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Improving treatment in patients scheduled for total knee arthroplasty

- the role of preoperative low-load blood flow restricted resistance training

PhD Dissertation
Stian Langgård Jørgensen

Health
Aarhus University

Department of Occupational & Physical Therapy
Horsens Regional Hospital
2024

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Acknowledgements

I would like to thank my three supervisors for tremendous and invaluable supervision during my PhD enrollment. Thank you, Inger, for your excellent mentorship in all aspects of the project. Thank you, Per, I have known you since my Master's Thesis, and without your guidance, I would never have become a PhD student in the first place. Thank you, Marie, for your invaluable help and guidance; it has been truly great to have you onsite and alongside me whenever needed.

Thank you to the Department of Physical and Occupational Therapy and the Department of Orthopedic Surgery at Horsens Regional Hospital. I am grateful for the opportunity to do this project. Also thanks to my colleagues at Horsens Regional Hospital, the personnel involved at Silkeborg Regional Hospital, and Lisa Urup Tønning at Aarhus University Hospital. You have all done a fantastic job, and it has always been a pleasure to chat or drop by for a visit. But most of all thank you for the support during my sick leave due to testicular cancer. I am truly grateful that you kept the project running.

I would also like to bring warm and sincere thank you to all the patients who were enrolled in the project. Without your participation, we would have no results.

To be a top researcher takes hard work with a busy schedule. Therefore, I am grateful that Prof. Jennifer Stevens-Lapsley and Prof. Michael Behringer agreed to evaluate my thesis.

I have enjoyed almost all aspects of being a PhD student. I would like to thank my loving wife, Cecilie, for supporting me and for patiently listening to me every time I have started rambling about the project. You and our two lovely daughters, Alberte & Astrid, provide a loving and peaceful sanctuary.

The scientific work presented in this thesis was conducted at the Department of Occupational and Physical Therapy, Regional Hospital Horsens during my enrollment as a PhD student at the Department of Clinical Medicine, Aarhus University (September 1, 2019 – March 27, 2024).

Originally the project was planned as a full-time, three-year project. However, due to the COVID-19 pandemic, it was impossible to achieve sample size within the original time frame. Therefore, we decided to extend the PhD period.

Data for this thesis was collected at the Department of Orthopedic Surgery, Regional Hospital Horsens (recruitment of patients); Department of Occupational and Physical Therapy, Regional Hospital Horsens (outcome assessments and exercise sessions); Elective Surgery Center, Regional Hospital Silkeborg (recruitment of patients); The Research Unit, Regional Hospital Silkeborg (outcome assessments and exercise sessions); and Department of Orthopedic Surgery, Aarhus University Hospital (exercise sessions).

Financial support for this trial was provided by the Central Denmark Region Research Foundation, Aase & Ejnar Danielsens Foundation, Elisabeth & Karl Ejnar Nis-Hanssens Mindeslegat, The Family Hede Nielsens Foundation, The Brother's Hartman Foundation, The Danish Physiotherapy Association Foundation, Helga & Peter Kornings Foundation, William Demants Foundation, Augustinus Foundation, Christian og Ottilia Brorsons Travel Grant for young scientists, The Graduate School of Health Travel Grant.

Thesis publications

I. Paper I: Jørgensen SL, Bohn MB, Aagaard P, Mechlenburg I. 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. BMJ Open 10(10): e034376: doi: 10.1136/bmjopen-2019-034376

II. Paper II: Stian Langgård Jørgensen, Inger Mechlenburg, Marie Bagger Bohn, Per Aagaard. Sit-to-stand power predicts functional performance and patient-reported outcomes in patients suffering from advanced knee osteoarthritis. Musculoskelet Sci Pract 69: 102899.

III. Paper III: Stian Langgård Jørgensen, Per Aagaard, Marie Bagger Bohn, Peter Hansen, Per Møller Hansen, Carsten Holm, Louise Mortensen, Mette Garval, Lisa Urup Tønning, Inger Mechlenburg. The efficacy of blood flow restriction exercise before total knee arthroplasty on sit-to-stand function 3 months postoperatively: A randomized controlled trial. *(in review)*

IV. Paper IV: Stian Langgård Jørgensen, Inger Mechlenburg, Per Aagaard, Peter Hansen, Per Møller Hansen, Marie Bagger Bohn. Pre-operative low-load blood flow restricted exercise induce persistent gains in knee extensor muscle strength 3 months after total knee replacement surgery: Secondary analysis of a randomized controlled trial. *(in review)*

Thesis overview

Study	Title	Aims	Methods	Conclusions
I	Efficacy of low-load blood flow restricted resistance EXercise in patients with Knee osteoarthritis scheduled for total knee replacement (EXKnee): protocol for a multicenter randomized controlled trial	To describe the rational and design of the randomized controlled trial.	This is a protocol paper, outlining the methods used in the randomized controlled trial.	
II	Sit-to-stand (STS) power predicts functional performance and patient-reported outcomes in patients with advanced knee osteoarthritis. A cross sectional study.	To examine i) the relationship of STS muscle power and maximal isometric knee extensor strength (KE MVC) on objective measures of physical function and patient-reported outcomes; ii) if STS power stronger correlated than knee extensor MVC with physical function and patient-reported outcomes.	Design: Cohort study. Cohort was divided into a male- and female cohort. Linear- and multiple regression analyses with and without adjusting for age. Pitman's test Dependent variables: STS Power and KE MVC Independent variables: Timed Up & Go (TUG), 40 meter fast paced walk test (40mFWT), Knee Injury & Osteoarthritis Outcome Score (KOOS) scales for Pain, Symptoms, Activities of Daily Living (ADL), Sport & Recreational Activities (Sport), Quality of Life (QoL).	Only STS Power was associated with physical function in male- and female patients with knee OA, and KOOS pain and ADL in male patients. STS power correlated better with measures of physical function and KOOS Pain and ADL-scores than the knee extensor MVC.
III	The efficacy of blood flow restriction EXercise prior to total Knee arthroplasty on sit-to-stand function three months postoperatively (EXKnee): A randomized controlled trial	To investigate the efficacy of eight weeks of preoperative low-load blood flow restricted resistance training (BFR-RT) compared with preoperative standard care total knee arthroplasty (TKA) on changes in 30-seconds chair stand test (30STS), patient-reported outcomes, and lower limb strength three months after surgery.	Eighty-six patients scheduled for TKA were randomized to eight weeks of preoperative BFR-RT 3x/week or usual preoperative medical care. Primary outcome: 30STS Intention-to-treat analysis	Eight weeks of preoperative BFR-RT yielded no superior effects on physical function or patient-reported outcomes three months after surgery. BFR-RT induced significant gains in leg press strength lasting up to three months after surgery.
IV	Eight weeks of preoperative low load blood flow restricted exercise induce gains in knee extensor muscle strength three months after total knee replacement surgery: Secondary analyses from a randomized controlled trial	To compare eight weeks of pre-operative BFR-RT with usual preoperative medical care on maximal knee extensor and flexor muscle strength, knee range of motion function, physical function, and EQ-5D-5L three months after TKA surgery.	Described in study III **Outcomes:** 1RM knee extension strength, maximal isometric knee extensor/flexor contraction strength, TUG, 40mFWTt, EQ-5D-L5	BFR-RT effectively prevented decreases in maximal knee extensor strength three months after TKA. No between-group changes in physical function and knee joint range of motion were observed three months postoperatively.

Summary in English

Improving treatment in patients scheduled for total knee arthroplasty. The role of preoperative low-load blood flow restricted resistance training.

Jørgensen SL

Background: The number of total knee arthroplasties (TKA) due to knee osteoarthritis (OA) increases worldwide. Despite being a successful surgery, ~20% of the patients perceive insufficient postoperative outcomes. Also, the majority of patients demonstrate long-lasting impairments in physical function following TKA compared with healthy peers. Improving preoperative knee extensor strength is proposed to enhance postoperative physical function. Low-load blood flow restricted resistance training (BFR-RT) increases skeletal strength and size and physical function with minimal stress on the knee joint.

Aims: The main aims of the overall PhD project were to

i. Outline the complete description of the trial protocol (Paper I)
ii. Evaluate the associations to lower limb sit-to-stand power (STS Power) or maximal isometric knee extensor strength (knee extensor MVC), respectively, with objective measures of physical function and patient-reported outcomes (Paper II).
iii. Determine if STS Power or knee extensor MVC would be differently related to physical function and patient-reported outcomes (Paper II)
iv. Investigate the efficacy of preoperative BFR-RT compared with usual preoperative medical care on physical function, lower limb strength, and patient-reported outcomes three months after TKA (Paper III & IV).

Methods: The intervention phase of the PhD project was designed as a randomized, controlled, assessor-blinded trial (RCT). Patients ≥50 years scheduled for TKA at Horsens- or Silkeborg Regional Hospital due to knee OA were randomly assigned to (i) eight weeks of preoperative BFR-RT or (ii) usual preoperative medical care. The primary endpoint was between-group mean change in 30-sec sit-to-stand (30STS) performance three months after TKA. Key secondary outcomes were: Timed Up & Go (TUG), 40-meter fast-paced walk test (40mFWT), 1 repetition maximum (RM) leg press and knee extensor strength, knee extensor and flexor MVC, the Knee Injury & Osteoarthritis Outcome Score (KOOS), and the EQ-5D-L5 questionnaire. **Paper II** was designed as a cross-sectional study comprising baseline data from all trial participants. Linear and multiple regression analyses and Pitman's test were applied with STS Power and knee extensor MVC as the dependent variables. The cohort was divided into a male- and female-patient cohort. **Papers III and IV** present intention-to-treat results from the RCT collected on the primary and secondary outcomes at baseline, pre-surgery, and three months after surgery.

Findings: At baseline, only STS Power was statistically associated with TUG and 40mFWT in our male- and female patient cohorts, and with KOOS subscales of Pain, Activities of Daily Living, and Sport & Recreational Activities in our male patient cohort (Study II). STS Power was equal or more strongly correlated to TUG, 40mFWT, and the KOOS subscales compared with the correlation coefficients derived with knee extensor MVC (Study II).

No significant between-group changes were observed in physical function or patient-reported outcomes from baseline to three months after surgery. Patients following usual preoperative medical care demonstrated significant postoperative decreases in leg extensor strength in the affected leg, while BFR-RT sustained preoperative levels of leg extensor strength (Paper III & IV).

Interpretation: STS Power can be used as a time-efficient and inexpensive measure to estimate ambulatory and walking speed in patients with advanced stages of knee OA (Study II).

The present preoperative BFR-RT protocol did not improve the postoperative measures of physical function or patient-reported outcomes compared with receiving usual preoperative medical care. The patients in the BFR-RT group only exercised the affected leg, which may, in part, explain the lack of significant between-group changes. However, preoperative BFR-RT protected against decreases in maximal knee extensor strength in the exercised leg (Paper III & IV).

Summary in Danish

Baggrund: Antallet af operationer, hvor der indsættes en total knæ alloplastik (TKA) grundet artrose i knæet, er stødt stigende. Selvom operationen er effektiv, har det vist sig at ~20% af patienterne ikke tilfredse med resultatet af operationen. Generelt oplever patienterne vedvarende forringelse af deres fysiske funktionsniveau sammenlignet med alderssvarende raske. Ved at forbedre muskelstyrken i lårets knæstrækkemuskel før operationen, kan man potentielt opnå bedre fysisk funktion efter operationen. Styrketræning med lette belastninger og samtidig delvis afklemning af blodets tilløb til det trænende ben (okklusionstræning) øger muskelstyrken, muskelmassen og det fysiske funktionsniveau samtidig med at knæleddet belastes minimalt.

Formål: Formålet med det overordnede PhD projekt var at

- i) Præsentere projektprotokollen i sin fulde længde (Studie I)
- ii) Evaluere om objektive mål for fysisk funktionsevne og patient-rapporterede udfaldsmål hænger sammen med muskelpower i benene og/eller maksimal isometrisk knæekstensionsstyrke (knæstrækker MVC) (Studie II)
- iii) Vurdere om fysisk funktionsevne og patient-rapporterede udfaldsmål har en statistisk bedre sammenhæng til muskelpower i underekstremiteterne sammenlignet med til knæstrækker MVC.
- iv) Undersøge effekten af præoperativ okklusionstræning sammenlignet med vanlige præoperative forløb målt på fysisk funktion, muskelstyrke i underekstremiteterne og patient-rapporterede udfaldsmål tre måneder efter en TKA (Studie III og IV) operation.

