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Efficacy of low-load blood flow restricted resistance EXercise in patients with Knee osteoarthritis scheduled for total knee replacement (EXKnee): protocol for a multicentre randomised controlled trial

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ABSTRACT

Introduction Up to 20% of patients undergoing total knee replacement (TKR) surgery report no or suboptimal pain relief after TKR. Moreover, despite chances of recovering to preoperative functional levels, patients receiving TKR have demonstrated persistent deficits in quadriceps strength and functional performance compared with healthy age-matched adults. We intend to examine if low-load blood flow restricted exercise (BFRE) is an effective preoperative method to increase functional capacity, lower limb muscle strength and self-reported outcomes after TKR. In addition, the study aims to investigate to which extent preoperative BFRE will protect against surgery-related atrophy 3 months after TKR.

Methods In this multicentre, randomised controlled and assessor blinded trial, 84 patients scheduled for TKR will be randomised to receive usual care and 8 weeks of preoperative BFRE or to follow usual care-only. Data will be collected before randomisation, 3–4 days prior to TKR, 6 weeks, 3 months and 12 months after TKR. Primary outcome will be the change in 30 s chair stand test from baseline to 3-month follow-up. Key secondary outcomes will be timed up and go, 40 me fast-paced walk test, isometric knee extensor and flexor strength, patient-reported outcome and selected myofiber properties.

Intention-to-treat principle and per-protocol analyses will be conducted. A one-way analysis of variance model will be used to analyse between group mean changes. Preintervention-to-postintervention comparisons will be analysed using a mixed linear model. Also, paired Student's t-test will be performed to gain insight into the potential pretraining-to-post-training differences within the respective training or control groups and regression analysis will be used for analysation of associations between selected outcomes.

Ethical approval The trial has been accepted by the Central Denmark Region Committee on Biomedical Research Ethics (Journal No 10-72-19-19) and the Danish Data Protection Agency (Journal No 652164). All results will be published in international peer-reviewed scientific journals regardless of positive, negative or inconclusive results.

Trial registration number NCT04081493.

Strengths and limitations of this study

- The trial is a multicentre, randomised controlled assessor blinded trial.
- This is the first clinical trial to investigate the effect of low-load ischaemic-resistance training as a preconditioning method prior to elective knee replacement surgery.
- Patients will not be blinded to their allocation into intervention groups (blood flow restricted vs control).
- This is a protocol paper.

INTRODUCTION

Knee osteoarthritis (OA) is a degenerative joint disease associated with pain, reduced physical activity and quality of life and affects almost 40% of all individuals ≥60 years of age.[1–5] Approaching end-stage knee OA, total knee replacement (TKR) is often the preferred treatment choice to reduce pain and regain functional capacity. That is, TKR is considered a highly successful treatment to improve quality of life and long-term function.[6] However, despite being considered highly successful, approximately 20% of the patients undergoing TKR experience a suboptimal outcome,[6] which has often been suggested to be related to incomplete restoration of physical function.[7] In addition, TKR patients typically demonstrate long-lasting deficits in quadriceps strength and functional performance.[2 4] This failure to return to 'normal' strength levels has been suggested

to be associated with preoperatively lower limb muscle strength and function.[2]

Preconditioning exercise designed to prepare the musculoskeletal system to better tolerate stressful events such as the impact of invasive surgery has been suggested to be applicable prior to elective TKR.[6] This is supported by the results of two randomised controlled trials indicating that preoperative heavy-resistance strength training (HRST) may enhance functional capacity and knee extensor muscle strength 3 months postoperatively.[7 8] Joint pain resulting from the high mechanical loads associated with HRST may represent a barrier to this type of training in some patients suffering from severe knee OA.[1 9] Therefore, a more tolerable, yet effective, alternative is needed for this population. Also, three recent systematic reviews investigating the topic of preoperative physiotherapy-based exercise before TKR all warrant high-quality, well-powered evidence to investigate the efficacy of preoperative physiotherapy before TKR.[10–12]

Resistance training with low exercise loads (~30% one repetition maximum) performed with concurrent partial blood flow restriction to the working limb (blood flow restricted exercise, BFRE) has received increasing clinical interest during the last decade.[1 13–32] The application of low muscle/tendon/joint forces in BFRE has been documented to increase human skeletal muscle size and to cause substantial strength gain in healthy young and old individuals, as well as some patient populations, despite the low magnitude of mechanical stress imposed on the trained tissue.[13 25 26] When applied in the clinical setting, BFRE has demonstrated positive effects on skeletal muscle hypertrophy, strength, and functional capacity in mild-degree knee OA patients[1 9 33 34] although not observed in all studies.[33] Importantly, BFRE appears to be feasible with a high training adherence in knee OA patients.[1 33 34] The use of different restrictive pressures (absolute restrictive pressures: 160–200 mm Hg and individualised pressure of 70%; the pressure needed to provide complete arterial blood flow restriction (total limb occlusion pressure, LOP) has been applied without any adverse events in mild-degree knee OA.[1 33 34] This is in line with Hughes *et al*[13] who suggested that when BFRE is performed correctly, it has been demonstrated to be as safe as free-flow exercise methods.[13]

Currently, no consensus exists about the appropriate restrictive pressure to induce favourable muscle adaptation in patients suffering from knee OA. This might be due to the fact that the effective occlusion pressure seems to be dictated by the exercise load/intensity.[35] Thus, the effective occlusion pressure varies between studies due to use of different exercises or differences in exercise load and intensity. Restrictive pressures ranging from 40% to 80% LOP have been suggested to be sufficient to evoke muscular adaptation in healthy adults.[14 17 18 36] If the load is less than 30% 1RM, higher restrictive pressures seems required to evoke muscle hypertrophy, while lower pressures (40% LOP) requires training loads of 30% 1RM or above to be performed.[36] Injury or joint pain (ie, from the knee) might limit the amount of resistance applied during strength testing, and may thus compromise the ability to rely fully on a given 30% 1RM estimation. Therefore, higher pressures than 40% LOP are suggested to be used in clinical settings.[36] On the other hand, higher pressures are associated with more discomfort during exercise and in between-set rest pauses,[14] which potentially can affect exercise motivation negatively in patients. Thus, an occlusion pressure sufficiently high to evoke measurable muscle adaptation despite potentially exercising at loads lower than 30% 1RM; yet tolerable to maintain a high adherence, seems a favourable choice for this particular patient population.

