to use a healthy contralateral leg as a control. Thereby, we could compare the tendinopathic tendon to the healthy tendon on various structural outcomes (e.g., thickness, hypoechoic area, patellar tendon volume). We thought this could provide valuable information on potential structural adaptations. Similarly, we only included participants with symptom duration of more than three months to ensure tendinopathic chronicity in the tendon. No limitation was set regarding the length of symptom duration, as we stratified for symptom duration and a recent study in Achilles tendinopathy suggests that symptom duration does not seem to influence clinical outcome (140).

Only participants with patellar tendinopathy located at the apex of the patella were included in the study. This was chosen as quadriceps and distal patellar tendinopathy often present with other coexisting conditions (51). Thus, quadriceps and distal patellar tendinopathy may present with different clinical features and management subtleties that could confound the clinical effect of the loading-based rehabilitation protocol.

Other inclusion criteria included pain of ≥ 4 during physical activity and local tenderness during palpation corresponding to the painful area at the apex patella. We only included participants with ≥4 pain (NPRS) during physical activity. This was chosen as an inclusion criterion to ensure a certain level of pain and functional limitation, thereby increasing the potential for achieving an effect of the rehabilitation protocol, as it could be speculated that participants with clinical patellar tendinopathy but with very limited pain and functional limitations would have limited benefits of the rehabilitation protocol. However, this could reduce

the external validity of the study as a population within the patient population was not included in this study, as also demonstrated by the relatively high number of participants screened and assessed for eligibility in this study.

Lastly, patellar tendinopathy should be verified by US examination with thickening of the anterior-proximal part at the patellar tendon (>1 mm compared to mid-tendon) and neovascularization visualized by Power Doppler and/or hypoechoic area. This was chosen to ensure confirmation of the clinical diagnosis of patellar tendinopathy, and to exclude any coexisting conditions that could affect the clinical condition. Likewise, a study reported a high degree of misdiagnosis if patellar tendinopathy is only diagnosed on patient history and clinical examination (55).

Table 1 – Inclusion and exclusion criteria for the Study I

Inclusion	Exclusion
Male athletes	Cardiovascular and metabolic diseases
Age 18-70 years	Smoking
Unilateral patellar tendinopathy	Previous surgery or trauma to the knee joint with an effect on the presenting clinical condition
Symptoms for ≥3 months	Enrolled in a resistance-based rehabilitation program for the affected patellar tendon within the previous 3 months
≥4 on the NPRS during physical activity	Injections with corticosteroid within the previous 12 months
Tenderness to palpation corresponding to the painful area	
Increased tendon thickness and power Doppler activity and/or hypoechoic area by ultrasonography examination	

Table of inclusion and exclusion criteria for Study I. NPRS, Numerical pain rating scale.

9.2.2 Study II

The systematic literature search was performed at Bispebjerg and Frederiksberg Hospital between September 2021 and March 2023, where the latest update was performed. The inclusion criteria were healthy males and females with or without previous training experience, aged between 18-55 years, and with an average body mass index (BMI) between 18.5-30 kg/m^2. We excluded studies performed in patients with any reported disease, operative treatments, or known

diagnoses. Inclusion and exclusion criteria for Study II are presented in Table 2.

We only included studies performed in a young-to-middle-aged population, as hormone and immune levels seem to decrease with age (141,142). We could have included all studies and performed sub-group analysis based on age; however, we expected a low number of hits. Similarly, obesity also affects the hormone balance and decreases the production of hormones, such as GH, estrogen, and testosterone (143,144). Therefore, we only included studies where participants had a mean BMI ranging from 18.5-30. Similarly, a patient population may have alterations in their hormone, immune, and oxidative stress levels due to, for example, medical treatment or post-operative responses (145). Lastly, the inclusion and exclusion criteria were also chosen to make a more homogenous population, as it may have been difficult to draw any conclusions in a very heterogenous population.

We chose to only investigate the acute hormonal, immune, and oxidative stress responses. Thus, these results may not be transferable to a continuous, long-term LL-BFRT protocol where physiological adaptations and acclimatization may occur and responses may diminish over time.

Table 2 – Inclusion and exclusion criteria for the systematic review and meta-analysis

	Inclusion	Exclusion
Population	Healthy trained and untrained adults >18 - <55 years of age BMI >18.5 - <30	Middle aged >55 years of age Populations with any cardiovascular, metabolic, or musculoskeletal diagnosis, any history of operative treatment, animal studies
Intervention	Low-Load Blood flow restricted resistance training (LL-BFRRE)	All other interventions
Comparator	Free flow conventional heavy-load resistance training (HL-FFRE) or free flow low-load resistance exercise (LL-FFRE)	Other training interventions e.g., vibration, electrical stimulation
Outcome	Hormonal, immune, and oxidative stress responses measured by blood, saliva, or muscle biopsy sampling Initial (<10 minutes post-exercise), intermediate (10-20 minutes post-exercise) and late (30+ minutes post-exercise)	Outcome of interest not reported
Study design	Randomized controlled trials, randomized crossover trials, non-randomized controlled trials, non-randomized crossover trials	No comparator/control group

Table of inclusion and exclusion criteria for studies included in Study II. BMI, body mass index. LL-BFRRE = LL-BFRT. The table is duplicated from Hjortshoej et al. (118) and used under the CC BY-NC 3.0 license.

9.2.3 Study III

This ancillary study was performed on baseline data from Study I and a previously published RCT study (5). A total of 57 male participants were included across the two studies, where baseline data from 26 participants was included from Agergaard et al. (5) and 31 participants were included from Study I.

In Agergaard et al. (5), the inclusion criteria were male athletes aged 20-45 with chronic (>3 month) patellar tendinopathy. The clinical diagnosis was confirmed by ultrasonography in the form of tendon swelling (1 mm difference compared to mid-tendon) and hypoechoic appearance with power doppler activity within the tendon. The exclusion criteria

were patellar tendinopathy >12 months, previous knee surgery, other knee joint diagnoses, diabetes or arthritis, previous corticosteroid injection for patellar tendinopathy, and smoking.

In study I, the inclusion criteria were as described in a previous section (section 9.2.1). The inclusion criteria were fairly similar between the two studies. However, there are some limitations with the applied inclusion and exclusion criteria. First, these studies only included male participants. The results presented in this study may not be transferable to a female population, although studies have found similar tendon thickness between sexes (146,147). Secondly, one study only included participants with symptom duration between 3 and 12 months (5), whereas the second study, study I, included participants with symptom duration for more than 3 months. In study I, the median symptom duration was 9.5 and 10 months for the LL-BFRT and HSRT group, respectively, and the participant with the longest symptom duration had had patellar tendinopathy for 36 months. Thus, these results are on a population with relatively short symptom duration, and they may not be transferable to a patient population with longer-lasting symptoms, e.g., several years.

The US settings and protocol were identical in the two studies, with the only changing variable being the operators. Both operators have experience with US examination of tendinopathic patellar tendons, and studies have found good-to-excellent inter-rater reliability for experienced operators (56,134). This indicates that operator variances may be limited and further validates the pooling of data from the two studies. A further limitation of Study III is that the US examinations were not performed for the purpose of evaluating tendon structure. Thus, some images, such as whole tendon and ROI echogenicity, was not obtained in order to evaluate echogenicity in the tendon. This is a limitation of Study III, as it may not truly reflect the echogenicity in tendinopathic patellar tendons. However, we chose to include whole tendon and ROI echogenicity as an exploratory analysis to see if it was feasible to perform and provide insights to the echogenicity following a 12-week loading-based rehabilitation protocol.

9.3 Overview of procedures and blinding (Study I, II, and III)

9.3.1 Overview of procedures

A flow of the procedures for each participant is illustrated in Figure 5. Participants, when cleared through a telephone interview, were assessed by a physician to be deemed eligible for study participation. Outcome assessments were performed at baseline, 3, 6, and 12 weeks with a 52-week follow-up (52-week follow-up is not included, as analysis of the data was not completed

prior to the deadline for submitting the thesis). The examination order was identical on all test days, and the participants were instructed not to perform physical activity 24 hours prior to the test days. Participants were asked to refrain from performing physical activity 24 hours prior to the test days in order to standardize the protocol between participants and groups. All US examinations were performed following a 10-minute seated rest period where participants filled out questionnaires. This was also performed to standardize test conditions as, for example, PD activity may be influenced by physical activity (148).

Figure 5: Overview of procedures in study I. SLDS, single-leg decline squat. VISA-P, Victorian Institute Sports Assessment – Patella. PPT, pain pressure threshold. iMVC, isometric maximal voluntary contraction. PD, power Doppler. MRI, magnetic resonance imaging. CSA, cross-sectional area. Structure indicates tendon thickness and echogenicity.

9.3.2 Blinding (Study I)

Blinding is an important aspect when conducting clinical research, as bias may otherwise influence the results, intentionally or unintentionally (149). In Study I, the primary outcome assessor was blinded to treatment allocation to minimize the risk of detection bias. In contrast, due to the nature of the study and the intervention program, it was not possible to blind the physiotherapists supervising the weekly session as well as blinding the participants for their treatment allocation. To minimize the risk of bias, the physiotherapists were instructed and received written information to ensure no favoritism of the treatment modalities. Likewise, participants, when presented to the study, received similar information regardless of their group

allocation to minimize bias. To minimize bias when performing and analyzing US and MRI obtained images and videos, the operators were only blinded for group allocation, as it was not possible to blind for time points. The outcome assessors performing image and video analyses were blinded to group allocation and time points.

9.4 Intervention protocol (Study I)

9.4.1. Training protocol

In this study, we aimed to investigate the rehabilitative effects of two different loading regimes based on either LL-BFRT or HSRT. The first study to investigate HSRT in a population with patellar tendinopathy used a training protocol consisting of three bilateral exercises: squat, leg press, and hack squat (4). However, in a more recent study, a different training protocol inspired by the original protocol was used and demonstrated similar clinical improvements (5). The training protocol consisted of two exercises: bilateral leg press and unilateral knee extension for both legs. We chose to use the protocol by Agergaard et al. (5) as leg press and knee extension are less technical exercises to perform and to reduce the training time for the participants and the physiotherapist supervising the weekly training session.

HSRT has demonstrated both clinical, mechanical, and morphological improvements and has increased in popularity, as described previously. At Bispebjerg and Frederiksberg Hospital, HSRT is the standard treatment in the rehabilitation of patellar tendinopathy, and as such, it was chosen as the loading-based control protocol in this Ph.D. thesis. Also, a recent study did not demonstrate any improvements in a “wait-and-see” control group (77), which has also previously been advised against in a systematic review (150). Therefore, we did not include a “wait-and-see” control group.

LL-BFRT has been investigated in other clinical populations (e.g., rehabilitation of ACL injuries and total knee arthroplasty) and has demonstrated significant clinical improvement (103). LL-BFRT has not been investigated in RCTs in the rehabilitation of tendinopathy; however, several case studies have investigated the effect of LL-BFRT in patellar tendinopathy (130–132). In general, the studies found significant improvements following exercises with LL-BFRT in tendinopathic patellar tendons. This study was primarily based on the novel results of Skovlund et al. (130); however, we made some alterations to the intervention program. Firstly, we chose to perform a 12-week rehabilitation period, which has been utilized in the current literature of patellar tendinopathy (4,5,76), thereby allowing for comparison of our results to

those of other studies. Secondly, we chose to apply a different total volume (sets x repetitions) compared to Skovlund et al. (130), where a protocol of 6 sets (30, 25, 20, 15, 10, 5 repetitions) was utilized. In contrast, we utilized a protocol of 4 sets (30, 15, 15, 15 repetitions). We chose a different total volume as the most commonly applied LL-BFRT protocol in the literature consists of four sets (30, 15, 15, 15 repetitions), and as we wanted to compare LL-BFRT to HSRT (99). Thirdly, we chose to use an individualized AOP for tourniquet cuff pressure. It has been recommended to use the individualized AOP as absolute pressures do not account for individual variances, such as limb circumference and blood pressure (99). Therefore, to account for individual variances and to standardize the training tourniquet cuff pressure, we applied the individualized AOP. Exercises are presented in Figure 6 and an overview of the training progression is presented in Table 3.

Figure 6: Depiction of the exercises performed with blood flow restriction in the LL-BFRT group. A) Leg press B) Knee extension. Both exercises where only performed on the injured leg.

The HSRT has demonstrated a significant clinically relevant effect in the treatment of patellar tendinopathy (4,5,76,93,94). This program was modified from the protocol utilized by Agergaard et al. (5). We included one extra set of each exercise in the HSRT group to equalize volume between groups. Exercises are demonstrated in Figure 7 and an overview of training progression is presented in Table 3. In the HSRT group, exercises were performed in a slow, controlled

manner with a total contraction time of six seconds (3 seconds concentric phase/3 seconds eccentric phase) as compared to the LL-BFRT group, which performed the exercises in a controlled manner with a total contraction time of three seconds (1.5 seconds concentric phase/1.5 seconds eccentric phase), but the total time-under-tension was approximately similar between groups.

Figure 7: Depiction of the exercises performed in HSRT group. A) Leg press B) Knee extension. Both exercises where only performed on the injured leg.

One session per week was supervised by experienced sports physiotherapists and performed at Bispebjerg-Frederiksberg Hospital, whereas the two individual training sessions were performed at a commercial training center. We chose one weekly supervised training session to increase compliance, ensure correct performance of the exercises, and ensure correct application of the tourniquet cuffs for the LL-BFRT group. We could have supervised all training sessions; however, due to practical reasons, such as limited time slots for the exercise machines, this was not possible. Additionally, if we had chosen three supervised training sessions per week, compliance may have dropped since not all participants would have been able to schedule three fixed training slots per week. This also meant that 5-RM tests and the supervised training sessions were performed on different exercise machines compared to the ones used by the participants in the commercial fitness center. These differences could influence the loads applied at the supervised training session compared to the independent training sessions due to the

different mechanics of individual machines. We could have performed all tests and training sessions (supervised and independent training sessions) in the commercial fitness center to ensure similarity between tests and training; however, this would have been logistically difficult as AOP measurements were performed using a US machine and not possible due to time constraints from the physiotherapists.

Table 3 – Overview of training progression for LL-BFRT and HSRT

Weeks	1	2	3	4	5	6-8	9-12
HSRT							
Number of sets	4	4	4	4	4	4	4
Repetitions	15	12	12	10	10	8	6
% of 1-RM	55	65	65	70	70	75	80
LL-BFRT							
Number of sets	4	4	4	4	4	4	4
Repetitions	75	75	75	75	75	75	75
% of 1-RM	30	30	30	30	30	30	30
% AOP	50	60	60	70	70	70	80

Table 3 presents the planned progression for the LL-BFRT and the HSRT rehabilitation program. LL-BFRT performed a total of 75 repetition structured as 30 repetitions in the 1st set and 15 repetitions in the 2nd – 4th set. LL-BFRT, Low-load blood flow restriction training; HSRT, Heavy-slow resistance training; AOP%, Arterial occlusion pressure percentage. The table is duplicated from Paper I.

9.4.2 Determination of 5-repetitions maximum and arterial occlusion pressure

During the 12-week intervention period, 5-RM and individual AOP were assessed at baseline and the start of every three weeks (baseline, 4-week, 7-week, and 10-week). These tests were performed to adjust for strength progression, and acclimatization to cuff pressure, e.g., decreased blood pressure and quadriceps muscle hypertrophy. A protocol was developed, and training sessions were conducted to ensure uniformity between the two physiotherapists.

The individual AOP was assessed after the participant had a 10-minute rest and prior to any warm-up. The participants were placed on the treatment table with the hip and knee in 90° flexion. A pneumatic tourniquet cuff was placed most proximally on the thigh and inflated to 100 mmHg. The cuff was incrementally increased by 10 mmHg until the popliteal artery was no longer visible on the US examination. We chose to perform the AOP assessment in a seated position instead of in a supine position, as the seated position resembled the position in the training exercises, and position seems to influence the AOP (151). The AOP is the absolute

pressure needed to totally occlude arterial blood flow and was then used to calculate the participants' AOP% throughout the study.

The 5-RM test was performed after a 5-minute warm-up on an ergonomic bicycle. The 5-RM tests started with the leg press followed by the knee extension, and both exercises were performed in a controlled manner. The participants were given a maximum of 4 attempts with a 3-minute inter-test rest period to avoid exhaustion. The participant's 5-RM was then used to calculate their 1-RM. The 5-RM tests were performed at a controlled tempo (1.5 seconds concentric phase/1.5 seconds eccentric phase), which is in contrast to the slow, controlled repetition tempo of the HSRT group. The repetition tempo has an impact on the relative submaximal lifting capacity, and as such, the load obtained during the 5-RM tests may not be transferable to the slow, controlled repetition tempo of the HSRT group (152). This is also applicable for the LL-BFRT group, where the restriction of blood flow may also impact the relative submaximal lifting capacity.

9.4.3 Pain during exercise, sport and physical activity

During the intervention period, a pain monitoring model was used. Participants were allowed to continue their participation in sports and physical activity if pain did not exceed 3 on the NPRS score during or after sport/physical activity. The pain monitoring model has previously been applied in studies investigating patellar and Achilles tendinopathy (5,153,154). However, a third study did not find any effect of an in-season loading-based rehabilitation protocol utilizing the pain monitoring model performed in volleyball players with patellar tendinopathy (155). In addition, pain during or after performing the rehabilitation protocol was allowed up to 5 on the NPRS, and participants were informed that tendon pain was normal; however, it should subside back to normal after completing the exercises. If the pain remained for more than six hours after completing the rehabilitation protocol, participants were instructed to reduce the load. We chose this pain monitoring model because pain for more than six hours probably does not indicate beneficial mechanical loading of the tendon but instead exacerbation of the clinical condition.

9.4.4 Training compliance

Training compliance was registered using an electronic training diary. The participants received an email at the start of every training week containing a direct link to REDCap, where sets, repetitions, and external loads were registered.

9.5 Clinical outcomes (Study I)

9.5.1 Primary outcome – Single-leg decline squat

The SLDS test is a functional clinical test used to assess subjective pain in patients with patellar tendinopathy using the NPRS (0 is no pain and 10 is the worst imaginable pain). In the ICON consensus statement of 2019, they recommended that functional tests should be included in future studies (156). We chose to include the SLDS test as it has demonstrated good test-retest reliability (157), and it has been used as a clinical functional test in several studies (5). Due to the functionality of the SLDS test, and the psychometric issues of the VISA-P (see section below), we decided to use the SLDS test as our primary outcome, with a 2-point NPRS difference considered a MCID.

In the present study, the SLDS test was performed without any warm-up, which is in contrast to other studies (5). This might influence the comparison with previous results, however, this approach was chosen to ensure that exercise-induced hypoalgesia did not affect the score (158). Prior to performing the SLDS test, the participants received instructions and the assessor demonstrated how to perform and score the test. In brief, the participants were instructed to stand on a 25° decline board on one leg, stabilize the hip, keep the trunk vertical, and keep the arms akimbo during the whole test. The heel was to be in contact with the board at all times, and the knee should follow the foot. When ready, the participants performed a 50° knee flexion and returned back to full extension at their own selected pace. The participants were then asked to score their tendon pain on the NPRS. The participants always started with the asymptomatic leg to familiarize themselves with the test before performing the SLDS test on the symptomatic leg. A total of two attempts were performed with a 2-minute seated rest between each attempt, and each attempt was scored on the NPRS. The mean of the two attempts on the symptomatic leg was then used for further analysis. The SLDS test is presented in Figure 8.

There are some limitations to the SLDS test. Firstly, the MCID of 2 points on the NPRS applied in this study was demonstrated in a population with musculoskeletal injuries, predominantly back injuries (135). Thus, the applied MCID of 2 points on the NPRS may not be applicable to this population. Secondly, there may be both significant floor and ceiling effects. None of the participants scored 10 at any time point during the study, and six participants scored 0 on the SLDS test at 12-week, but their VISA-P score ranged from 57 to 100, which may indicate both ceiling and floor effects, respectively. Thirdly, the SLDS test requires technique and balance to perform, and there may be a significant familiarization period before performing the SLDS test optimally. Lastly, participants may experience a relief in pain during repeated

loading due to the warm-up effect, which is a common characteristic in patients with patellar tendinopathy.

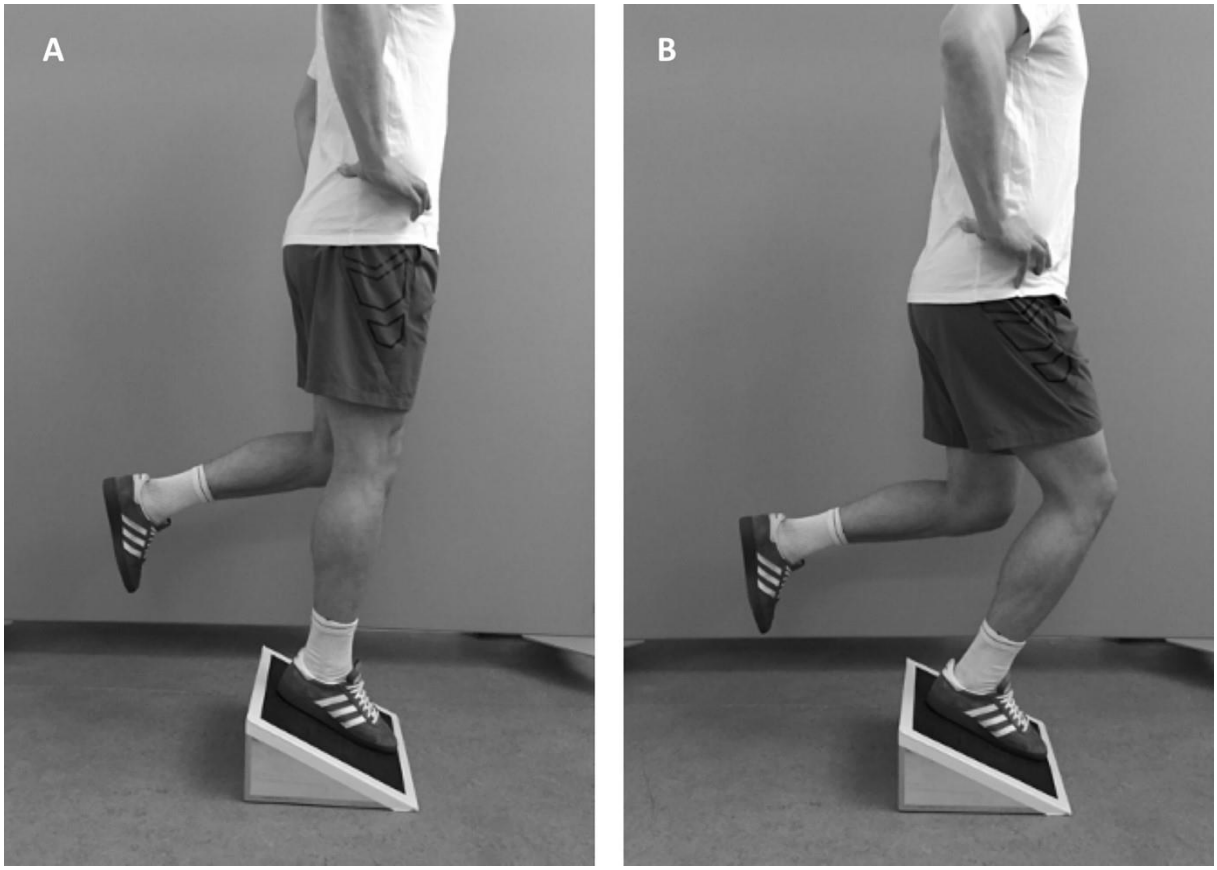


Figure 8: Illustration of the single-leg decline squat (SLDS) test. A) is the starting position of the SLDS test and B) is the end position of the SLDS test.