Metoder: Projektet blev udført som et randomiseret, kontrolleret, tester-blindet forsøg. Patienter ≥50 år, skrevet op til TKA på Regionshospitalerne Horsens eller Silkeborg på grund af artrose i knæet blev randomiseret til enten i) præoperativ okklusionstræning eller ii) det vanlige præoperative forløb. Den primære analyse var baseret på om gennemsnitsændringen i 30-sekunders rejse/sætte sig-testen (30STS) 3 måneder efter operationen var forskellig mellem grupperne. Vigtige sekundære effektmål var Timed Up & Go (TUG), 40-meter gangtest (40mFWT), 1 repetition maksimum (RM) benpres og knæekstensions styrke, knæstrækker MVC og maksimal isometrisk knæbøjer styrke, the Knee Injury & Osteoarthritis Outcome Score og EQ-5D-L5-spørgeskemaet. **Studie II** var

et tværsnitsstudie på baselinedata fra alle projektdeltagerne. Vi anvendte lineær og multipel regressionsanalyser samt Pitman's-testen med STS Power og knæstrækker MVC som de afhængige variable. Vi delte kohorten op i mænd og kvinder. **Studie III & IV** præsenterer resultaterne fra vores *intention-to-treat* analyser på det primære og sekundære effektmål, som vi indsamlede data ved baseline, før operationen og tre måneder efter operationen.

Fund: Ved baseline viste kun muskelpower i benene en statistisk sammenhæng med TUG og 40mFWT i både den mandlige og kvindelige patientkohorte, samt yderligere for KOOS subskalaerne smerte, dagligdagsaktiviteter og sport- og fritidsaktiviteter i den mandlige patientkohorte (Studie II). Der kunne ikke observeres nogle forskelle mellem patientgrupperne (interventionsgruppen og kontrolgruppen) i fysisk funktion eller patient-rapporterede udfaldsmål tre måneder efter operationen. Patienterne der fulgte det vanlige præoperative forløb blev svagere i knæekstensorerne efter operationen, mens patienterne i gruppen der udføre okklusionstræning fastholdt muskelstyrkeniveauet i knæekstensorerne svarende til baselinemålingerne (Studie III & IV).

Fortolkning: Muskelpower i benene målt ud fra en rejse-sætte-sig test kan let anvendes til at estimere ganghastighed og fysisk funktionsevne i patienter med svær grad af artrose i knæet (Studie II). Vores studie viser at præoperativ okklusionstræning ikke forbedrer fysisk funktion eller patient-rapporterede udfaldsmål mere end den vanlige præoperative forløb. Dette kan skyldes at patienterne kun trænede det ben, der skulle opereres, mens benet uden symptomer ikke modtog nogen træning. Ligesom i tidligere studier, så vi, at vores præoperative okklusionstræningsprotokol beskyttede mod tab af maksimal muskelstyrke i lårets knæstrækkemuskel i det trænende ben (Studie III & IV)

List of abbreviations

30STS	30-seconds sit-to-stand-test
40mFWT	40-meter fast paced walk test
ADL	Activities of daily living
BFR-RT	Low-load blood flow redistricted resistance training
BMI	Body mass Index
CI	Confidence Interval
Cm	centimeter
CON	Control Group
CONSORT	Consolidated Standards of Reporting Trials
Deg	Degree
DOMS	Delayed Onset of Muscle Soreness
EQUATOR	Enhancing the QUAlity and Transparency Of health Research
EQ-VAS	EuroQol Visual Analog Scale
HHD	Hand held dynamometer
HL-PRT	Heavy-load progressive resistance training
HRQOL	Health-related quality of life
Kg	Kilo
Knee extensor MVC	Maximal isometric voluntary contractions of the knee extensors
Knee flexor MVC	Maximal isometric voluntary contractions of the knee flexors
KOOS	Knee Injury & Osteoarthritis Outcome Score
AOP	Arterial occlusion pressure
m	meter
MetS	Metabolic Syndrome
Nm	Newton meter
NRS	Numeric ranking scale
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
PhD	Doctor of Philosophy
QoL	Quality of life
r	Pearson correlation coefficient

r^2	coefficient of correlation
RCT	Randomized controlled trial
REDCap	Research Electronic Data Capture online database
Reps	Repetitions
RM	Repetition maximum
ROM	Range of motion
ROS	Reactive oxygen species
Sec	Seconds
Sport	Sport & Recreational Activities
STS Power	Sit-to-stand power
THA	Total hip arthroplasty
TKA	Total knee arthroplasty
TUG	Timed Up and Go
VAS	Visual analog scale
W	Watt

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Table A-4 Patient characteristics of the patients included in the trial versus the observational cohort

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resistance training (BFR-RT) and the control group (CON) receiving usual preoperative medical care.

* within-group change $p < 0.05$

BACKGROUND

Osteoarthritis

Osteoarthritis (OA) is one of the world's most prevalent diseases causing joint pain, disability, and reduced levels of physical function (Bade, Kohrt, and Stevens-Lapsley 2010; Cross et al. 2014; Hunter and Bierma-Zeinstra 2019). OA most commonly affects the knee, hip, spine, or hand (March et al. 2014; Murray et al.) with 528 million people worldwide suffering from mild-to-more advanced stages of OA. According to the World Health Organization, 73% of the subjects affected by OA are ≥55 years old, 60% are females, and 344 million people would benefit from treatment (i.e. rehabilitation) to alleviate symptoms and prevent further impairments in physical function (www.who.org). With the aging population increasing worldwide, a global obesity pandemic, and a high prevalence of knee joint injuries, the OA burden is projected to rise (Cross et al. 2014; Hunter and Bierma-Zeinstra 2019).

OA pathogenesis

Information Box

The cartilage is non-vascularized and not neurally innervated. It consists mainly of collagen fibrils embedded in a proteoglycan matrix containing ~70% water (Martel-Pelletier et al. 2016). A small population of chondrocytes controls the cartilage tissue turnover (Martel-Pelletier et al. 2016). Healthy cartilage is characterized by sophisticated resilience to withstand and distribute compressive forces evenly between bone plates, and, thus, sustains a healthy equilibrium between cartilage tissue synthesis and degradation (Martel-Pelletier et al. 2016; Abramoff and Caldera 2020)

Historically, OA has been considered to be a result of *wear* and tear (Abramoff and Caldera 2020). However, our current understanding of the disease has developed and today we know that OA pathogenesis involves a complex interplay of mechanical, inflammatory, and metabolic factors (Hunter and Bierma-Zeinstra 2019; Abramoff and Caldera 2020;

Lespasio et al. 2017; Martel-Pelletier et al. 2016). Despite cartilage degeneration is a primary factor in OA progression, the disease affects the whole joint and alters the remodeling processes of its structures, including the bone, subchondral bone, muscles, ligaments, capsules, synovia, menisci, and cartilage (Sharma 2021; Hunter and Bierma-Zeinstra 2019).

Onset of the OA disease is typically characterized by a gradual negative imbalance in the cartilage tissue turnover, which increases cartilage fragility and vulnerability to physical compression forces (Hunter and Bierma-Zeinstra 2019). As a result, a cascade of downstream factors is initiated to repair the damaged regionss (Hunter and Bierma-Zeinstra 2019; Martel-Pelletier et al. 2016; Abramoff and Caldera 2020). Chondrocytes, which are responsible for cartilage tissue turnover (Martel et al. 2005) elevate their synthesis-activity, leading to increased levels of matrix degrading products that negatively affect the adjacent synovium causing tissue hypertrophy and vascular infiltrations. In the subchondral bone regions, bone marrow lesions and vascular infiltration occur due to an elevated bone tissue turnover and development of osteophytes occurs due to accumulation of inflammatory biological factors and mechanical overloading (Figure 1) (Hunter and Bierma-Zeinstra 2019; Martel-Pelletier et al. 2016; Abramoff and Caldera 2020).

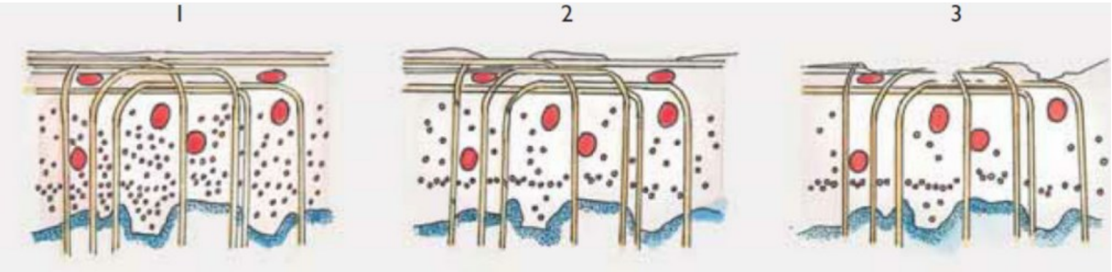

Figure 1. Yellow lines = Collagen; Red ovals = chondrocytes; dots = proteoglycans. To aid repair processes, the chondrocytes upregulate the synthesis activity. This results in the generation of matrix degradation products and proinflammatory mediators negatively affecting the function of the chondrocytes. (Illustration borrowed from Idrætsskadebogen 1st edition)

Knee Osteoarthritis

More than half of the OA prevalence worldwide is due to knee OA (Lespasio et al. 2017). The prevalence peaks in subjects ≥50 of age (Cross et al. 2014; Abbassy, Trebinjac, and Kotb 2020) Primary knee OA consists of articular degeneration of one or more compartments of the knee joint without any specific underlying reason, but is strongly associated with age, female gender, obesity, joint malalignment, increased biomechanical joint-loading (incl. body overweight), genetics, and lower limb muscle weakness (Sen R 2023; Hunter and Bierma-Zeinstra 2019; Martel-Pelletier et al. 2016). Secondary knee OA occurs due to joint morphology/deformity or injury (i.e. anterior cruciate ligament rupture, knee fractures, tibia plateau fractures or meniscus injury) triggering articular joint degeneration (Sen R 2023). Additionally, occupations involving prolonged standing, repetitive squatting, and kneeling increases the risk of developing knee OA (Johnson and Hunter 2014; Hunter and Bierma-Zeinstra 2019; Lespasio et al. 2017). By the age of 75, some degree of knee OA is observed in 75% of all people (Lespasio et al. 2017).

Symptoms and diagnostics

Pain is the overwhelming self-perceived symptom of symptomatic knee OA, which often occurs at the onset of movement, then alleviates during locomotion (within 30 minutes), and returns after prolonged periods of joint-loading (the OA Triade) (Hunter and Bierma-Zeinstra 2019; Bliddal 2020). Further, knee OA-related pain reduces locomotive function (i.e. reduced walking distance and gait speed) compared with healthy peers and impairs the motivation for sports- and leisure-time physical activities (Gay et al. 2016; Lespasio et al. 2017). In the advanced stages of knee OA, joint pain even appears at rest, during load-bearing activities, and at night which hampers the sleep quality (Sharma 2021)

Clinically, OA can be diagnosed based on symptoms and a physical examination involving: crepitus; joint tenderness with palpation; visible bony enlargements; reduced joint range of motion (ROM) with pain at maximal knee joint extension and flexion; knee joint pain; morning stiffness; impairments in physical function; impairments in maximal lower limb muscle strength; and muscle atrophy in the muscles surrounding the affected joint (Hunter and Bierma-Zeinstra 2019; Sharma 2021; Bade, Kohrt, and Stevens-Lapsley 2010; Taylor et al. 2014; Calatayud et al. 2016; Skoffer, Dalgas, and Mechlenburg 2015). Inflammation, effusion, warmth, and synovitis are not always present in patients with knee OA (Sharma 2021). Also, disease progression increases the risk of obvious joint deformities such as varus or valgus of the knee joint (Leopold 2009). Ultimately, the above-mentioned signs and symptoms result in impairments in quality of life (QoL) (Lespasio et al. 2017).

