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High-load strength training compared with standard care treatment in young adults with joint hypermobility and knee pain: study protocol for a randomised controlled trial (the HIPEr-Knee study)

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ABSTRACT

Introduction Patients with generalised joint hypermobility, including knee hypermobility (GJHk), often experience knee pain and are typically managed with low-intensity strength training and/or proprioceptive training as part of standard care. However, not all patients experience satisfactory outcomes. High-load strength training may offer additional benefits, such as increased muscle cross-sectional area, neural drive and tendon stiffness, which may reduce pain and improve active knee joint stability during movement tasks and daily activities. So far, no randomised controlled trials (RCTs) have compared high-load strength training with traditional treatment strategies (standard care) for this patient group.

Methods and analysis In this RCT, we aim to recruit patients with GJHk and knee pain from primary care physiotherapy clinics in the Region of Southern Denmark and via social media. Patients with competing injuries or experience with high-load strength training will be excluded. Patients will be randomised (1:1 ratio) to either 2 weekly sessions of high-load strength training or standard care for 12 weeks. The primary outcome is self-reported knee pain during an activity nominated by the patient as the most aggravating for their present knee pain measured using the Visual Analogue Scale for Nominated Activity (VAS_{NA}, 0–100; 0=no pain and 100=worst imaginable pain). This will be collected at baseline, 6 weeks, 12 weeks and 12 months. Secondary outcomes include self-reported knee function and adverse events (collected at baseline, 12 weeks and 12 months), objective measurements including a 5-repetition maximum single-leg press, proprioception and single-leg-hop for distance (collected at baseline and 12 weeks), and a range of other outcome measures such as fear of movement, tendon stiffness and global perceived effect. We aim to recruit 90 patients in total to detect a 10 mm group difference in the primary outcome with 80% power.

Ethics and dissemination This study was funded by Independent Research Fund Denmark (grant number 2034-00088B) on 14 June 2022; the Regional Committees on Health Research Ethics for Southern Denmark approved it (S-20230050) on 30 August 2023. The first recruitment site opened on 15 February 2024, and the final results will be submitted to a peer-reviewed journal to inform rehabilitation strategies for symptomatic GJHk. Protocol version 1, dated 4 July 2024.

Trial registration number NCT06277401.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study uses a combination of self-reported and objective inclusion criteria for generalised joint hypermobility including knee hypermobility, based on international recommendations.
⇒ The interventions are specifically designed for clinical settings and delivered by trained primary care physiotherapists.
⇒ The standard care used in this study may differ from standard care used in other Danish primary care clinics.
⇒ Blinding of interventions and outcome assessors was not possible.

INTRODUCTION

Generalised joint hypermobility (GJH), a condition characterised by an excessive range of motion, is common in the adult population. In a population-based survey of 2056 Danish adults, 13% reported GJH including knee joint hypermobility (GJHk), of which one-half reported knee complaints with greater pain than those without the condition.[1] In addition to chronic knee pain, individuals with GJHk often experience decreased physical function, reduced quality of life and increased risk of developing osteoarthritis.[2] Little is known about the underlying mechanisms causing symptoms in individuals with GJHk. However, reduced stiffness of passive

tissues (tendons and ligaments) and impaired neuromuscular function are likely to play an important role in joint stability.[3–6]

Individuals with symptomatic GJHk are often treated with low-intensity strength training and/or proprioceptive training to reduce knee pain and improve function, but not all patients experience satisfactory outcomes.[7 8] High-load strength training has similar benefits as low-intensity training for reducing knee pain and improving proprioception and function.[9] However, high-load strength training offers additional benefits such as a marked increase in muscle cross-sectional area,[10 11] neural drive[12–15] and increased tendon stiffness.[16–23] In theory, the increase in muscle cross-sectional area strengthens the muscles surrounding the knee, providing optimal stability and muscular capacity. The enhancement of neural drive, by improving the nervous system's ability to activate muscles more quickly and effectively, as well as enhancing fine motor control—expressed as improved force steadiness and accuracy at low force—may improve active joint stability, helping to prevent injuries. Additionally, increased tendon stiffness, particularly in the patellar tendon, may improve joint stability, proprioception and force transmission. These adaptations are crucial to achieving active knee joint stability during movements and daily life by controlling excessive movements and providing a solid foundation for pain reduction. For individuals with symptomatic GJHk, these potential mechanisms may improve joint health, physical function and quality of life.