The adaptive mechanisms evoked by BFRE seem to involve accumulation of metabolites, ischemia (transient tissue hypoxia), which may increase recruitment of higher threshold (type II) fibres through stimulation of group III and IV afferent nerve fibres,[37 38] and also activation of myogenic muscle stem cells (satellite cells, SC).[13 26 31] SC are cells positioned between the sarcolemma and the myofiber basal lamina.[31 39] SCs play an important role in human skeletal muscle growth due to their ability to donate new myonuclei to the muscle fibres.[31 40–44] That is, the human skeletal muscle fibres are multinucleated cells with each myonucleus controlling the protein synthesis of a certain cytoplasmatic area in the muscle fibre.[40–42 45] Myonuclei transcriptional activity can be fully maximised with exercise, hence requiring new myonuclei to support further muscle tissue accretion.[41 42 44] It has been suggested that exercise-related addition of SC and myonuclei by means of BFRE might reduce the muscle atrophy related to bedrest and/or prolonged inactivity.[31 46] Previous studies applying short-term (10 days) preoperative BFRE before an anterior cruciate ligament rupture–reconstruction found no atrophy protective effect or higher postoperative muscle strength compared with performing a low-load exercise without blood flow restriction (placebo). However, it might be questionable if the applied training frequency, intensity and training period have been sufficient to promote SCs and myonuclei addition. Thus, longer periods of intensive training might be necessary to promote the desired muscle morphological adaptations (addition of myonuclei and increased SC content).

Aim and hypothesis of the trial

The primary aim of this trial is to investigate the efficacy of 8 weeks of BFRE compared with receiving usual care prior to TKR on postoperative chair stand performance. We hypothesise that 8 weeks of preoperative BFRE will lead to increased 30 s chair stand performance (30 s chair stand test: 30 s CST) when assessed 3 months postoperatively. Secondary aims are to investigate the efficacy of preoperative BFRE on lower limb muscle strength 3 months after TKR and investigate the potential relationship to functional capacity and quality of life. Furthermore, it will be investigated to which extent 8 weeks of BFRE

induce myofiber hypertrophy and gain in SC number and myonuclei content in the knee extensor musculature.

MATERIAL AND METHODS

Design

The trial is designed as a multicentre (two sites), randomised, assessor blinded, controlled trial following the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[47] Primary endpoint will be 3 months after TKR. Additional and secondary endpoints will be evaluated during the week of TKR, 6 weeks after TKR (questionnaires only) and 12 months after TKR. Muscle biopsies will be obtained from all patients undergoing surgery at Horsens Regional Hospital at baseline, during surgery and 3 months after TKR.

Participants

Patients will be recruited from the Departments of Orthopedic Surgery at Horsens and Silkeborg Regional Hospitals in Denmark. Patient enrolment will start 2 September 2019 at Horsens Regional Hospital and 1 October 2019 at Silkeborg Regional Hospital. Patient recruitment is expected to be completed in June 2021. All patients are expected to have completed baseline testing in September 2021. To account for surgery and intervention, the 3-month follow-up will be concluded in April 2022. Thus, at the end of September 2022, all patients are expected to have completed 12-month follow-up testing.

Inclusion criteria

(1) Patients ≥50 years scheduled for TKR due to knee OA at Horsens or Silkeborg Regional Hospital.

Exclusion criteria

(1) Severe cardiovascular diseases (New York Heart Association class III and IV), previous stroke incident, thrombosis incident; (2) traumatic nerve injury in affected limb (3) unregulated hypertension (systolic ≥180 or diastolic ≥110 mm Hg) (4) spinal cord injury; (5) planned other lower limb surgery within 12 months; (6) cancer diagnosis and currently undergoing chemotherapy-, immunotherapy or radiotherapy; (7) inadequacy in written and spoken Danish; (8) an existing prosthesis in the index limb; (9) living more than 45 min from either Horsens Regional Hospital or Silkeborg Regional Hospital and (10) pregnancy.

All patients will be screened for eligibility by four orthopaedic chief physicians at Horsens Regional Hospital and by three orthopaedic chief physicians at Silkeborg Regional Hospital who will perform the initial inclusion of study participants and hand out written project information. All patients accepting to participate will be asked to complete a written informed consent allowing the physiotherapist (at Horsens Regional Hospital and Silkeborg Regional Hospital) to contact the patients by phone for a final eligibility and exclusion criteria-screening and book an appointment for baseline testing. If the patient agrees to participate in the trial, he/she will sign a written informed consent to participate in the project. Subsequently, the patient will be baseline tested at the hospital by a blinded (to group allocation) assessor. Patients declining to participate in the RCT will be offered the option of participating in a parallel observational cohort trial. All patients included in the project will be scheduled for a TKR. Two to three weeks before surgery, all patients will be invited to a, preoperative information meeting where nurses, surgeons and physiotherapists will provide detailed information on pain management, nutrition, the surgical procedure, physical activity, postoperative home-based rehabilitation (table 1A,1B), load management (usual care).[48] On the day of surgery, patients will be hospitalised at Horsens Regional Hospital or Silkeborg Regional Hospital where an orthopaedic chief physician will perform the TKR procedure. The day after surgery all patients will receive physiotherapy-supervised training once or twice per day by a physiotherapist in order to fulfil the discharge criteria (table 2).[48] Patients will generally be discharged within 1–2 days after fulfilling all the discharge criteria listed above. After discharge, all patients will receive a standard home-based rehabilitation programme focusing on improving knee joint mobility, increasing the tolerance for standing without assistive devices and lower extremity muscle strength. Variations in the selection of exercises and exercise variables exist in the standard home-based rehabilitation programmes between the respective hospitals; however, the purpose of the programmes is identical. If the patients do not fulfil the discharge criteria, they will be offered supervised knee-specific exercise therapy at a municipal rehabilitation centre or specialised hospital-based rehabilitation after discharge from the hospital.