Radiographic imaging is used to confirm the OA diagnosis and grade the severity of OA (Lespasio et al. 2017). Typical radiographic signs of OA are joint-space narrowing, subchondral bone sclerosis, osteophyte formation, and cyst formation (Figure 2) (Taruc-Uy and Lynch 2013; Lespasio et al. 2017).

The most frequent radiographic grading system is the Kellgren & Lawrence scale (Kellgren and Lawrence 1957) ranging from 0-4 based on the degree of joint space narrowing with 0 = no joint space narrowing and osteophytes; 1: doubtful-; 2: minimal- ; 3: moderate-; 4: Severe joint space narrowing and osteophyte formation (Lespasio et al. 2017; Kellgren and Lawrence 1957).

Figure 2. Illustration of the joint space knee in a non-affected knee and an osteoarthritic knee joint with joint-space narrowing, osteophytes, and sclerosis (Borrowed from Gornale et al. (Gornale, Patravali, and Hiremath 2020)

Knee extensor and flexor strength in patients with knee OA

Maximal knee extensor- and flexor muscle strength, muscle activation, and proprioception all represent factors that are impaired in patients with advanced stages of knee OA - both compared with the contralateral leg and with healthy age-matched peers - ultimately increasing the risk of physical disability and falling episodes in these patients (Skoffer et al. 2015; Zeng et al. 2021; Sharma 2021; Bade, Kohrt, and Stevens-Lapsley 2010). This is often due to progressively increasing patterns of symptom-related disuse (i.e. pain-avoidance) (Johnson and Hunter 2014; Skoffer et al. 2015; Skoffer, Dalgas, and Mechlenburg 2015; Bade, Kohrt, and Stevens-Lapsley 2010; Dreyer et al. 2013). Notably, improving knee extensor strength can reduce perceived knee pain and increase physical function in patients suffering from knee OA (DeVita et al. 2018; Bartholdy et al. 2017), but the underlying biomechanical mechanisms for these positive adaptations in pain perception remain largely unknown (DeVita et al. 2018). Nonetheless, due to the positive features associated with improving lower limb strength, exercise training to increase maximal lower limb muscle strength is a recommended treatment modality for subjects with knee OA (Zeng et al. 2021; Skoffer et al. 2015). Increased levels of preoperative physical function and maximal knee extensor strength are suggested as therapeutic key targets prior to total knee arthroplasty (TKA) surgery while shown to correlate positively with postoperative physical function (Mizner, Petterson, and Snyder-Mackler 2005; Mizner et al. 2005; Stevens, Mizner, and Snyder-Mackler 2003; Kwok, Paton, and Haddad 2015; Gill and McBurney 2013; Wang et al. 2016).

However, pain, swelling, and increased joint stiffness associated with knee OA affect the tolerance to perform physical exercise at high loading intensities, thereby rendering the patients even more prone to disuse muscle atrophy, loss in muscle strength, and impairments in physical function (Kwok, Paton, and Haddad 2015).

Total knee arthroplasty

When non-invasive treatments fail to attenuate pain, improve or maintain physical function, or sustain QoL in subjects with advanced stages of knee OA, TKA surgery is offered to the patients (Gränicher et al. 2022; Sharma 2021; Hunter and Bierma-Zeinstra 2019). TKA is a highly effective treatment for reducing pain and improving quality of life in patients with advanced stages of knee OA (Canovas and Dagneaux 2018; Rolfson et al. 2016).

Both globally and in Denmark, the number of TKA procedures is increasing (Carr et al. 2012). In Denmark ~8,000 subjects underwent TKA in 2015, ~10,000 in 2019, and ~13.000 in 2022 (Odgaard et al. 2019; S.; Østergaard S.E.; Jakobsen T.L.; Christensen T.M. 2023).

Despite being considered an effective treatment, ~20% of the patients remain dissatisfied with pain and physical function following TKA surgery (Bourne et al. 2010; Noble et al. 2006; Hunter and Bierma-Zeinstra 2019). Notably, impairments in physical function and lower limb strength have been demonstrated to persist for years following surgery and to stay below levels of healthy peers (Noble et al. 2005; Meier et al. 2008; Mizner, Petterson, and Snyder-Mackler 2005; Mizner et al. 2005; Alnahdi, Zeni, and Snyder-Mackler 2012; Paxton et al. 2015). Thus, despite relieving knee joint pain, TKA surgery may not reverse preexisting impairments in physical function and muscle strength (Bade, Kohrt, and Stevens-Lapsley 2010; Walsh et al. 1998; Capin et al. 2022).

Treatment guarantee

In Denmark, the healthcare system is obliged to provide the recommended treatment within four weeks after being diagnosed (the so-called 'treatment guarantee'). However, this treatment guarantee is often exceeded, and the majority of patients scheduled for TKA typically wait several months before undergoing surgery. The waiting time prolongs their suffering and, may, negatively influence health-related quality and life (Gill and McBurney 2013). On the other hand, this preoperative waiting period provides a window of opportunity to introduce preoperative muscle strengthening exercises to improve postoperative physical function.

Muscle strengthening exercises before total knee arthroplasty

Prehabilitation involves a structured preoperative intervention protocol aiming to improve holistic fitness (Sutton et al. 2023) and optimize postoperative recovery (Franz et al. 2019; Franz et al. 2018; Topp et al. 2002). Within orthopedic elective surgery, prehabilitation efforts primarily have focused on exercise programs (Jørgensen et al. 2022; Husted et al. 2020), weight loss programs (Liljensøe et al. 2021), and/or patient education programs (Sutton et al. 2023; Skou et al. 2015). The present Thesis focuses on prehabilitation protocols involving muscle strengthening exercises, referred to below as "prehabilitation" or "preoperative muscle strengthening exercises".

To induce gains in maximal muscle strength it is essential to systematically overload the target musculature, which is typically achieved by means of progressively adjusted resistance training exercise (Minshull and Gleeson 2017; Garber et al. 2011). Traditionally, resistance training regimes using heavy loading intensities (>60-80% 1 repetition maximum (RM)) have been deemed necessary to induce gains in muscle strength in healthy and older individuals (Garber et al. 2011; Chodzko-Zajko et al. 2009). In line with this notion, preoperative heavy-load progressive resistance (HL-PRT) training has been demonstrated effective in improving physical function and lower limb strength in patients undergoing TKA, when compared with usual preoperative medical care (i.e. no exercise) (Skoffer et al. 2016; Calatayud et al. 2016; Jørgensen et al. 2022). However, Ferraz et al. (Ferraz et al. 2018) reported that about 25% of patients with moderate-degree knee OA allocated to HL-PRT were unable to tolerate the heavy exercise loads imposed by their training protocol due to exercise-related exacerbations in knee pain (Ferraz et al. 2018).

Recommendations for improving preoperative fitness in patients with knee osteoarthritis scheduled for total knee arthroplasty

Due to the absence of Danish national clinical guidelines on how to physically prepare patients for TKA surgery, Danish regional hospitals typically apply locally developed preoperative guidelines. At Horsens Regional Hospital, patients are recommended "*to exercise to improve fitness before the TKA surgery. I.e. by walking or cycling*". At Silkeborg Regional Hospital the local preoperative guidelines encourage patients to follow the national dietary guidelines, stop smoking, and exercise as seen fit, "*i.e. by walking or cycling"*. Intuitively, these exercise guidelines appear insufficient to induce gains in patient's musculoskeletal fitness levels before surgery in patients with advanced stages of knee OA (Chodzko-Zajko et al. 2009; Garber et al. 2011).

In 2020, *The Journal of Physical Therapy* published a set of clinical practice guidelines entitled "Physical Therapist Management of Total Knee Arthroplasty", outlining various treatment recommendations for patients scheduled for TKA (Jette et al. 2020). These guidelines recommended preoperative exercise programs involving strengthening and flexibility exercises since these activities were presumed to positively enhance the rate of postoperative recovery in physical function and self-reported outcomes (i.e. pain and QoL) (Jette et al. 2020). Specifically, the recommendations stated that preoperative exercises should be safe to perform, while targeting activities such as postural balance, knee flexion and extension range of motion (ROM), lower limb strength, and QoL, respectively, while concurrently decreasing pain and reducing the length of inpatient stay (Jette et al. 2020).

Low-load blood flow restricted resistance training

Resistance training exercises using low loading intensities (30%1RM) and concurrent partial blood flow restriction to the active muscles (BFR-RT) (Figure 3) have been shown to produce gains in maximal muscle strength, muscle size, physical function, and self-reported outcomes in patients with mild-to-moderate knee OA (Ferraz et al. 2018; Segal et al. 2015; Bryk et al. 2016). Muscle perfusion is typically restricted using pressure cuffs positioned proximally on the exercising limb (Figure 3). Furthermore, BFR-RT is considered safe and feasible in various patient populations (Petersson et al. 2020;

Jørgensen and Mechlenburg 2021; Petersson et al. 2022; Høgsholt et al. 2022; Mortensen, Mechlenburg, and Langgård Jørgensen 2023; Jørgensen et al. 2023; Jørgensen 2023; Bentzen et al. 2023; Jønsson et al. 2024)

Current recommendations suggest to use cuff pressures between 40-80% of the total arterial occlusion pressure (AOP) during BFR-RT exercise (Patterson et al. 2019). Thus, BFR-RT typically allows an initial and partial arterial inflow to the exercising limb while venous outflow is largely obstructed (Cuyul-Vásquez et al. 2020).

Despite the low loading intensities (20-40% 1RM), BFR-RT appears effective in producing gains in maximal muscle strength, muscle size, and physical function that are comparable to that achieved with HL-PRT in both patients and healthy subjects (Jørgensen et al. 2023; Grønfeldt et al.). Importantly, BFR-RT appears to induce less knee-related discomfort than HL-PRT during exercise while leading to more marked relieve in self-reported knee pain in patients suffering from knee-joint disorders (Ferraz et al. 2018; Hughes et al. 2019; Giles et al. 2017).

The adaptive mechanisms evoked by BFR-RT are not fully understood. It is hypothesized that the hypoxic environment resulting from high metabolic stress along with mechanical tension induces increased levels of systematic hormone production, muscle cell swelling, production of reactive oxygen species (ROS), activation and proliferation of myogenic stem cells (so-called satellite cells), and increased fast-twitch myofiber recruitment (Hughes et al. 2017; Wernbom and Aagaard 2019; Wernbom, Augustsson, and Raastad 2008; Rossi et al. 2018; Pearson and Hussain 2015; Vissing et al. 2020)

Although the physiological mechanisms remain under scrutiny, BFR-RT has been recommended as a viable treatment method across multiple clinical patient populations, especially in conditions where high mechanical loading is contraindicated or intolerable due to excessive joint pain (Hughes et al. 2017; Lim and Thahir 2021; Franz et al. 2018).