Clinicians often hesitate to use high-load strength training for individuals with symptomatic GJHk due to uncertainty about patient safety, treatment effectiveness and because current guidelines recommend against high-load strength training.[24] However, in a pilot study including 16 young women with GJHk and knee pain, we observed that high-load strength training was well tolerated, and patients experienced substantial reductions in knee pain during self-nominated activities, improved muscle strength, functional performance and knee proprioception, as well as increased patellar tendon stiffness. These results suggest that high-load strength training may be a viable treatment alternative to current practice for individuals with symptomatic GJHk.[25]

The present randomised controlled trial (RCT) aims to investigate if high-load strength training is superior to standard care in improving pain, function and quality of life in young patients (18–45 years) with symptomatic GJHk. We hypothesise that patients randomised to 12 weeks of high-load strength training will experience greater reductions in knee pain compared with patients randomised to standard care.

METHODS AND ANALYSIS

Study design

This study protocol (version 1, dated 4 July 2024) describes the design of a multicentre, parallel-group superiority RCT (1:1 ratio) to be conducted in primary care physiotherapy clinics in the Region of Southern Denmark. The study acronym is the HIPEr-Knee study (High-Intensity Progressive ExeRcise for Knee hypermobility).

The study protocol follows the Standard Protocol Items: Recommendations for Interventional Trials,[26] and the RCT will conform to the Consolidated Standards of Reporting Trials statement for reporting RCTs.[27] The interventions are reported according to the TIDieR template for intervention description and replication (online supplemental file 1) and the Consensus on Exercise Reporting Template (online supplemental file 2).

The study is registered at www.clinicaltrial.gov (NCT06277401), enrolment started on 15 February 2024 and recruitment is expected to finish in September 2025.

Patients

The study includes patients with GJHk and knee pain. The criteria for symptomatic joint hypermobility—in 2017 defined as hypermobility spectrum disorder (HSD)—have been described broadly,[28] but in this study, a combination of self-reported and objective criteria will be used to identify patients with GJHk and knee pain. A diagnosis of HSD is typically given when a patient does not meet the criteria for hypermobile Ehlers-Danlos Syndrome (hEDS). However, hEDS is rarely diagnosed in Denmark. Therefore, we asked patients if they had been diagnosed with EDS, and in addition, excluded patients with signs of connective tissue frailty (ie, suspected hEDS) during the patient screening, as the intervention has not been pilot-tested in patients with confirmed or suspected hEDS.

Inclusion criteria are as follows:

- Adults aged 18–45 years.
- Persistent knee pain (all types of knee pain for ≥3 months, including pain during movement and rest) (self-reported).
- Average knee pain during the past week ≥30 mm using a 0–100 mm Visual Analogue Scale (VAS; 0=no pain and 100=worst imaginable pain) (self-reported).
- GJH will be assessed during the online screening using the Five-Part Hypermobility Questionnaire (positive ≥2/5) (self-reported).[29] We will also evaluate the Beighton score[30] at baseline testing, but for pragmatic reasons, this will not be part of the inclusion criteria.
- Knee joint hypermobility will be assessed as passive hyperextension of the knee in standing as described in the Beighton tests and confirmed in supine with the heel resting on a 20 cm block with a goniometer (positive >10 degrees) (objectively measured).[31]

Exclusion criteria are as follows:

- Diagnosed with patellar tendinopathy.
- Pregnancy or childbirth within the past year (due to increased levels of relaxin that could affect joint stability), or planning to become pregnant during the 12-week intervention period.
- Knee surgery within the past year.
- Participation in regular structured strength training within the past 6 months.
- Inability to speak and understand Danish.
- Diagnosed with EDS (all types).

- Other heritable connective tissue disorders such as Marfan syndrome, osteogenesis imperfecta, Loeys-Dietz syndrome, Stickler syndrome and skeletal dysplasias.
- Autoimmune rheumatic connective tissue disorders such as lupus, rheumatoid arthritis and Chromosomal conditions such as Fragile X syndrome, Kabuki syndrome and Down syndrome.
- Neuromuscular disorders that can cause joints to become unstable, such as multiple sclerosis and myopathies.