Randomisation

After baseline assessment, patients will be randomised (1:1) using the Research Electronic Data Capture (REDCap) randomisation system to either the training (BFRE) group or the control (CON) group. Prior to randomisation, all patients will be booked for follow-up test sessions and surgery. All randomisation procedures will be performed by the physiotherapists in charge of the BFRE training. Assessors performing the tests will be blinded to group allocation until completion of the trial. A flow chart of the patient allocation procedures is depicted in figure 1.

CON group

Participants in CON will receive usual care (see above) prior to TKR and be encouraged to continue their usual lifestyle up until TKR.

BFRE group

In addition to receiving usual care (cf. above), participants in the BFRE group will perform supervised BFRE sessions three times per week for 8 weeks supervised by a physiotherapist educated in administering BFRE. All BFRE training will be performed at Horsens Regional Hospital and Silkeborg Regional Hospital.

Table 1A Postoperative rehabilitation programme, Horsens Regional Hospital

Step	Exercise	Repetitions	Sets	Resistance
Week 0–3				
Step 1 and 2	Supine peristaltic pump exercise with feet above heart level	20 min	3–4/day	–
Step 1	Supine knee extension mobilisation	20 s	3 sets	–
Step 1	Supine unilateral knee and hip extension and flexion mobilisation with slipper under the heel	5 repetitions	3 sets	Slipper minimises floor friction
Step 2	Seated knee extension and flexion mobilisation with slipper under the foot	5 repetitions	3 sets	Slipper minimises floor friction
Step 2	Standing weight transfer exercise	15 repetitions each side	1 set	Body weight
Step 2	Sit to stand from a high chair or the edge of table	5 repetitions	3 sets	Body weight
Week 3 and onwards				
Step 1 and 2	Supine peristaltic pump exercise with feet above heart level	20 min	3–4/day	–
Step 1	Seated knee extension mobilisation	20 s	4 rounds	Arms can be used to apply pressure onto the knee to help extend the knee
Step 1	Step up exercise	10–15 repetitions	2–3 sets	Bodyweight
Step 1	Standing knee isometric knee towel press	10–15 repetitions	2–3 sets	Ball/towel rolled together
Step 1	Sit to stand from a chair	10–15 repetitions	2–3 sets	Body weight
Step 1	One leg standing	30 s	1 set	Body weight
Step 2	Standing hip flexion	Not informed	Not informed	Elastic band
Step 2	Standing hip abduction	Not informed	Not informed	Elastic band
Step 2	Partial frontal plane sliding lunge	10 repetitions	3 sets, 2–3/day	Body weight
Step 2	Partial back sliding lunge	10 repetitions	3 sets, 2–3/day	Body weight
Optional	Cycling	10–20 min	1 set	Light resistance can be added when it is possible to perform a full round with the operated limb.

Step 1 is performed in the morning and step 2 is performed in the afternoon. All exercises are performed once per day.

Table 1B Postoperative rehabilitation programme, Silkeborg Regional Hospital

Step	Exercise	Repetitions	Sets	Resistance
Week 0–2				
Optional	Cycling	5–10 min	2/day	
–	Supine peristaltic pump exercise	Not informed	Not informed	–
–	Rest with leg above heart level	30 min	4/day	–
–	Seated isometric knee extension	3 s	10 sets	Lower leg and the foot
–	Seated knee flexion mobilisation	3 s	10 sets	–
–	Seated knee extension mobilisation	30 s	3 sets	Apply pressure to the knee joint using the arms
–	Supine isometric knee extension	3 s	10 sets	Lower leg and the foot
–	Supine passive knee extension mobilisation			Gravity will extend the knee joint
Week 2 and onwards				

Continued

Table 1B Continued

Step	Exercise	Repetitions	Sets	Resistance
–	Supine knee isometric knee towel press	3 s hold	10 sets	Lower leg and the foot
–	Sit to stand	10 repetitions	1 set	Body weight
–	Standing knee flexion mobilisation	3 s	10 sets	Body weight
–	Step up exercise	10 repetitions	1 set	Body weight

All exercises are performed twice per day. Cycling ergometer exercise is optional.

Intervention procedures

BFRE

Each BFRE session will consist of a 10 min warm up (ergometer cycling), followed by two different unilateral lower-limb-resistance training exercises: (1) leg press and (2) knee extension performed on standard strength training machines. Each exercise will be performed with the affected lower limb only and consist of four rounds interspaced by 30 s of rest (table 3). First round: 30 repetitions (reps); second round: 15 reps; third round: 15 reps; fourth round: until exhaustion (table 1A,1B). If patients can perform more than 15 repetitions in the fourth exercise set, the exercise load will be increased with the minimum extra load possible.[30] Participants will be instructed to perform both the eccentric and concentric contraction phases using a steady 2 s pace duration. The fourth and final exercise set will be performed to the point of exhaustion defined as being unable to complete the final concentric contraction phase in 2 s. During the 30 s rest period, patients will rest in a standardised resting position while maintaining the initial cuff-pressure. Between each exercise, patients will have a 5 min 'free-flow' rest period. The 5 min rest period applied between exercises was chosen based on experiences from a previous pilot project (Jorgensen & Bohn 2019, unpublished data) and experience with applying BFRE in clinical practice. In both situations, we often experienced that patients stayed seated in the leg press machine for >2 min after the last (fatiguing) set to feel sufficiently rested and confident to walk from one exercise machine to another. The cuff will be released immediately after completion of the final exercise set.