9.5.2 Patient reported outcome measure – Victorian Institute of Spots Assessment - Patella

The Victorian Institute of Spots Assessment-Patella questionnaire (VISA-P) is a patient reported outcome measure (PROM) used to assess pain and function of the patellar tendon in patients with patellar tendinopathy (159). The VISA-P is a PROM with eight questions regarding pain, function, and sports participation and has been recommended by the 2019 consensus statement (156). The use of PROMs in clinical trials has increased over time (160,161), and has been recommended to be included in studies by regulatory bodies as PROMs may assist clinicians and patients to select the best treatment, enhance the understanding of patients' experiences, and improve future methodology in clinical trials (162). The VISA-P has been translated into several languages and has demonstrated acceptable cross-cultural adaptation (163–166). In addition, the VISA-P demonstrated sufficient reliability, measurement error, construct validity, and

responsiveness with moderate-to-high quality evidence (167,168), however, recent studies have questioned the validity of the VISA questionnaires for Achilles and patellar tendinopathy (169,170). In addition, working with the VISA-P within its intended population, we and the patients experienced several issues, such as a time element when answering questions 7 and 8. Due to these issues, we decided to use the VISA-P as a secondary outcome in this study, as it is the recommended PROM in patients with patellar tendinopathy. Also, since it is the primary PROM in patellar tendinopathy research, most studies have included it as an outcome. We therefore included it to enable comparison between studies.

The VISA-P was completed prior to any paraclinical and clinical assessments (except magnetic resonance imaging) so as not to influence their score. The VISA-P was administered in paper form, and participants were briefly guided through the questionnaire by the primary investigator but answered the questionnaire without any assistance. This was done to minimize the assessors influence on the participants answers.

9.5.3 Pain pressure threshold

In patients with patellar tendinopathy, tendon tenderness during manual palpation is a clinical hallmark and is often located at the inferior pole of the patella (51). However, it may be difficult to standardize and quantify pressure using manual palpation when evaluating the patient's pain pressure threshold (PPT). Thus, the pain pressure algometer has been proposed as an alternative to quantify and standardize the measurement. Two studies have demonstrated that the pain pressure algometer is a feasible and reliable tool when evaluating PPT in patients with patellar tendinopathy (171,172).

In the present study, PPT was assessed using a handheld pain algometer (Algometer Type II; Somedic AB, Sollentuna, Sweden) with a 1 cm^2 probe. The probe was placed perpendicular to the skin, and pressure was increased at a rate of 30 KPa/s. To prevent adverse effects, such as soft tissue damage, a maximum pressure of 1000 KPa/s was applied. The PPT was assessed at four different locations on the symptomatic side and three different locations on the asymptomatic side. The locations were the most painful area (MPA), which was only performed on the symptomatic leg, the free patellar tendon just distally from the apex patella (AP), the muscle belly of the tibialis anterior (TA), and the muscle belly of the extensor carpi radialis brevis (ECR). We chose these four locations as they have previously been used in the literature (173), and we chose the ECR to assess if the potential effects on PPT were peripheral or systematic. Two consecutive tests were performed at each site, with a 1-minute rest

in between tests. The mean of the two tests was used for further analysis. PPT was performed following the SLDS test (primary outcome) but before isometric strength measurements. The participants were informed in the same manner at each time point to limit bias and enhance their comprehension of the test. This was done as a study demonstrated that verbal information may alter the PPT response in healthy participants (174), and as such, a standard information protocol was established.

In this study, we chose to employ the pain pressure algometer in order to assess the PPT throughout a training intervention protocol that has previously been done in a randomized crossover trial (173), although several limitations have to be considered. Firstly, the test seems to be highly operator-dependent, as there seems to be a learning curve in administering the correct pressure and operating the device. Also, it seems highly affected by participants familiarizing themselves with the test, as it may be difficult to comprehend due to the subjective nature of pain, e.g., what is pain and when is it pain? Secondly, there seems to be a large variation in the test's scores (171), and therefore it could be difficult to evaluate longitudinal data on PPT. Lastly, the test measured mechanical stimuli (pressure). Although mechanical stimuli (manual pressure) are a hallmark of patellar tendinopathy, it may not accurately reflect the pain patients experience during loading-based activities.

9.5.4 Isometric maximal voluntary contraction of the quadriceps muscles

Isometric maximal voluntary contraction (iMVC) of the quadriceps muscle was performed to assess potential strength gains in the two intervention groups. iMVC has demonstrated excellent intra-rater, inter-rater, and test-retest reliability in a healthy population (175,176).

In the study, participants were positioned with 90° flexion in the hip and knee and a straight back in a custom-made rig. The participants were strapped to the rig with their hands placed in their lap, and a stiff metal rod was attached to their ankle. Using a wireless transmitter (8-channel TeleMyo 2400T G2 Telemetry System), force recordings were captured using a MyoResearch XP Master Edition Version 1.07 (Noraxon). A total of 4 trials were performed on each leg, with a 2-minute rest between each trial. Each trial lasted for approximately 5 seconds with maximal effort. The length of the tibia was measured to estimate the maximal knee extensor torque (peak force x tibia length).

We chose to perform this as the last test on each test day. This was done so the iMVC would not influence the results from the other clinical and structural tests. In contrast, fatigue could be a factor when performing this test, as the participants had performed the SLDS

test prior to this. In addition, iMVC may not correctly translate muscle strength gains obtained by dynamic strength training exercises (177). Lastly, pain or pain expectation could potentially influence the result, as some participants may not provide maximum effort due to pain or fear of pain.

9.6 Structural outcomes (Study I and III)

9.6.1 Ultrasonography imaging

The same protocol and settings were utilized in Study I and Study III for US examination of the tendon structure and will be outlined in brief. All US images were captured using a HI VISION Ascendus ultrasound machine (Hitachi Medical Systems). The examinations were performed by the same operator in Study I and the same two operators in Study III, and both studies utilized the same protocol and US settings. The examination consisted of two protocols capturing B-mode (grey-scale) images and PD video. Participants were instructed to refrain from strenuous physical activity 24 hours prior to the US examination.

The B-mode images were captured with the participants in a seated position with a straight back and the hips and knees in 90° flexion. We chose to measure the tendon thickness with the participant in a seated position to induce a pull on the tendon so that it is stretched. In a relaxed tendon, the tendon would “fold”, thus making any length or thickness measurements difficult to perform. An 8-cm probe (EUP-L53L, Hitachi Medical Systems) held perpendicular to the skin was used, and for the US settings, the depth was set to 4.5 cm, a dynamic range of 70, and a gain of 20. Images were captured where the tendon was visually thickest, and both the patella and the tibiae tubercle were visible in the image. A total of two images were captured at each leg, with the probe removed between each image.

The PD videos were captured with the participant in a supine position and with a straight and completely relaxed knee. For the examination of PD activity, we chose a completely relaxed knee, as a study has demonstrated that PD is less visible on stretched tendons compared to relaxed tendons (178). A 4-cm probe (EUP-L75, Hitachi Medical Systems) was used to locate the area with the most PD activity in the sagittal plane. When located, PD activity was captured by recording a 4-second sine-loop. A standardized setting for all measurements was utilized, with a fixed depth of 2.0 cm, a dynamic range of 70, a color doppler frequency of 10 MHz, a pulse repetition frequency of 250 Hz, and a gain of 37.

9.6.2 Analysis of ultrasonography images and videos

The same protocol for assessing PD activity and tendon structure was applied in both study I and study III. Tendon structure was assessed by the same assessor in both study I and study III, whereas two different assessors assessed the PD activity but used the same protocol. In study I, tendon structure and PD activity were assessed at baseline, 3, 6, and 12 weeks. In study III, only baseline data from the two RCTs was assessed.

Tendon structure was defined as tendon length, tendon thickness, and tendon echogenicity. Tendon length was measured from the apex patellar to the insertion at the tibiae tubercle. Tendon thickness was measured at 0.5 cm distally from the apex patella (proximal), the middle of the tendon length (mid), and 0.5 cm proximally from the insertion at the tibiae tubercle (distal). We chose to measure at 0.5 cm as previous studies have used this site, thus enabling comparison between studies (4,5), and also as tendinopathic patellar tendon thickness seems to be most pronounced roughly 0.5 cm from the apex of the patella (56). In addition, the whole tendon echogenicity, and the echogenicity for the region of interest (ROI) were evaluated, where the ROI was defined as the injury site at the apex patella. A blinded assessor performed all measurements in Fiji ImageJ (Version 1.53; National Institutes of Health) using a custom-made macro. The average value between the two B-mode images was used for further analysis. To increase the standardization of tendon structure assessment, a protocol was developed. Similarly, the assessor has previously undergone training, and it was the same assessor that performed the measurement in Study I and Study III.

For PD activity, a blinded assessor completed all assessments in Fiji ImageJ (Version 1.53; National Institutes of Health) and installed a custom-made macro to identify the frame in each video with the most PD activity. Each frame was manually evaluated, and only PD within the tendon proper was included. PD outside the tendon and PD subjectively evaluated as noise were excluded. The frame with the most PD activity was used for further analysis. A representation of tendon structure and PD activity is presented in Figure 9.

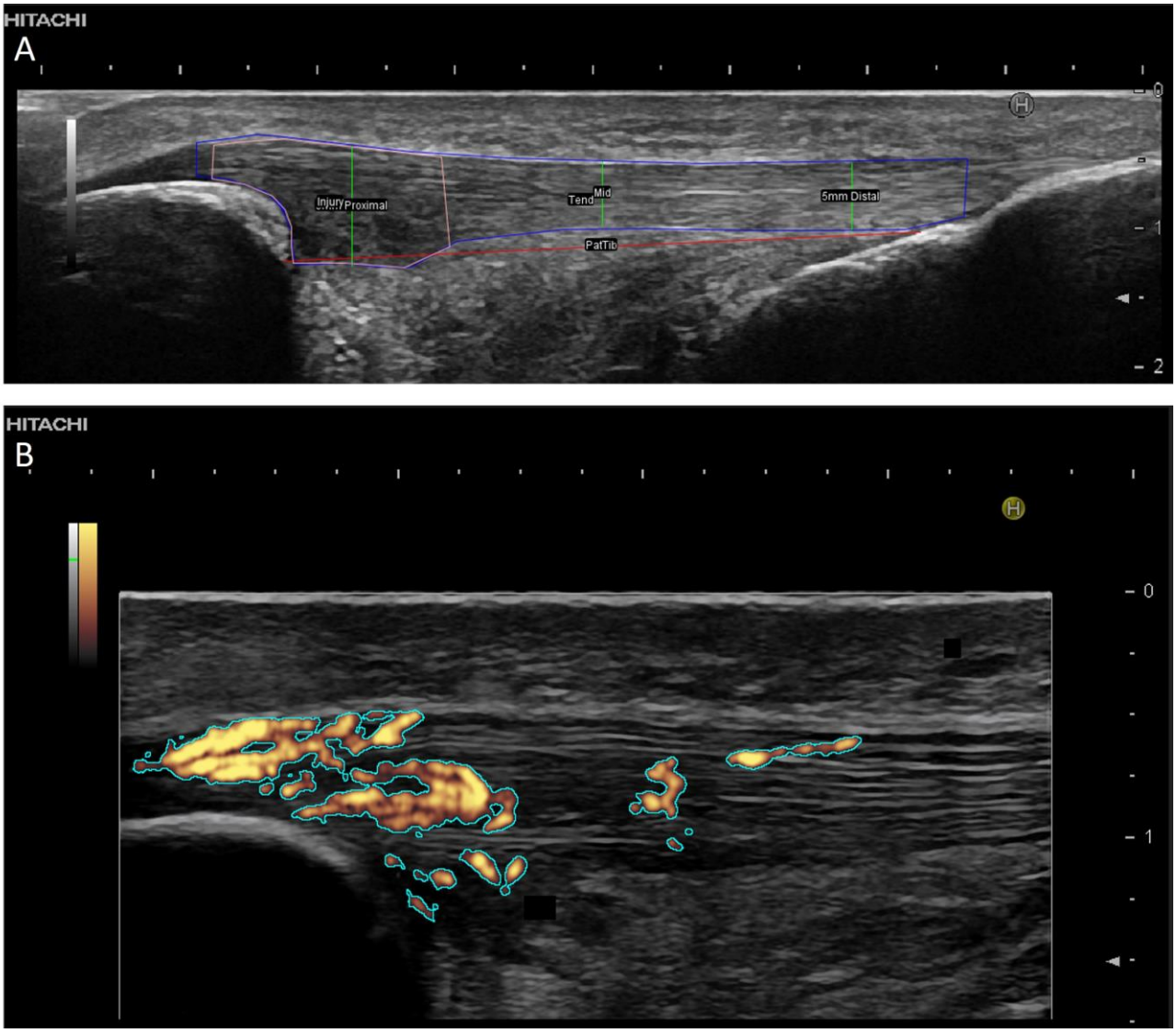


Figure 9: A) Demonstrates different sites measured using US imaging in the symptomatic tendon in Study I and Study III. The red line (PatTib) indicates the tendon length. The green lines (5 mm Proximal, Mid, 5mm Distal) are the measurement sites for tendon thickness based on tendon length. The blue outline indicates whole tendon echogenicity, and the grey outline indicates echogenicity in the region of interest measured at the injury site only. B) Demonstrates PD activity measured in the symptomatic tendon. Only PD activity within the tendon was included in the analysis. For both A and B, the same protocol was applied for the asymptomatic tendon. The figure is modified from Paper III. The figure is used under the CC BY-NC 3.0 license and published in Hjortshoej et al. (179).

9.6.3 Magnetic resonance imaging

In Study I, magnetic resonance imaging (MRI) was performed at baseline and at the end of the 12-week rehabilitation protocol. The MRI was performed in a Phillips Ingenia Ambition 1.5T scanner (software version 5.6.1.2, Eindhoven, The Netherlands). The participants were placed in a supine position with their legs closely positioned together by a strap, and their feet placed against a plastic foot plate. A coronal isotropic 3D T1 weighted sequence was performed starting

at the tibiae tubercle and as proximally as possible to ensure capture of the quadriceps muscle. These images were used to quantify the quadriceps cross sectional area (CSA) and the patellar tendon volume. We chose to measure patellar tendon volume, as the tendon is conical-shaped that tapers towards the tibia tubercle (8,9). Therefore, CSA measurements may not accurately reflect the patellar tendon, as the patellar tendon CSA is often only measured at one or three locations (4,5,66).

9.6.4 Analysis of the magnetic resonance imaging

Analysis of the quadriceps muscle CSA was performed in Horos open-source software (v.3.3.6) by a single, blinded assessor. The quadriceps muscle CSA was measured 200 mm from the tibiae plateau and encompassed all the different muscles in the extensor compartment. The images were analyzed in grey-scale and in combination with the National Institutes of Health color scheme to optimize the accuracy of the muscle's boundaries, thereby increasing reliability and minimizing the risk of underestimation of the muscle CSA (180).

Patellar tendon volume was measured by the same assessor and estimated using the open-source software ITK-SNAP (v4.0.1, Cognitica, Philadelphia, PA, USA). The patellar tendon volume was measured in just the free patellar tendon. The free patellar tendon was defined as just distally from the apex patella to just proximally from the insertion at the tibiae tubercle. The assessor selected images of the patellar tendon at different locations throughout the entirety of the tendon length and placed "seed-bubbles" in the selected region of interest. The artificial intelligence (AI) software then extrapolated the "seed-bubbles" in the structure of interest to assess patellar tendon volume. The assessor manually removed any overflow to ensure that only the free patellar tendon volume was included. The assessor was blinded to the injury site and time point to minimize observer bias. Quadriceps muscle CSA and patellar tendon volume are presented in Figure 10.

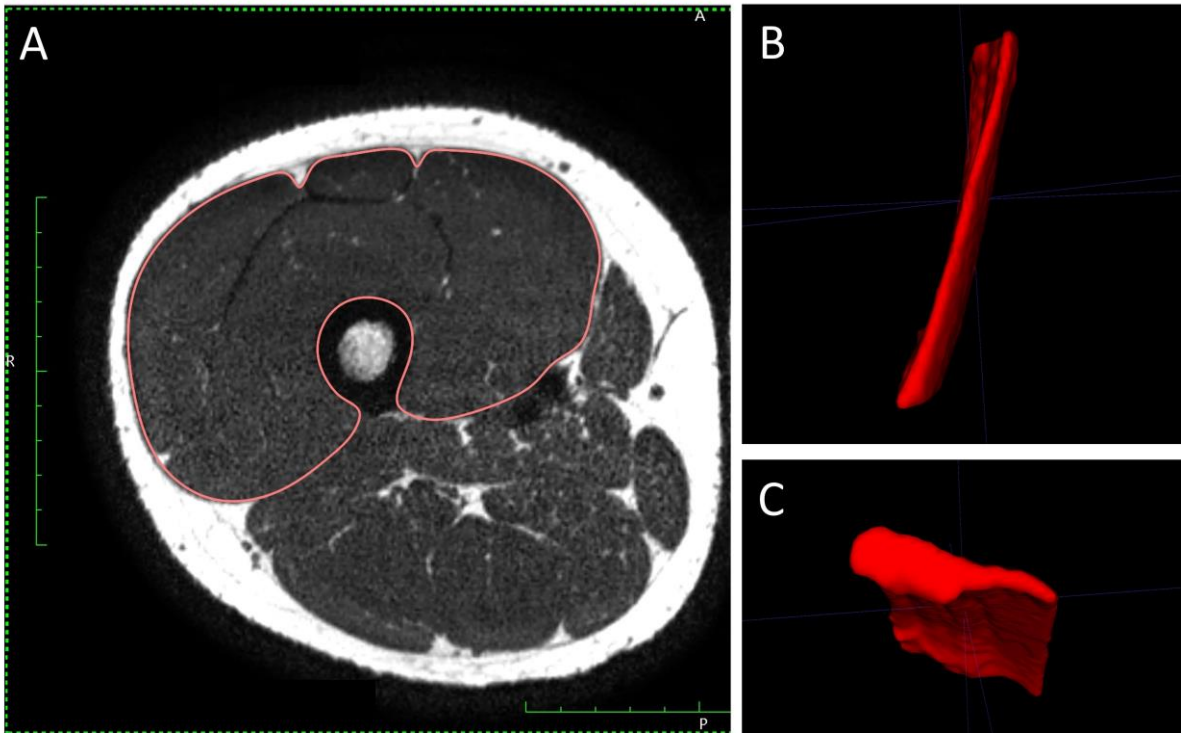


Figure 10: Illustration of A) magnetic resonance imaging axial grey-scale outline of quadriceps muscle cross-sectional area measured in Horos. Red line indicates muscle outline. B) patellar tendon volume in a sagittal view and C) a top-down view of the proximal part of the tendon at injury site. Image A was analyzed in Horos and B + C was analyzed in ITK-SNAP.

9.7 Systematic review and meta-analysis (Study II)

9.7.1 Databases

In Study II, Medline through PubMed (PubMed), Embase, Cochrane CENTRAL, CINAHL, and SPORTDiscus were chosen as databases in which the structured literature search was performed. The databases were chosen for different reasons. PubMed, Embase, and Cochrane Central were chosen as those are the most applied databases when performing a systematic literature search (181). PubMed is the primary health scientific database (182) and, with the addition of Embase, it increases the coverage by a mean of 6.8 percentage points (183), and by also adding Cochrane CENTRAL we believed most studies would be identified (181). Further, we added CINAHL and SPORTDiscus to increase our coverage and potentially identify specialized studies.

9.7.2 Search terms and study records

The search terms were developed in consensus with all the involved authors. Three different search strategies were developed in order to identify relevant studies within each category

(hormone, immune, and oxidative stress). Each specific strategy was customized to fit each individual database, and the search strategies for PubMed are presented in Table 4. Search terms were searched in Title/abstract and in each database's medical subject heading (MeSH-terms).

Study records derived from the systematic search were exported into Mendeley Citation Manager version 1.19.4, and duplicates were removed using semi-automated tools provided in Mendeley. Two independent assessors screened all records for eligibility. Disagreements were resolved by consensus and, if necessary, by group discussions.

Two assessors assessed all the study records to reduce the risk of missing potential studies, which is commonly used in systematic reviews and meta-analyses. The assessors assessed all records in dependently in order to not influence each other, thus likely reducing bias. Also, we used a semi-automated tool to screen for duplicates. The semi-automated tool most likely did not identify all duplicates. Thus, the reported studies assessed for title and abstract may not be truly accurate. Group discussions were used to assess any disagreements between the two primary assessors. This is common practice and is performed in order to reduce the risk of excluding otherwise eligible studies. Only one study was evaluated by group discussions.

Table 4 – Search strategy for hormone, immune, and oxidative stress in MEDLINE through PubMed

Search strategy for hormonal responses in MEDLINE through PubMed	
Focus 1	Focus 2
Blood flow restriction	Hormon*
BFR	Physiolog*
Kaatsu	Endocrin*
Occlusion training	Inflammation #
Occlusion exercise	Metaboli*
Vascular Occlusion	Plasma #
Vascular restriction	

Search strategy for immune system responses from MEDLINE through PubMed	
Focus 1	Focus 2
Blood flow restriction	Cytokin* # cytokines
BFR	Chemokin*
Kaatsu	Autocrin*
Occlusion training	Neurocrin*
Occlusion exercise	Paracrin* # Intercellular Signaling Peptides and Proteins
Vascular Occlusion	Immune # Immune system
Vascular restriction	

Search strategy for oxidative stress responses in MEDLINE through PubMed	
Focus 1	Focus 2
Blood flow restriction	Oxidative # oxidative stress, advanced oxidation protein products
BFR	Oxidant
Kaatsu	Oxidation # oxidation-reduction
Occlusion training	Nitric Oxide # Nitric oxide, Nitric oxide synthases
Occlusion exercise	Nitrite
Vascular Occlusion	reactive oxygen species
Vascular restriction	

All terms were searched with the Boolean operator OR within each focus group and the Boolean operator AND was used between the two focus groups.
* indicates open ended terms. # indicates terms searched using the medical subject heading (MeHS). The table is duplicated from supplementary data from Hjortshoej et al. (118) and used under the CC BY-NC 3.0 license.

9.7.3 Risk of bias and quality assessment of studies

Risk of bias assessments were performed on randomized trials using the Risk of bias 2 (ROB2) by Higgins et al. (184) and the Risk of bias in non-randomized studies-of intervention (ROBINS-I) by Sterne et al. (185) for non-randomized trials. However, the ROB2 has demonstrated poor inter-rater reliability, which demonstrates several challenges, such as independent researchers reaching different assessments of risk of bias using the ROB2 (186). ROB2 and ROBINS-I were

utilized as they are recommended by the Cochrane Handbook and because they are the most applied assessment tools to evaluate the risk of bias in systematic reviews and meta-analyses. Likewise, the ROB2 and ROBINS-I may lack the specificity needed to evaluate training intervention studies, as blinding participants to intervention is not feasible.
As the application for the risk of bias assessment is limited in training intervention studies, the Tool for the assEssment of Study qualiTy and reporting in EXercise (TESTEX) was also used to assess study quality and reporting (187). The TESTEX is a relatively new assessment tool in training intervention studies, and the score ranges from 0 to 15, where 5 is the maximum score for study quality and 10 is the maximum score for study reporting. The TESTEX item inter-rater reliability ranged from moderate-to-excellent, and the summated TESTEX score demonstrated excellent inter-rater reliability (187). Due to the lack of specificity of the ROB2 and ROBINS-I, the TESTEX was included as it likely provides a more relevant rating of study quality and reporting. Further, the two assessors met to align and discuss the application of the individual assessment tools before they were applied to each individual study. This has likely increased the agreement between the two assessors.