Recruitment procedure

Patients with knee pain attending the recruiting clinics will be asked to answer an online prescreening questionnaire, including the Five-Part Hypermobility Questionnaire for GJH[29] and questions about knee symptoms, through the web-based Research Electronic Data Capture (REDCap). From the prescreening, the treating physiotherapists will identify potentially eligible patients with knee symptoms and complete the physical screening for local knee joint hypermobility. As an additional strategy for achieving adequate patient enrolment, we will use social media to invite people with knee pain to answer the online prescreening questionnaire and, if found eligible, be referred to primary care physiotherapy clinics free of cost.

All eligible patients will receive verbal and written information about the study. If eligible and willing to join the study, a consent form (online supplemental file 3) will be signed following a face-to-face inclusion session with the primary care physiotherapist.

Randomisation

The allocation sequence will be computer-generated with permuted block randomisation (block size 4 or 6), set up by a data manager outside the project. Before randomisation, eligible patients will be appointed a time for baseline testing by the primary care physiotherapist. Following the baseline testing session, the project manager will complete the randomisation automatically in REDCap and reveal the group allocation (A or B) to the patient and physiotherapist. Patients will be randomly assigned to either high-load strength training or standard care with a 1:1 allocation ratio, stratified for sex. To ensure allocation concealment, the principal investigator, outcome assessors and the project manager will be blinded to block size and unaware of the following assignment in the allocation sequence.

Blinding

Due to the pragmatic nature of the study, investigators and treating physiotherapists—also outcome assessors of objective measurements—cannot be blinded to group allocation. To minimise the risk of detection and performance bias (as blinding to the intervention is not possible), patients only receive general information about the aim of the study (ie, to compare two different exercise interventions that aim to reduce knee pain and improve knee function) but receive no information about the content of the two exercise interventions and the study hypotheses during the study.

An independent biostatistician blinded to group allocation will perform the primary analysis. To reduce the risk of interpretation bias, blinded results from the analyses (group A compared with group B) will be presented to all authors, who will agree on two alternative written interpretations before the data manager unblinds the randomisation code.

Emergency unblinding is not relevant as this study includes two exercise-based interventions with clear modification guidelines related to the patients' symptom response. Instead, in case of unexpected serious adverse events reported by patients or treating physiotherapists, we will follow the standard procedure in Denmark and refer the patients to their general practitioner.

Interventions

All patients will receive a printed exercise leaflet including exercise descriptions and images, an exercise logbook, registration of knee pain, recommendations about warm up—and general recommendations about joint hypermobility, pain and pain management, activity modification, maintaining a physically active life, and the purpose of performing knee-specific exercises. The intervention will be delivered by 14 physiotherapists across five clinics close to the patient's home, and the project will cover all treatment expenses. The physiotherapists involved have undergone a comprehensive 3-hour training session. The first hour introduced the study protocol and overall design. The second hour focused on the baseline and follow-up physical assessments. The final hour concentrated on the intervention strategies, particularly the exercise programmes, with an emphasis on quality of movement, lower extremity alignment and control of the hip and knee.

High-load strength training

Within 7–10 days after baseline testing, patients randomised to high-load strength training will start a supervised progressive high-load strength training programme designed following the American College of Sports Medicine guidelines on progression and intensity to elicit a physiological response (online supplemental file 4). The high-load strength training programme has previously been described in detail and feasibility tested.[25] The programme consists of five exercises: leg press, seated calf raise, leg extension, leg curl and forward lunge. The individual's initial workload will be established by conducting a 5-repetition maximum (5-RM) strength test. During the intervention period, the workloads will be regularly adjusted to align with the weekly RM goals with acceptable symptoms below 5/10 on a Numerical Pain Rating Scale (NPRS) and good movement quality compared with unloaded movement (eg, no knee valgus motion or pelvis drop). Each set will be performed until failure, except

Table 1 Description and progression of the high-load strength training and standard care