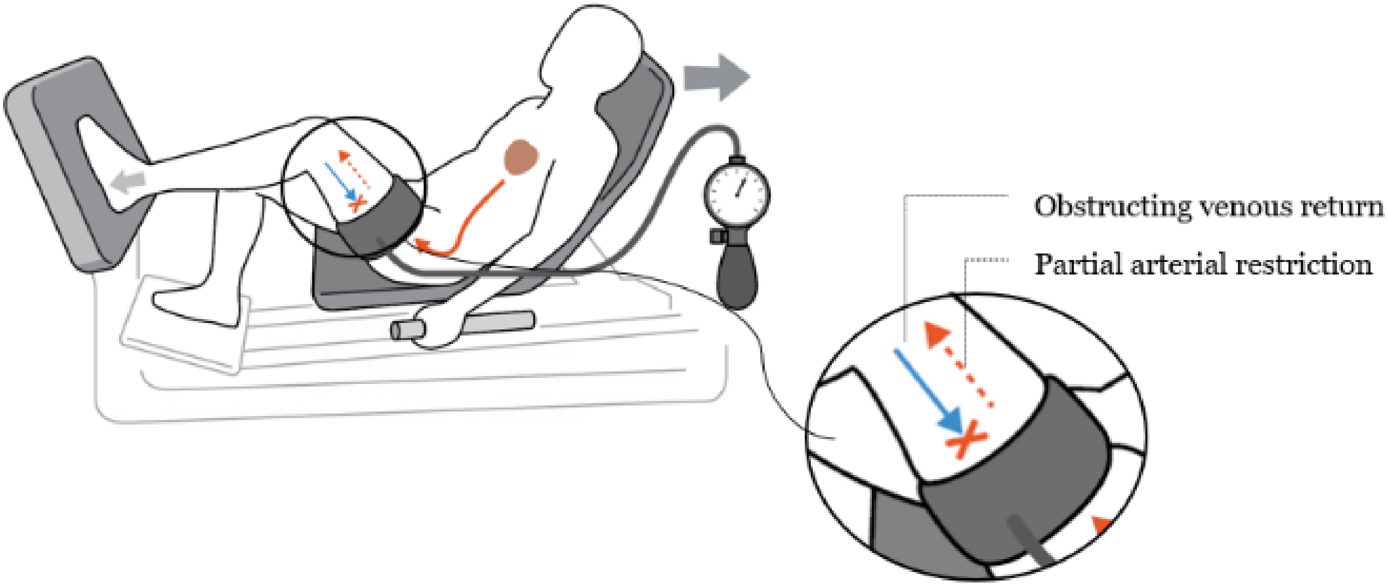

Figure 3. Illustration of leg press exercise with blood flow restriction. The pneumatic cuff is inflated to achieve partial arterial inflow while obstructing the venous return. Adapted from Jørgensen & Bohn (Jørgensen 2023)

Assessment procedures in patients with knee osteoarthritis

Physical function

The Osteoarthritis Research Society International (OARSI) has recommended five objective measures to monitor and evaluate various skills-related mobility statuses in persons with knee OA (Dobson et al. 2013).

Measures of physical function typically comprise the 30-second sit-to-stand test (30STS), the 40-meter fast-paced walk test (40mFWT), stair negotiation, the Timed Up & Go (TUG), and the 6-min walk test (Dobson et al. 2013). The 30STS, 40mFWT, and stair tests form the recommended minimal core set for evaluating the physical function in patients with knee OA. However, no standardized assessment protocol for the star test exists (Dobson et al. 2013). Therefore, as stair cases can differ markedly between sites, assessing stair test performance can be challenging in trials with multiple assessments sites.

Assessing muscle power in patients with knee OA

Mechanical muscle power is the product of contractile force and contraction velocity (force · velocity = power (Watt)) (Caserotti et al. 2008; Caserotti et al. 2001; Cormie, McGuigan, and Newton 2011). High lower limb muscle power represents an important prerequisite for unassisted rising from a chair, negotiating stairs, and crossing the street by foot (Aagaard et al. 2010). Evaluating lower limb muscle power has been suggested to be equally or more important for various mobility tasks than maximal knee extensor strength in both older adults and patients with knee OA (Bean et al. 2003; Reid et al. 2015; Accettura et al. 2015; Langgård Jørgensen et al. 2023). Moreover, maximal lower limb muscle power appears more strongly correlated to given measures of physical function and patient-reported pain and quality of life compared with knee extensor strength in patients with knee OA (Reid et al. 2015). However, assessing muscle power has historically rarely been available nor readily affordable in clinical settings. Notably, Alcazar et al. (Alcazar, Kamper, et al. 2020; Suetta et al. 2019; Alcazar, Aagaard, et al. 2020; Alcazar et al. 2021; Alcazar et al. 2018) demonstrated that lower limb muscle power can be derived from sit-to-stand testing (STS Power) in healthy young-to-old adults (i.e. employing the 30STS) with strong similarity to more established measures of mechanical muscle power (i.e. Nottingham power rig) (Alcazar, Kamper, et al. 2020; Alcazar et al. 2018). Thus, implementation of the STS Power test provides clinicians and researchers with an unique, simple, and affordable tool to evaluate and monitor muscle power in individuals with knee OA, including before and after TKA.

Knee joint range of motion (ROM)

Restoring knee ROM after TKA is a highly important clinical objective, while also used as an essential discharge parameter and marker of recovery progression (Jørgensen et al. 2020; Capin et al. 2022). In practical terms, and to sufficiently engage in daily life activities such as negotiating stairs and riding a bike, a 110° ROM in knee flexion is required (Rowe et al. 2000; Capin et al. 2022).

Lower limb muscle strength

Strength improvements often appear to be highly task-specific (i.e. leg press exercise will mostly improve 1RM leg press strength) (Spitz et al. 2023). Consequently, in the present PhD project it was deemed important to include measures of maximal isometric knee extensor- and flexor strength which would represent strength measures to which the patients were unaccustomed (non-specific strength) (Spitz et al. 2023).

Patient-reported outcomes

Patient-reported outcomes is considered an important part of the overall patient evaluation before and after TKA as they evaluate the patient perceptions and perspectives within specific domains (Collins et al. 2011; Dobson et al. 2013). Thus, the patient-reported outcomes provide (i) insights about the specific aspects the patients perceive as important, and (ii) the surgery success rates (Rolfson et al. 2016; Most et al. 2022). The International Society of Arthroplasty Registries have recommended to apply both patient-specific questionnaires and generic to evaluate the effectiveness of TKA treatment (Rolfson et al. 2016). The Knee Injury & Osteoarthritis Outcome Score (KOOS) was suggested one of several possible patient-specific questionnaires to apply before and after TKA surgery

(Rolfson et al. 2016). The KOOS has been extensively used to monitor and evaluate the current patient-perceived disease status before and after undergoing TKA (Collins et al. 2016; Collins and Roos 2012; Skou and Roos 2017; Skou et al. 2015).

Furthermore, the 5-level EuroQol 5 dimension (EQ-5D-L5) was suggested as one of the generic questionnaires (Rolfson et al. 2016). The EQ-5D-L5 is a widely used generic questionnaire to assess health-related quality of life and health-status (Jensen et al. 2023) compared with the general population (Jensen et al. 2023). Recently, preference values of the general Danish population has been developed for the EQ-5D-L5 (Jensen et al. 2023). Ultimately, to assess a broad range of dimensions, the utilization of the generic and patient-specific questionnaires have been suggested as good complements (Collins and Roos 2012).

AIMS AND HYPOTHESIS

Aims

Paper I: The protocol paper aimed to outline the entire RCT project protocol. Parts of the methods and aims included in the protocol paper will be covered in my subsequent postdoc period (muscle biopsy data: under preparation at the University of Southern Denmark, and 12-month follow-up data).

Paper II: To examine the relationship between STS muscle power and knee extensor MVC in the affected leg, respectively, versus TUG, 40m-FWT, and the KOOS subscales of pain, symptoms, ADL, Sport, QoL, respectively, in a cohort of male and female patients with advanced knee OA. Secondly, we aimed to determine if STS muscle power was a stronger predictor (i.e. correlated more strongly) than maximal isometric knee extensor strength (MVIC) for the above objective and subjective outcome measures.

Paper III and IV: To investigate the efficacy of eight weeks of preoperative BFR-RT compared with usual preoperative medical care on the postoperative recovery in 30STS, TUG, 40m-FWT, KOOS, and EQ-5D-L5, 1RM leg press strength, 1RM knee extensor strength, knee extensor MVC, and knee flexor MVC when assessed three months after TKA.

Hypotheses:

Paper I: In this protocol paper we outline the hypotheses related to the entire project.

Paper II: STS Power and knee extensor MVC on the affected leg, respectively, will both be positively associated with outcomes of physical function and patient-reported outcomes, however STS power will be more strongly correlated with these outcomes compared with knee extensor MVC on the affected leg.

Paper III and IV: Eight weeks of preoperative BFR-RT will improve physical function, patient-reported outcomes, and lower limb strength both before and three months after TKA surgery compared with usual preoperative medical care.

STUDY DESIGN, MATERIALS AND METHODS

The present section summarizes the overall study design, materials and the methods. More detailed descriptions on the methods are provided in Paper I (Jørgensen et al. 2020).

Study Design

The trial was designed as a multicenter, randomized, assessor-blinded controlled trial conducted at Horsens Regional Hospital, Silkeborg Regional Hospital, and Aarhus University Hospital. In brief, eligible patients scheduled for TKA were randomized to either eight weeks of preoperative BFR-RT (BFR-RT) or usual preoperative medical care (control group (CON)). Data were collected on physical function, lower limb strength, and patient-reported outcomes at baseline (~10 weeks before surgery), 3-5 days before surgery (pre-surgery), and three months after surgery by the PhD student and two research staff members at Silkeborg Regional Hospital, respectively. The primary end-point was three months after surgery. Follow-up assessments 12 months after surgery are expected to be completed June 2024.

The trial was (i) approved by the Central Denmark Region Committee on Health Research Ethics (Journal No 10-72-19-19), (ii) registered at the Central Denmark Region's internal list of research projects (Journal No 652164), and (iii) registered at clinicaltrial.gov (NCT 04081493). Before enrolment, participants signed an informed consent. All data retrieved from the enrolled patients were handled by Danish law (databeskyttelses-forordningen, databeskyttelsesloven, lov om patientens retsstilling), treated confidentially by the research staff, and securely stored in the Research Electronic Data Capture (REDCap) online databases.

Systematic instructions and monitoring of both the physiotherapists in charge of the assessment protocol and the physiotherapists in charge of the exercise protocol was performed regularly by the PhD-student during the trial period to reduce the effect of heterogeneity between sites. An overview of trial responsibilities for the participating hospital is presented in Table 1.

Table 1. Overview of hospitals involved the PhD study

Hospitals	**Patient enrollment**	**Baseline- & follow-up assessments**	**Exercise sessions**	**Surgery**
Horsens Regional Hospital	X	X	X	X
Silkeborg Regional Hospital	X	X	X	X
Aarhus University Hospital			X	

Participants

Patients fulfilling the following eligibility criteria were invited into the RCT:

Enrollment criteria:

- Patients aged ≥50 years scheduled for TKA at Horsens- or Silkeborg Regional Hospital.

Exclusion criteria:

- Cardiovascular disease classified as New York Heart Association class III-IV (Dolgin and New York Heart Association Criteria 1994)
- Former suffering from stroke- or thrombosis event(s)
- Systolic blood pressure ≥180 or diastolic blood pressure ≥110 mmHg
- Traumatic nerve injury in leg scheduled for surgery
- Spinal cord injury
- Pregnancy

- Existing arthroplasty in the leg scheduled for surgery
- Other plans for lower extremity surgery within 12 months after the TKA surgery
- Currently receiving chemo-, immuno-, or radiotherapy treatment due to cancer
- Other reasons for exclusion (i.e. unable to understand written and spoken Danish, mental unable to participate, etc.)

Enrolment Procedures

The initial eligibility screening was conducted by orthopedic surgeons in the outpatient clinics at Horsens- and Silkeborg Regional Hospital (Table 1, Figure 4). The orthopedic surgeons briefly introduced the project and provided written information about the project to the patients. The assessment flow is illustrated in Figure 4.

Patients motivated to participate were provided 24 hours of consideration. Subsequently, the PhD-student or the project coordinator at Silkeborg Regional Hospital contacted the patients and provided detailed project information. Patients accepting to participate were booked for baseline testing. Eligible patients declining to participate were invited to complete the baseline questionnaires sent by email (observational cohort).