9.7.4 Data extraction

Data extraction was performed in Excel (Microsoft Corporation, Redmond, Washington) in a standardized data extraction form, and all data was extracted by the primary investigator. To investigate the effects of interventions, $mean_{change}$ and SD_{change} were collected if available. The corresponding authors were contacted by email if the data were unretrievable. If the corresponding authors were unable to retrieve data or did not respond, mean differences and pooled SD were estimated. If only graphics are reported (figures and graphs), WebPlotDigitizer (version 4.4, Pacifica, California, USA) was used to estimate data.

The standardized extraction form was developed in order to minimize the risk of extraction errors from the studies. Also, to minimize extraction errors, a second assessor could have validated the extraction data from the primary assessor. However, due to pragmatic reasons, such as time constraints, this was not chosen. For graphic information, the WebPlotDigitizer software was utilized to be able to retrieve data in studies only reporting graphs or figures. The WebPlotDigitizer software was only used if data was otherwise unavailable, and authors did not respond. Using the WebPlotDigitizer software, erroneous estimation could be a possibility, but it is preferable to exclude studies based on data unavailability.

9.8 Statistics

Study I

In Study I, all statistical analyses were performed using SAS software (version 7.15, SAS Institute Inc., Cary, NC, USA) and graphs were performed in GraphPad PRISM (version 9.5.1, GraphPad Software, San Diego, California, USA). To assess the data distribution for normality, it was visually assessed by using Quantile-Quantile plots together with histograms. Data are presented as least square means ± standard deviation to account for missing values. For normally distributed outcome data, a mixed effects model was employed to assess for between-group differences at all four time points. Likewise, a mixed effects model was used on change scores to assess any interaction of time. A Pearson correlation coefficient was used to assess the correlation of changes from baseline to 12 weeks between clinical outcomes (SLDS and VISA-P) and structural outcomes (patellar tendon volume, muscle quadriceps CSA, proximal patellar tendon thickness, and Doppler). The analyses were performed as. Alpha was set to 0.05 and beta to 0.80.

Study II

In Study II, all meta-analyses were performed using the software Review Manager (RevMan, version 5.4.1) provided by the Cochrane Collaboration. The meta-analysis was performed on the initial (>10 minutes post-exercise), intermediate (10-20 minutes post-exercise), and late (<30 minutes post-exercise) hormone, immune, and oxidative stress responses following an acute bout of LL-BFRT compared to conventional free flow resistance exercise being either LL-FFRE or HL-FFRE. The meta-analyses were performed on $\text{mean}_{\text{change}}$ and $\text{standard deviation}_{\text{change}}$ scores. Data were collected from included studies, if available. To estimate missing data for SD_{change}, the following formula was used:

$$SD_{\text{change}} = \sqrt{SD^2_{\text{baseline}} + SD^2_{\text{final}} - (2 \times correlation \times SD_{\text{baseline}} \times SD_{\text{final}})}$$

A correlation coefficient of 0.8 has been proposed as a standard to compute SD_{change} if correlations were not reported in the study. Meta-analyses were performed using standardized mean difference (SMD) due to differences in methodology applied to measure hormone, immune, and oxidative stress responses. A random-effects model was used to summarize data, and the data are presented using SMD and 95% CI. SMD was computed based on Hedge's G, and a SMD between 0.2-0.5 was considered a small effect, an SMD between 0.5-0.8 was considered a moderate effect, and an SMD >0.8 was considered a large effect. In addition,

heterogeneity between studies was estimated using I^2, and was interpreted as an I^2 between 0-40% may not be important heterogeneity, an I^2 between 30-60% may represent moderate heterogeneity, an I^2 between 50-90% may represent substantial heterogeneity, and an I^2 between 75-100% represent substantial heterogeneity.

Study III

In study III, all statistical analyses were performed using SAS software (version 7.15, SAS Institute Inc., Cary, NC, USA). Quantile-Quantile plots and histograms were used to assess the distribution of data. Data are presented as mean ± standard deviation and 95% confidence interval when appropriate. For parametric distributed outcomes (tendon length, proximal, mid, and distal tendon thickness, hypoechoic area, and ROI), a two-tailed dependent t-test was used to analyze differences between symptomatic and non-symptomatic tendon. For non-parametric distributed outcomes (Doppler), a Wilcoxon signed-rank test was utilized. Data were reported in median, 1st quartile, 3rd quartile, range, and p-value.

The interclass correlation coefficient (ICC) was used to assess intra-rater reliability and was performed on raw and delta values. A single measurement, two-way mixed-effect model, absolute agreement (ICC 2.1) was used as recommended (188). An ICC score below 0.50 was considered poor, an ICC score of 0.50-0.75 was considered moderate, an ICC score of 0.75-0.90 was considered good, and an ICC score above 0.90 was considered excellent. In addition, a dependent t-test was performed to measure bias, while typical error and typical error in percent were calculated to estimate absolute reliability.

10. RESULTS

In this section, the results from the three studies that comprise this thesis will be presented.

10.1. Summary of main findings in study I

Paper I

A total of 263 persons were screened for eligibility through telephone interviews. Of the 263 screened through telephone interviews, 75 potential participants were assessed for eligibility by a physician at the outpatient clinic at the Institute of Sports Medicine Copenhagen. Of those

assessed for eligibility by the physician, 36 participants were included in the study. A flow-chart of the study is provided in Figure 11, and the participants baseline demographics are presented in Table 5. The two groups were comparable at baseline for all variables.

Table 5 – Demographic data

	LL-BFRT (n= 16)	HSRT (n= 20)
Age	29.9 ± 9.2	32.7 ± 10.8
Height	184.6 ± 6.1	186.7 ± 7.4
Weight	83.8 ± 9.2	85.5 ± 12.9
Symptom duration (months)†	10.0 (1st quartile 5; 3rd quartile 12.5)	9.5 (1st quartile 6; 3rd quartile 18.0)
Pain during physical activity (NPRS)	5.9 ± 1.4	5.7 ± 1.6
Physical activity (h/wk)	4.8 ± 3.4	3.6 ± 4.0

Data are presented in means ± standard deviations unless stated otherwise. NPRS, numeric pain rating scale. h/wk, hours per week. LL-BFRT, low-load blood flow restriction training. HSRT, heavy-slow resistance training. † Data er presented in median, 1st and 3rd quartile. The table is duplicated from Paper I.

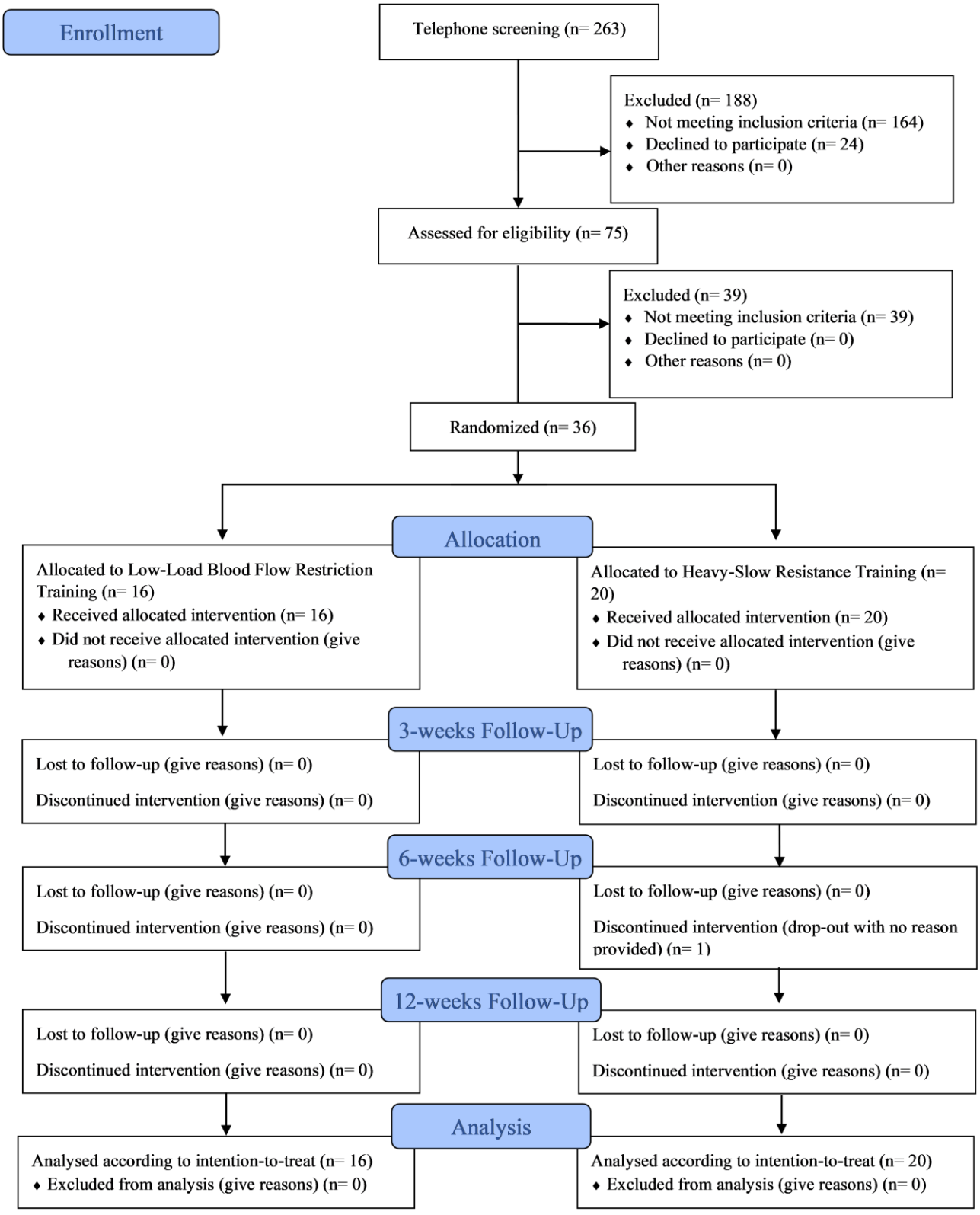


Figure 11: An illustrative representation of the flow of participants throughout the study. The figure is duplicated from Paper I.

10.1.1 Training data and physical activity

The mean overall training compliance was 77.3 ± 28.8% and 81.5 ± 24.2% for the LL-BFRT and HSRT group, respectively. There was no statistically significant between-group difference (4.27 ± 26%; 95% CI: -13.69, 22.23; P= 0.63). Similarly, there was no significant group-differences for total leg press and knee extension repetition, load, or volume. Training data is presented in Table 6.

Table 6 – Training data for LL-BFRT and HSRT

	LL-BFRT	HSRT	Between-group difference
Leg press completed sessions %	77.3 ± 28.8	81.3 ± 24.8	-04.0 ± 26.6; 95% CI 14.2, -22.2); P= 0.66
Leg press repetition %	74.6 ± 28.6	82.0 ± 26.7	-07.4 ± 27.6; 95% CI 11.4, -26.2); P= 0.43
Leg press load %	75.6 ± 28.9	68.9 ± 26.8	06.8 ± 27.7; 95% CI 25.7, -12.2); P= 0.47
Leg press volume %	67.5 ± 29.9	64.7 ± 28.5	02.9 ± 29.1; 95% CI 22.7, -17.0); P= 0.77
Knee extension completed sessions %	76.9 ± 28.6	81.1 ± 24.1	-04.2 ± 26.2; 95% CI 13.7, -22.1); P= 0.64
Knee extension repetition %	73.1 ± 28.6	79.6 ± 24.6	-06.5 ± 26.5; 95% CI 11.5, -24.5); P= 0.47
Knee extension load %	77.3 ± 28.4	71.4 ± 28.0	05.9 ± 28.2; 95% CI 25.1, -13.3); P= 0.53
Knee extension volume %	68.4 ± 29.9	65.2 ± 28.0	-03.2 ± 28.8; 95% CI 22.9, -16.5); P= 0.74
Overall compliance %	77.3 ± 28.8	81.5 ± 24.2	-04.3 ± 26.4; 95% CI 13.7, -22.2); P= 0.63

Tabel 6 demonstrates the average percentage completion of sessions, repetitions, load, and volume for leg press and knee extension, respectively. Also, total overall compliance is presented. Values are presented in mean ± standard deviation percentage. LL-BFRT, low-load blood flow restriction training (n=16); HSRT, heavy-slow resistance training (n=20). CI, confidence interval. The table is duplicated from Paper I.

For leg press 5-RM, there was a significant effect of time (P< 0.0001) but no significant group (P= 0.87) or group x time (P= 0.18) effect. For knee extension 5-RM, there was a significant effect of time (P< 0.0001) but no significant group (P= 0.46) or group x time (P= 0.35) effect. Leg press 5-RM increased by 19.0 ± 20.8% and 21.8 ± 13.8% from baseline to 10 weeks for LL-BFRT and HSRT, respectively. Knee extension 5-RM increased by 20.3 ± 15.8% and 27.9 ± 26.0% from baseline to 10 weeks for LL-BFRT and HSRT, respectively.

Similarly, there was a significant effect of time (P= 0.034) for AOP. AOP at baseline was 186.9 ± 11.4 mmHg and significantly decreased to 180.7 ± 10.0 mmHg at 10 weeks. Data for 1-RM and AOP are presented in Figure 12.

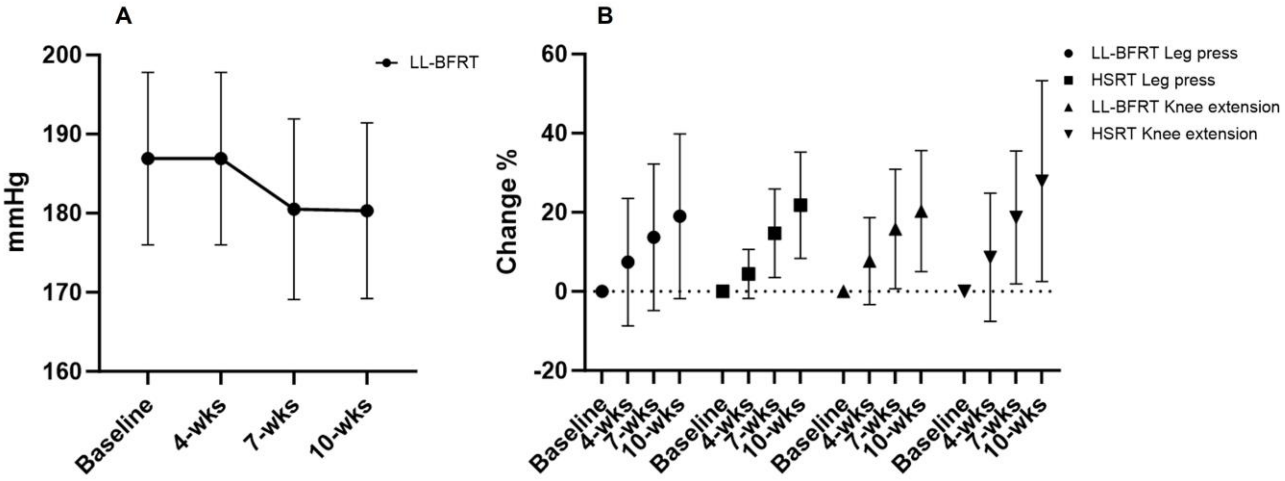


Figure 12: Illustration of total arterial occlusion pressure (AOP) and 5-repetition maximum (RM) test. A) presents total AOP and data are presented as lest squares means ± standard deviation. B) represents 5-RM change score in percent from baseline and data are presented in least squares means mmHg, millimeter of mercury; LL-BFRT, low-load blood flow restriction training (n=16); HSRT, heavy-slow resistance training (n=20). Leg press P-values: group (P= 0.87), time (P< 0.0001), and group x time (P= 0.18). Knee extension P-values: group (P= 0.46), time (P< 0.0001), and group x time (P= 0.35). AOP P-value: time (P= 0.034).

For physical activity, there was a significant effect of time (P< 0.01) but no significant group (P= 0.38) or group x time (P=0.81) effect. Physical activity increased from baseline to 12 weeks from 4.8 to 6.2 hours per week (23%) for the LL-BFRT group, and from 3.6 to 5.2 hours per week (31%) for the HSRT group. Physical activity is presented in Figure 13.

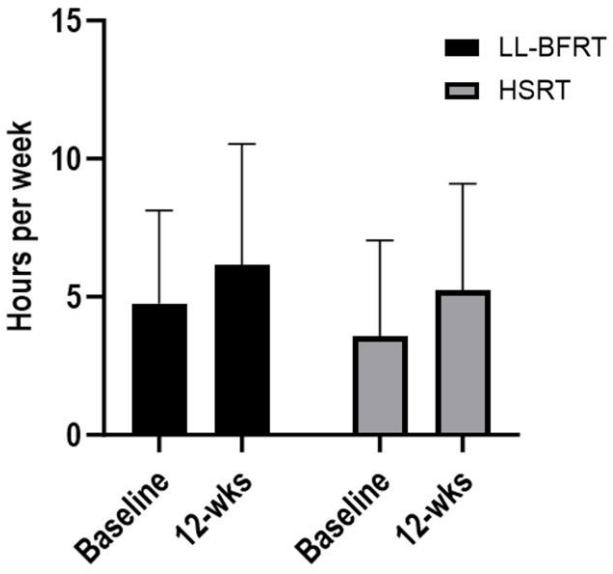


Figure 13: Physical activity measured at baseline and 12 weeks. Values are presented as least squares means and standard deviations. LL-BFRT, low-load blood flow restriction training (n=16); HSRT, heavy-slow resistance training (n=20). Physical activity P-values: group (P= 0.37), time (P< 0.01), and group x time (P= 0.81). The figure is duplicated from Paper I.

10.1.2 Clinical outcomes

For the NPRS during the SLDS test, no significant between-group difference was observed at 12 weeks (0.2 ± 1.9 mean difference; 95% CI -1.1, 1.5; P= 0.74) or at any other time points. There was a significant decrease in the NPRS score from baseline to 12 weeks in both groups. There was a significant decrease of -1.8 ± 1.7 (95% CI -2.6, -1.0; P< 0.0001) and -2.0 ± 2.2 (95% CI -3.0, -1.0; P< 0.001) NPRS from baseline to 12 weeks for the LL-BFRT and the HSRT group, respectively.

Data from the VISA-P demonstrated a similar pattern, and no significant between-group difference was observed at 12 weeks (0.1 ± 15.8 mean difference; 95% CI -10.7, 10.5; P= 0.99) or at any time point. There was a significant increase of 16.2 ± 14.5 (95% CI 9.0, 23.4; P< 0.001) and 16.3 ± 17.3 (95% CI 8.5, 24.0; P< 0.001) on the VISA-P score from baseline to 12 weeks for the LL-BFRT and the HSRT group, respectively. The NPRS during SLDS test and the VISA-P score are illustrated in Figure 14.

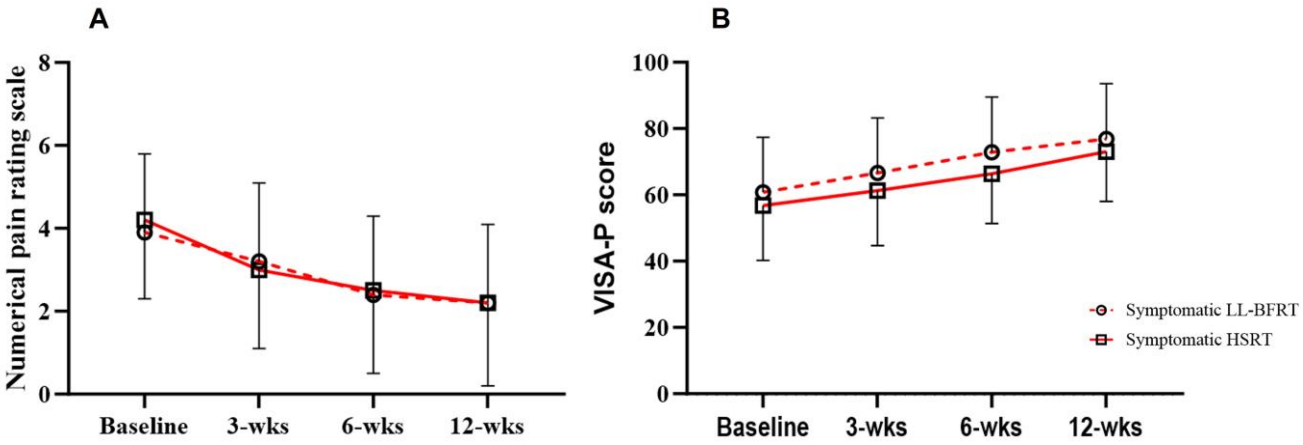


Figure 14: Graphs illustrating the clinical improvement in A) NPRS during SLDS and B) VISA-P score. Values are presented in least squares mean ± standard deviation at baseline, 3, 6, and 12 weeks.
VISA-P, Victorian Institute of Sports Assessment – Patella. NPRS, numeric pain rating scale. SLDS, single-leg decline squat. LL-BFRT, low-load blood flow restriction training (n=16). HSRT, heavy-slow resistance training (n=20). A) SLDS: P-values group (0.94), time (< 0.0001), and group x time (0.91). B) VISA-P: P-values group (0.32), time (< 0.0001), and group x time (0.93).

The PPT data are presented in Figure 15. For the symptomatic tendon, there were no between-group differences at any time point for any sites. However, there was a significant increase in PPT at the AP (P= 0.040) but no effect of group or group x time. There was a significant increase in PPT from baseline to 12 weeks (P= 0.02). The MPA, TA, and the ECR did not change at any time point. For the asymptomatic tendon, there was no significant effect of time, group, or time x group for any location and at any time point.