Week	Load magnitude	Repetitions	Sets	Rest between sets	Sessions /week	Duration in weeks	Contraction mode (exercise tempo)	Rest between repetitions	Time under tension	Muscular failure	Range of motion	Recovery time	Anatomical form
High-load strength training													
1	14 RM	10	3	1–1.5 min	2	1	0-3-0-3	0 s	180 s	No	Full	48 hours	Yes
2	12 RM	10	3	1–1.5 min	2	1	0-3-0-3	0 s	180 s	No	Full	48 hours	Yes
3	10 RM	10	3	1–1.5 min	2	3	0-3-0-3	0 s	180 s	Yes	Full	48 hours	Yes
6	9-8-7-6 RM	9-8-7-6*	4	2–3 min	2	3	0-3-0-3	0 s	180 s	Yes	Full	48 hours	Yes
9	8-7-6-5 RM	8-7-6-5*	4	2–3 min	2	3	0-3-0-3	0 s	156 s	Yes	Full	48 hours	Yes
12	10 RM	6	3	2–3 min	2	1	0-3-0-3	0 s	108 s	No	Full	48 hours	Yes
Standard care													
1–12	Bodyweight	10–15	2	1–1.5 min	2	12	0-3-0-3	0 s	120–180 s	No	Full	48 hours	Yes

*The number of repetitions decreases for every set.

for the familiarisation and tapering weeks (table 1). The programme will be performed twice weekly for 12 weeks, with at least 48 hours between sessions at a gym in the physiotherapy clinics. Patients will be offered face-to-face supervision once weekly (12 times in total) by trained physiotherapists.

Standard care

The standard care programme replicates the standard treatment by combining clinical experience with current guidelines for managing hypermobile joints, as the Danish Rheumatism Association and the Ehlers-Danlos Society recommended. Moreover, it includes components from standard care programmes used in comparable knee studies to enhance its effectiveness.[32] The programme was developed by the principal investigator (BL) (15 years of clinical experience), in collaboration with two primary care physiotherapists. One physiotherapist had 22 years of clinical experience and specialised knowledge in working with hypermobile knees, while the second had 7 years of general clinical experience but was less experienced in treating hypermobile joints. To make sure that the developed programme was representative of usual care in patients with hypermobile joints and knee pain, 13 Danish primary care physiotherapists outside the study took part in an online survey, where they were asked to consider the statement: 'The exercise programme is suitable for training patients with hypermobile joints and knee pain' and to indicate their level of agreement. In total, 11/13 physiotherapists (85%) expressed agreement or strong agreement to this statement.

The standard care programme focuses on knee stability and function performed at low intensities, to be conducted twice weekly for 12 weeks (table 1).[33] The programme consists of 3–5 exercises performed with 2 sets of 10–15 repetitions and does not require special advanced training equipment. The exercises are squat, lunge, bridging, side lying hip abduction and standing balance drills, each with three levels (online supplemental file 5). The trained physiotherapist and the patient will collaboratively determine the number of exercises, exercise intensity and the number of physiotherapy sessions throughout the 12 weeks, mimicking clinical practice. Progression will be assured by changing exercise levels towards more weight bearing and increased demands for balance and stability while keeping acceptable symptoms below 5/10 on an NRS pain scale and maintaining good movement quality (eg, no knee valgus motion or pelvis drop).

Strategies to improve adherence to interventions

Patients are informed that the aim is to complete at least 18 out of 24 sessions (75%). The project manager will monitor a dashboard report in REDCap weekly regarding the completion of the weekly questionnaire completion, exercise adherence and adverse events. If a patient misses a treatment session, the physiotherapist will call to emphasise the importance of protocol adherence.

Exercise sessions will be scheduled for convenience with at least 1 day (48 hours) in between. If a patient does not comply for two consecutive weeks, the project manager will follow up by email and phone encouraging the patient to continue the protocol.

Criteria for discontinuing or modifying allocated interventions

The project manager will contact patients who express to their physiotherapist or the project staff that they want to discontinue participation. The reason for discontinuation will be registered, and all patients will be included in the intention-to-treat (ITT) analysis. We will encourage discontinuing patients to respond to patient-reported outcomes for the rest of the study period, with priority given to the primary endpoint.

Knee pain will be monitored before, during (when supervised) and after each training session. In case patients experience symptoms or pain above the acceptable threshold (5/10 on NRS) or swelling during the exercise session for more than 2–3 hours, for example, until the next day or the next exercise session, then the training intensity will be modified, and if required, the treating physiotherapist will perform a clinical examination.[25] Modification rules for both groups include changing load, range of motion, sets and repetitions, number of weekly exercise sessions, and excluding exercises that aggravate symptoms, and all changes will be noted. The exercises will then be performed at that level until the symptoms decrease below the threshold of 5/10. After that, increases in load will follow the progression as initially planned. For patients with symptoms at rest above 5/10 at baseline, no increase in symptoms will be allowed during exercise.