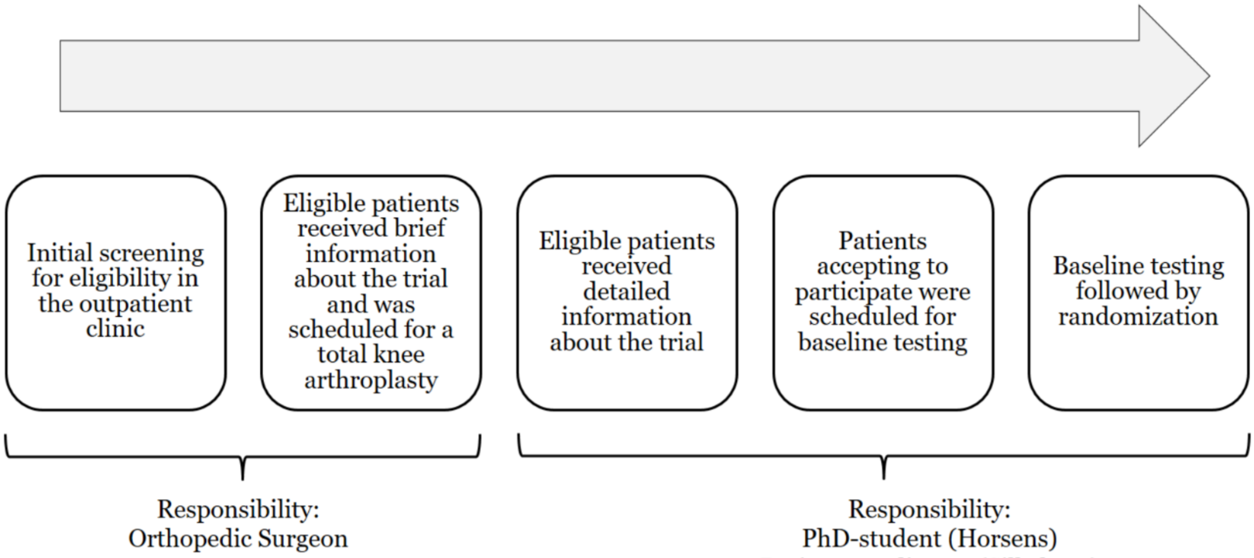

Figure 4. Illustration of the enrollment flow.

Randomization, allocation concealment, and blinding

After baseline testing, a research staff member uninvolved in the data collection procedures block-randomized (stratified by site) the patients to either (i) preoperative BFR-RT or (ii) CON using a random number matrix (RedCap randomization tool).

It was not possible to blind the patients, involved surgeons, and the physiotherapist in charge of exercise sessions for treatment allocation. In contrast, the PhD-student and the assessors at Silkeborg Regional Hospital were blinded to patient allocation during all follow-up tests to avoid performance bias. All participants were carefully instructed to withhold information about group allocation at all follow-up assessments.

Intervention procedures

Determination of limb occlusion pressure

At the baseline test session, individual AOP was determined for each participant with an Ultrasound Doppler probe (EDAN Instruments, inc., China) placed over the posterior tibial artery to capture the auscultatory pulse (Ferraz et al. 2018; Rodrigues et al. 2020; Jørgensen et al. 2020). Cuff pressure (mmHg) was measured with the patient seated on an examination table (Jørgensen et al. 2020; Petersson et al. 2022). The cuff was incrementally inflated until the auscultatory pulse was interrupted, defined as AOP. The procedure was repeated until two identical AOPs were identified consecutively (Jørgensen et al. 2020; Petersson et al. 2022).

Low-load blood flow restricted resistance training (BFR-RT)

In addition to receiving usual preoperative medical care, the BFR-RT group performed eight weeks of supervised exercises three times per week. Each session consisted of 10-min low-intensity ergometer cycling followed by a unilateral leg press exercise and a unilateral knee extension exercise. All exercises were performed using a 12 cm pneumatic nylon cuff (Occlude Aps, Denmark) positioned around the proximal part of the exercising thigh (affected limb) inflated to 60% AOP. A physiotherapist educated in administering the BFR-RT protocol performed on-site supervision in all training sessions.

All exercise variables are presented in Table 2. Each exercise consisted of four sets: set 1: 30 repetitions (reps); set 2-3: 15 reps, set 4: as many reps as possible, with 30 seconds rest between sets. The cuff remained inflated between sets (Nielsen et al. 2012; Hughes et al. 2019). A preset position for cuff inflation and resting was established for leg press exercise to ensure the 60% AOP between sets (Figure 5).

Figure 5. Illustration of the standard resting position during the leg press exercise to ensure 60% limb occlusion pressure during the rest periods. The cuff was inflated to 60% limb occlusion pressure in the same position.

The fourth exercise set was performed until the concentric contraction phase exceeded two seconds which was defined as failure. If the patients completed >15 reps in the fourth set, the exercise load was increased with the minimum extra load possible in the following session (Jørgensen et al. 2016). Between each exercise, a 5-min rest pause without cuff compression was provided. The patients only exercised the limb scheduled for surgery. All exercise machines as progression models were similar between all three sites.

Table 2. Exercise variables in the low-load blood-flow restricted exercise protocol

Exercise variable	
Weeks	8
Level of AOP	60% AOP
Sets	4
Load intensity	30% 1RM
Repetitions 1st set	30
Repetitions 2nd & 3rd set	15
Repetitions 4th set	To failure
Contraction modes per repetition	
Concentric	2 seconds
Isometric	0 seconds
Eccentric	2 seconds
Rest between repetitions	0 seconds
Time under tension per repetition	4 seconds
Range of movement	maximum
Rest between sets	30 seconds
Rest between sessions	≥36 hours
Progression	>15 repetitions in set 4 = progression with the minimal possible load
Minimal additional load, leg press	10 kilo
Minimal additional load, knee extension	0.6 kilo

AOP = Arterial occlusion pressure; RM = Repetition maximum

Control group

The CON group was encouraged to live their lives as usual until TKA surgery, according to local preoperative recommendations, involving no hospital led prehabilitation activities. They received usual preoperative medical care approximately two weeks before surgery, which is described below.

Usual Preoperative Medical Care

All patients were invited to a standard preoperative information- and educational meeting ~2 weeks before surgery where the patients gained knowledge about pain management, nutrition, the surgical procedure, physical activity, postoperative home-based rehabilitation, and load management (Jørgensen et al. 2020).

Total knee arthroplasty

On the day of TKA surgery, the patients were hospitalized. The day after surgery, the participants received mild rehabilitation (mobilization) activities by a hospital physiotherapist to (i) achieve the discharge criteria set out by the local hospital (Table 3) and (ii) learn the home-based rehabilitation exercise program (the home-based rehabilitation exercise programs differed between sites; descriptions of each home-based rehabilitation exercise program is available in Paper I, Table 1a & Table 1b (Jørgensen et al. 2020)). Normally, patients were discharged within ~1-2 days postoperatively. Before discharge, the physiotherapists and orthopedic surgeons considered if the patients were suited for handling the home-based rehabilitation exercise program, or if the patient needed supervised physiotherapy to achieve a sufficient postoperative recovery of physical function. If the physiotherapist or orthopedic surgeon considered supervised postoperative physiotherapy necessary for the patient to achieve sufficient postoperative recovery, the patient was referred to a municipal rehabilitation center or specialized hospital-based rehabilitation.

Two to three weeks postoperatively all patients who performed the home-based rehabilitation exercise program (usual postoperative care) visited the hospital outpatient physiotherapy clinics for an examination of physical function, knee joint mobility, knee pain, -swelling and symptoms, and understanding of how to perform the exercises. If the patients recovered sufficiently, the home-based rehabilitation exercise program was progressed, and no follow-up assessment at the hospital was scheduled. If the patient demonstrated insufficient recovery based on the examination, the patients were referred to a municipal rehabilitation with no follow-up assessment at the hospital or specialized hospital-based rehabilitation.

The patients referred to supervised postoperative rehabilitation were evaluated by the physiotherapists in charge of the supervised postoperative rehabilitation without any follow-up examination in the hospital outpatient clinics.

Table 3. Discharge criteria at Horsens Regional Hospital and Silkeborg Regional Hospital

	Hospital	
Outcome	**Horsens**	**Silkeborg**
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 program	Sufficient	Sufficient

Borrowed from Jørgensen et al. (Jørgensen et al. 2020)

OUTCOME MEASURES

Outcomes measures were collected at baseline (~10 weeks before surgery), again pre-surgery (in the week before surgery), and finally three months after surgery. The primary end-point was three months after surgery.

Demographics

At baseline we collected the following demographic data from all patients: Age, sex (female/male), weight (kg), height (cm), civil status, smoking status, alcohol consumption, education level beyond high school, employment status, previous TKA (left/right/no), previous total hip arthroplasty (left/right/no), duration of knee symptoms, knee planned for surgery (right/left), medication in the past week, and the AOP.

An overview of the primary and secondary outcomes and data collection time points is presented in Table 4.

Primary outcome

The 30-second sit-to-stand test

The primary outcome was the between-group difference in change in 30STS performance from baseline to three-month follow-up. The patients were instructed to perform as many sit-to-stands as possible in 30 seconds from seated to standing with full hip- and knee extension (seat height 44 cm) while the arms were crossed on the chest (Jones, Rikli, and Beam 1999; Gill and McBurney 2008). Three practice repetitions were allowed before performing the test (Dobson et al. 2013).

Secondary outcome variables

Timed Up & Go

The patients were instructed to (i) rise from a chair on the command "Go", (ii) walk as fast as possible to mark two meters ahead (iii) turn 180° around (iv) walk rapidly back to sit down on the chair seat. The use of armrests was allowed. The test was demonstrated to the patient. The patient initiated the test with the command "go" and the time was stopped at initial contact with the chair seat (seat height 44 cm). The fastest of the three trials was included in the statistical analyses. One minute rest was allowed between trials (Bloch, Jonsson, and Kristensen 2017; Kristensen et al. 2010).

4x10 meter walk test meter walk test

The patients were instructed to walk as fast and safely as possible to a visible mark 10 m away excluding 2 meters in each end to turn around (Wright et al. 2011; Dobson et al. 2013). The patients were allowed to use assistive walking devices if necessary. One practice trial was provided to check understanding (Dobson et al. 2013).

Sit-to-stand Power (STS Power)

STS Power (watt/kg) was only reported in Paper II. STS Power was derived from 30STS repetitions, body height (m), and body weight (kg) (Alcazar et al. 2018; Suetta et al. 2019; Alcazar, Kamper, et al. 2020; Alcazar, Aagaard, et al. 2020; Alcazar et al. 2021) as presented in the equation:

$$STS\ \ power = \frac{Body\, mass\ (kg)\ \cdot 0.9\ \cdot [Height\ (m) \cdot 0.5 - Chair\ height(m)]}{[\frac{Time\ (\text{sec})}{number\ of\ repetitions}] \cdot 0.5}$$

The 0.9 represents the fraction of body mass that is vertically displaced during the STS movement, 0.5 in the numerator denotes the estimated ratio of leg length relative to body height, and 0.5 in the denominator denotes the relative duration (ratio) of the concentric movement phase relative to each cyclic STS repetition (Alcazar et al. 2021).

Knee joint range of motion (ROM)

Maximal active knee joint flexion and extension ROM were measured with the patient lying supine on the examination table with a 360° plastic goniometer. The fulcrum of the goniometer was visually aligned to the medial epicondyle of the knee joint, and the moveable arms pointed towards the greater trochanter and the lateral malleolus (Jakobsen et al. 2010). To allow hyperextension of the knee, the heel was placed on a firm square box (height 5 cm, width 8 cm; length 15 cm).

Estimated 1RM leg press strength and 1RM knee extensor strength

All patients performed the leg press strength testing before the knee extensor strength testing. Patients first performed three low-load warm-up sets of 12-, 12, and eight repetitions before 5-8RM leg press testing and 5-8RM knee extensor testing, respectively. The load in each warm-up set increased by 5-10 kilos. After the warm-up, the load was increased to determine the 5-8 RM load. If the 5-8 RM load was undetermined within three trials, a final all-out trial was performed. Estimated 1RM strength was calculated as [1RM = load (kg)/1.0278-0.0278·number of repetitions)] (Hansen 2012). The tests were performed unilaterally.