Table 2 Discharge criteria at Horsens regional hospital and Silkeborg regional hospital

Outcome	Horsens Regional Hospital	Silkeborg Regional Hospital
Minimum knee flexion range of motion	60°	90°
Maximal knee extension deficit	15°	5°
In-and-out of bed	Independent	Independent
Sit-to-stand	Independent	Independent
Walking with/without assistive devices	Independent	Independent
Stair negotiation with/without assistive devices	Independent	Independent
Activities of daily living	Independent	Independent
Understanding of the home-based postoperative exercise programme	Sufficient	Sufficient

The occlusion pressure during both exercises will be set at 60% of LOP and the starting load intensity will be 30% with 1 repetition maximum (1RM) in both exercises.

Individual LOP will be determined using a pneumatic, conically shaped, 12 cm wide, rigid cuff (Occlude Aps, Denmark) attached to the patient's most proximal area of the thigh on the affected side. While sitting on an examination table with the ankle and 1/3 of the lower limb off the table, a vascular Doppler probe (EDAN Instruments, China) will be placed posterior to the medial malleolus over the posterior tibial artery to capture the auscultatory pulse. To determine the cuff pressure (mm Hg) needed for total blood flow occlusion, the cuff will gradually be inflated in 20 mm Hg steps until reaching the pressure where the auscultatory pulse is interrupted (ie, LOP). The first time the auscultatory pulse is interrupted, the examiner releases 10–20 mm Hg pressure from the cuff until the auscultatory pulse is present again. When the auscultatory pulse reappears, the cuff is inflated with 10 mm Hg until the LOP is found again. If the second LOP is identical to the first, it will be defined as the LOP for that specific patient. Otherwise, the procedure will be repeated until determining an identical LOP two consecutive times.

Outcome variables

Outcome assessments will be performed at baseline (before randomisation), 3–4 days before surgery, 6 weeks after TKR, 3 months after TKR and 12 months after TKR. To reduce the number of postoperative visits, only questionnaires; The Knee disability and Oteoarthritis Outcome Score (KOOS), EuroQol Group 5-dimensions-Level 5 (EQ-5D-L5) and reporting of adverse event or receiving supervised physiotherapy postoperatively will be sent via email 6 weeks after surgery. Two testers (two trained physiotherapists) blinded to group allocation will perform all baseline and follow-up measurements. Bergström needle muscle biopsies[49] will be taken from vastus lateralis of the quadriceps muscle in both lower limbs from patients included at Horsens Regional Hospital only at baseline, during surgery, and 3 months after TKR by doctors trained in performing the procedure. An overview of the data collection parameters is presented in table 4.