Relevant concomitant care during the trial

Patients can take pain medication during the study and continue with existing medical treatments as their general practitioner advises. Patients will be encouraged to limit concomitant interventions for knee joint pain, such as manual therapy and other treatments delivered by healthcare professionals. However, if a patient finds supplementary treatment necessary to be able to complete the current interventions (eg, manual treatment for exercise-induced muscle soreness), the patient will be encouraged to receive as few treatments as possible and to report concomitant interventions on the weekly questionnaire.

Provisions for post-trial care

No post-trial care will be provided to the patients. However, participants are not restricted from getting other treatments after the trial.

Fidelity of treatment delivery and patient receipt

To enhance the reporting and conduct of the study, fidelity will be assessed following contemporary recommendations focusing on how clinicians deliver the programme and the patients' receipt of the programme.[34 35]

The treatment delivery assessment entails clinical observations of how the physiotherapists deliver the programme. A research assistant performs two to three observations of each clinician placed at the start, middle and end of an exercise programme. To ensure a systematic and thorough assessment, an a priori designed checklist is used for the clinical observations (The HIPEr-Knee Fidelity Checklist; online supplemental file 6). The HIPEr-Knee Fidelity Checklist addresses the differentiation between high-load strength training and standard care, physiotherapists' adherence to the programme and their competence to deliver it, thereby ensuring the evaluation of various aspects of treatment delivery.

Patient receipt is assessed by use of data from the patients' weekly questionnaire and exercise logs. We plan to publish a secondary paper with details about the fidelity measures described here.

The principal investigator will contact the clinics regularly (every 2–3 months) to review the project procedures, go through the interventions and answer any questions related to the project completion.

Data collection

The baseline and follow-up assessments will be conducted at the participating physiotherapy clinics. Further measurements, such as assessment of tendon stiffness, will be performed on a subsample of 30 patients due to time constraints at the Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark, at baseline and 12-week follow-up. We will use REDCap to collect and store data in adherence to international guidelines for protecting confidential information. All questionnaires are answered by the patient directly in REDCap using range checks for data values. The objective measurements will be performed by the treating physiotherapists who will be trained, and where possible, double entries will be used. Clean data collection forms can be obtained from the principal investigator on request. Regardless of discontinuation or deviation from protocols, all patients will be asked to complete the follow-up questionnaires.

Outcomes

The timing of all outcomes collected is shown in table 2.

Baseline characteristics

Patient characteristics such as height, weight, pain intensity, symptom duration and symptom onset will be collected. Physical activity is self-reported using the Saltin-Grimby Physical Activity Level Scale[36] and the Tegner score.[37]

Primary outcome

The primary outcome is self-reported knee pain during an activity nominated by patients to be the most aggravating for their present knee pain (VAS nominated activity—VAS_{NA}, 0–100, 100=worst imaginable pain).[38] The primary outcome will be completed at baseline, 6 weeks, 12 weeks and 12 months follow-up. The primary endpoint will be at the 12-week follow-up.

Table 2 Time schedule of enrolment, interventions, assessments and visits for patients

	Study period					
	Preallocation		Allocation	Postallocation		
	Enrolment	Baseline	Week 0	Week 6	Week 12	Week 52
Time point	**–*t***	**t_0**	**0**	**t_1**	**t_2**	**t_3**
Enrolment						
Eligibility screening	x					
Informed consent	x					
Allocation			x			
Intervention						
Intervention		←	—	→		
Comparator						
Assessments						
Initial questionnaire and demographics	x					
Saltin-Grimby Physical Activity Level Scale	x					
Tegner score	x					
Anthropometry		x				
Primary outcome measure						
VAS pain $_{NA}$, 0–100 mm		x		x	x	x
Secondary outcomes						
KOOS		x			x	x
Adverse events					x	x
Dynamic strength (5 RM single-leg press), kg		x			x	
Proprioception (reposition), error (°)		x			x	
Single-Leg-Hop for distance, cm		x			x	
Other outcome measures						
VAS pain past week, 0–100 mm		x		x	x	x
TSK-11, 11–44		x			x	x
EQ-5D-5L, <0–1		x			x	x
Global perceived effect					x	x
Patient Acceptable Symptom State, yes/no					x	x
Treatment failure, yes/no					x	x
American College of Rheumatology response criteria 20% and 50%					x	x
Tendon stiffness, N/mm (subgroup)		x			x	
Knee extension RTD (subgroup)		x			x	
Knee extension isometric MVC (subgroup)		x			x	
Moving patellar apprehension test (subgroup)		x			x	
Knee instability questions		x			x	

EQ-5D-5L, The European Quality of life-5-Dimension 5-level; KOOS, Knee injury and Osteoarthritis Outcome Score; MVC, maximal voluntary contraction; RTD, Rate of Torque Development; TSK, Tampa Scale of Kinesiophobia; VAS, Visual Analogue Scale.