Maximal isometric knee extensor and flexor strength

Knee isometric extensor- and flexor strength (MVC) were measured with a hand-held dynamometer (HDD) (MicroFet2) setup. The patient was seated upright on an examination table with arms crossed on the shoulders to avoid compensation (Koblbauer et al. 2011). The HHD was fixated with a rigid adjustable strap allowing MVC testing to be performed at 90° knee flexion. For knee extensor MVC, the HHD was fixed to the leg of the examination table and positioned on the anterior part lower leg 5 cm above the medial malleolus (111). For the knee flexor MVC, HHD was fixed to a wall-mounted rib and was placed on the posterior aspect of the calcaneus (111). The HHD-stain gauge automatically converted the signal into newton which was multiplied with the lever arm length to calculate the moment of force (torque) (Aagaard et al. 2002). The tests were performed unilaterally and normalized to bodyweight (Nm/kg).

Knee disability and Osteoarthritis Outcome Score (KOOS)

Patients were instructed to complete the five KOOS subscales; pain, symptoms, activities of daily living (ADL), sport and recreational activities (Sport), and quality of life (QoL) with a total of 42 questions scored from zero to four on a Likert-type scale boxes (Roos and Lohmander 2003). The total sum of each subscale was converted into a numeric score of zero (worst) to 100 (best) on a 0-100 continuous scale (Roos and Lohmander 2003).

EuroQol Group 5-dimension (EQ-5D-5L)

Patients also were instructed to complete the EQ-5D-L5 questionnaire. The EQ-5D-5L is a generic questionnaire containing two separate parts: (I) an evaluation of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (no problems, slight problems, moderate problems, severe problems, and extreme problems), yielding a health state ranging from -0.624 (worst) to 1.000 (best), using a Danish preference value set (Herdman et al. 2011; Wittrup-Jensen et al. 2009; Jensen et al. 2023; Mandy van Reenen 2019); (II) a visual analog self-rating scale (EQ-VAS) of the overall current health status from 0 (worst imaginable health) to 100 (best imaginable health) (Mandy van Reenen 2019; Herdman et al. 2011).

Numeric Rating Scale Pain (NRS pain)

Patients reported pain intensity using a segmented unidimensional 11-item measure of pain intensity in adults (Numeric ranking scale (NRS,0-10) for pain at each testing session at rest, and after all lower limb strength tests. Further, NRS pain was measured at each exercise session, before-, after 1st set- and after the last set of each exercise. Zero was no pain and 10 representing worst pain (Hawker et al. 2011).

Exercise adherence and progression

Project physiotherapists registered all exercise session attendances and loading progressions during BFR-RT sessions. Exercise adherence was calculated as:

$adherence\ (\%) = \frac{scheduled\ sessions}{completed\ sessions} \cdot 100$ (Høgsholt et al. 2022; Petersson et al. 2022)

Adverse events

Patients completed an open-labeled questionnaire to describe any unexpected or unintended events occurring during the period from enrolment until the 3-month follow-up resulting in contact with the healthcare system regardless of whether related or unrelated to the intervention or outcome assessments.

Declining surgery

The patients revealed if they decided to undergo surgery. Patients declining to be operated followed all prescheduled follow-up assessments.

Postoperative supervised physiotherapy

Participation in postoperative supervised training was recorded at the three-month follow-up assessments by using patient-reported questionnaires (yes/no; type of exercise).

Table 4. Overview of the primary and secondary outcomes

Measure	**Outcome**		**Time point**
Primary Outcome			
30-sec sit-to-stand test	More repetitions represents better physical function	Measures the number of sit-to-stands performed with full hip- and knee extension when standing within 30 seconds with the hands crossed in front of the chest (Jones, Rikli, and Beam 1999; Gill and McBurney 2008). The 30STS is associated with lower limb strength and physical function with good to excellent intra- and inter-rater reliability (Dobson et al. 2013; Gill and McBurney 2008; Jones, Rikli, and Beam 1999; Wright et al. 2011). The chair height was 44 cm high. The patients were allowed three practice repetitions before performing the trial (Dobson et al. 2013).	T0 T1 T2
Secondary Outcomes *Physical function*			
Timed Up & Go	Fewer seconds represents better ambulatory function	An ambulatory test measuring the time required to stand from a chair (seat height 44 cm) walk around a tape mark 3 meters away and return to sitting. The test has good inter-rater reliability (Bloch, Jonsson, and Kristensen 2017; Kristensen et al. 2010).	T0 T1 T2
40 meter fast paced walk test	Fewer seconds represents better walking speed	Measures the time spent to walk as fast as possible for 4x10 meters excluding 2 meters in each end to turn around (107). The test is valid and responsive for assessing short-distance maximum walking speed with excellent inter-rater reliability (Wright et al. 2011).	T0 T1 T2
Sit-to-stand Power	Higher watts represents better performance	Lower limb muscle power derived from sit-to-stand testing (STS Power) in healthy young-to-old adults (i.e. employing the 30STS) is strongly correlated to more established measures of mechanical muscle power (i.e. Nottingham	T0

		power rig) (Alcazar, Kamper, et al. 2020; Alcazar et al. 2018).	
Knee joint range of motion	0° represents full knee extension range of motion. 130° represent full knee flexion range of motion.	Maximal active knee joint flexion and extension range of movement (ROM) were measured with the patient lying supine on the examination table with a 360° plastic goniometer. High intra-tester reliability has been observed for this test (Jakobsen et al. 2010). A 6.6°-change in knee ROM is considered to reflect a true change when assessing maximal knee joint flexion and extension (Jakobsen et al. 2010).	T0 T1 T2
Lower limb strength			
1 Repetition maximum leg press- and knee extensor strength	More kilos represents stronger lower limbs	The load was gradually increased to determine the 5-RM load. One RM strength was estimated [1RM = load (kg)/1.0278-0.0278·number of repetitions)] (Hansen 2012). The tests were performed unilaterally.	T0 T1 T2
Isometric maximal knee extensor- and flexor torque	Higher force production (Nm/kg) represents stronger lower limbs	Knee extensor- and flexor MVC force output was measured with a standardized hand-held dynamometer (HDD) setup. The method has good-to-excellent inter- and intra-rater reliability in patients scheduled for TKA (111). The tests were performed unilaterally.	T0 T1 T2
Patient-reported outcomes (questionnaires)			
The Knee Osteoarthritis Outcome Score	Scores closer to 100 represents better self-perception in each subscale	The questionnaire is intended for, among other knee-injury populations, subjects suffering from knee OA and after TKA (Collins et al. 2016). The KOOS is valid and reliable in patients on the waiting list for TKA for knee OA with adequate content validity, and construct validity (Roos and Lohmander 2003; Lyman et al. 2018; Collins et al. 2016).	T0 T1 T2
The EQ-5D-L5	An EQ-Index score -0.624 I worst and 1.000 is best. An EQ-VAS score closer to 100 is better.	The EQ-5D-L5 is a generic questionnaire but has been demonstrated to be responsive in terms of detecting changes in health-related QoL (HRQoL) in patients undergoing TKA with a small ceiling- and floor effect (Jin et al. 2019). The EQ-5D-L5 has been found reliable and valid in patients with knee OA eligible for TKA (Herdman et al. 2011; Buchholz et al. 2018; Bilbao et al. 2018; Conner-Spady et al. 2015). The patients completed both parts of the EQ-5D-L5.	T0 T1 T2

Adverse Events	No = no adverse events Yes = adverse event	The patients completed an open-labeled questionnaire with the possibility to describe the adverse event in 5-8 words.	T2
Pain during testing and exercise sessions	Lower pain scores represent lower perceived pain.		T0 TE T1 T2
Declining surgery	Yes = received total knee arthroplasty surgery No = declined total knee arthroplasty surgery		T2
Postoperative supervised physiotherapy	No = performed the postoperative home-based rehabilitation exercise program Yes; type = Description of the postoperative supervised physiotherapy received		T2
Exercise related variables			
Exercise adherence	Higher exercise adherence represents more attendance to planned sessions		TE
Exercise progression	Higher loading intensity represent exercise progression		TE

Knee extensor MVC = maximal isometric knee extensor torque; knee flexor MVC = maximal isometric knee flexor torque; T0 = baseline; TE = during exercise sessions; T1 = pre-surgery; T2 = Three months after surgery; Nm = newton meter; kg = kilo

SAMPLE SIZE CALCULATION

No data were available in the literature on changes in 30STS following BFR-RT in patients scheduled for TKA or on the minimal clinically relevant change in 30STS in patients suffering from knee OA. Skoffer et al. (Skoffer et al. 2016) found a 3-4-rep improvement in 30STS three months after TKA following four weeks of preoperative HL-RT compared with usual preoperative medical care, which was applied in our calculation along with a 4.7 standard deviation (Skoffer et al. 2016). Assuming a statistical power of 0.80 and a significance level of 0.05, it was calculated that 39 patients were required in each group yielding 78 patients in total. With an expected 10% dropout rate, a total sample size of 86 patients was deemed required.

STATISTICAL CONSIDERATIONS AND METHODS

Paper II

Descriptive statistics are presented as group means and 95% Confidence Interval (CI). Continuous data were checked for normality using histograms and QQ plots. Dependent variables were: STS Power knee extensor MVC, and independent variables were TUG, 40mFWT, and KOOS subscales Pain, Symptoms, Sport, ADL, QOL (Langgård Jørgensen et al. 2023).

We performed all analyses with each dependent variable separately for the male patient cohort and the female patient cohort using linear and multiple regression analysis (Pearson product-moment method) with age as the covariate (Langgård Jørgensen et al. 2023).

The assumption of the multiple regression analyses was verified using plots of observed versus predicted values, residual plots, histograms, and QQ plots. β coefficients with 95%CI were calculated along with the correlation coefficient (r), the unadjusted and adjusted coefficients of determination (r^2) (Foldager et al. 2022; Langgård Jørgensen et al. 2023).

To compare the strength of the r-values based on STS Power and knee extensor MVC as a predictor of physical function and patient-reported outcomes, respectively, the Pitman's test was performed on the unadjusted r-values (Skoffer et al. 2015). The level of statistical significance was set at $P \leq 0.05$.

Papers III and IV

Recommendations listed in the “Enhancing the QUAlity and Transparency Of health Research” (EQUATOR) network (Christensen, Bliddal, and Henriksen 2013), the

CONSORT statement (Moher et al. 2012), and a Checklist for statistical Assessment of Medical Papers (Mansournia et al. 2021) were followed using the *intention-to-treat* principle including all 86 patients. A pre-specified *per-protocol* analysis on the primary outcome variable was performed. The *per-protocol* population included patients in the intervention group attending ≥80% of the supervised exercise sessions (≥19 sessions), and all control subjects. Between-group comparisons from baseline to three months postoperatively were analyzed using a mixed linear model with patient ID as a random effect and time, hospital site, and subject group as fixed effects. Student t-tests were applied to compare the pre-to-post-training differences within the respective training or control groups (Jørgensen et al. 2020). Patients with missing values were excluded from the specific analyses (complete case-analysis) (Heymans and Twisk 2022) The level of statistical significance was set at P≤0.05.

RESULTS

Participant enrollment and flow

From September 2019 to June 2023, a total of 2805 patients were scheduled for a TKA at Horsens Regional Hospital and Silkeborg Regional Hospital (Figure 6). Of these, 612 were assessed for eligibility. Eighty six patients were enrolled in the trial and randomized to BFR-RT (n = 42) or CON (n = 44). Forty-three patients were enrolled from each site.

The most frequent reason for ineligibility was unwillingness to participate due to too much time spent on transportation (n = 223).

A total of 16 (19%) patients were lost to follow-up pre-surgery, and 16 patients were lost to follow-up after surgery. Lost to follow-up was defined as not completing the primary outcome at the respective follow-up tests (Figure 6). Of the 42 patients allocated to BFR-RT, 2 (5%) patients declined to participate in the exercise sessions due to (i) too much time spent on transportation (n=1) and (ii) personal reasons (n=1).

Patient characteristics

Paper II

Baseline characteristics of included patients in the RCT (males and females) are presented in Table 5.

The included patients comprised of 14% more females than males (37 males versus 49 females). The males were significantly higher and heavier compared with the females ($p<0.05$) while no differences were observed in age and body mass index (BMI) between genders (Table 5).