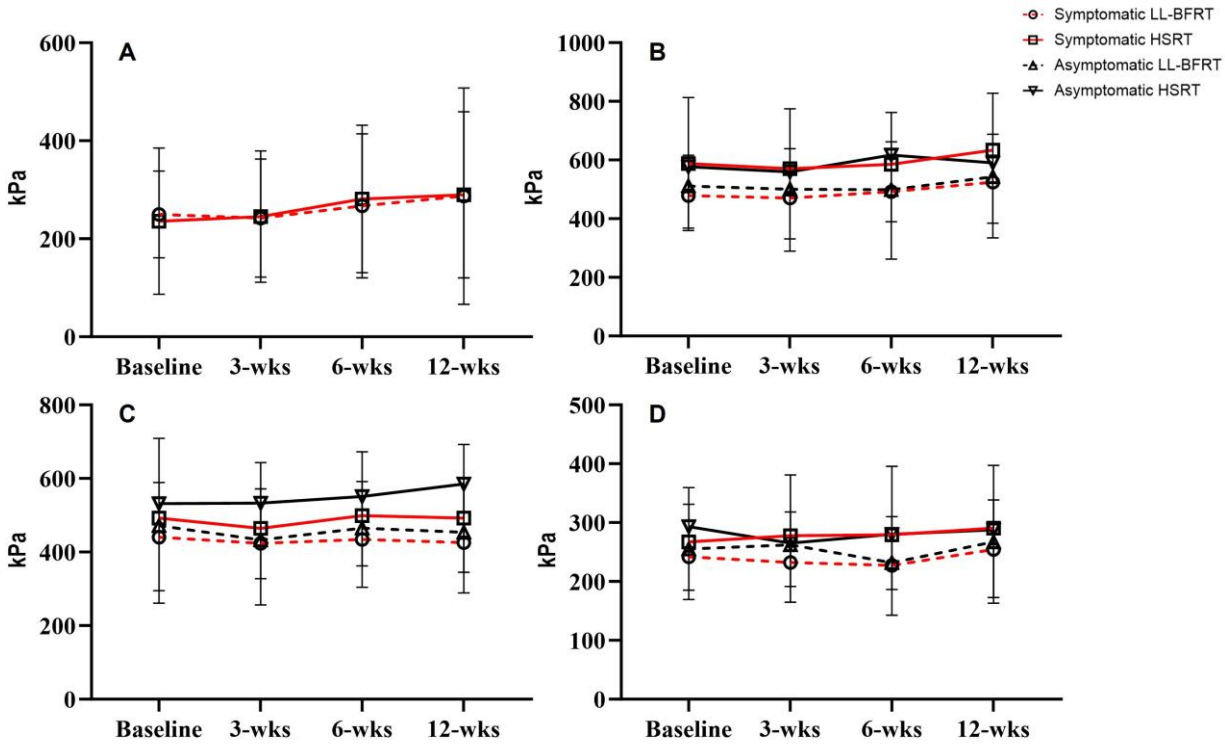


Figure 15: Graphs illustrating the PPT score for the symptomatic and asymptomatic tendon. A) most painful area (MPA) (only symptomatic side), B) Apex patella (AP), C) Tibialis anterior (TA), D) Extensor carpi radialis brevis (ECR). Values are presented in mean and standard deviation at baseline, 3, 6, and 12 weeks. kPa, kilopascal; LL-BFRT, Low-load blood flow restriction training (n=16); HSRT, Heavy-slow resistance training (n=20). Symptomatic side: MPA: P-values group (0.97), time (0.14), and group x time (0.97). AP: P-values group (0.06), time (0.040), and group x time (0.96). TA: P-values group (0.31), time (0.55), and group x time (0.95). ECR: P-values group (0.16), time (0.39), and group x time (0.70). Asymptomatic side: AP: P-values group (0.28), time (0.55), and group x time (0.48). TA: P-values group (0.16), time (0.48), and group x time (0.37). ECR: P-values group (0.35), time (0.06), and group x time (0.12). The figure is duplicated from Paper I.

The maximal knee extensor torque demonstrated no between-group differences at any time points. A significant effect of time (P= 0.049) with a significant increase was observed for the symptomatic leg, but no significant effect of group (P= 0.94) and group x time (P= 0.31). There was a significant increase from baseline to 12 weeks (P= 0.049). For the asymptomatic leg, there was no significant effect of group (P= 0.53), time (P= 0.71), or group x time (P= 0.44). Maximal knee extensor torque is illustrated in Figure 16.

Overall, LL-BFRT did not demonstrate superiority compared to HSRT during the SLDS, VISA-P, PPT, and iMVC at 12-week follow-up.

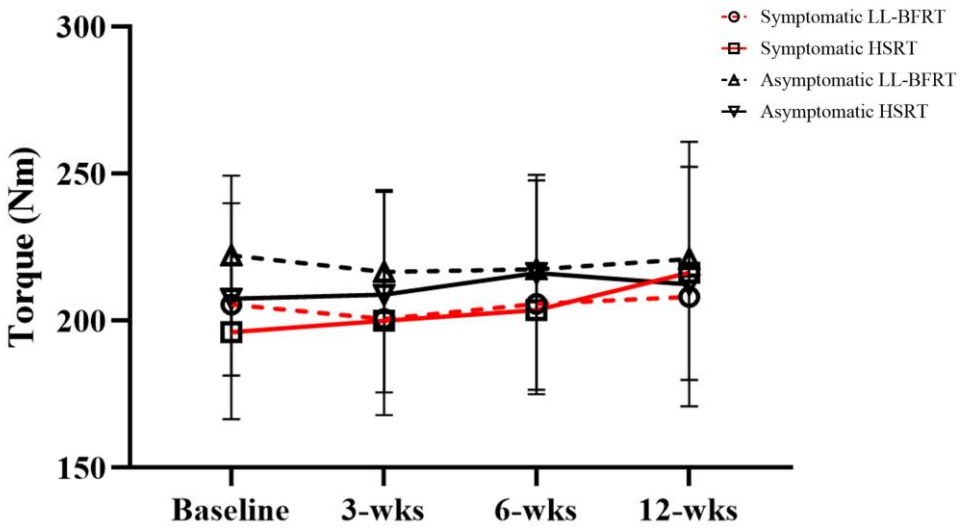


Figure 16: Graphs illustrating the iMVC data at baseline, 3, 6, and 12 weeks. Values are presented in mean and standard deviation. LL-BFRT, low-load blood flow restriction training (n=16); HSRT, heavy-slow resistance training (n=20). Symptomatic side iMVC P-values: group (P= 0.94), time (P= 0.049), and group x time (P= 0.31). Asymptomatic side iMVC P-values: group (P= 0.53), time (P= 0.71), and group x time (P= 0.44).

10.1.3 Ultrasound imaging

For the PD activity in the symptomatic tendon, there was no effect of group (P= 0.38) or time (P= 0.59) but a significant effect of group x time (P=0.004). For the LL-BFRT group, there was a significant decrease in PD activity from 3-week to 6-week (-7.1 ± 8.5; 95% CI -11.4, -2.9; P< 0.01) and for HSRT group there was a significant decrease from baseline to 3-week (-5.2 ± 7.6; 95% CI -10.0, -0.5; P= 0.032) and an increase from 3-week to 6-week (6.5 ± 7.8; 95% CI 1.5, 11.5; P= 0.015). PD activity is presented in Figure 17.

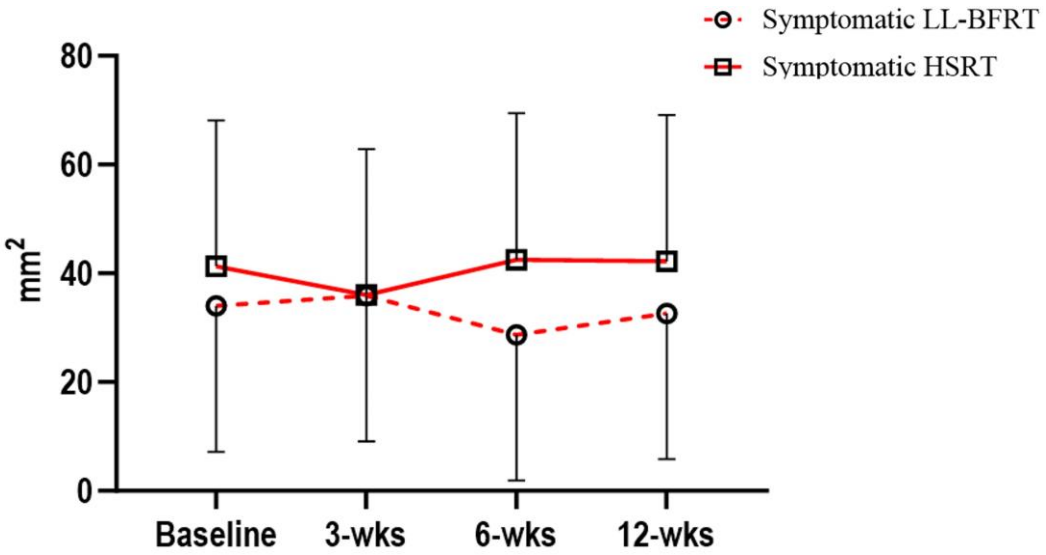


Figure 17: Power Doppler (PD) activity in the symptomatic tendon at baseline, 3, 6, and 12 weeks. There was a significant group x time effect (P< 0.01), but no group (P= 0.38) or time effect (P= 0.59). LL-BFRT, low-load blood flow restriction training (n=16); HSRT, heavy-slow resistance training (n=20).

For the US data on structural adaptations of the tendon, data are presented in Figure 18 and 19. For proximal tendon thickness, there were no significant group (P= 0.32), time (P= 0.23), and group x time (P= 0.11) effect for the symptomatic tendon. Similarly, no significant effect of time (P= 0.99), time (P= 0.09), or group x time (P= 0.98) were demonstrated for the asymptomatic tendon. For the mid-tendon, there was a significant effect of time (P= 0.03) but no effect of group (P= 0.40) and group x time (P= 0.75) for the symptomatic tendon whereas the asymptomatic tendon did not demonstrate any effect of group (P= 0.59), time (P= 0.37), or group x time (P= 0.38). For the distal tendon thickness, there was a significant effect of time for both groups and for both the symptomatic (P= 0.049) and asymptomatic tendon (P= 0.03) with no group or group x time effect. There was a significant decrease from 6 weeks to 12 weeks for both the symptomatic (P= 0.01) and asymptomatic tendon.

For the whole tendon echogenicity, there were no significant group (P= 0.19), time (P= 0.93) or group x time (P= 0.10) effect for the symptomatic tendon. Similarly for the ROI echogenicity, there were no significant group (P= 0.19), time (P= 0.93) or group x time (P= 0.10) effect for the symptomatic tendon.

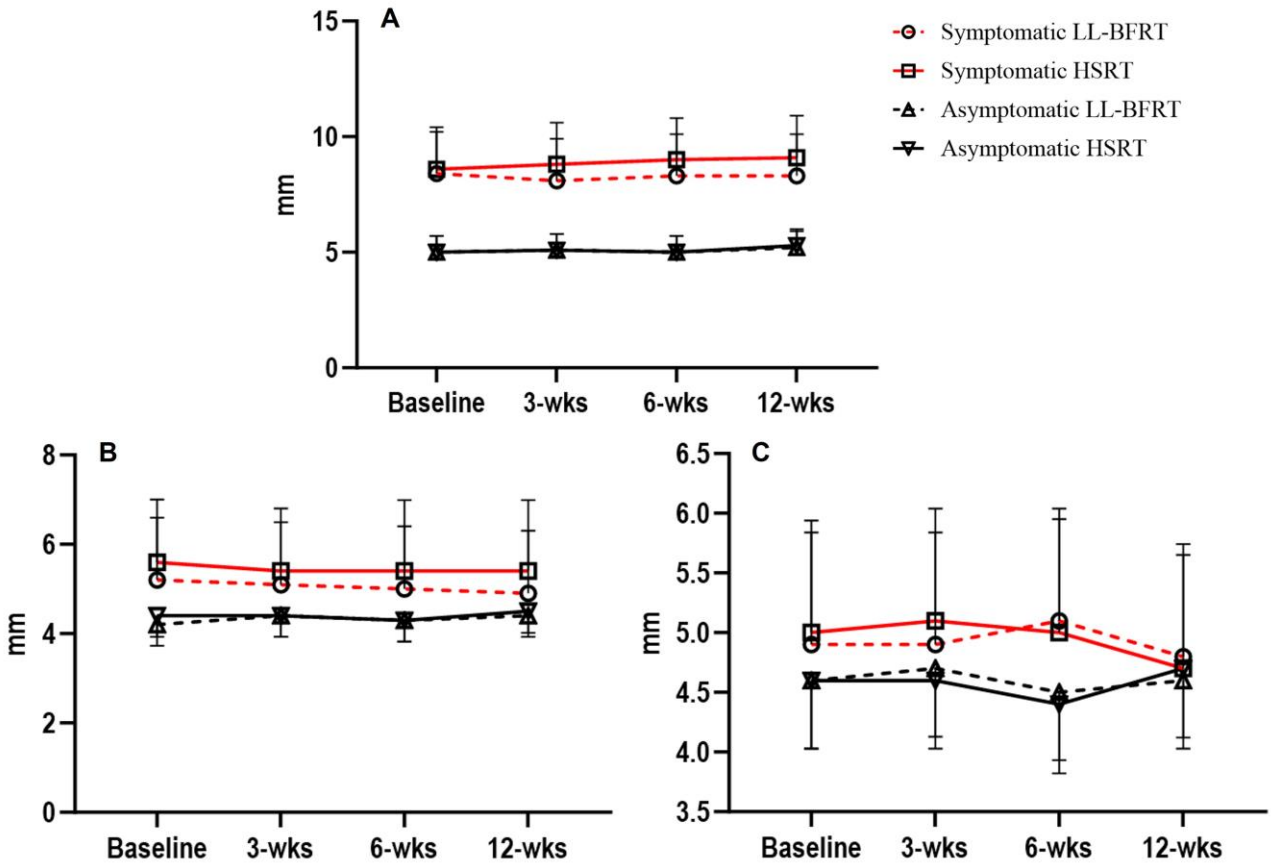


Figure 18: Graphs of tendon thickness. A) Tendon thickness measured 0.5 cm distally from apex of the patella (proximal). B) Tendon thickness measured mid-tendon (mid). C) Tendon thickness measured 0.5 cm proximally from the tibia tubercle (distal). Measurements were performed at baseline, 3, 6, and 12 weeks. Values are presented in least squares means ± standard deviations. mm; millimeters. LL-BFRT, low-load blood flow restriction training (n=16); HSRT, heavy-slow resistance training (n=20). Symptomatic tendon: Proximal: group (P= 0.32), time (P= 0.23), and group x time (P= 0.11); mid: group (P= 0.40), time (P= 0.026), and group x time (P= 0.75); distal: group (P= 0.96); time (P= 0.049); group x time (P= 0.31). Asymptomatic tendon: proximal: group (P= 0.99), time (P= 0.09), group x time (P= 0.98); mid: group (P= 0.59), time (P= 0.37), and group x time (P= 0.38); distal: group (P= 0.94), time (P= 0.028), and group x time (P= 0.79).

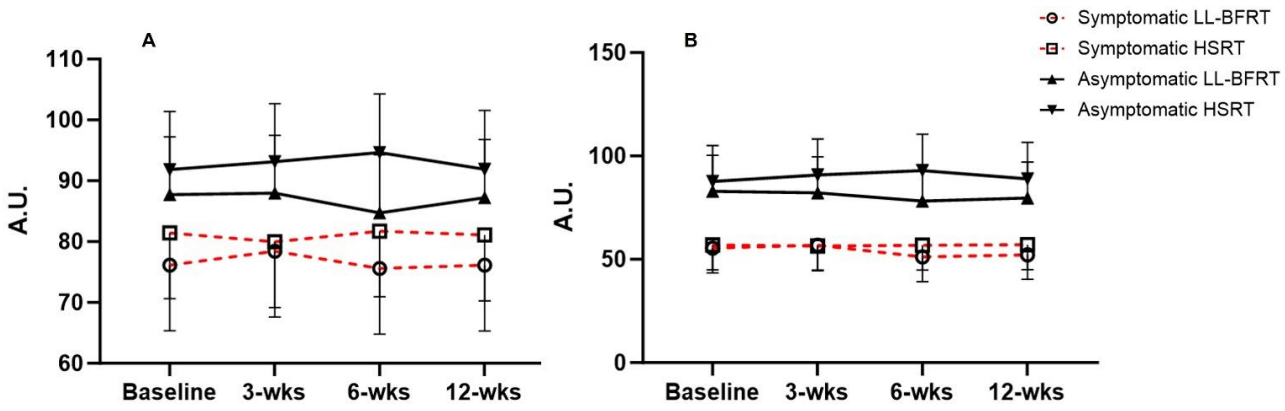


Figure 19: Illustrating whole tendon and region of interest (ROI) echogenicity. A) whole tendon echogenicity and B) ROI echogenicity was measured at baseline, 3, 6, and 12 weeks. Values are presented as least squares means ± standard deviations. mm; millimeters. LL-BFRT, low-load blood flow restriction training (n=16); HSRT, heavy-slow resistance training (n=20). A) whole tendon echogenicity symptomatic tendon: group (P= 0.19), time (P= 0.93), and group x time (P= 0.10). Whole tendon echogenicity asymptomatic tendon: group (P= 0.027), time (P= 0.91), and group x time (P= 0.19). B) ROI echogenicity symptomatic tendon: group (P= 0.42), time (P= 0.21), and group x time (P= 0.12). ROI echogenicity asymptomatic tendon: group (P= 0.06), time (P= 0.94), and group x time (P= 0.23). The figure is duplicated from Paper I.

10.1.4 Magnetic resonance imaging

For quadriceps CSA of the symptomatic leg, there were no between-group differences observed at any time point. There was a significant effect of time (P= 0.02) with a significant increase in quadriceps muscle CSA, but no significant effect of group (P= 0.52) or group x time (P= 0.96). For the asymptomatic leg, there were no between-group differences observed at any time point. There was a significant effect of time (P= 0.048) with a decrease in quadriceps muscle CSA, but no significant effect of group (P= 0.15) or group x time (P= 0.24).

For the symptomatic patellar tendon volume, there were no between-group differences at any time point. There was no significant effect of time (P= 0.46), group (P= 0.08) or group x time (P= 0.96). For the asymptomatic patellar tendon volume, there were no between-group differences at any time point. There was no significant effect of group (P= 0.15), time (P= 0.41) or group x time (P= 0.17). Quadriceps muscle CSA and patellar tendon volume are presented in Figure 20.

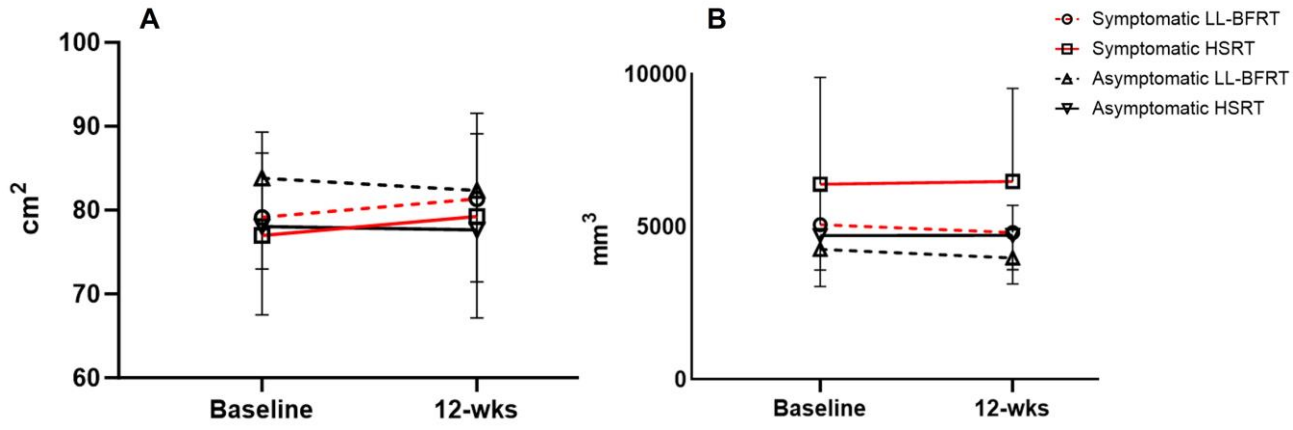


Figure 20: Graph illustrating quadriceps muscle CSA and patellar tendon volume. A) quadriceps muscle CSA and B) patellar tendon volume was measured at baseline and 12 weeks. Measurements were performed at baseline and 12 weeks. Values are presented in least square means ± standard deviations. mm; millimeters. LL-BFRT, low-load blood flow restriction training (n=16); HSRT, heavy-slow resistance training (n=20). A) Quadriceps muscle CSA symptomatic side: group (P= 0.52), time (P< 0.01), and group x time (P= 0.96). Quadriceps muscle CSA asymptomatic side: group (P= 0.15), time (P= 0.048), and group x time (P= 0.24). B) Patellar tendon volume symptomatic tendon: group (P= 0.08), time (P= 0.46), and group x time (P= 0.13). Patellar tendon volume asymptomatic tendon: group (P= 0.15), time (P= 0.41), and group x time (P= 0.17). The figure is duplicated from Paper I.

10.1.4 Correlations

There was no significant correlation between clinical outcomes (the SLDS test and VISA-P) and structural outcomes (patellar tendon volume, proximal tendon thickness, and PD activity). The correlations were considered low and ranged from -0.14 to 0.17.

10.2 Summary of main findings in study II

Paper II

A total of 12525 study records were identified, of which 4664 were identified as duplicates using a semi-automated tool. After removing duplicates, 7861 were screened for eligibility in the study. Of those, 274 went through full text screening, of which 29 studies were included in the final systematic review and meta-analysis (122,189,198–207,190,208–216,191–197). A schematic illustration of the flow of the included studies is presented in Figure 21.

A total sample population of 427 participants was included across all studies, of which the majority were males. Of the total population, 362 were males and 25 were females; 40 participants were not classified by sex. The overall population was generally young, with a mean

age across studies of 23.2 years, and mostly physically active (69% of the population). Biological samples comprised the withdrawal of blood (27 studies) and muscle biopsies (3 studies), while a single study collected both blood and muscle biopsy samples.

10.2.1 Risk of bias and study quality assessment

All 29 studies were assessed for risk of bias using ROB2 or ROBINS-1. 20 studies were assessed for risk of bias using ROB2, where 10 studies were assessed as having “Some concerns” and the other 10 studies were assessed as having “High risk of bias”. For the nine studies assessed by ROBINS-1, six were assessed as having “Moderate risk of bias” and three studies were assessed as having “High risk of bias”.

Using the TESTEX to evaluate study quality and reporting in training intervention studies, the average TESTEX score for study quality was 2.71 out of 5 and the average score for study reporting was 4.89 out of 10. Thus, the total average TESTEX score for study quality and reporting was 7.60 out of 15. An in-depth assessment of the individual studies using TESTEX is presented in Table 7.

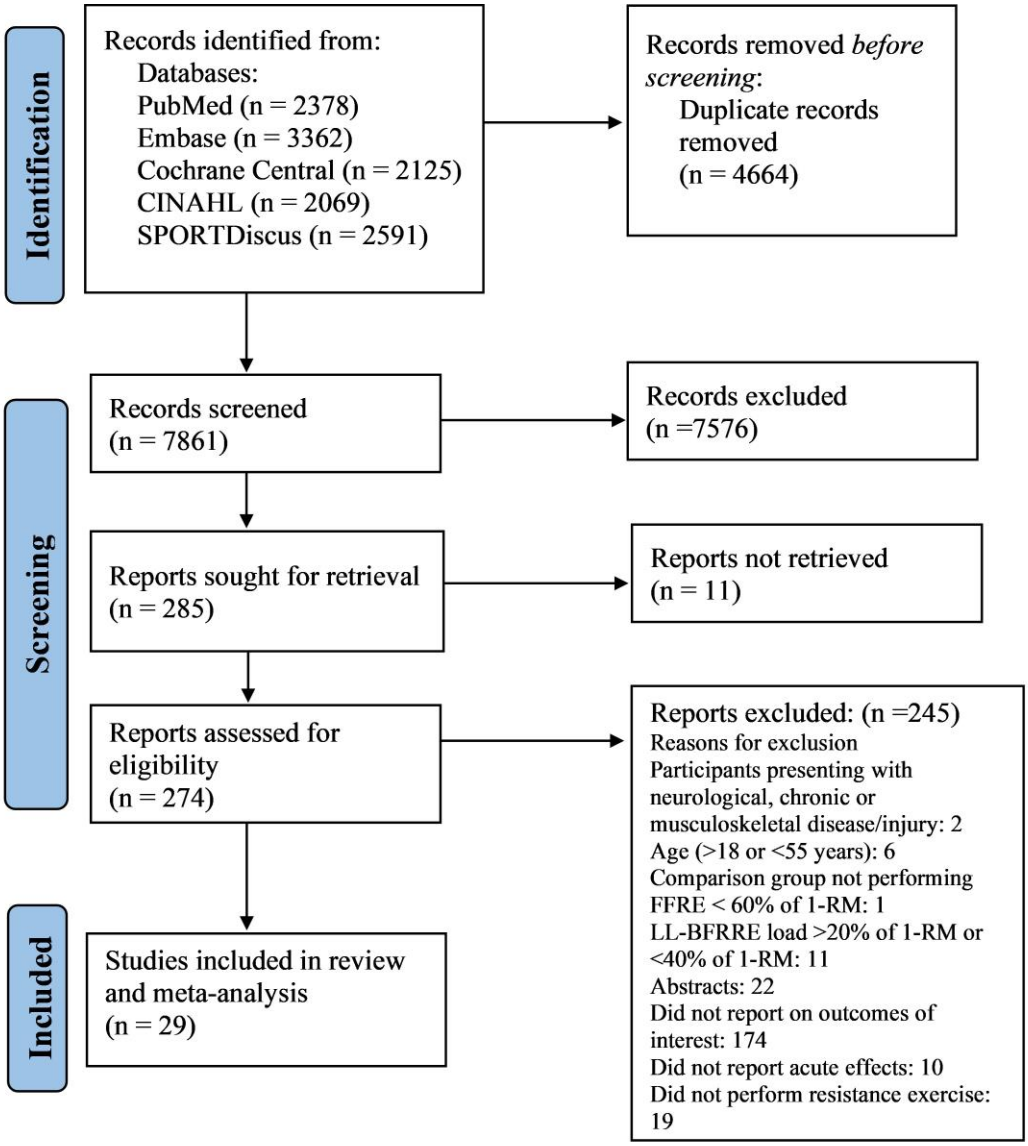


Figure 21: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow chart that presents the number of studies involved at each step of the search and screening process with reasons for exclusion. The figure is duplicated from Hjortshoej et al. (118) and used under the CC BY-NC 3.0 license.