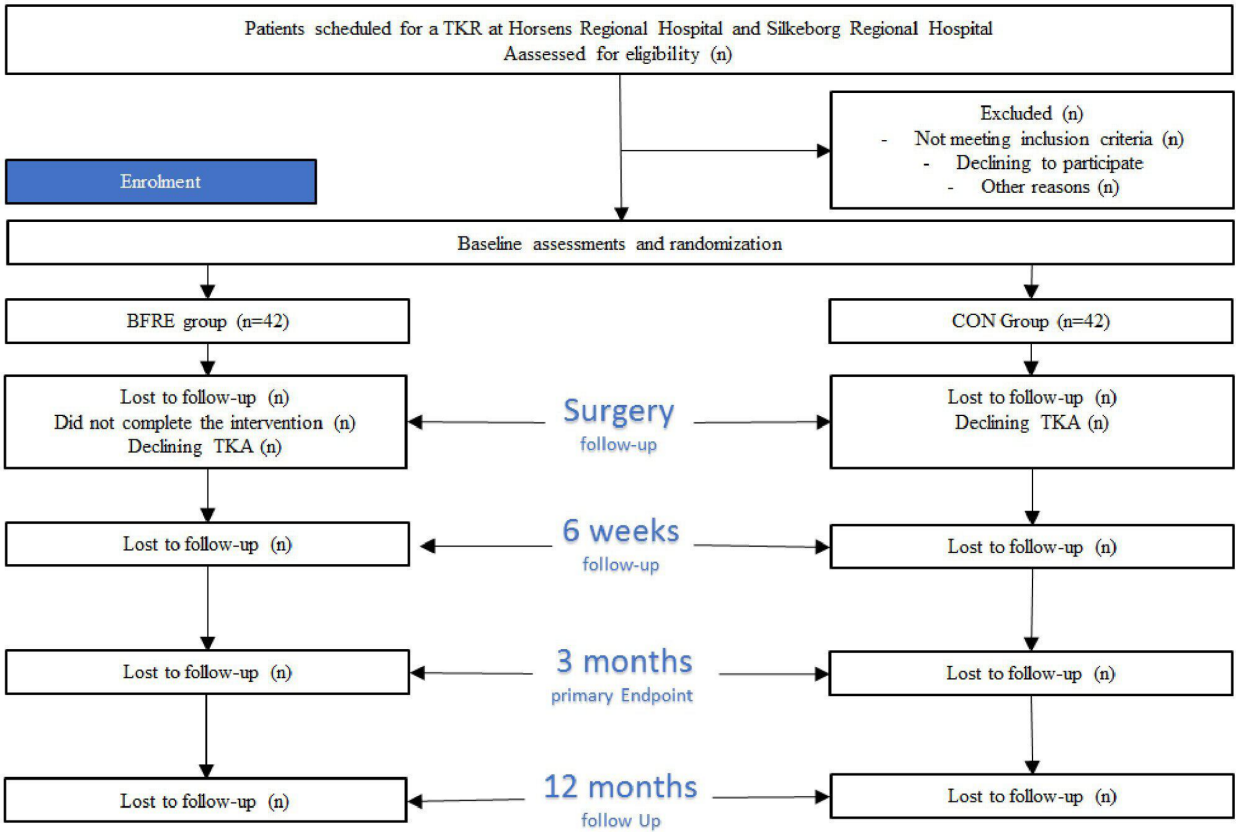

Figure 1 Flow chart of the enrolment, treatment and follow-up phases. BFRE, low-load blood flow restricted exercise; CON, control; TKR, total knee replacement.

Before starting the baseline testing, all assessors will be thoroughly trained in performing the tests according to the standardised test procedures for each test method. All assessors will be blinded to intervention allocation (presurgery BFRE training or usual care). Further, assessors will be trained in how to communicate with the participants at follow-up test sessions to avoid break of blinding due to miscommunication. Also, all cases where blinding is being broken will be registered. Also, the physiotherapist in charge of LL-BFRE will be thoroughly trained in performing the exercise on healthy subjects before applying LL-BFRE on study-patients. At the last scheduled exercise session (ie, 24th session), the physiotherapists in charge of LL-BFRE will carefully remind the participants not to reveal their group allocation to any assessors at any time point during post-testing.

The primary investigator will be in weekly contact with the physiotherapists supervising the LL-BFRE at Horsens Regional Hospital and Silkeborg Regional Hospital where day-to-day-retraining and supervision can be arranged. Furthermore, physiotherapists supervising the LL-BFRE will receive in-depth retraining every 3 months.

Outcomes

Primary outcome

The 30s-CST

The 30s-CST will be assessed using a 44 cm (seat height) chair with armrests. The 30s-CST measures the number of sit-to-stand repetitions completed within 30 s. The 30s-CST is considered a valid and sensitive measure of lower-extremity sit-to-stand function with good to excellent intraobserver and interobserver reliability.[50–52]

Secondary outcomes

The timed up and go test

The timed up and go test (TUG) assesses the time required for patients to stand from a 44 cm (seat height) chair walk around a tape mark 3 m away and sit into the chair at return. The patients will be instructed to walk as fast and safely as possible towards the tape mark (and touch the tape mark (with at least one foot), turn around and return to the chair and sit down. Use of armrests is allowed. The fastest of two trials will be used for further analysis. Up to 1 min of rest will be allowed between trials.[53 54] Good inter-rater reliability has been demonstrated with the TUG test.[52]

4×10 m walk test

4×10 m walk test (40m-FWT) measures the total time it takes to walk 4×10 m excluding turns (m/s).[52] Patients will be instructed to walk as quickly and as safely as possible without running to a visible mark 10 metres away, return and repeat for a total distance of 40 m.[52] Prior to the test, one practice trial will be provided to check understanding. The 40m-FWT is a valid and responsive measure

Table 3 Exercise variables for the blood-flow restricted exercise (BFRE) protocol

Exercise variable	Weeks 1–8
Level of LOP	60% LOP
Sets	4
Load intensity	30% 1RM
Repetitions 1st set	30
Repetitions 2nd and 3rd set	15
Repetitions 4th set	To volitional failure
Contraction modes per repetition	
Concentric	2 s
Isometric	0 s
Eccentric	2 s
Rest between repetitions	0 s
Time under tension per repetition	4 s
Range of movement	Maximum
Rest between sets	30 s
Rest between sessions	≥36 hours
Progression	The minimal possible load (5 kg) is added when patients perform >15 repetitions in 4th set

LOP, total limb occlusion pressure; RM, repetition maximum.

for assessing short distance maximum walking speed with excellent inter-rater reliability.[52]

1RM leg press strength

1RM leg press strength will be estimated from a 5-8RM leg press test. Patients perform three low-load warm-up sets. The first and second warm-up sets consist of 12 repetitions, and the third warm-up set consists of eight repetitions. The load of each warm-up set will be increased with 10 kilos. After warm-up, the load will be increased to determine the 5RM. If the 5RM cannot be determined within three trials, a fourth all-out trial (as many repetitions as possible) will be performed. The 1RM will be calculated as [1RM=load (kg)/1.0278–0.0278·number of repetitions)].[55]

1RM knee extension strength

1RM knee extension strength will be estimated from 5-8RM knee extension test as described above for the estimation of 1RM leg press test (55).

Maximal isometric voluntary contraction of the knee

Maximal isometric voluntary contraction (MVC) of the knee will be measured using a handheld dynamometer (HHD). The patients will be seated on an examination table with knees and hips positioned at 90° flexion. The patients will be instructed to remain seated in an upright position and place both hands on the shoulder to avoid compensation. The HHD will be fixed with a rigid belt to the examination table. Adjustable straps will be used to allow MVCs of the knee extensors to be performed at 90° knee flexion in all patients. The HDD will be positioned 5 cm above the medial malleolus.[56] The patients will be instructed to produce as much force as possible into the HHD. Good to excellent inter-rater and intrarater reliability has previously been demonstrated on group-level in patients suffering from knee OA for maximum knee extensor muscle strength testing with HDD.[56] Patients will receive four trials. For analysis, the mean maximal strength of the second, third and fourth measures will be calculated and corrected for bodyweight[56]