CONSORT FLOW CHART

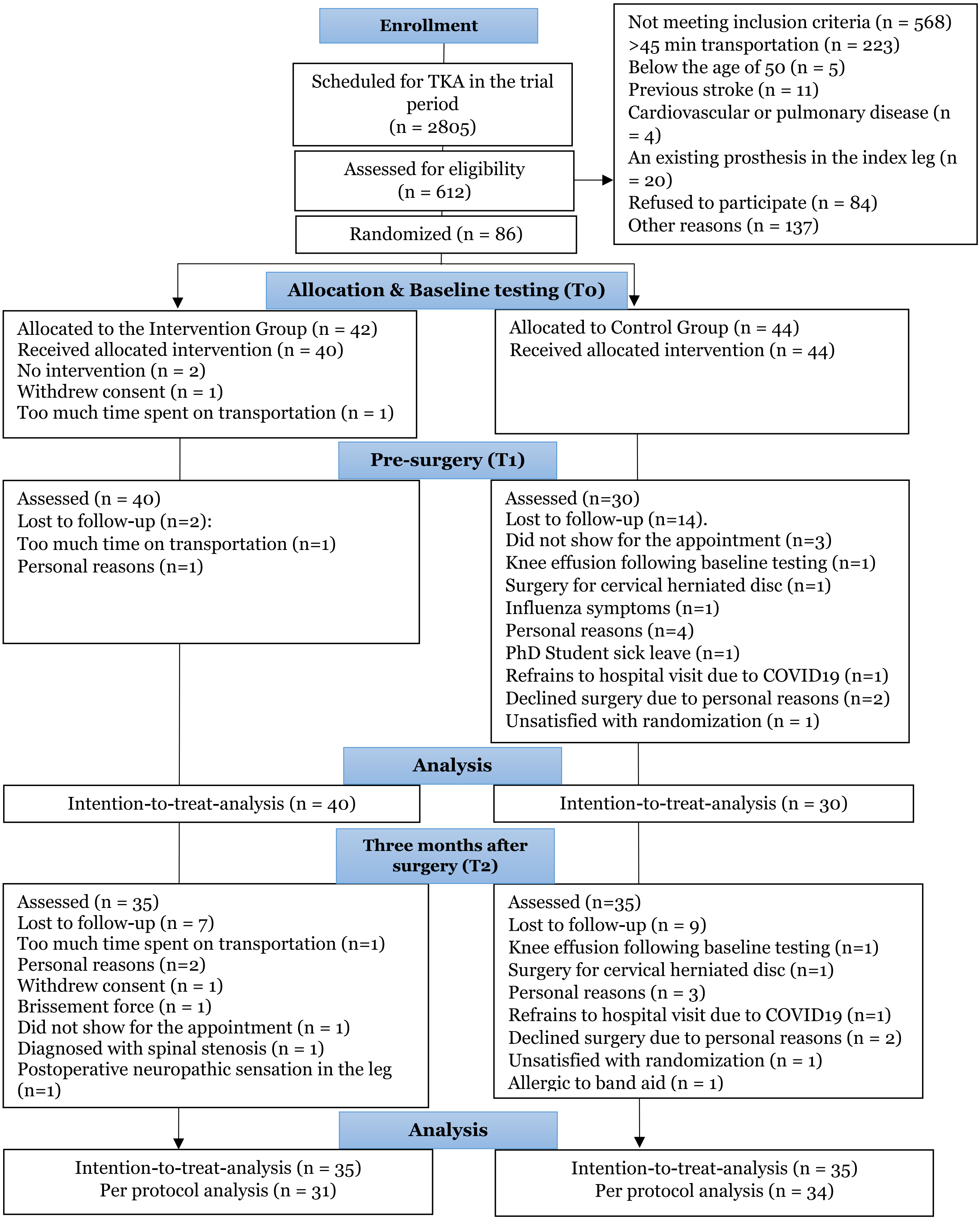

Figure 6. Consort study flow chart until three months follow-up. N represent the number of patients who was assessed for the primary outcome.

Equal distributions between genders were scheduled for right leg TKA (males: 48%; females 53%) and left leg TKA (males: 51%; females: 47%), patient with a total hip arthroplasty in the contralateral limb (males: 8%; females 4%), and symptom duration were observed (Table 5). The female patient cohort demonstrated 9% more patients with an existing TKA in the contralateral knee (males: 13%; females: 22%) (Table 5).

No differences were observed at baseline in the five KOOS subscales between genders. Also, no between-group differences were observed for 30STS or 40mFWT. The males were faster during the TUG test ($p<0.05$) compared with the female patients (Table 5). Males and females demonstrated similar STS power values, but the males produced higher knee MVC torque on the affected limb ($p<0.01$) compared with the female patients (Table 5).

Table 5. Baseline characteristics of the male and female trial participants (n=86)

Outcome	**Males** (n=37) Mean [95%CI]	**Females** (n=49) Mean [95%CI]
Height (cm)	178.2 [172.9; 183.6]*	165.6 [162.9;166.3]
Weight (kg)	94.5 [89.5; 99.5]*	86.6 [81.1; 92.1]
Age (years)	65.9 [63.2; 68.6]	67.2 [64.9; 69.4]
BMI	30.8 [27.2; 34.4]	31.9 [30.1; 33.8]
Knee Osteoarthritis Outcome Score		
Pain (0-100)	47.6 [42.3; 53.0]	47.5 [43.1: 51.9]
Symptoms (0-100)	53.8 [47.5; 60.0]	51.8 [46.6: 57.0]
Activities of daily living (0-100)	54.7 [49.3; 60.1]	53.4 [49.0; 57.9]
Sport & Recreational (0-100)	23.7 [17.6; 29.8]	16.8 [12.1; 21.4]
Quality of life (0-100)	30.7 [26.2; 35.2]	29.2 [25.3; 33.1]
Physical Function		
Sit to stand (repetitions)	12.4 [11.1; 13.6]	12.3 [11.3; 13.4]
Timed Up & Go (seconds)	6.6 [5.8; 7.4]*	7.8 [6.9; 8.6]
40 meter fast paced walk test (meter)	25.8 [23.4; 28.3]	28.8 [26.8; 30.9]
STS power production (W/kg)	3.22 [2.81; 3.63]	2.72 [2.46; 2.97]
Maximal isometric knee extensor strength, affected leg (Nm/kg)	2.99 [2.67; 3.31]**	2.03 [1.83; 2.23]
Knee scheduled for surgery (n)	Counts	Counts
Right	18	26
Left	19	23
Existing total knee replacement in the contralateral knee (n)		
Yes/No	5/32	11/38
Existing total hip replacement in the contralateral leg (n)		
Yes/No	3/34	2/47
Symptoms duration (n)		
0-6 months	0	2
6-12 months	4	3
1-3 years	5	11
>3 years	28	33

*Male/female are presented as the absolute number of males and females, respectively; Cm= centimeter; kg = kilo; CI = confidence interval *: p<0.05, **=<0.01

Paper III and IV

Baseline characteristics of all 86 patients, the BFR-RT group, and CON are presented in Table 6. No between-group differences were observed for age, height, weight, or BMI (Table 6). There were 10% more males in the CON group (48%) compared with the BFR-RT group (38%). The number of patients scheduled for a TKA on the right limb and left limb, living with an existing TKA or THA in the contralateral limb, civil status, smoking status, duration of knee symptoms, and pain medication were similar between the groups (Table 6).

Table 6. Baseline patient characteristics of the intervention group and control group

	All (n=86) Mean [95%CI]	**BFR-RT** (n=42) Mean [95%CI]	**CON** (n=44) Mean [95%CI]
Age (years)	66.6 [64.9; 67.7]	67.1 [64.6; 69.7]	66.1 [63.8; 68.5]
Height (cm)	170.5 [167.6; 173.3]	169.1 [164.2; 174.1]	171.7 [168.7; 174.8]
Weight (kg)	90.0 [86.2; 93.8]	90.3 [85.1; 95.6]	89.7 [83.9; 95.5]
Body mass index (weight (kg) • height (cm)^2)	31.4 [29.6; 33.3]	32.5 [29.2; 35.7]	30.5 [28.6; 32.4]
	Count	Count	Count
Males/females	37/49	16/26	21/23
Knee scheduled for surgery (n)			
Right	44	23	21
Left	42	19	23
Existing total knee replacement in the contralateral knee (n)			
No	70	33	37
Yes	16	9	7
Existing total hip replacement in the contralateral leg (n)			
No	81	40	43
Yes	5	2	3
Civil status			
Married/in a relationship	69	33	36
Single/divorced/widow/widower	17	9	8
Smoking			
Never smoked	43	21	22
Former smoker	23	16	17
Occasional smoker	3	1	2
Smoking	5	4	1
Duration of knee symptoms			
0-6 months	2	1	1
6-12 months	7	3	4
12-36 months	16	9	7
More than 36 months	61	29	32
Pain medication			
Paracetamol	65	33	32
Ibuprofen	34	17	17
Morphine	6	3	3
Did not use pain medication	15	6	9

BFR-RT = intervention group; Con = control group; cm = centimetre; kg = kilo; CI = confidence interval

At baseline, the BFR-RT and CON groups displayed similar performance in all measures of physical function, knee joint range of motion, patient-reported outcomes, and lower limb strength (Table 7).

Table 7. Baseline measures of physical function, patient-reported outcomes and lower limb strength in the intervention group and control group

Outcome	**BFR-RT** Mean [CI95%]	**CON** Mean [CI95%]
Physical function and knee range of motion		
30-sec sit-to-stand (repetitions)	12.8 [11.4; 14.1]	12.0 [10.9; 13.1]
Timed Up & Go (seconds)	6.9 [6.1; 7.7]	7.7 [6.9; 8.5]
40 meter fast paced walk test (seconds)	26.4 [24.2; 28.6]	28.7 [26.6; 30.8]
Knee flexion, affected leg (degrees)	115 [111; 120]	116 [112; 120]
Knee extension, affected leg (degrees)	7 [2; 11]	6 [2; 10]
Patient-reported outcomes		
KOOS Pain (0-100)	50.5 [45.7; 55.3]	45.0 [40.5; 59.4]
KOOS Symptoms (0-100)	52.8 [47.3; 68.4]	52.5 [47.2; 57.8]
KOOS Activities of daily living (0-100)	54.3 [49.4; 59.1]	53.0 [48.5; 57.6]
KOOS Sport & Recreational Activities (0-100)	17.1 [11.8; 22.4]	21.1 [16.1; 26.1]
KOOS Quality of Life (0-100)	31.0 [26.9; 35.1]	28.3 [24.5; 32.2]
EQ-5D-5_Index (-0.624-1)	0.69 [0.65; 0.73]	0.65 [0.61; 0.69]
EQ-VAS (0-100)	61.4 [53.9; 69.0]	64.0 [56.8; 71.3]
Lower limb strength		
1RM Leg press, affected (Kg)	56 [48; 65]	57 [49; 65]
1RM Leg press, non-affected (Kg)	77 [66; 87]	75 [64; 85]
1RM Knee extensor, affected leg (Kg)	17 [14; 20]	21 [19; 24]
1RM Knee extensor, non-affected leg (Kg)	24 [20; 28]	26 [22; 29]
Isometric knee extensor torque, affected leg (Nm kg $^{-1}$)	2.3 [2.0; 2.6]	2.6 [2.3; 2.9]
Isometric knee extensor torque, non-affected leg (Nm kg $^{-1}$)	2.4 [2.1; 2.7]	2.7 [2.4; 3.0]
Isometric knee flexor torque, affected leg (Nm kg $^{-1}$)	1.3 [1.2; 1.5]	1.3 [1.2; 1.5]
Isometric knee flexor torque, non-affected leg (Nm kg $^{-1}$)	1.5 [1.3; 1.6]	1.4 [1.3; 1.6]

CI95% = 95% confidence interval; rep = repetition; KOOS = Knee Injury & Osteoarthritis Outcome Score; RM = repetition maximum; kg = kilo; pre = pre-surgery; pre = prior to surgery; 3 months = 3 months postoperative

Associations with STS Power vs knee extensor strength when adjusted to age to physical function and patient-reported outcomes

STS power was better associated with TUG and 40mFWT compared with knee extensor

MVC in both the male- and female patient cohort (Table 8a, Table 8b).