Table 7 – Study quality and reporting assessment tool (TESTEX)

		Study quality						Study reporting								
Study	Year	Eligibility criteria specified	Randomization specified	Allocation concealment	Groups similar at baseline	Blinding of assessor	SUM	Outcome assessed in 85% of participants	Intention-to-treat analysis	Between-group statistical comparison reported	Point measures and measures of variability for all reported outcome	Activity monitoring in control groups	Relative exercise intensity remained constant	Exercise volume and energy expenditure	SUM	TOTAL
Bemben et al.	2022	1	0	0	0	0	1	1	1	2	1	0	1	0	6	7
Boeneo et al.	2018	0	0	1	1	0	2	0	0	2	0	0	1	1	4	6
Burgera et al.	2018	1	0	1	1	0	3	2	0	2	1	0	1	1	7	10
Centner et al.	2018	1	0	0	1	0	2	2	0	2	1	0	1	0	6	8
Drummond et al.	2008	1	0	1	1	0	3	1	0	2	0	0	1	0	4	7
Ellefsen et al.	2015	0	0	1	1	1	3	1	0	2	0	1	1	1	6	9
Ferguson et al.	2018	0	0	0	1	0	1	0	0	2	0	0	1	1	4	5
Fujita et al.	2007	0	0	1	1	0	2	0	0	2	0	1	1	1	5	7
Garten et al.	2015	1	0	0	1	0	2	0	0	2	0	0	1	1	4	6
Goldfarb et al.	2008	1	0	0	1	0	2	2	0	2	0	0	1	0	5	7
Hughes et al	2020	0	1	1	1	0	3	3	1	2	1	1	1	1	10	13
Kim et al.	2014	1	0	1	1	0	3	0	0	2	1	1	1	1	6	9
Kraemer et al.	2005	1	0	0	1	0	2	2	0	1	0	0	1	0	4	6
Larkin et al.	2012	1	0	1	1	0	3	2	0	2	1	1	1	1	8	11
Laurentino et al.	2022	1	0	0	1	0	2	1	0	2	0	0	1	0	4	6
Lima et al.	2021	1	0	1	1	0	3	2	1	2	1	1	1	1	9	12
Madarame et al.	2008	0	0	1	1	0	2	0	0	2	0	0	0	1	3	5
Manini et al.	2012	1	0	1	1	0	3	0	0	2	0	0	1	1	4	7
Neto et al.	2018	1	0	1	1	0	3	0	0	2	0	0	1	1	4	7
Ozaki et al.	2013	1	0	1	1	1	4	0	0	2	1	1	0	1	5	9
Ramis et al.	2020	1	0	1	1	1	4	2	0	2	1	0	0	1	6	10
Reeves et al.	2006	1	0	0	1	0	2	2	0	1	0	0	1	1	5	7
Shariffi et al.	2020	1	0	1	1	0	3	0	0	2	1	0	0	1	4	7
Takano et al.	2005	1	0	0	1	0	2	0	0	2	1	0	1	0	4	6
Takarada et al.	2004	0	0	0	1	0	1	1	0	0	0	0	1	0	2	3
Takarada et al.	2000	0	0	0	1	0	1	1	0	0	0	0	0	0	1	2
Vilaça-Alves	2023	1	0	0	1	0	2	1	0	2	1	0	1	1	6	8
Yinghao et al.	2021	1	1	0	1	1	4	2	1	2	0	0	1	0	6	10
Zhao et al.	2020	1	1	1	1	0	4	0	0	2	1	0	1	0	5	8

Table 7 is a presentation of study quality and study reporting using the Tool for assEssment of Study qualiTy and reporting in EXercise (TESTEX) assessment tool for training intervention studies. The score ranges from 0 – 15. The table is duplicated from Hjortshoej et al. (118) and used under the CC BY-NC 3.0 license.

10.2.2 Hormone responses

A total of six different hormones were included in the meta-analysis at one or more time point (initial, intermediate, and late). The hormones included: GH, testosterone, cortisol, insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), and noradrenalin (NA).

GH was investigated by a total of 13 studies (194,196,213–215,200,202,204,205,209–212), of which 11 investigated the initial response, nine investigated the intermediate response, and seven investigated the late response post-exercise time intervals. GH plasma production demonstrated no difference between LL-BFRT and overall FFRE in the initial post-exercise phase (SMD = 0.64 [95% CI -0.23, 1.51]). However, significant increases were demonstrated in the intermediate (SMD = 2.04 [95% CI 0.87, 3.22]) and late (SMD = 2.64 [95% CI 1.13, 4.16]) post-exercise time intervals. Sub-group analysis based on load intensity demonstrated a borderline significant increase in GH plasma production at the initial time interval (SMD = 1.69 [95% CI -0.03, 3.42]) for LL-BFRT compared to LL-FFRE, whereas significant increases were demonstrated at the intermediate (SMD = 3.39 [95% CI 1.54, 5.24]) and late (SMD = 3.55 [95% CI 1.59, 5.52]) post-exercise time intervals. Comparing LL-BFRT to HL-FFRE, no significant differences were observed at any time point. Data from the meta-analysis is presented in Figure 22 which is duplicated from Hjortshoej et al. (118).

Testosterone was investigated by eight studies (a reference was mistakenly included in the published article but it was not included in the analysis, results, and discussion) (189,196,202,204,209,210,214,215), of which seven investigated the initial response, six investigated the intermediate response, and three investigated the late response post-exercise time intervals. Testosterone plasma levels demonstrated no differences in the initial (SMD = 0.35 [95% CI -0.34, 1.05]) and intermediate (SMD = 0.55 [95% CI -0.26, 1.36]) post-exercise time intervals when comparing LL-BFRT to overall FFRE. For LL-BFRT compared to either HL-FFRE and LL-FFRE, sub-group analysis based on load intensity demonstrated no significant differences at the initial and intermediate post-exercise time intervals; However, a significant increase in testosterone plasma levels was observed at the late (SMD = 0.60 [95% CI 0.09, 1.10]) post-exercise phase for LL-BFRT compared to LL-FFRE.

Cortisol was investigated by seven studies (189,194,196,200,202,209,214), of which six investigated the initial response, four investigated the intermediate response, and one study investigated the late response post-exercise. Cortisol plasma levels did not differ between LL-BFRT and overall FFRE at the initial (SMD = 0.65 [95% CI -0.00, 1.31]) and intermediate (SMD = 0.60 [95% CI -0.47, 1.68]) post-exercise time intervals. Sub-group analysis based on load intensity did not reveal any differences in cortisol plasma levels at the initial and

intermediate post-exercise time intervals when comparing LL-BFRT to LL-FFRE and HL-FFRE, respectively. One study investigated the late post-exercise response and found an increase in plasma cortisol levels for LL-BFRT compared to LL-FFRE.

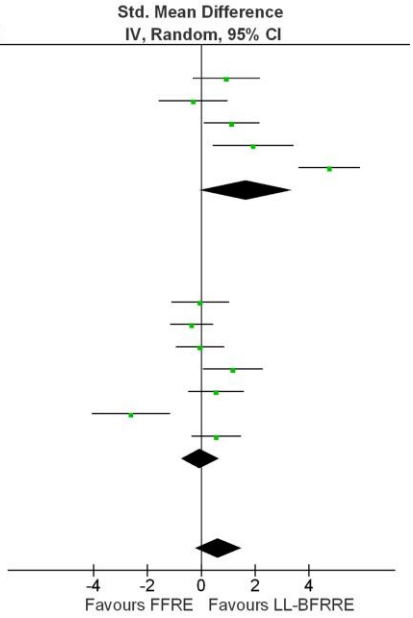
IGF-1 was investigated by a total of seven studies (189,193,196,202,205,211,215). Six studies investigated the initial response, and three investigated the intermediate and late responses post-exercise, respectively. However, meta-analysis could only be performed at the initial and intermediate post-exercise responses. There was no significant difference in IGF-1 plasma levels at the initial (SMD = 0.61 [95% CI -0.43, 1.65]) and intermediate (SMD = 0.34 [95% CI -0.41, 1.09]) post-exercise time intervals when comparing LL-BFRT to overall FFRE. Sub-group analysis based on load intensity showed a borderline significant increase in IGF-1 plasma levels at the initial (SMD = 1.14 [95% CI -0.15, 2.42]) and intermediate (SMD = 0.88 [95% CI -0.14, 1.91]) post-exercise time point in LL-BFRT compared to LL-FFRE.

VEGF was investigated by four studies (122,210,211,216). Three studies investigated the initial response, one investigated the intermediate response, and two investigated the late post-exercise response. In the initial post-exercise time interval, VEGF production increased to a similar extent with LL-BFRT and overall FFRE (SMD = 1.54 [95% CI -0.47, 3.55]).

NA was investigated by a total of four studies (204,207,211,213), of which four investigated the initial response, three investigated the intermediate response, and four investigated the late response post-exercise. Comparing LL-BFRT to overall FFRE, there was no significant difference during the initial (SMD = 2.06 [95% CI -0.12, 4.24]) and late (SMD = 0.01 [95% CI -0.85, 0.86]) post-exercise time intervals. NA plasma levels increased in the initial post-exercise phase in favor of LL-BFRT when compared to LL-FFRE (SMD = 2.89 [95% CI 1.13, 4.65]) with no differences observed in the intermediate and late post-exercise time intervals.

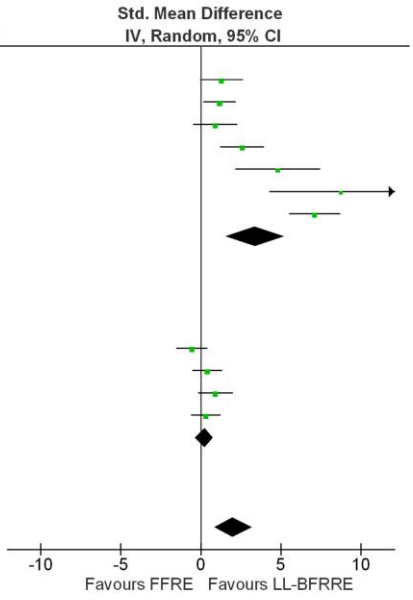
Initial phase

Study or Subgroup	LL-BFRRE Mean	SD	Total	FFRE Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 LL-BFRRE vs LL-FFRE								
Fujita et al. 2007	1.6	1.63	6	0.37	0.59	6	8.1%	0.93 [-0.29, 2.14]
Madarame et al. 2008	2.21	2.98	5	3.18	2.85	5	8.0%	-0.30 [-1.55, 0.95]
Takano et al. 2005	0.38	0.27	9	0.15	0.05	9	8.5%	1.13 [0.11, 2.14]
Takarada et al. 2000	14.2	4.98	6	5.42	3.27	6	7.6%	1.92 [0.45, 3.39]
Yinghao et al. 2021	6.38	0.7	25	3.23	0.6	25	8.3%	4.76 [3.64, 5.87]
Subtotal (95% CI)			**51**			**51**	**40.5%**	**1.69 [-0.03, 3.42]**
Heterogeneity: Tau² = 3.47; Chi² = 41.33, df = 4 (P < 0.00001); I² = 90%								
Test for overall effect: Z = 1.93 (P = 0.05)								
1.1.2 LL-BFRRE vs HL-FFRE								
Ellefsen et al. 2015	0.65	0.81	7	0.68	0.39	7	8.5%	-0.04 [-1.09, 1.00]
Kim et al. 2014	4.23	5.05	13	6.34	6.2	13	8.9%	-0.36 [-1.14, 0.41]
Manini et al. 2012	1.15	1.62	10	1.25	2.24	10	8.8%	-0.05 [-0.93, 0.83]
Reeves et al. 2006	8.11	6.11	8	2	3.37	8	8.4%	1.17 [0.09, 2.26]
Shariffi et al. A 2020	1.95	1.43	8	1.33	0.5	8	8.5%	0.55 [-0.46, 1.55]
Shariffi et al. B 2020	1.41	0.51	8	3.35	0.85	8	7.6%	-2.62 [-4.05, -1.18]
Vilaça-Alves et al. 2023	1.91	2.36	10	0.82	1.22	10	8.7%	0.56 [-0.34, 1.45]
Subtotal (95% CI)			**64**			**64**	**59.5%**	**-0.04 [-0.73, 0.66]**
Heterogeneity: Tau² = 0.61; Chi² = 20.73, df = 6 (P = 0.002); I² = 71%								
Test for overall effect: Z = 0.10 (P = 0.92)								
Total (95% CI)			**115**			**115**	**100.0%**	**0.64 [-0.23, 1.51]**
Heterogeneity: Tau² = 2.05; Chi² = 89.39, df = 11 (P < 0.00001); I² = 88%								
Test for overall effect: Z = 1.44 (P = 0.15)								
Test for subgroup differences: Chi² = 3.33, df = 1 (P = 0.07), I² = 70.0%								



Intermediate phase

Study or Subgroup	LL-BFRRE Mean	SD	Total	FFRE Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.1.1 LL-BFRRE vs LL-FFRE								
Fujita et al. 2007	5.53	4.91	6	0.6	0.88	6	9.6%	1.29 [-0.00, 2.59]
Laurentino et al. A 2022	7	5.42	10	2.05	1.96	10	10.1%	1.16 [0.20, 2.13]
Madarame et al. 2008	11.17	7.66	5	5.29	3.24	5	9.5%	0.90 [-0.44, 2.24]
Takano et al. 2005	3.09	1.43	9	0.32	0.2	9	9.5%	2.58 [1.26, 3.91]
Takarada et al. 2000	32.57	5.84	6	6.33	4.1	6	7.1%	4.80 [2.20, 7.40]
Takarada et al. 2004	32.64	0.96	6	6.21	3.83	6	4.3%	8.74 [4.32, 13.15]
Yinghao et al. 2021	10.6	0.96	25	5.05	0.51	25	9.1%	7.11 [5.55, 8.66]
Subtotal (95% CI)			**67**			**67**	**59.3%**	**3.39 [1.54, 5.24]**
Heterogeneity: Tau² = 5.21; Chi² = 60.45, df = 6 (P < 0.00001); I² = 90%								
Test for overall effect: Z = 3.59 (P = 0.0003)								
2.1.2 LL-BFRRE vs HL-FFRE								
Laurentino et al. B 2022	7	5.42	10	11.39	9.33	9	10.2%	-0.56 [-1.48, 0.36]
Manini et al. 2012	2.88	1.73	10	2.14	1.87	10	10.2%	0.39 [-0.49, 1.28]
Reeves et al. 2006	6.87	8.37	8	1.16	1.22	8	10.0%	0.90 [-0.14, 1.95]
Vilaça-Alves et al. 2023	3.19	3.02	10	2.28	2.79	10	10.2%	0.30 [-0.58, 1.18]
Subtotal (95% CI)			**38**			**37**	**40.7%**	**0.24 [-0.34, 0.81]**
Heterogeneity: Tau² = 0.12; Chi² = 4.55, df = 3 (P = 0.21); I² = 34%								
Test for overall effect: Z = 0.81 (P = 0.42)								
Total (95% CI)			**105**			**104**	**100.0%**	**2.04 [0.87, 3.22]**
Heterogeneity: Tau² = 3.30; Chi² = 99.78, df = 10 (P < 0.00001); I² = 90%								
Test for overall effect: Z = 3.41 (P = 0.0006)								
Test for subgroup differences: Chi² = 10.20, df = 1 (P = 0.001), I² = 90.2%								



Late phase

Study or Subgroup	LL-BFRRE Mean	SD	Total	FFRE Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.1.1 LL-BFRRE vs LL-FFRE								
Fujita et al. 2007	4.47	3.37	6	0.55	0.66	6	15.2%	1.49 [0.14, 2.84]
Madarame et al. 2008	10.14	5.12	5	3.28	2.55	5	14.7%	1.53 [0.02, 3.04]
Takano et al. 2005	8.49	1.08	9	0.24	0.14	9	8.1%	10.20 [6.32, 14.09]
Takarada et al. 2000	16.15	4.37	6	5.7	2.39	6	14.0%	2.74 [0.99, 4.49]
Yinghao et al. 2021	10.38	1.78	25	4.25	0.6	25	15.9%	4.54 [3.46, 5.62]
Subtotal (95% CI)			**51**			**51**	**68.0%**	**3.55 [1.59, 5.52]**
Heterogeneity: Tau² = 4.05; Chi² = 29.51, df = 4 (P < 0.00001); I² = 86%								
Test for overall effect: Z = 3.55 (P = 0.0004)								
3.1.2 LL-BFRRE vs HL-FFRE								
Ellefsen et al. 2015	0.66	0.47	7	0.49	0.38	7	15.9%	0.37 [-0.69, 1.43]
Manini et al. 2012	4.38	1.7	10	2.13	1.79	10	16.1%	1.23 [0.26, 2.21]
Subtotal (95% CI)			**17**			**17**	**32.0%**	**0.83 [-0.01, 1.67]**
Heterogeneity: Tau² = 0.10; Chi² = 1.38, df = 1 (P = 0.24); I² = 27%								
Test for overall effect: Z = 1.93 (P = 0.05)								
Total (95% CI)			**68**			**68**	**100.0%**	**2.64 [1.13, 4.16]**
Heterogeneity: Tau² = 3.47; Chi² = 51.39, df = 6 (P < 0.00001); I² = 88%								
Test for overall effect: Z = 3.41 (P = 0.0006)								
Test for subgroup differences: Chi² = 6.26, df = 1 (P = 0.01), I² = 84.0%								

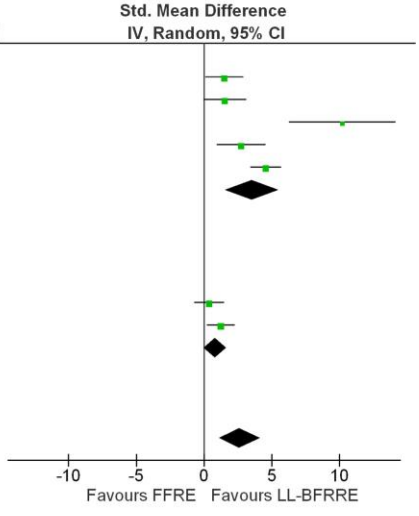


Figure 22: Forest plot for growth hormone production initial (<10 minutes), intermediate (10-20 minutes), and late (>30 minutes) phase post-exercise. Data are based on change scores (pre – post-exercise). A random effects model was utilized for statistics and data are presented using standardized mean difference, SMD. Sub-group analysis was performed on load intensity with the total combined effect presented with the lowest rhombi. Parentheses, 95% confidence interval.
FFRE, free flow resistance exercise. LL-FFRE, low-load free flow resistance exercise. HL-FFRE, heavy-load free flow resistance exercise. LL-BFRRE, low-load blood flow restriction resistance exercise. LL-BFRRE = LL-BFRT. The figure is duplicated from Hjortshoej et al. (118) and used under the CC BY-NC 3.0 license.

10.2.3 Immune responses

Interleukin-6 response was investigated by a total of three studies (191,213,216). All studies investigated the initial response post-exercise, and one study also evaluated the intermediate and late responses post-exercise. The sub-group analysis demonstrated no significant difference between LL-BFRT and LL-FFRE (SMD = 1.79 [95% CI -0.58, 4.17]).

Creatine phosphokinase was investigated by two studies in the initial and late post-exercise time intervals (206,213). LL-BFRT and overall FFRE demonstrated no differences at the initial (SMD = -0.03 [95% CI -0.57, 0.52]) or late (SMD = -1.32 [95% CI -2.72, 0.09]) post-exercise time intervals. However, an elevated response was observed for HL-FFRE compared to LL-BFRT in the late post-exercise time interval (SMD = -2.03 [95% CI -2.83, -1.24]). Data from the meta-analysis are presented in Figure 23 which is duplicated from Hjortshoej et al. (118).

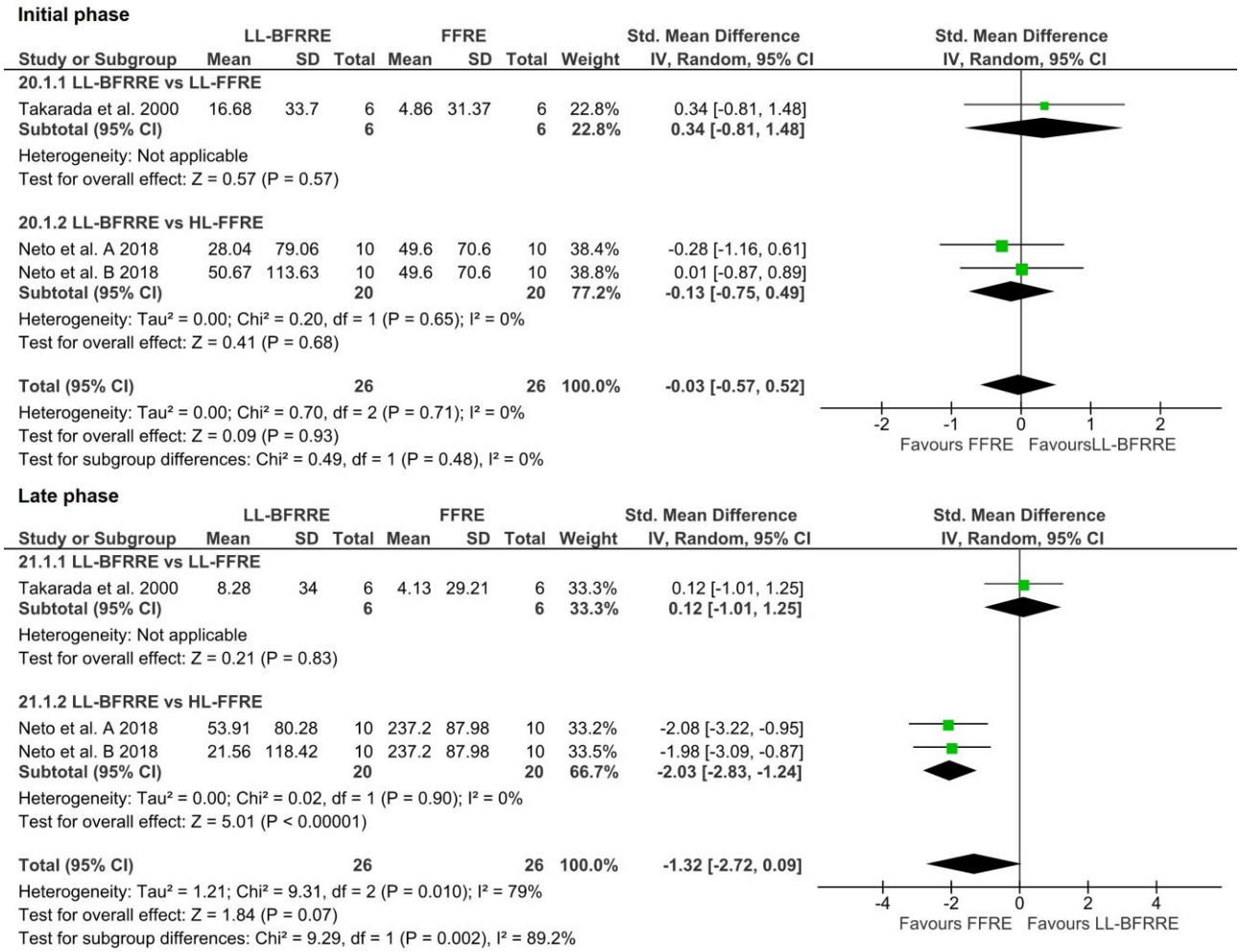


Figure 23: Forest plot for creatine phosphokinase production initial (<10 minutes), and late (>30 minutes) phases post-exercise. Data are based on change scores (pre – post-exercise). A random effects model was utilized for statistics and data are presented using standardized mean difference, SMD. Sub-group analysis was performed on load intensity with the total combined effect presented with the lowest rhombi. Parentheses, 95% confidence interval.
FFRE, free flow resistance exercise. LL-FFRE, low-load free flow resistance exercise. HL-FFRE, heavy-load free flow resistance exercise. LL-BFRRE, low-load blood flow restriction resistance exercise. LL-BFRRE = LL-BFRT. The figure is duplicated from Hjortshoej et al. (118) and used under the CC BY-NC 3.0 license.