MVC of the knee flexors

MVC of the knee flexors will be measured and performed using HHD at 90° knee flexion with the patients seated identically as during MVC for the knee extensors.[56] The HHD will be positioned posterior aspect of calcaneus[56] and patients will be instructed to produce as much force as possible into the HHD. Good to excellent inter-rater and intrarater reliability has previously been demonstrated on group-level in patients suffering from knee OA for maximum knee flexor muscle strength testing with HDD.[56] Patients will receive four trials. For analysis, the mean maximal strength of the second, third and fourth measures will be calculated and corrected for bodyweight[56]

Myofiber cross-sectional area, muscle fibre type composition, SC content and myonuclei number

Myofiber cross-sectional area (CSA), muscle fibre type composition, SC content and myonuclei number will be assessed by obtaining needle biopsies (100–150 mg) from all patients enrolled at Horsens Regional Hospital. The biopsies will be obtained bilaterally from the middle portion of the vastus lateralis muscle using the percutaneous needle biopsy technique of Bergström.[49 57 58] Biopsies will be performed by two experienced orthopaedic surgeons (chief physicians) trained in performing the needle muscle biopsy technique at Horsens Regional Hospital. Efforts will be made to extract tissue from the same region (2–3 cm apart) and depth (~1–2 cm).[49] The tissue samples will be dissected of all visible blood, adipose tissue and connective tissue and mounted in Tissue-Tec (4583, Sakura Finetek, Alphen aan den Rijn, The Netherlands), frozen in isopenate precooled with liquid nitrogen, and stored at −80°C.[31 49 59] All muscle samples will be analysed as previously described by Nielsen *et al*[31] using immunofluorescence microscopy. Transverse serial sections (8 µm) of the embedded muscle biopsy specimen will be cut at −22°C using a cryostat (HM560; Microm, Walldorf, Germany) and will be mounted on glass slides for subsequent analysis as described in detail elsewhere.[31] Myogenic stem cells ((SC) will be visualised with an antibody against Pax7.[31] Type I (stained) and type II (unstained) myofibers will be differentiated, and muscle fibre area will be determined[31]: MSC-derived nuclei will

Table 4 Outcome measures to be collected

Outcome measures	Data collection instrument	Time points of assessment
Primary outcome		
Sit-to-stand function	30 s chair stand test	B, S, 3 and 12 months
Secondary outcomes		
Ambulatory capacity	Timed up and go	B, S, 3 and 12 months
Gait speed	4x10 m walk test	B, S, 3 and 12 months
1RM leg press strength	Leg press machine	B, S, 3 and 12 months
1RM knee extension strength	Knee extension machine	B, S, 3 and 12 months
Isometric knee extensor muscle strength	Handheld Dynamometer	B, S, 3 and 12 months
Isometric knee flexion muscle strength	Handheld Dynamometer	B, S, 3 and 12 months
Myofiber morphology	Muscle Biopsies	B, S, 3 months
Myogenic stem cell content	Muscle Biopsies	B, S, 3 months
Pain	KOOS	B, S, 6 weeks, 3 and 12 months
Symptoms	KOOS	B, S, 6 weeks, 3 and 12 months
Activities of daily living	KOOS	B, S, 6 weeks, 3 and 12 months
Sports and recreation	KOOS	B, S, 6 weeks, 3 and 12 months
Quality of life	KOOS	B, S, 6 weeks, 3 and 12 months
Socioeconomic costs	EQ-5D	B, S, 6 weeks, 3 and 12 months
Adverse events	Questionnaire and medical records	3 months
Exercise compliance and progression	Physiotherapist records	BFRE
Pain during visits	NRS for pain	B, BFRE, S, 3 and 12 months
Declining to be operated	Questionnaire	3 months
Postoperative supervised physiotherapy	Questionnaire	6 weeks, 3 and 12 months
Knee joint range of motion	Goniometer	B, S, 3 and 12 months
Patient characteristics and related	Questionnaire	B
Measurements	Questionnaire	B
Gender	Tape measure	B
Age	Electronic body mass scale	B
Height	Questionnaire	B
Body mass	Questionnaire	B
Civil status	Questionnaire	B
Educational level	Questionnaire	B
Employment status	Questionnaire	B
Substance use (alcohol, smoking)	Questionnaire	B
Duration of knee symptoms	Questionnaire	B
Pain medication during the last week	Questionnaire	B
Comorbidities	Questionnaire	B

B, baseline; BFRE, low-load blood flow restricted exercise; D, during surgery; EQ-5D, EuroQol Group 5-dimension; KOOS, knee disability and osteoarthritis outcome score; 12 months, 12 months after TKR; 3 months, 3 months after TKR; NRS, Numeric Rating Scale; RM, repetition maximum; S, 0–2 days before surgery.

stain positive for Pax7 and be within the basal lamina; nuclei (DAPI stained) with a sublaminar placement will be considered myonuclei.[31]

Knee disability and osteoarthritis outcome score

KOOS is a patient-administered knee-specific questionnaire comprising five subscales: Pain; Symptoms; Activities of daily living; Sport & Recreation and Knee-Related Quality of Life. Each item is scored from 0 to 4.[60] The raw score for each of the five subscales is the total sum of the associated item scores. Scores can be transformed to a 0–100 scale. The scores of the five subscales can be expressed as a composite outcome profile, higher scores indicating fewer problems.[61] The KOOS questionnaire is valid and reliable in patients suffering from knee OA and patients on the waiting list for TKA for knee OA.[60 62 63]

EuroQol Group 5-dimension-Level 5

EQ-5D-5L is a self-completion questionnaire consisting of two parts; the first part of the EQ-5D-5L comprises five dimensions involving mobility, self-care, usual activities, pain/discomfort and anxiety/depression. All dimensions have five response categories (no problems, slight problems, moderate problems, severe problems and extreme problems) resulting in a five digit descriptive health state,[64] which will be converted into a summary index ranging from −0.624 (worst) to 1.000 (best), using a Danish value set.[65] The second part, EQ-VAS rates the overall current health status from 0 (worst imaginable health) to 100 (best imaginable health).[64] The EQ-5D-5L is reliable and valid in patients with knee OA eligible for TKA.[66 67]

Adverse events

Adverse events will be defined as unpredicted or unintended events, signs or disease occurring during the period from inclusion until the 3-month follow-up (primary endpoint) resulting in contact with the healthcare system (hospital or general practitioner) independent of whether or not the event is related to the intervention or outcome assessments. Adverse events will be recorded and categorised in accordance with the definitions established by the US Food and Drug Administration. Continuous registration of adverse events will be performed and a short open-ended questionnaire will be administered at 3 months follow-up.