Secondary outcomes

The secondary objective outcomes will be collected at baseline (except perceived effect), 12 weeks and 12 months follow-up.

The Knee injury and Osteoarthritis Outcome Score is a validated knee-specific questionnaire used to assess

patient-reported outcomes in the continuum from knee injury to osteoarthritis and is widely used for different types of knee pathology.[39]

A sitting active knee joint repositioning (proprioception) test will be performed to assess mean absolute angle error (AAE). Patients will sit on an elevated couch, and an electric goniometer (Biometrics, NP11, UK) will be attached to the lateral side of the affected knee. The patients will be blindfolded and asked to actively extend their knees while guided to a predetermined angle position and to hold that position for 5 s. After returning the leg to a passively hanging position, the patients will be asked to replicate the joint angle actively. The test will be performed twice at 30°, 50° and 70°, respectively (0°=fully extended, randomised order). The mean AAE of the six attempts will be used.

A single-leg maximal hop for distance will be performed to assess knee function.[40] The patients will be asked to hop as long as possible, landing and balancing on the same leg long enough for the examiner to determine the distance measured by a tape measure fixed to the floor. The distance will be measured (in cm) from the toe in the starting position to the heel in the landing position. The best of three hops will be recorded. An additional hop will be performed if the patient improves more than 10 cm between the second and third hop.

A standardised protocol will be followed to establish dynamic leg strength by a 5-repetition maximum leg press test.[41] All settings on the leg press available at the included clinics will be noted and replicated for follow-up testing.

Adverse events

Adverse events will be defined as any unintended, negative findings, symptoms or illnesses that occur during the study assessments or interventions, whether attributable to the project or not. Minor adverse events include symptom flare-ups, subluxations and exercise-induced pain or fatigue. Serious adverse events are unexpected but cover life-threatening events, disability and permanent damage.[42] Adverse events are recorded in the exercise logbook at every exercise session and in the weekly questionnaire. The treating physiotherapists are familiar with the modification guidelines to reduce the exercise load if patients experience short-lasting minor adverse events. An acute increase in knee symptoms, such as severe knee pain (eg, 8 or higher on the NPRS), including pain during rest or dislocation of the knee or patella, will be reported to the project manager by patients or treating physiotherapists. We will report the frequency of adverse events and the number of patients experiencing adverse events during the study.

Other outcome measures

Average self-reported knee pain for the past week using the VAS (0–100, 100=worse) will be collected at baseline, 6 weeks, 12 weeks and 12 months.[38] The remaining self-reported other outcome measures will be collected at baseline, 12 weeks and 12 months: The Tampa Scale of Kinesiophobia-11,[43] EQ-5D-5L, <0–1, Global perceived effect,[44] Patient Acceptable Symptom State,[45] Treatment failure[45] and the American College of Rheumatology response criteria,[46] and questions about knee instability.[47] Other objective outcome measures will be collected at baseline and 12 weeks and include tendon stiffness (subgroup),[25 48] knee extension isometric Maximal Voluntary Contraction and Rate of Torque Development (subgroup)[25] and moving patellar apprehension test[49] to assess patella instability (subgroup) (online supplemental file 7).

Statistical methods

Sample size calculation

As we compare two active interventions, we consider a difference in change between treatments of 10 mm VAS_{NA} to be clinically meaningful.[50] We will need a total sample of 74 patients to detect a between-group difference in change of 10 mm in VAS_{NA}, assuming an SD of 15 mm, a power of 80% and a significance level of 0.05. Anticipating 20% dropouts, we will include a sample size of 90 patients (45 in each group). Because assessment of tendon stiffness is resource-heavy and takes time, we will assess tendon stiffness in a subgroup of patients (15 from each group).