10.2.4 Oxidative stress responses

Nitric oxide was investigated in two studies in the initial and one study in the late post-exercise time intervals (190,207). No differences were observed when comparing LL-BFRT to overall FFRE (SMD = -0.44 [95% CI -0.34, 1.22]). Sub-group analysis demonstrated no differences when comparing LL-BFRT to LL-FFRE (SMD = 0.25 [95% CI -0.59, 1.09]) nor when comparing LL-BFRT to HL-FFRE (SMD = -0.53 [95% CI -0.83, 1.89]).

Protein carbonyls was assessed by three studies (198,203,206), of which three investigated the initial response and one study investigated the intermediate and late responses

post-exercise. All studies compared LL-BFRT to HL-FFRE, revealing borderline significant increased plasma levels of PC for HL-FFRE compared to LL-BFRT in the initial post-exercise time interval (SMD = -1.50 [95% CI -3.19, 0.20]). Data from the meta-analysis are presented in Figure 24 which is duplicated from Hjortshoej et al. (118).

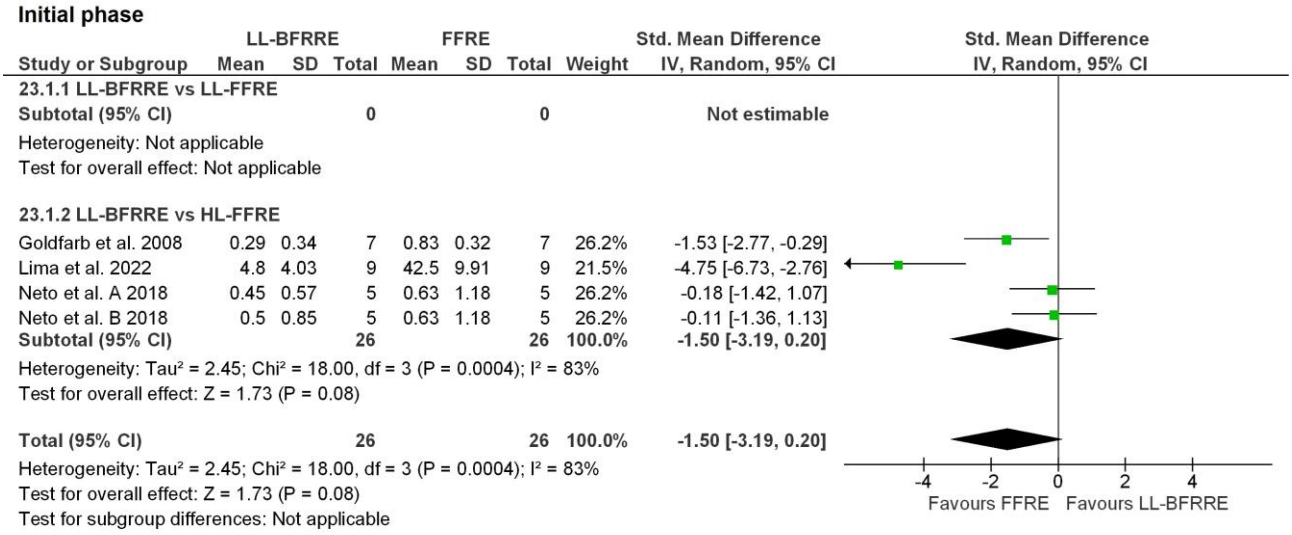


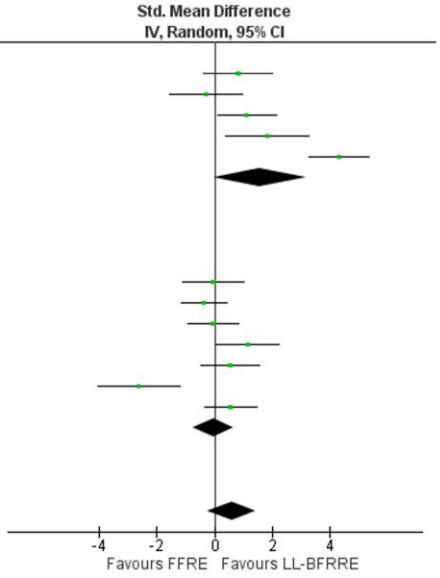
Figure 24: Forest plot for protein carbonyls production initial (<10 minutes) phase post-exercise. Data are based on change scores (pre – post-exercise). A random effects model was utilized for statistics and data are presented using standardized mean difference, SMD. Sub-group analysis was performed on load intensity with the total combined effect presented with the lowest rhombi. Parentheses, 95% confidence interval.
FFRE, free flow resistance exercise. LL-FFRE, low-load free flow resistance exercise. HL-FFRE, heavy-load free flow resistance exercise. LL-BFRRE, low-load blood flow restriction resistance exercise. LL-BFRRE = LL-BFRT. The figure is duplicated from Hjortshoej et al. (118) and used under the CC BY-NC 3.0 license.

10.2.4 Sensitivity analyses

In this section, sensitivity analyses using a correlation coefficient of 0.6 were used to determine SDchange and are presented in figure 25-29. The following analyses that will be presented are GH, testosterone, NA, creatine phosphate and protein carbonyls. Testosterone at the late phase was the only change due to the sensitivity analysis. The reported analysis using a correlation coefficient of 0.8 demonstrated a significant increase in testosterone plasma levels was observed at the late (SMD = 0.60 [95% CI 0.09, 1.10]) post-exercise phase for LL-BFFT compared to LL-FFRE. In contrast, the sensitivity analysis demonstrated a borderline significant increase (SMD = 0.45 [95% CI -0.03, 0.92]) in favor of LL-BFRT compared to LL-FFRE. The other variables investigated in Study II are presented in the appendix.

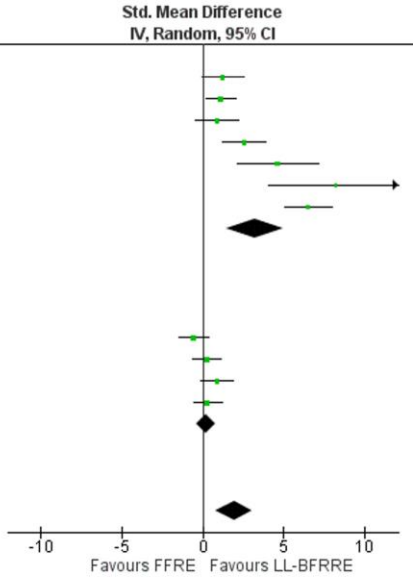
Initial phase

Study or Subgroup	LL-BFRRE Mean	SD	Total	FFRE Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 LL-BFRRE vs LL-FFRE								
Fujita et al. 2007	1.6	1.79	6	0.37	0.77	6	8.1%	0.82 [-0.38, 2.02]
Madarame et al. 2008	2.21	3.13	5	3.18	3.02	5	8.0%	-0.28 [-1.53, 0.97]
Takano et al. 2005	0.38	0.27	9	0.15	0.07	9	8.5%	1.11 [0.10, 2.12]
Takarada et al. 2000	14.2	5.16	6	5.42	3.47	6	7.5%	1.84 [0.40, 3.29]
Yinghao et al. 2021	6.38	0.77	25	3.23	0.66	25	8.4%	4.32 [3.28, 5.37]
Subtotal (95% CI)			**51**			**51**	**40.6%**	**1.58 [-0.03, 3.18]**
Heterogeneity: Tau² = 2.98; Chi² = 37.40, df = 4 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 1.93 (P = 0.05)								
1.1.2 LL-BFRRE vs HL-FFRE								
Ellefsen et al. 2015	0.65	0.85	7	0.68	0.47	7	8.4%	-0.04 [-1.09, 1.01]
Kim et al. 2014	4.23	5.05	13	6.34	6.2	13	9.0%	-0.36 [-1.14, 0.41]
Manini et al. 2012	1.15	2.29	10	1.25	2.47	10	8.8%	-0.04 [-0.92, 0.84]
Reeves et al. 2006	8.11	6.25	8	2	3.4	8	8.4%	1.15 [0.07, 2.23]
Shariffi et al. A 2020	1.95	1.43	8	1.33	0.5	8	8.5%	0.55 [-0.46, 1.55]
Shariffi et al. B 2020	1.41	0.51	8	3.35	0.85	8	7.6%	-2.62 [-4.05, -1.18]
Vilaça-Alves et al. 2023	1.91	2.38	10	0.82	1.23	10	8.7%	0.55 [-0.35, 1.45]
Subtotal (95% CI)			**64**			**64**	**59.4%**	**-0.04 [-0.73, 0.65]**
Heterogeneity: Tau² = 0.60; Chi² = 20.56, df = 6 (P = 0.002); I² = 71%								
Test for overall effect: Z = 0.11 (P = 0.92)								
Total (95% CI)			**115**			**115**	**100.0%**	**0.60 [-0.24, 1.44]**
Heterogeneity: Tau² = 1.90; Chi² = 84.65, df = 11 (P < 0.00001); I² = 87%								
Test for overall effect: Z = 1.39 (P = 0.16)								
Test for subgroup differences: Chi² = 3.28, df = 1 (P = 0.07), I² = 69.5%								



Intermediate phase

Study or Subgroup	LL-BFRRE Mean	SD	Total	FFRE Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.1.1 LL-BFRRE vs LL-FFRE								
Fujita et al. 2007	5.53	5.05	6	0.6	1.05	6	9.6%	1.25 [-0.04, 2.53]
Laurentino et al. A 2022	7	5.56	10	2.05	2.09	10	10.1%	1.13 [0.17, 2.09]
Madarame et al. 2008	11.17	7.79	5	5.29	3.41	5	9.5%	0.88 [-0.45, 2.22]
Takano et al. 2005	3.09	1.43	9	0.32	0.22	9	9.5%	2.58 [1.25, 3.91]
Takarada et al. 2000	32.57	6.02	6	6.33	4.28	6	7.1%	4.64 [2.11, 7.17]
Takarada et al. 2004	32.64	0.98	6	6.21	4.06	6	4.4%	8.26 [4.07, 12.45]
Yinghao et al. 2021	10.6	1.03	25	5.05	0.58	25	9.3%	6.54 [5.09, 7.98]
Subtotal (95% CI)			**67**			**67**	**59.4%**	**3.23 [1.47, 4.99]**
Heterogeneity: Tau² = 4.70; Chi² = 56.81, df = 6 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 3.60 (P = 0.0003)								
2.1.2 LL-BFRRE vs HL-FFRE								
Laurentino et al. B 2022	7	5.56	10	11.39	9.49	9	10.2%	-0.55 [-1.47, 0.37]
Manini et al. 2012	2.88	2.42	10	2.14	2.64	10	10.2%	0.28 [-0.60, 1.16]
Reeves et al. 2006	6.87	8.51	8	1.16	1.25	8	10.0%	0.89 [-0.15, 1.93]
Vilaça-Alves et al. 2023	3.19	3.04	10	2.28	2.8	10	10.2%	0.30 [-0.58, 1.18]
Subtotal (95% CI)			**38**			**37**	**40.6%**	**0.20 [-0.35, 0.76]**
Heterogeneity: Tau² = 0.10; Chi² = 4.28, df = 3 (P = 0.23); I² = 30%								
Test for overall effect: Z = 0.72 (P = 0.47)								
Total (95% CI)			**105**			**104**	**100.0%**	**1.95 [0.81, 3.10]**
Heterogeneity: Tau² = 3.14; Chi² = 96.91, df = 10 (P < 0.00001); I² = 90%								
Test for overall effect: Z = 3.35 (P = 0.0008)								
Test for subgroup differences: Chi² = 10.35, df = 1 (P = 0.001), I² = 90.3%								



Late phase

Study or Subgroup	LL-BFRRE Mean	SD	Total	FFRE Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.1.1 LL-BFRRE vs LL-FFRE								
Fujita et al. 2007	4.47	3.51	6	0.55	0.84	6	15.2%	1.42 [0.09, 2.74]
Madarame et al. 2008	10.14	5.26	5	3.28	2.72	5	14.7%	1.48 [-0.01, 2.97]
Takano et al. 2005	8.49	1.08	9	0.24	0.14	9	8.1%	10.20 [6.32, 14.09]
Takarada et al. 2000	16.15	4.56	6	5.7	2.59	6	14.1%	2.60 [0.90, 4.30]
Yinghao et al. 2021	10.38	1.84	25	4.25	0.66	25	15.9%	4.37 [3.32, 5.41]
Subtotal (95% CI)			**51**			**51**	**68.0%**	**3.44 [1.52, 5.36]**
Heterogeneity: Tau² = 3.87; Chi² = 29.37, df = 4 (P < 0.00001); I² = 86%								
Test for overall effect: Z = 3.51 (P = 0.0004)								
3.1.2 LL-BFRRE vs HL-FFRE								
Ellefsen et al. 2015	0.66	0.5	7	0.49	0.46	7	15.9%	0.33 [-0.73, 1.39]
Manini et al. 2012	4.38	2.39	10	2.13	2.53	10	16.2%	0.88 [-0.05, 1.80]
Subtotal (95% CI)			**17**			**17**	**32.0%**	**0.64 [-0.06, 1.34]**
Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 1 (P = 0.45); I² = 0%								
Test for overall effect: Z = 1.80 (P = 0.07)								
Total (95% CI)			**68**			**68**	**100.0%**	**2.51 [1.00, 4.02]**
Heterogeneity: Tau² = 3.45; Chi² = 53.36, df = 6 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 3.26 (P = 0.001)								
Test for subgroup differences: Chi² = 7.22, df = 1 (P = 0.007), I² = 86.2%								

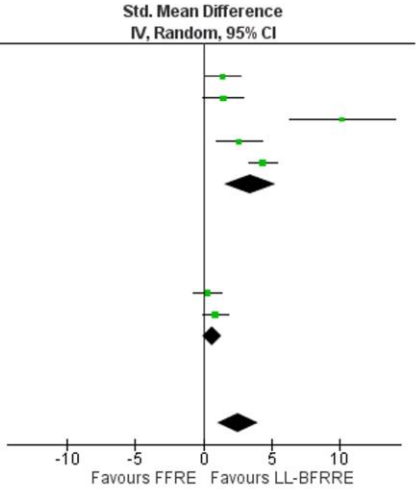


Figure 25: Sensitivity analysis demonstrating forest plot for growth hormone production initial (<10 minutes), intermediate (10-20 minutes), and late (>30 minutes) phases post-exercise. Data are based on change scores (pre – post-exercise). A random effects model was utilized for statistics and data are presented using standardized mean difference, SMD. Sub-group analysis was performed on load intensity with the total combined effect presented with the lowest rhombi. Parentheses, 95% confidence interval.
FFRE, free flow resistance exercise. LL-FFRE, low-load free flow resistance exercise. HL-FFRE, heavy-load free flow resistance exercise. LL-BFRRE, low-load blood flow restriction resistance exercise. LL-BFRRE = LL-BFRT.

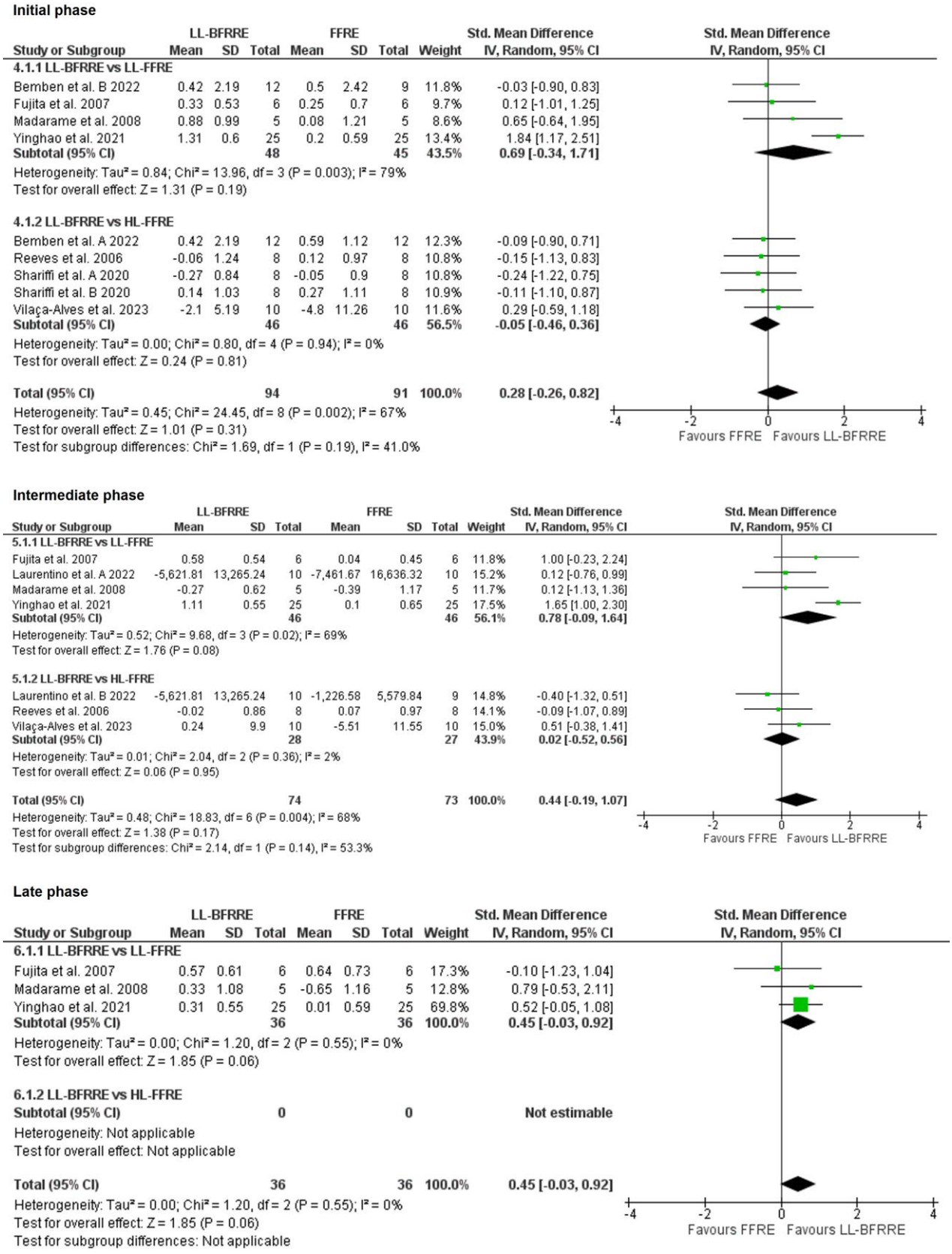


Figure 26: Sensitivity analysis demonstrating forest plot for testosterone production initial (<10 minutes), intermediate (10-20 minutes) and late (>30 minutes) phases post-exercise. Data are based on change scores (pre – post-exercise). A random effects model was utilized for statistics and data are presented using standardized mean

difference, SMD. Sub-group analysis was performed on load intensity with the total combined effect presented with the lowest rhombi. Parentheses, 95% confidence interval.
FFRE, free flow resistance exercise. LL-FFRE, low-load free flow resistance exercise. HL-FFRE, heavy-load free flow resistance exercise. LL-BFRRE, low-load blood flow restriction resistance exercise. LL-BFRRE = LL-BFRT.

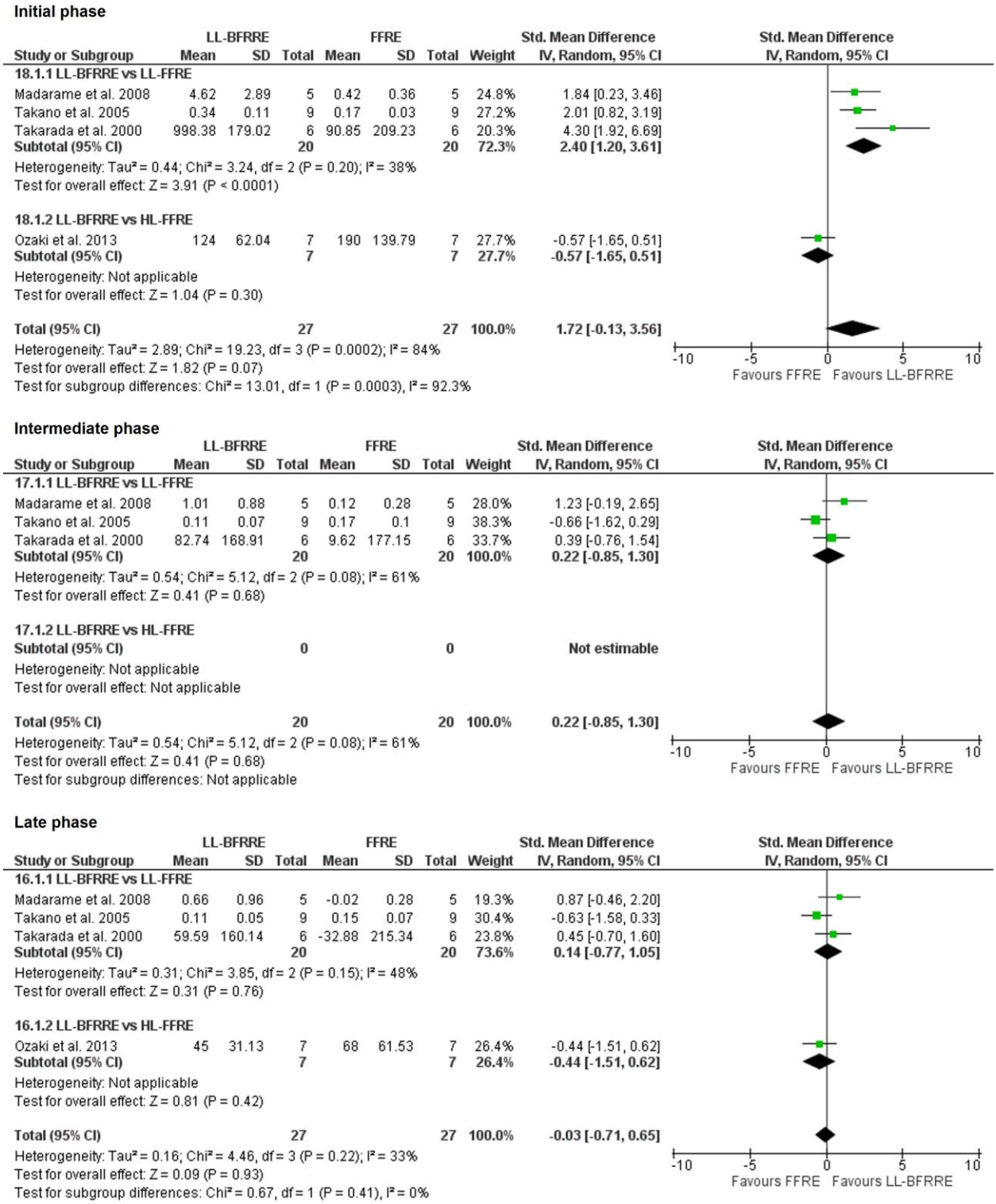


Figure 27: Sensitivity analysis demonstrating forest plot for noradrenaline production initial (<10 minutes), intermediate (10-20 minutes) and late (>30 minutes) phases post-exercise. Data are based on change scores (pre – post-exercise). A random effects model was utilized for statistics and data are presented using standardized mean difference, SMD. Sub-group analysis was performed on load intensity with the total combined effect presented with the lowest rhombi. Parentheses, 95% confidence interval.