Other outcome measures

Blood pressure

Blood pressure will be measured by the orthopaedic chief physicians when patients are visiting the outpatient clinic. Blood pressure will be used to determine eligibility to participate in the project.

Exercise compliance and progression

Exercise compliance and progression will be obtained by the physiotherapist in charge of the training sessions and entered directly into the REDCap-system. The progression will be monitored as the total load lifted by the patient for exercise session.

Numeric rating scale for pain

Numeric Rating Sscale (NRS) for pain is a segmented unidimensional 11-item measure of pain intensity in adults[68] that will be used to rate pain intensity during both testing and exercise sessions.[68] The number '0' represents no pain while '10' represents worst pain imaginable.[68]

Declining to be operated

Declining to be operated will be measured at 3-month follow-up, where patients will be asked whether they decided to be operated or not. Patients who declined to be operated will be invited to participate in all prescheduled follow-up assessments.

Postoperative supervised physiotherapy

Postoperative supervised physiotherapy will be measured at 6 weeks, 3 months and 12 months follow-up by answering a questionnaire. If patients have participated in postoperative supervised physiotherapy, the patient must specify whether the treatment was related to the TKR or due to other circumstances.

Knee joint active range of motion

Knee joint active range of motion will be measured with a 360° plastic goniometer (scale 1°) with 16.5 cm moveable arms at baseline in the week of surgery, 3 months, and 12 months after surgery. Laying supine on an examination table, the knee joint flexion and knee joint extension will be measured separately.[69] The tester then identifies the most prominent part of the trochanter, the lateral epicondyle of the femur, the lateral head of fibula and the lateral malleolus. When identified, the patient is asked to flex the knee as much as possible with the heel maintaining contact to the surface at all time.[69] Second, the patients will be asked to extend the knee joint as much as possible. To allow the knee to extend as much as possible, a firm quadratic box (height: 5 cm, width: 8 cm, length: 15 cm) will be placed under the heel of the patient. The procedure of measuring knee extension will be similar to knee flexion, as the patients increases the degree of knee extension maximally[69] The fulcrum of the goniometer will correspond visually to the transepicondylar axis of the knee joint. The moveable arms of the goniometer will be pointed towards the greater trochanter and the lateral malleolus.[69]

Data management

All data from the physical function tests will be entered into RedCap by the assessors using double data entry to ensure data quality. All patient-reported outcome data (KOOS, NRS Pain, EQ-5D-5L) will be entered directly into RedCap by the patients, and usage of the 'required fields' will ensure no missing items from the completed questionnaires. To reduce missing data, a reminder email will be sent automatically from the RedCap-system. All patient data will be anonymised by assigning study numbers to each patient (coding). Personal data about the patient will be located separately from the main dataset to protect confidentiality during all trial phases.

The raw dataset will be maintained for ten years after completion of the trial with indefinite restricted access due to sensitive data. After publication of the trial, a fully anonymised patient-level dataset and corresponding statistical description will be made publicly available if required by the scientific journal, in which the results are published.

Sample size

The power and sample size calculation is based on the expected differences between the two subject groups from baseline to 3-month follow-up.[8] Due to lack of data on the primary outcome for investigations applying LL-BFRE before a surgical procedure, we decided to base

our sample size calculation on Skoffer *et al*[8] who investigated the efficacy of 4 weeks of preoperative and 4 weeks postoperative HRST (intervention group) compared with 4 weeks of postoperative HRST only (CON group) on 30 s CST 3 months in patients receiving a TKR.[8] The authors found a between-group difference of 3–4 repetition difference (14.7±4.7 repetitions vs 11.0±4.4 repetitions) 3 months after TKR surgery.[8]

To reduce the probability of type I errors and enable detection of a between-group difference also, α-level is set at 0.05 ($p<0.05$) and β-level is set at 0.20 (80% power). Expecting a 3-repetition between-group difference 3 months postoperatively and assuming an SD of 4.7 in both groups, 39 patients are required in each group (yielding 78 patients in total). With an anticipated dropout rate of 10%, 84 patients will be recruited for the trial.

Statistical considerations

The primary efficacy analysis will be an assessment of the between group difference in change in the 30 s CST from baseline to 3-month follow-up (primary endpoint).

All descriptive statistics and tests will be reported in accordance with the recommendations of the 'Enhancing the QUAlity and Transparency Of health Research' network[70] and the CONSORT statement.[47] Intention-to-treat principle (ie, all patients as randomised independent of departures from allocation treatment, compliance and/or withdrawals) and per-protocol analysis will be conducted. A one-way analysis of variance model will be used to analyse between group mean changes in continuous outcome measures.[31] The model includes changes from baseline to 12 month follow-up. Between-intervention comparison from baseline to 3 months after surgery will be analysed using a mixed linear model with patient ID as a random effect and time, group and hospital as fixed effects.[31 71] Also, to gain insight into the potential pretraining-to-posttraining differences within the respective training or CON groups, paired Student's t-test will be performed. Level of statistical significance is $p<0.05$.