Statistical analysis

Before any analysis will commence, a statistical analysis plan will be made publicly available. Descriptive analysis will be used to present the baseline characteristics with categorical data presented as proportion (%) and continuous data presented as median (IQR) or mean (SD). Continuous data will be checked for normality using the visual inspection of histogram and quantile-quantile plot.

The primary outcome, VAS_{NA}, will be analysed using a linear mixed model. The model will include the group arm (high-load strength training and standard care), time (6 weeks, 12 weeks), the interaction between group and time, baseline value and randomisation stratification factor (sex) as fixed effects. The physiotherapy clinics will be added as random effects in the model to take the clustering into account. The primary analysis will follow the ITT principle, using data from all randomised patients and assuming missing at random based on the variables included in the model. Model assumptions, including normality of residuals and random effects, will be assessed.

For secondary outcomes, average self-reported knee pain for the past week will be analysed similarly to the primary outcome. Other secondary continuous data will be analysed on available data using a multivariable linear regression model to assess the outcomes at 12 weeks, adjusting for baseline value of the outcome of interest and randomisation stratification factor (sex) and physiotherapy clinics. The assumptions underlying the regression models, including normality of residuals, homogeneity of variance of residuals and linearity for quantitative predictors, will be assessed. Categorical outcomes will be presented with proportion (%) and

statistical differences between groups will be analysed using χ^2 test or Fisher's exact test as appropriate.

Per-protocol analyses will be applied using the same methods. The per-protocol population for both groups is defined as those attending at least 18/24 planned exercise sessions (75%), completing the intervention and not receiving steroid injections or surgery during the intervention period. The proportion of patients with satisfactory treatment attendance/effect and response criteria will be analysed as detailed in the statistical analysis plan. An alpha level of 0.05 (two sided) will be considered statistically significant. We will use Stata version 18 or later for the analysis.

Data management

The data collection and management procedures have been approved by the Danish Data Protection Agency (University of Southern Denmark, 5 September 2023). Personal information about patients will be kept separate from the main dataset and will not be shared. All personal data will be stored securely to protect confidentiality before, during and after the trial. Data entry and coding of the deidentified data will be conducted by trained staff at the University of Southern Denmark.

Data monitoring

A formal data monitoring committee will not be established, as the severity of adverse events is expected to be noncritical, and the intervention is not considered a high-risk intervention based on the feasibility study. Any unexpected serious adverse events or outcomes will be discussed by the trial management committee (identical to the authors of this protocol). Furthermore, the trial management committee will monitor recruitment, treatment and attrition rates as well as any concerns related to the study.

End of trial

The trial will end when all patients have completed their 12-month follow-up. In the case of slow recruitment, we will terminate the trial after 2 years once a minimum of 37 patients in each arm have completed it, based on the power calculation.

Patient and public involvement

Patient experiences from the feasibility study investigating the intervention programme have been included to adjust the programme. Primary care physiotherapists provided feedback about the standard care programme.

ETHICS AND DISSEMINATION

Before study initiation, the study was approved by The Regional Scientific Ethics Committee for Southern Denmark (S-20230050, 30 August 2023), and the study will be conducted in agreement with the Helsinki Declaration. If patients sustain any trial-related harm, they are covered by the Danish Patient Compensation. The Regional Committees on Health Research Ethics annually select studies for auditing. The audit process is independent of investigators and sponsors.

The primary RCT results will be submitted for publication to an international, peer-reviewed journal, regardless of whether the results are positive, negative or inconclusive about the study hypothesis. The principal investigator will ensure publication, with authorship eligibility following the International Committee of Medical Journal Editors guidelines. Any important protocol amendment will be reported to the Regional Committees on Health Research Ethics for Southern Denmark, registered at ClinicalTrials.Gov and communicated in the primary RCT report. The results will be communicated to patients and the public through the media and workshops. The patients can ask about our findings after the study is completed.

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Contributors BL and JBT conceived the study idea and initiated the study design. BL and BDH developed the fidelity checklist. BL, JBT and AM drafted the statistical analysis plan. BL and JBT drafted the study protocol, and JB-M, BJ-K, PH, AM and BDH contributed to protocol refinement and approved the final version. JBT is the grant holder, and BL is the principal investigator and the guarantor of the study; accepts full responsibility for conducting the study and will draft the manuscripts for publication with contributions and approval of final versions from all authors.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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