FFRE, free flow resistance exercise. LL-FFRE, low-load free flow resistance exercise. HL-FFRE, heavy-load free flow resistance exercise. LL-BFRRE, low-load blood flow restriction resistance exercise. LL-BFRRE = LL-BFRT.

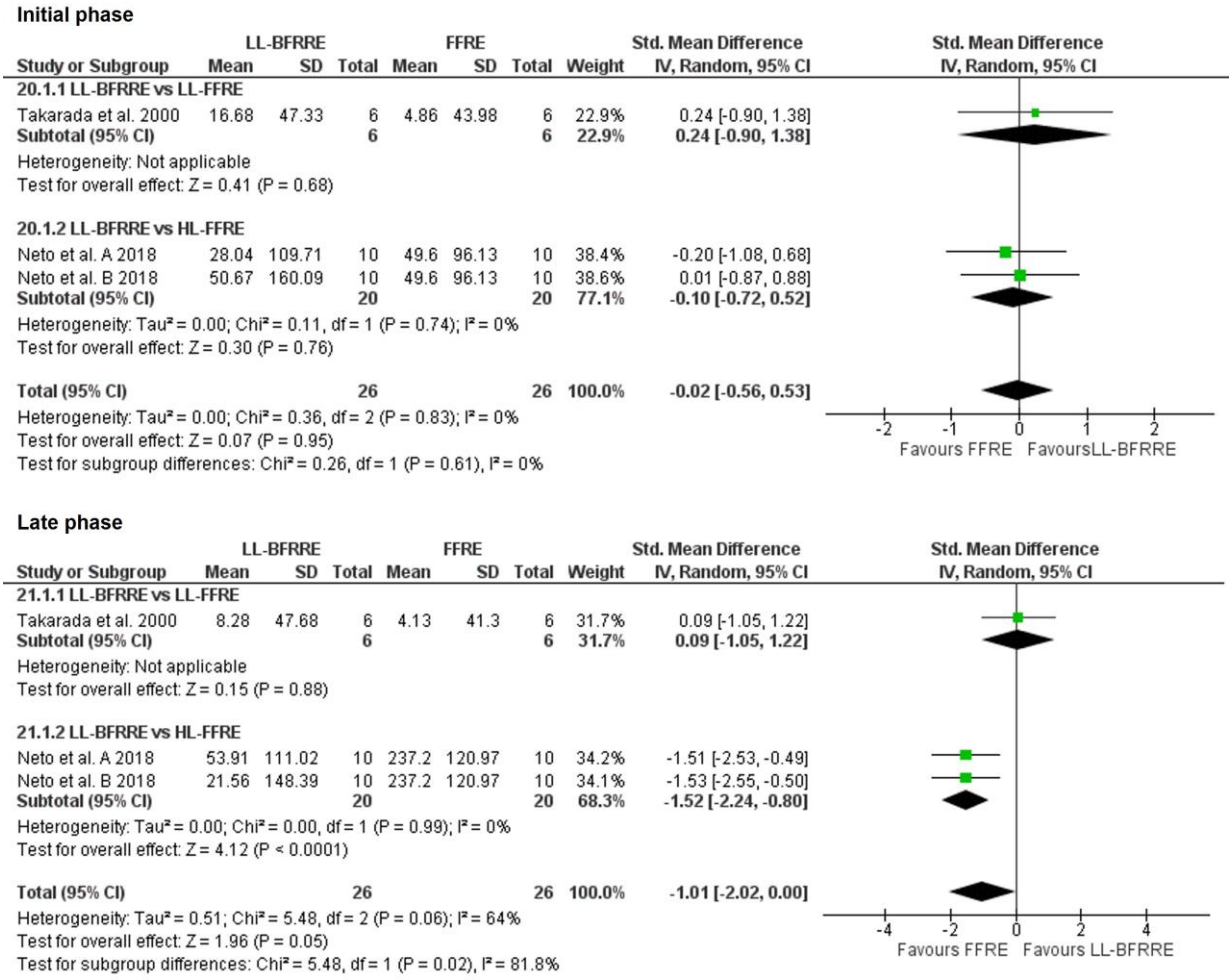


Figure 28: Sensitivity analysis demonstrating forest plot for creatine phosphokinase production at initial (<10 minutes), and late (>30 minutes) phases post-exercise. Data are based on change scores (pre – post-exercise). A random effects model was utilized for statistics and data are presented using standardized mean difference, SMD. Sub-group analysis was performed on load intensity with the total combined effect presented with the lowest rhombi. Parentheses, 95% confidence interval.
FFRE, free flow resistance exercise. LL-FFRE, low-load free flow resistance exercise. HL-FFRE, heavy-load free flow resistance exercise. LL-BFRRE, low-load blood flow restriction resistance exercise. LL-BFRRE = LL-BFRT.

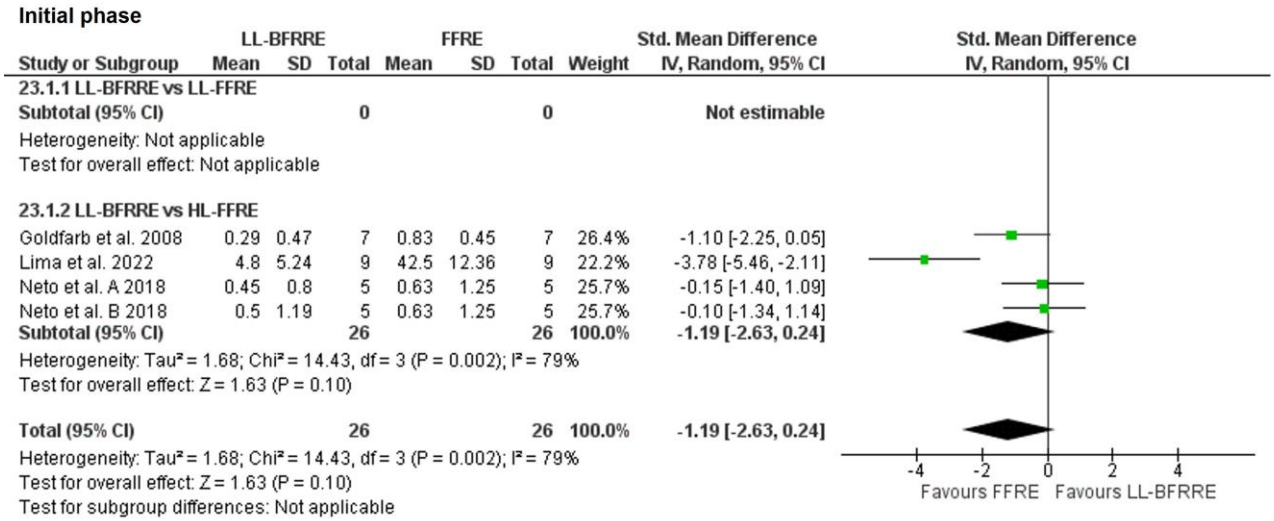


Figure 29: Sensitivity analysis demonstrating forest plot for protein carbonyls production at initial (<10 minutes) phase post-exercise. Data are based on change scores (pre – post-exercise). A random effects model was utilized for statistics and data are presented using standardized mean difference, SMD. Sub-group analysis was performed on load intensity with the total combined effect presented with the lowest rhombi. Parentheses, 95% confidence interval.
FFRE, free flow resistance exercise. LL-FFRE, low-load free flow resistance exercise. HL-FFRE, heavy-load free flow resistance exercise. LL-BFRRE, low-load blood flow restriction resistance exercise. LL-BFRRE = LL-BFRT.

10.3 Summary of main findings in study III

Paper III

Baseline data from a total of 57 participants from two randomized clinical trials were included in the study. The participants all had symptomatic unilateral patellar tendinopathy. US imaging was all performed using the same US protocol and settings. The participant's demographic characteristics are presented in Table 8.

Table 8 – Participant demographic Study III

Age (years)	30.59 ± 8.24
Height (cm)	184.88 ± 7.51
Weight (kg)	84.45 ± 10.12
BMI (m^2/kg)	24.71 ± 2.63
VISA-P score	59.44 ± 15.55
SLDS Score*	4.0, 1st quartile 2.5, 3rd quartile 5.5, range 1-7.5
Symptom duration (months)*	8.0, 1st quartile 5.0, 3rd quartile 11.0, range 3.0-36.0
Physical activity (hours pr. week)	6.38 ± 4.60

Table 8 represents demographic data (n=57). Data are presented as mean and standard deviation unless otherwise stated. *For SLDS score and Symptom duration median, 1st and 3rd quartile, and range are presented. BMI, body mass index. VISA-P, Victorian Institute of Sports Assessment – Patella Questionnaire. SLDS, single-leg decline squat. Table is duplicated from Paper III. The table is used under the CC BY-NC 3.0 license and published in Hjortshoej et al. (179).

10.3.1 Power Doppler activity

There was significantly greater PD activity in the symptomatic tendon compared to the asymptomatic tendon. The data were distributed in a non-parametric fashion. The median PD activity was 25.6 mm^2 (interquartile range 14.9, 41.6; range: 0.1, 109.1) for the symptomatic tendon compared to 0.00 mm^2 (0.00, 0.00; range: 0.00, 12.6) with a p-value of $p< 0.001$. The data for PD activity are presented in Table 9.

10.3.2 Tendon structure

Tendon structure was evaluated at both the symptomatic and asymptomatic tendon and included tendon length, tendon thickness (proximal, mid, and distal), and tendon echogenicity (whole tendon and ROI). Tendon length did not demonstrate any difference between symptomatic and asymptomatic tendon (mean difference 0.4 ± 2.9 mm; 95% CI -0.4, 1.2). Tendons were significantly thicker at the symptomatic tendon compared to the asymptomatic tendon at the proximal (mean difference 2.5 ± 1.9 mm; 95% CI 2.0, 3.0), mid (mean difference 0.8 ± 1.3 mm; 95% CI 0.5, 1.1), and distal (mean difference 0.2 ± 0.6 mm; 95% CI 0.1;0.4) part of the tendon. Likewise, whole tendon and ROI echogenicity were lower for the symptomatic tendon compared to the asymptomatic tendon. The data for tendon structure are presented in Table 9.

Table 9 – Absolute values for PD activity and tendon structure

	Symptomatic tendon (n=57) Mean ± SD	Asymptomatic tendon (n=57) Mean ± SD	Ratio	Mean difference ± SD	95% CI	p-value
Power Doppler activity (mm^2)*	25.6 (14.9; 41.6) (range: 0.1 – 109.1)	0.00 (0.00; 0.00) (range: 0.00 – 12.6)		Na	Na	p< 0.001
Tendon length (mm)	53.3 ± 5.3	52.9 ± 5.1		0.4 ± 2.9	-0.4; 1.2	P= 0.284
Tendon thickness – proximal (mm)	7.6 ± 1.9	5.1 ± 0.6	1.50 ± 0.38	2.5 ± 1.9	2.0; 3.0	p< 0.001
Tendon thickness – mid (mm)	5.2 ± 1.4	4.4 ± 0.5	1.18 ± 0.26	0.8 ± 1.3	0.5;1.1	p< 0.001
Tendon thickness – distal (mm)	4.9 ± 0.7	4.6 ± 0.5	1.06 ± 0.13	0.2 ± 0.6	0.1;0.4	P= 0.004
Echogenicity whole tendon (A.U.)	80.7 ± 11.1	92.0 ± 9.5	0.88 ± 0.10	-11.4 ± 9.6	-13.9; -8.8	p< 0.001
Echogenicity ROI (A.U.)	62.1 ± 14.3	85.9 ± 18.6	0.75 ± 0.21	-23.8 ± 20.1	-29.1; -18.5	p< 0.001

Table 9 demonstrates the average absolute measurement value. All analyses are performed using a paired t-test unless stated otherwise. SD, standard deviation. *, Wilcoxon signed rank test and values are presented as median (1^{st} quartile; 3^{rd} quartile) and range. Na, not applicable. ROI, region of interest (echogenicity intensity at injury site only). A.U., arbitrary units. The table is duplicated from Paper III. The table is used under the CC BY-NC 3.0 license and published in Hjortshoej et al. (179)

10.3.3 Intra-rater reliability

Intra-rater reliability was assessed on raw values and delta values for PD activity and tendon structure for both the symptomatic and asymptomatic leg. Intra-rater reliability for raw values demonstrated good-to-excellent reliability, and the ICC scores ranged from 0.81-0.99 on the symptomatic tendon. On the asymptomatic tendon, intra-rater reliability demonstrated moderate-to-excellent reliability, and the ICC scores ranged from 0.74-0.99. The TE% ranged from 1.09-37.72 for measurements on the symptomatic and asymptomatic tendon. The TE was 1.53 and 0.25 for PD activity on the symptomatic and asymptomatic tendon, respectively. TE for tendon length and tendon thickness ranged from 0.30-0.96 and 0.23-0.85 for the symptomatic and asymptomatic tendon. Lastly, TE for echogenicity ranged from 1.09-1.33 for the symptomatic and the asymptomatic tendon, respectively. Data for intra-rater reliability are presented in Table 10.

Intra-rater reliability for delta values demonstrated poor-to-excellent reliability, and the ICC scores ranged from 0.37-0.99. The TE was 1.50 for PD activity, 0.46-1.81 for tendon length and thickness, and 3.46-8.33 for tendon echogenicity.

Table 10 – Intra-rater reliability for PD activity and tendon structure measurements

	Symptomatic tendon				Asymptomatic tendon			
	ICC 2.1 (95% CI)	T-test (p-value)	TE	TE%	ICC 2.1 (95% CI)	T-test (p-value)	TE	TE%
Power Doppler activity	0.99 (0.99; 0.99)	0.699	1.53	4.89	0.99 (0.98; 0.99)	0.218	0.25	37.72
Tendon length	0.96 (0.94; 0.98)	0.946	0.96	1.80	0.97 (0.96; 0.98)	0.698	0.85	1.61
Tendon thickness – proximal	0.96 (0.94; 0.98)	0.131	0.38	4.90	0.79 (0.66; 0.87)	0.429	0.31	6.15
Tendon thickness – mid	0.96 (0.93; 0.98)	0.779	0.30	5.84	0.82 (0.71; 0.89)	0.048	0.23	5.36
Tendon thickness – distal	0.81 (0.70; 0.88)	0.487	0.36	7.41	0.74 (0.60; 0.84)	0.113	0.25	5.52
Echogenicity whole tendon	0.99 (0.99; 0.99)	0.582	1.00	1.10	0.99 (0.98; 0.99)	0.244	1.00	1.10
Echogenicity ROI	0.99 (0.99; 0.99)	0.582	1.07	1.33	0.99 (0.98; 0.99)	0.244	1.00	1.09

Table 10 demonstrates intra-rater reliability between measurements. ICC, Interclass correlation coefficient. 95% CI, 95% confidence interval. T-test, paired t-test. TE, typical error (absolute values). TE%, typical error in percent. ROI, region of interest (echogenicity intensity at injury site only). The table is duplicated from Paper III.

11. DISCUSSION

In this section, the results from the three studies will be discussed against the current available literature.

11.1 Study I

11.1.2 Clinical outcomes

The main finding demonstrated no between-group difference for the NPRS during the SLDS test at 12-week follow-up between LL-BFRT and HSRT. However, there was a similar clinically significant symptom improvement after 12 weeks for both groups. Thus, LL-BFRT did not demonstrate clinical superiority compared to HSRT at 12 weeks based on the SLDS test. These novel data suggests that LL-BFRT clinically improve symptoms equally to HSRT after 12 weeks of rehabilitation.

This study was based on the findings from a pilot study investigating the effect of LL-BFRT in patients with patellar tendinopathy (130). In the pilot study, there was a 50% pain reduction on the NPRS during SLDS, a significant 4% increase in iMVC, and a 31% reduction in PD activity. The results from the SLDS test are comparable, despite the fact that the pilot study only consisted of a 3-week rehabilitation protocol compared to the 12-week rehabilitation protocol. In this study, we included a 3-week follow-up to directly compare the results from the pilot study. At 3-week follow-up, a significant decrease in the NPRS during the SLDS test was demonstrated, but those results were not comparable to the pilot study (decrease in NPRS LL-BFRT ~20%; HSRT ~ 30%). A possible explanation for the difference in results at 3-week follow-up could be due to the greater total volume per training session in the pilot study, where the rehabilitation protocol (repetitions: 30/15/15/15) in Study I was chosen as it is the predominantly applied protocol for LL-BFRT (99,105,109). Another explanation could be that the participants were instructed not to participate in other sports or physical activities outside of the pilot study, whereas participants were allowed to continue participating in sports or physical activities in Study I based on the principles of the pain monitoring model (153). Continued physical activity has been shown to be feasible in the rehabilitation of tendinopathy (5,153,154); however, this could impact the NPRS score during the SLDS test, as participants may have continued to perform activities that provoked symptoms.

A study investigating a 12-week rehabilitation protocol of moderate-slow

resistance training (-2.0 NPRS) and HSRT (-2.2 NPRS) found a similar clinical reduction in NPRS on the SLDS test compared to the results from Study I (5). Another study performing progressive isometric, isotonic, and energy storage exercises also found a similar reduction in NPRS (-2.2 NPRS) (217). Lastly, a study performing HSRT and inertial flywheel rehabilitation demonstrated a greater decrease in NPRS (-3.3), however, they also had higher baseline scores (flywheel group: 7.2 NPRS; HSR group: 6.2 NPRS), which may explain the difference compared to the other studies (76). Thus, the comparable effect at 12-week demonstrated in previous studies (5,76,217), and those in Study I, suggest that the HSRT rehabilitation protocol is effective in reducing symptoms in patients with patellar tendinopathy and that LL-BFRT is equally effective.

Similarly, the VISA-P increased with a clinically significant increase of 16.2 and 16.3 for the LL-BFRT and the HSRT group, respectively. Baseline values and increases in VISA-P at 12-week follow-up are in congruence with those reported previously by other studies utilizing a similar mechanical loading-based rehabilitation protocol as the HSRT protocol (4,5,76,78,217). This further reaffirms the notion that LL-BFRT is a viable rehabilitation option. The VISA-P was included as a secondary outcome as it is the only PROM specifically designed to measure pain and function in patients with patellar tendinopathy, and to compare the clinical effects of LL-BFRT and HSRT found in Study I to those reported in other studies. Although there was clinically relevant improvement, participants did fully recover (did not reach 100 on the VISA-P). This could be explained by the relatively short rehabilitation period, where changes in chronic, degenerative tissues may need longer time to fully recover, but it could also be that the VISA-P has been found to lack validity and may thus not accurately report the “true” state of patients with patellar tendinopathy (170).

The results seem to indicate that load magnitude does not influence clinical outcome if the total volume is sufficiently high, as LL-BFRT is performed with a relatively low external mechanical load (30% of 1-RM), which corresponds with previous data where moderate load magnitude resulted in equal results as HSRT (5). However, it cannot be concluded based on this study, what effect blood flow restriction had on tendinous tissue, as we did not include a control group performing only low-load training without blood flow restriction. Based on the results in Study II, LL-BFRT probably induces similar increases in, e.g., GH, compared to HL-FFRT (118). These similar increases in hormone production could potentially be a factor in explaining the similar clinical effects between LL-BFRT and HSRT.

There was a significant increase in PPT at the AP site from baseline to 12 weeks, but no effect of group or group x time. There were no significant changes in PPT at the MPA, TA, and ECR sites from baseline to 12 weeks.

No other RCT studies have investigated the long-term effect of PPT in a 12-week mechanical loading-based rehabilitation protocol in patients with patellar tendinopathy. However, one study has investigated the immediate effect of isometric and dynamic exercise on PPT at the patellar tendon, tibialis anterior, and extensor carpi radialis brevis (173). They found no significant changes for the patellar tendon and extensor carpi radialis brevis, whereas they found a significant increase in PPT for the tibialis anterior immediately post-exercise. This could indicate a modulated pain mechanism in patients with patellar tendinopathy, as EIH is supposed to work systemically. This is in congruence with a cohort study that found evidence of peripheral and central sensitization in Achilles tendinopathy (218). However, another cohort study did not report any evidence for centralized sensitization but only found evidence of peripheral sensitization in patellar and Achilles tendinopathy (219). Our results support the evidence of peripheral sensitization (reduction with 12 weeks exercise), as only localized significant changes were observed for the AP, whereas no changes were observed for TA and ECR at any time point throughout the study.

The iMVC results shown in this study demonstrated a total increase in iMVC of 5.5% across both groups. This is supported by a systematic review and meta-analysis that showed similar strength gains between LL-BFRT and heavy-load resistance training (102). In the pilot study, a significant increase in iMVC of 4% was demonstrated, which is comparable to the strength gains reported in our study. However, these gains were demonstrated following a 12-week compared to a 3-week rehabilitation protocol. Likewise, several studies have demonstrated a significant increase in MVC following a rehabilitation protocol of HSRT in patients with patellar tendinopathy (4,5,76). This study utilized an identical protocol to the study of Agergaard et al. (5), which demonstrated a significant increase in iMVC of 15%. Thus, there seems to be a difference between the studies in the strength gains reported. A possible explanation could be that dynamic loading protocols have some limitations in their translation into isometric strength measurement, which may result in large variances between studies (177). Additionally, pain during iMVC may have limited the participants' maximal effort during the iMVC test. In contrast, pain during the SLDS test decreased significantly from baseline to 12 weeks, and the VISA-P improved significantly from baseline to 12 weeks; thus, this does not support the notion that pain may have influenced the results. However, it could be that these tests do not accurately

measure pain during peak loads, as anecdotally, some of the participants reported pain during the iMVC, and some were unable to perform all 4 trials due to exacerbation of pain.

These increases in strength gains are further supported by other variables, e.g. increases in 5-RM and increase in muscle quadriceps CSA, which indicate significant adaptations of the mechanical loading-based rehabilitation protocols. Firstly, there were significant increases in 5-RM for both leg press and knee extension for both groups. This indicates that significant neurological and muscular adaptations to the respective protocols occurred. Lastly, there was a significant increase in muscle quadriceps CSA for both groups from baseline to 12 weeks. These data suggest that the applied training volume was sufficient to induce tissue adaptation and that the participants complied with the respective protocols.