Secondary outcome variables: Between-intervention comparison from baseline to the week of surgery, 6 weeks after surgery, three and 12 months after surgery will be analysed as described for the primary outcome. Regression analysis will be used to analyse the potential associations between preoperative strength and postoperative lower extremity function and self-reported outcome as well as between preoperative functional capacity and postoperative functional capacity. Additionally, regression analysis will be used to analyse the association between preoperative number of SCs and myonuclei on postoperative isometric knee extensor muscle strength, muscle fibre CSA, and functional capacity. All statistical analyses will be performed by the primary investigator using Stata (Stata 16.1, StataCorp LLC, Texas, USA).

Ethical aspects and dissemination

The trial has been accepted by the Central Denmark Region Committee on Biomedical Research Ethics (Journal No 10-72-19-19) and by the Danish Data Protection Agency (Journal No 652164). Before inclusion, all patients will provide their written informed consent in accordance with the Declaration of Helsinki. All data and information collected in regard to this trial will be treated confidentially (blinded and encrypted) by the researchers and staff connected to the trial.

All results from the trial will be published in international peer-reviewed scientific journals regardless of the results being considered positive, negative or inconclusive.

Patient and public involvement

Before developing this clinical trial, a pilot project was performed to determine the feasibility and efficacy of BFRE in patients suffering from lower limb injuries. The experiences with the training modality and the verbal feedback from patients on training duration, frequency and intensity resulted in useful knowledge that certainly has improved the development of the present clinical trial.

DISCUSSION

To the best of our knowledge, this is the first trial to investigate the effect of preoperative BFRE on functional capacity, self-reported outcome, lower limb muscle strength and myofiber morphology/stem cell abundance in patients scheduled for TKR. Only few studies have investigated (short-term [10 days]) preoperative BFRE without finding an atrophy protective effect or difference in muscle strength compared with a CON group performing a placebo intervention (SHAM group).[72] However, patients performing short term preoperative BFRE before ACL-R demonstrated higher muscle endurance compared with a SHAM group.[73] Therefore, results of this trial are expected to provide novel information on longer periods of BFRE that will enable researchers to design effective exercise-based preconditioning protocols for elective TKR patients. The LL-BFRE protocol applied in the present project is widely used and follows the recommendations from a recent position stand by Patterson *et al*.[74] The authors suggested that exercising 2–3 times per week at 20%–40% of 1RM in 2–4 sets (eg, 30-15-15-15 or sets to failure) using pressures between 40% and 80% of LOP has demonstrated to be effective when aiming at increasing muscle strength and promoting muscle hypertrophy.[74]

The trial is designed as an assessor blinded randomised controlled trial, thus representing the highest evidence level. However, the nature of the trial does not allow blinding of the participants which is an inherent limitation of the trial. The trial is conducted at two hospitals that consistently perform a high number of TKR procedures annually (225 and 460, respectively), thus securing a strong expertise in terms of surgery and infrastructure. Both hospitals have all equipment needed available for surgery, postoperative hospitalisation, training and testing. All outcome variables are considered valid and reliable measures and consist of both objective outcomes and self-reported patient outcomes.

No adverse health-related events have been reported in previous studies applying BFRE in patients' suffering from knee OA or in healthy older adults.[1 9 13 23 33 34] Further, in a recent review and meta-analysis, it was stated that exercise with concurrent blood-flow restriction is a safe exercise modality when occlusion procedures are applied correctly.[13] The inherent invasive procedure of muscle biopsies may cause adverse events in rare occasions. Therefore, all muscle biopsy samples will be collected by trained medical doctors and performed following administration of local anaesthesia and in fully sterile conditions. The needle muscle biopsy protocol has been applied in a large number of previous investigations including very old frail subjects (97 years of age) without any reporting of adverse events besides occasional muscle soreness.[31 49 57 75 76]

There are some limitations of the project that must be taken into account. First, our primary end point is 3 months postoperatively. The (uncontrolled) period discharge to 3 months postoperatively renders the project vulnerable to external variabilities. However, from a pragmatic point of view, this uncontrolled period from discharge to 3-month follow-up reflects the reality that Danish patients face postoperatively. Thus, the results at 3-month follow-up will, indeed, reflect the impact of performing preoperative LL-BFRE on the postoperative outcome regardless of the external variable that can hamper the results. Second, the discharge criteria at Horsens Regional Hospital and Silkeborg Regional Hospital withhold slight differences. That is, the acceptable knee joint ROM at discharge differs between the sites, thus it can be speculated that more patients from Silkeborg Regional Hospital will be offered a postoperative, supervised rehabilitation programme. This might affect the number of patients receiving supervised physiotherapy after discharge between sites. However, all patients included in the present project will report whether they have received postoperative supervised physiotherapy at all follow-up assessments. Thus, we will be able to determine (and normalise) a potential between-site difference in patients receiving supervised physiotherapy after TKR. Also, site-specific differences in the postoperative rehabilitation protocols (table 1A,1B) may be considered a limitation. That is, the protocols contain both identical but also different exercises and progression steps. However, a recent review and meta-analysis found no difference in effectiveness between clinic-based or inpatient programmes compared with home-based rehabilitation programmes in the early subacute period after TKA[27] and studies in other knee patient populations have also been unable to observe differences in main outcome variables when comparing home-based postoperative rehabilitation to supervised postoperative rehabilitation.[28 29] We feel confident, therefore, that the apparent differences between the postoperative rehabilitation protocols are not highly likely to affect the results of the present study. Nonetheless, to verify this notion we will introduce site allocation (Horsens Hospital vs Silkeborg Hospital) as a separate independent variable in the mixed linear model used for the statistical analysis.

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