11.1.3 Tendinopathy and imaging

Ultrasonography

The results did not demonstrate any significant changes in PD activity from baseline to the 12-week follow-up, which are in line with a previous study (5) and in contrast to another study investigating PD activity in patellar tendinopathy (4). The rehabilitation protocol for HSRT was relatively similar between Study I and Agergaard et al. (5); thus, it seems that HSRT does not reduce neovascularization in the tendon following a 12-week rehabilitation protocol. In contrast, Kongsgaard et al. (4) found a significant decrease in PD activity (45%) from baseline to 12 weeks. A possible explanation for the difference in results could be that in Kongsgaard et al. (4), tendon biopsies were performed at baseline and at 12 weeks and may thereby have affected tendon rehabilitation, as biopsies in healthy tendons have demonstrated an increase in cell activity (220). Additionally, the US settings were different between studies, which may have affected the sensitivity to detect PD activity as US sensitivity is highly influenced by its settings (221).

This is the first RCT study to investigate the effect of LL-BFRT on PD activity in a prolonged rehabilitation protocol for patellar tendinopathy. Skovlund et al. (130), investigated the effect of a 3-week rehabilitation protocol on PD activity and found a significant 31% reduction in PD activity from baseline to 3-week follow-up. This is in contrast to our results, where no decrease in PD activity was demonstrated. This could be explained by the fact that participants were asked to refrain from participation in sport/physical activity outside of the pilot study, as studies have demonstrated that physical activity may increase PD activity (148,222). In

summary, it does not seem that PD activity changes following a 12-week training-based rehabilitation protocol, regardless of modality.

Proximal tendon thickness did not demonstrate any significant difference from baseline to 12-week follow-up for any group. This is in congruence with the findings of other mechanical loading-based interventions (5,76,217), however, another study did find a significant decrease in tendon thickness from baseline to 12-week follow-up (4). A potential explanation could be that tendon biopsies were performed at baseline and at 12 weeks, which could have affected the tendon thickness. Thus, there were no changes in tendon structure despite a significant improvement in function and pain. This supports the notion that other mechanisms than structural changes may play a vital part in symptom manifestation in patellar tendinopathy.

Magnetic resonance imaging

The results did not demonstrate any significant changes in patellar tendon volume from baseline to 12 weeks for either group. These results are also in congruence with the results for tendon thickness measured by US, which have been previously presented. Seemingly, no longitudinal RCT studies have investigated the patellar tendon volume in chronic patellar tendinopathy, however, several studies have investigated the tendon CSA in both healthy and tendinopathic tendons (4,5,127,129). For LL-BFRT, no studies have investigated its effect and tendon structure using MRI in a population with patellar tendinopathy. However, the effect of LL-BFRT on tendon tissue has been investigated in healthy Achilles and patellar tendons (127,128). In both studies, there was a significant increase in tendon CSA from baseline to 16-week follow-up. Likewise, HSRT has also been demonstrated to increase tendon CSA in healthy tendons in several studies (127,128,223,224). These results demonstrate that both protocols induce tendon hypertrophy in healthy tendons. However, similar rehabilitation protocols have been applied to tendinopathic tendons, but no significant changes in tendon CSA have been demonstrated (4,5,89). These results indicate that tendinopathic tendon tissue may not be as responsive as healthy tendon tissue, as studies have demonstrated no significant changes, even in the seemingly unaffected part of the tendinopathic patellar tendon (4,5). Likewise, in order to change patellar tendon CSA/volume in patients with patellar tendinopathy, a prolonged rehabilitation program may be beneficial. Thus, future studies are needed to better understand the morphological adaptations that occur during a mechanical loading-based rehabilitation protocol.

There was a significant increase in quadriceps CSA from baseline to 12-weeks of 3% for both groups, respectively, but no significant between-group differences. These results are

in line with previous results that have also demonstrated a significant hypertrophy response of 7% following a 12-week rehabilitation protocol of HSRT (4). The same methodology was used to assess quadriceps CSA, as it was measured 20 cm from the tibia plateau in both studies. This again indicates that the training volume was sufficiently high, as it is comparable to other studies.

Correlations were performed for the clinical and structural outcomes. The correlations were generally weak (range -0.14, 0.17) and there were no significant correlations between clinical outcomes (NPRS on the SLDS test and VISA-P) and structural outcomes (patellar tendon volume, PD activity, and tendon thickness). These results are further supported by studies that also demonstrated no correlation between VISA-P and PD activity (5), and likewise, studies have reported no association with clinical and structural outcomes (225,226). In contrast, other studies have reported significant correlations between structural and mechanical outcomes and VISA-P (66). However, these contradicting results and generally low correlations between clinical and structural outcomes may not be surprising, as variation in symptom manifestation between individuals may vary greatly (227).

11.1.4 Implications to other tendinopathic tendons

This study was performed on tendinopathic patellar tendons, however, tendinopathy also occur in other tendons in the body, such as Achilles tendinopathy, adductor tendinopathy, rotator cuff tendinopathy and lateral elbow tendinopathy (1,35,228,229). The transferability of the presented results to other tendons may depend on the location, as there may be considerable differences between tendons and tendinopathy e.g. comparing lower extremity to upper extremity tendinopathy. Tendons in the lower limb may behave differently compared to the upper limb as the tendons in the lower limb are weight-bearing tendons that are exposed to constant load. Furthermore, it seems that upper limb tendinopathy demonstrates local sensitization whereas lower limb tendinopathy does not, although the level of evidence is low (230,231). Additionally, there also seem to be an age difference as patients presenting with Achilles tendinopathy (35,89) and upper limb tendinopathy (232,233) generally tend to be older compared to patients with patellar tendinopathy (4,35,76).

The patellar tendon is also referred to as the patellar ligament because the most superficial layer is regarded as a tendon connecting muscle to bone whereas the deeper layers can be regarded as a ligament as it connects from bone to bone (12,234). Additionally, the

Achilles tendon also exhibits a larger paratenon which may improve the healing of the tendon; however, the paratenons role in healing and repair of the tendon remains unknown (235) but a study in rats indicates that the paratenon promotes healing of the Achilles tendon (236). Thus, the patellar tendon may be structurally different and as such, a direct extrapolation of the results in Study I on patellar tendinopathy to other tendinopathies in the lower and upper extremities should be done with caution.

11.1.5 The role and extent of inflammation in tendinopathy

To what extent the role of inflammation plays in tendinopathy is still debated (45). In injured tissue, for example, connective tissue, healing occurs in an overlapping pattern and can be subdivided into three phases: the inflammatory phase, proliferation, and remodeling (237). Inflammation is a normal response to tissue injury and plays a critical role in tissue healing and repair through an intricate mediation of macrophages, pro- and anti-inflammatory mediators (238). In the inflammatory phase, the necrotic tissue is removed by monocytes and macrophages (239), and the immune system initiate the recruitment of immune cells and cytokines that activates cell proliferation and remodeling of the tissue. A shift from the inflammatory phase to the proliferative phase is essential for tissue healing and to restrict the persistence of inflammation in the injured tissue. Inflammation may be involved and peak in the early stages of tendinopathy and gradually evolve into a low-grade chronic matter in chronic tendinopathy. This is supported by several studies that have found markers of inflammation to be present in early phase tendinopathy (58,240). In chronic tendinopathy, macrophage infiltration has been demonstrated in both chronic Achilles tendinopathy and in healthy Achilles tendon; however, the cell fractional area was significantly higher in the tendinopathic tendon than those in the healthy tendons (241). In contrast, a study in patellar tendinopathy, found negligible infiltrations in both tendinopathic patellar tendons and in healthy patellar tendons (242). Additionally, the type of tendon may be of importance, as many studies have investigated rotator cuff tendinopathy, where many studies included total or partial tendon ruptures and exclusively tendinopathic tendons (52). Further, clinical studies that have investigated the effect of anti-inflammatory medical treatments in early and chronic tendinopathy, have failed to demonstrate long-term effect (240,243). Finally, in a recent meta-analysis, the authors concluded *that "...inflammatory cells are observed in a proportion of tendinopathic tendons but not in all"* and *"Further controlled studies using comparable methods and sufficient sample sizes for various phases of tendon symptomatology are needed to allow any firm conclusion in regard to a potential common*

presentation of inflammation, and common pathway for the development of Tendinopathy" (52). Thus, the extent and role of inflammation in tendinopathy are still debatable and warrants further research.

11.1.6 General clinical implications

The findings suggest that LL-BFRT can be another rehabilitation protocol in the clinician's toolbox, as the clinical and structural outcomes were similar between rehabilitation protocols. The clinician should consider the patient's preference when administering rehabilitation treatment for patellar tendinopathy. Other considerations could be the utility of LL-BFRT in patients with severe symptom manifestation, in-season athletes, and in patients with coexisting conditions where heavy peak loads may be contraindicated, such as reconstruction of the anterior cruciate ligament, as LL-BFRT decreases peak loads on tendons, muscles, joints, and bones.

11.2 Study II

11.2.1 Estimating SD_{change}

In the meta-analysis, we estimated the SD_{change} using the proposed formula by the Cochrane Handbook (244): $SD_{\text{change}} = \sqrt{SD^2_{\text{baseline}} + SD^2_{\text{final}} - (2 \times correlation \times SD_{\text{baseline}} \times SD_{\text{final}})}$

In order to estimate the SD_{change} based on the above-mentioned formula, we imputed a fixed correlation coefficient of 0.8 for all analyses (245). In addition, sensitivity analyses were also performed using an imputed correlation coefficient of 0.6.

However, another approach could have been used to estimate SD_{change}, as SD can be estimated from, e.g., P-values. P-values for change were sometimes reported by the trial authors, but this was almost only for statistically significant results. The exact P-values were rarely reported but referred to as being "$P < 0.05$" or "$P < 0.01$" in the text and/or as an asterisk in a figure. The true correlation coefficient can be estimated from trials where all three standard deviations are reported, that is, the baseline, change, and re-test standard deviations. The median correlation coefficient can be used instead of an assumed correlation, but for this to be appropriate, there should be a reasonable number of trials providing this data, and the intervention groups should be reasonably methodologically similar. Our meta-analysis included a maximum of seven trials.

Finally, the statistical heterogeneity indicated that the trials were methodologically heterogeneous.

Therefore, we estimated the change score standard deviations for meta-analysis using a fixed correlation coefficient of 0.8. According to the Cochrane Handbook *"... a sensitivity analysis should be undertaken, trying different values of Corr, to determine whether the overall result of the analysis is robust to the use of imputed correlation coefficients*" (Cochrane Handbook 14.4.6.3) (244). We conducted a sensitivity analysis with a correlation coefficient of 0.6, which was lower than 0.7 that has been reported as a conservative estimate by Rosenthal (246), and it did not change the results meaningfully.

11.2.2 Small sample size bias

In the presented systematic review and meta-analysis (Study II), several studies with small sample sizes were included in the analysis. This may pose a problem for the validity of Study II, and any definitive conclusion should be made with caution when there are a limited number of studies with a low number of participants in each group (247). Additionally, it could be difficult to assess the assumptions of the model if the number of studies is small and the assessment of heterogeneity, I^2, in the random-effect model is biased in meta-analysis with a low number of studies.

11.2.3 Publication bias

In the literature, it has repeatedly been demonstrated that there is a tendency for increased publication rates in studies with positive results, e.g., studies demonstrating statistically significant effects of treatment (248–250). Funnel plots do not only assess publication bias, but several other factors may also influence a potential asymmetry in a funnel plot, such as methodological heterogeneity, small-study effect, or chance alone (251). Currently, it is recommended that at least 10 studies are needed in order to assess funnel plot asymmetry (244). To reduce the influence of methodological heterogeneity in funnel plots, the analysis should arguably be conducted on the meta-analysis subgroup level. In our systematic review (Study II), only a single overall meta-analysis included >10 (n=11) studies (GH analysis). However, this analysis was based on two subgroups of studies (n = 5 and 6) with substantial methodological heterogeneity between them. Also, all the studies in the review included a relatively low number of participants ($n \leq 50$). Therefore, a funnel plot assessment was deemed inappropriate.

11.2.4 Strength and limitations

The strength of this systematic review and meta-analysis is its thorough search matrix and systematic literature search in several databases. Likewise, Study III also included sub-group analyses based on exercise protocol (low-load free flow resistance exercise vs. heavy-load free flow resistance exercise), research design (randomized trials vs. non-randomized trials), and sensitivity analyses using a correlation coefficient of 0.6.

The main limitation of this systematic review and meta-analysis is the relatively low number of participants included in each study and the total population included in the analysis. Combining all the included studies, a total of 427 participants were included, but only the analysis on GH included more than 100 participants in the LL-BFRT and FFRE groups, respectively. This is also reflected in the relatively large confidence intervals for most of the analyses. Another limitation is the high heterogeneity, where only two sub-group analyses demonstrated low heterogeneity, whereas the rest demonstrated moderate-to-substantial heterogeneity. This could be due to the variability in the study population, methods of analysis, and collection of data. Lastly, data extraction and data analyses were performed by a single author, which may introduce some risk of error.

11.2.4 Implications

This systematic review and meta-analysis have pooled existing data on the hormone, immune, and oxidative stress responses following LL-BFRT compared to FFRE. This can provide valuable knowledge regarding the potential physiological responses of LL-BFRT that could explain the similar tendon and muscular hypertrophy and strength gains associated with LL-BFRT (127,129). This could give clinicians a basic understanding of the potential mechanisms of LL-BFRT and identify any knowledge gaps for researchers.

11.2.5 Funding, conflict of interest, and data availability statement

Study II was supported by RegionH, Bispebjerg Hospital, Center for Healthy Aging (Nordea Foundation), University of Copenhagen, The Association of Danish Physiotherapists, University College Absalon, and the Danish Medical Research Council. The funding parties played no role in any part of the study.

For all authors in Study II, no financial or other conflicts of interest are declared by any of the authors.

11.3 Study III

11.3.1 PD activity and structural outcomes

In Study III, there was a significantly greater difference in PD activity and structural outcomes, except tendon length, for the symptomatic tendon compared to the asymptomatic tendon.

PD activity was significantly greater, with a median PD area of 25.6 mm^2 and 0.00 mm^2 for the symptomatic and asymptomatic tendon, respectively. The vast majority of studies (59,76,217,252,253) have evaluated PD activity using the Öhberg score (254), which is an ordinal score ranging from 0 (indicating no blood vessels) to 4 (indicating four or more vessels throughout the tendon), and thus no direct comparison can be made. Compared to other studies that have quantified PD activity, this study had a much higher PD area (4,255). Kongsgaard et al. (4) measured PD activity in a quantifiable way but reported the results in pixels, which makes direct comparisons difficult as pixels are sensitive to, e.g., resolution and zoom. A cross sectional study (255) has quantified PD activity in a similar fashion to this study, and they reported values of approximately 2.0 mm^2, which is significantly lower compared to our study. A possible explanation could be the inclusion criteria, the included population, and the US settings, as PD activity is dependent on the settings applied (221). Additionally, the greater PD activity in Paper III could be explained by the relatively low functional scores and high pain scores, as a study found lower functional scores and increased pain scores in patients with PD activity in abnormal tendons compared to abnormal tendons without PD activity (252). This could indicate that PD activity plays a role in symptom manifestation. In Study III, most of the participants did not demonstrate any PD activity in their contralateral asymptomatic tendon, and we found a median PD activity of 0.00 (1^{st} quartile 0.00, 3^{rd} quartile 0.00). This seems to be in line with previous studies that have also found PD activity in a small number of asymptomatic tendons (59,256). However, PD activity has been demonstrated to be a good prognostic factor for the development of symptoms in asymptomatic tendons (58,257). Thus, it remains unclear to what extent PD activity plays a role in symptom manifestation and whether it is the cause or response of patella tendinopathy.

11.3.2 Structural outcomes

There was significantly greater patellar tendon thickness at all three sites (proximal, mid, and distal) of the patellar tendon for the symptomatic tendon compared to the asymptomatic tendon. Other cross-sectional studies using both US and MRI that investigated the thickness or CSA of the tendinopathic patellar tendon compared to a healthy control group reported a similar pattern

in the tendon thickness as those reported in Study III (9,62,66). This indicates that the morphological changes of patella tendinopathy are not only localized at the proximal injury site of the tendon but also affect the tendon systematically. This also indicates that using a ratio between the proximal and mid-tendon thickness in the evaluation of the symptomatic tendon may underestimate the "true" alterations when evaluating tendon pathology. Thus, it may be more appropriate to use the contralateral tendon.

Lastly, in an exploratory analysis of echogenicity, Study III demonstrated significantly lower echogenicity in the symptomatic tendon compared to the asymptomatic tendon. As lower echogenicity represents more fluids within the tendon, it could be speculated that more fluids within the tendon create an internal pressure that affects the pain mediating receptors and could potentially explain the pain associated with patellar tendinopathy (47).

11.3.2 Intra-rater reliability

Study III demonstrated good-to-excellent intra-rater reliability for PD activity and tendon structure in the symptomatic tendon, whereas the asymptomatic tendon demonstrated moderate-to-excellent intra-rater reliability. The results from Study III are comparable to other studies investigating intra-rater reliability in patellar tendinopathy that have also reported moderate-to-excellent intra-rater reliability in healthy and tendinopathic patellar tendons (10,61). Likewise, Study III found acceptable typical error % (TE%) ranging from 1.10-7.41% for the symptomatic tendon and 1.09-37.72% for the asymptomatic tendon. The high TE% for the asymptomatic tendon was for PD activity, which was likely due to the relatively high number of participants without PD activity; thus, small differences in PD activity may contribute more to the TE%. For the absolute TE, the differences were negligible, with TE ranging from 0.30 to 0.28 mm and 0.23 to 0.31 mm for the symptomatic and asymptomatic tendon thickness. Likewise, the TE for PD activity was 1.53 and 0.25 mm^2 for the symptomatic. These results demonstrate that US measurements of PD activity and tendon structure can be reliably assessed in patients with chronic patellar tendinopathy.

11.3.3 General clinical implications

The results from Study III demonstrated significantly greater tendon thickness at the proximal and mid-part of the patellar tendon, which was not surprising. However, somewhat surprisingly, the distal part of the patellar tendon also demonstrated significantly greater tendon thickness, indicating that the whole tendon may be affected and not just the injured part of the patellar

tendon. Thus, clinicians should evaluate the whole tendon. Secondly, the results from this study demonstrated that US imaging of structural outcomes of the patellar tendon has moderate-to-excellent intra-rater reliability. This indicates that clinicians can use US imaging to monitor morphological structural changes, e.g., structural changes throughout a rehabilitation intervention. Additionally, these results can be used by the clinician to disseminate the severity of structural morphology to patients with chronic patellar tendinopathy.

12. CONCLUSION

This Ph.D. thesis includes three different papers: i) a randomized clinical trial; ii) a systematic review and meta-analysis; iii) an ancillary study based on baseline data from Study I and a previously published randomized clinical trial (5). The overall aim of this Ph.D. thesis was to investigate a potential new treatment modality and its possible mechanisms, and to establish the structural differences between the symptomatic tendinopathic and the asymptomatic healthy tendon.

The main finding of this Ph.D. thesis was that LL-BFRT did not demonstrate superiority at the primary endpoint using the NPRS during the SLDS test as the primary outcome, and both groups demonstrated equal clinically and borderline clinically improvements. Likewise, no between-group difference was demonstrated for the PROM VISA-P; however, a clinically improvement was observed for LL-BFRT and HSRT, respectively. There were no between-group differences in any other secondary clinical or structural outcomes at any time point. Secondly, this thesis demonstrated that LL-BFRT induces increased hormone and immune responses compared to volume-matched LL-FFRE and similar responses compared to HL-FFRE in healthy adults. Specifically, LL-BFRT demonstrated increases in GH (intermediate and late post-exercise time interval), testosterone (late post-exercise time interval), and NA (late post-exercise time interval) production compared to volume-matched LL-FFRE. No significant differences were observed for any hormone comparing LL-BFRT to HL-FFRE. For immune responses, no differences were observed between LL-BFRT and LL-FFRE; however, HL-FFRE demonstrated an increase in creatine phosphokinase at the initial post-exercise phase. For oxidative stress, no differences were observed for LL-BFRT and HL-FFRE. Lastly, this thesis demonstrated greater PD activity in the symptomatic patellar tendon compared to the asymptomatic contralateral tendon. Additionally, a greater tendon thickness and lower echogenicity was observed in the symptomatic compared to the asymptomatic tendon. Lastly, a

moderate-to-good intra-rater reliability were demonstrated for all measurements on the tendinopathic tendon.

In conclusion, LL-BFRT demonstrated no superiority compared to HSRT in a 12-week rehabilitation protocol in elite and recreational male athletes with unilateral patellar tendinopathy. LL-BFRT demonstrated increased production in hormone responses compared to volume-matched LL-FFRE but similar responses compared to HL-FFRE in healthy adults. Lastly, the symptomatic tendinopathic tendon demonstrated greater PD activity, a greater tendon thickness, and lower echogenicity compared to the contralateral asymptomatic tendon, while demonstrating good-to-moderate intra-rater reliability.

13. PERSPECTIVES

In the following section, future perspectives emerging from the results of this Ph.D. thesis will be presented. In this Ph.D. thesis, one-year follow-up data was not analyzed and therefore not included in the thesis, which may provide valuable insights into the long-term effects of LL-BFRT and HSRT, respectively.

From a clinical perspective, based on the results from Study I, it can be concluded that LL-BFRT and HSRT induce similar clinical and structural responses. Thus, the choice of rehabilitation modality should be based on the patient's preference. Another consideration could be that LL-BFRT may be more feasible and tolerable to perform in athletes during in-season as it reduces peak loads on the muscles, joints, and tendons. Lastly, LL-BFRT could be utilized in the early stages of patellar tendinopathy or in patients with severe symptom manifestation, as it may be more tolerable to perform compared to HSRT. Based on the results from Study I and other studies, an intervention period of 12 weeks is not long enough to fully recover from chronic patellar tendinopathy. Likewise, it could be speculated that a prolonged intervention period may have resulted in improved clinical outcomes and structural changes. Therefore, future studies should include longer training interventions in order to investigate the length of recovery following mechanical loading.

Training intervention studies have been investigated in great depth regarding chronic patellar tendinopathy. However, it seems that the current research in training interventions alone is insufficient to fully recover the patients. As mentioned previously, prolonged intervention periods should be investigated. Likewise, other modalities, such as

corticosteroid injections and the reduction in physical activity, should also be investigated further, as a recent study demonstrated significant improvement in patients with plantar fasciitis in the short-term and long-term (258,259). Further research in these modalities may help improve clinical outcomes for the benefit of the patient.

Future research should investigate if blood flow restriction attenuates clinical outcomes or if similar results in outcomes could have been induced by performing low-load resistance exercise to exhaustion. It could be that the important aspect of rehabilitation in tendinopathy is to ensure sufficient mechanical volume is transferred through the affected tendon, and that treatment modality is of little importance. This would also be beneficial knowledge for clinicians, who would be able to tailor the rehabilitation protocol best suited to the patient.

There were a limited number of studies available investigating the hormonal, immune, and oxidative stress responses following LL-BFRT compared to FFRE. Future studies should further investigate the physiological responses following LL-BFRT to elucidate potential mechanisms for the similar muscle and tendon hypertrophy response and strength gains, as well as the clinical improvement in different clinical populations.

Albeit this thesis provides valuable clinical knowledge in the treatment of patellar tendinopathy, further research is still warranted as the current rehabilitation of patellar tendinopathy still seems to have the potential for optimization.

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15. PAPERS