Significant associations to KOOS subscales were only found with STS Power to pain, sport, and ADL in the male patient cohort (Table 8a, Table 8b).

Overall, knee extensor MVC was not significantly associated with any of the selected outcomes (Table 8b).

Table 8a. Associations to STS Power (watt/body mass)

	Crude		Adjusted	
	Males	**Females**	**Males**	**Females**
Timed Up & Go (Seconds)				
β	-1.3**	-1.4**	-1.1**	-1.4**
95%CI	[-1.3; -0.8]	[-2.3; -0.5]	[-1.6; -0.6]	[-2.3; -0.5]
R	0.68	0.41	0.68	0.43
r^2	0.46	0.17	0.47	0.19
p-value r^2	<0.01	<0.01	<0.01	<0.01
n	37	49	36	49
40 meter fast paced walk test (seconds)				
β	-4.3**	-2.7*	-4.4**	-2.6*
95%CI	[-5.8; -2.9]	[-5.0; -0.5]	[-6.0; -2.7]	[-4.8; -0.5]
R	0.72	0.34	0.74	0.43
r^2	0.52	0.12	0.55	0.18
p-value r^2	<0.01	0.02	<0.01	0.01
n	37	49	36	49
KOOS Pain				
β	5.2*	3.5	6.5**	3.5
95%CI	[1.2; 9.2]	[-1.4; 8.3]	[2.2; 10.8]	[-1.3; 8.4]
R	0.42	0.22	0.50	0.28
r^2	0.18	0.05	0.25	0.08
p-value r^2	0.01	0.16	<0.01	0.17
n	34	45	33	45
KOOS Symptoms				
β	1.1	-0.7	3.5	-0.6
95%CI	[-4.0; 6.2]	[-6.6; 5.2]	[-1.4; 8.5]	[-6.6; 5.3]
R	0.08	0.03	0.49	0.11
r^2	>0.00	<0.00	0.24	0.01
p-value r^2	0.65	0.82	0.17	0.77
n	34	46	33	46
KOOS Sport				
β	2.2	3.2	4.6*	3.3
95%CI	[-2.7; 7.1]	[-1.9; 8.4]	[0.0 9.2]	[-1.6; 8.3]
R	0.18	0.19	0.55	0.35
r^2	0.03	0.03	0.29	0.12
p-value r^2	0.36	0.21	<0.01	0.07
n	34	45	33	45
KOOS ADL				
β	7.1**	2.7	7.2**	2.8
95%CI	[3.6; 10.7]	[-2.2; 7.7]	[3.3; 11.0]	[-2.3; 7.8]
R	0.58	0.17	0.58	0.17
r^2	0.34	0.03	0.33	0.03
p-value r^2	<0.01	0.27	<0.01	0.54
n	34	45	33	45
KOOS QOL				
β	1.4	3.1	2.1	3.2
95%CI	[-2.2; 5.1]	[-1.2; 7.4]	[-1.6; 5.9]	[-0.9; 7.3]
R	0.15	0.21	0.32	0.37
r^2	0.02	0.05	0.10	0.14
p-value r^2	0.43	0.16	0.12	0.04
n	34	46	33	46

β = β–coefficient; KOOS = Knee Injury & Osteoarthritis Outcome Score; Sport = sport and recreational activities; ADL = activities of daily living, QoL = quality of life * $p<0.05$ ** $p<0.01$

Table 8b. Associations to knee extensor MVC strength in the affected leg (Nm/kg)

	Crude		Adjusted	
	Males	**Females**	**Males**	**Females**
Timed Up & Go (Seconds)				
β-	-0.9*	-1.0	-0.6	-1.0
95%CI	[-1.7; -0.2]	[-2.3; 0.2]	[-1.5; 0.3]	[-2.2; 0.3]
R	0.39	0.24	0.39	0.26
r^2	0.15	0.06	0.15	0.07
p-value r^2	0.02	0.10	0.08	0.20
n	35	48	34	48
40 meter fast paced walk test (seconds)				
β	-2.9*	-3.0*	-2.7	-2.6
95%CI	[-5.5; -0.3]	[-3.0; -0.0]	[-6.0; 0.5]	[-5.5; 0.3]
R	0.37	0.29	0.37	0.36
r^2	0.14	0.08	0.14	0.13
p-value r^2	0.03	<0.05	0.08	0.04
n	35	48	34	48
KOOS Pain				
β	-2.9	-0.0	-2.0	0.3
95%CI	[-8.7; 3.0]	[-6.6; 6.5]	[-9.1; 5.1]	[-6.3; 6.9]
R	0.18	>0.00	0.23	0.17
r^2	0.03	>0.00	0.05	0.03
p-value r^2	0.32	0.99	0.45	0.54
n	32	44	31	44
KOOS Symptoms				
β	-4.4	-1.1	-2.3	1.4
95%CI	[-11.2; 2.3]	[-6.3; 8.4]	[-0.0; 0.0]	[-6.1; 8.9]
R	0.24	0.04	0.38	0.10
r^2	0.06	>0.00	0.14	0.01
p-value r^2	0.19	0.77	0.11	0.81
n	32	45	31	45
KOOS Sport				
β	0.3	1.9	3.6	2.5
95%CI	[-6.1; 6.8]	[-5.0; 8.8]	[-3.5; 10.8]	[-4.2; 9.2]
R	0.02	0.09	0.39	0.29
r^2	<0.00	0.01	0.15	0.09
p-value r^2	0.91	0.58	0.10	0.16
n	32	44	31	44
KOOS ADL				
β	1.4	1.9	-0.1	1.9
95%CI	[-4.6; 7.4]	[-4.8; 8.5]	[-7.2; 7.0]	[-4.9; 8.7]
R	0.09	0.09	0.07	0.09
r^2	0.01	<0.01	<0.01	<0.01
p-value r^2	0.63	0.57	0.94	0.16
n	32	44	31	44
KOOS QOL				
β	-0.7	-1.4	0.3	-0.6
95%CI	[-5.9; 4.6]	[-7.1; 4.2]	[-5.7; 6.3]	[-6.2; 4.9]
R	0.05	0.08	0.25	0.30
r^2	>0.00	0.01	0.06	0.09
p-value r^2	0.80	0.61	0.41	0.61
n	32	45	31	45

β = β–coefficient; KOOS = Knee Injury & Osteoarthritis Outcome Score; Sport = sport and recreational activities; ADL = activities of daily living, QoL = quality of life * $p<0.05$ ** $p<0.01$

Pitman's test

Table 9 presents the comparison of the crude r-values of STS Power and knee extensor MVC to each outcome parameter.

For the male patient cohort, TUG, 40mFWT, KOOS Pain, KOOS Sport, KOOS ADL, and KOOS QOL displayed a significantly stronger correlation to STS Power compared with knee extensor MVC (Table 9). Only KOOS Symptoms revealed a stronger correlation to knee extensor MVC compared with STS Power in the male patient cohort (Table 9).

For the female patient cohort, TUG, KOOS Pain, KOOS Sport, KOOS ADL, and KOOS QOL were significantly stronger correlated to STS Power compared with knee extensor MVC (Table 9). The correlation with 40mFWT and KOOS Symptoms displayed no significant differences in STS Power compared with knee extensor MVC (Table 9).

Table 9. Correlations of sit-to-stand power vs. maximal knee extensor strength as crude predictors of physical function and patient-reported outcomes

	Sex	STS Power		Knee extensor MVC
Timed Up & Go	Male	r = 0.68	> p < 0.01	r = 0.39
	Female	r = 0.41	> p = 0.01	r = 0.24
40 meter fast paced waling	Male	r = 0.72	> p < 0.01	r = 0.37
	Female	r = 0.34	= p = 0.48	r = 0.29
KOOS Pain	Male	r = 0.42	> p < 0.01	r = 0.18
	Female	r = 0.22	> p = 0.01	r = 0.00
KOOS Symptoms	Male	r = 0.08	< p = 0.03	r = 0.24
	Female	r = 0.03	= p = 0.07	r = 0.04
KOOS Sport & Recreation	Male	r = 0.18	> p < 0.01	r = 0.02
	Female	r = 0.19	> p = 0.05	r = 0.09
KOOS Activities of daily living	Male	r = 0.58	> p < 0.01	r = 0.09
	Female	r = 0.17	> p = 0.01	r = 0.09
KOOS Quality of life	Male	r = 0.15	> p = 0.01	r = 0.05
	Female	r = 0.21	> p = 0.01	r = 0.08

> favors STS power, < favors knee extensor MVC strength, = no significant difference between STS power and knee extensor MVC strength

STS power: mean 30-s sit-to stand power; MVC knee extensor MVC strength: maximal isometric knee extensor torque; KOOS=Knee Injury & Osteoarthritis Outcome Score

Changes in physical function

Paper III and Paper IV

Raw data for the primary and secondary outcomes at each follow-up are presented in Paper III and Paper IV (appendix).

Primary outcome

For the primary outcome (30STS), the between-group mean change at the primary endpoint (three months after surgery) was 0.01 [-1.6; 1.6] (Table 10, Figure 7). Likewise, no between-group difference was observed pre-surgery (Table 10, Figure 7).

Both groups revealed significant within-group improvements three months after surgery (Table 10).

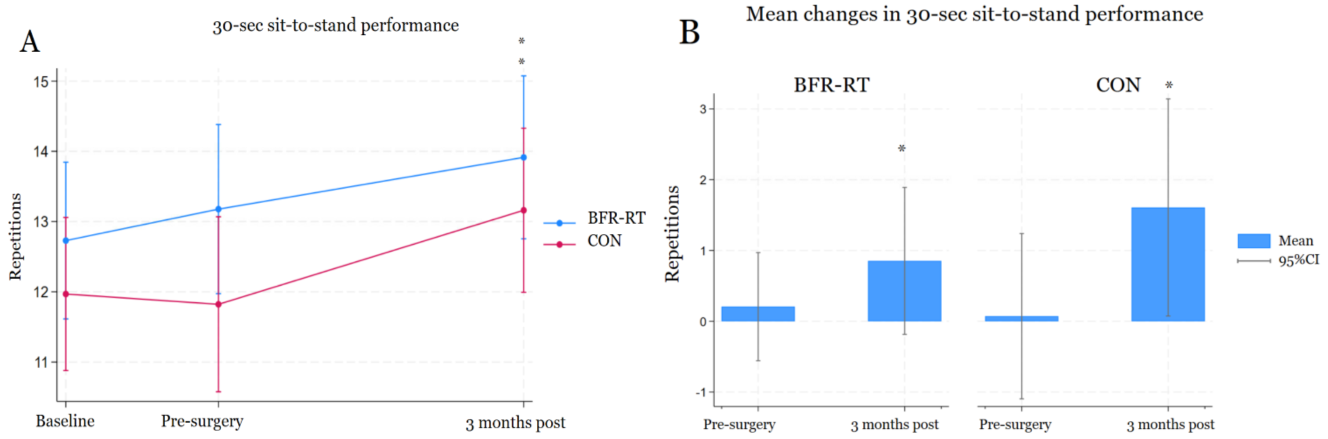

Figure 7. A. Absolute numbers of repetitions and Between-group differences in the 30 seconds sit-to-stand test at the three measurement points. B. Mean changes in the primary outcome, 30 seconds sit-to-stand test from baseline to pre-surgery, and from pre-surgery to three months after total knee arthroplasty for the group engaging in eight weeks of preoperative low-load blood flow restricted resistance training (BFR-RT) and the control group (CON) receiving usual preoperative medical care.
* = within-group change p <0.05

Table 10. Mean change in the primary and secondary outcomes with BFR-RT vs. usual preoperative medical care

	BFR-RT		CON		Between-group	
Outcome	**Mean change T1** [CI]	**Mean change T2** [CI]	**Mean change** T1 [CI]	**Mean change T2** [CI]	**T1** [CI]	**T2** [CI]
Physical function						
30-sec sit-to-stand (reps)	0.4 [-0.4; 1.3]	1.2 [0.03; 2.3]*	-0.1 [-1.1;0.8]	1.2 [0.03;2.4]*	-0.6 [-1.9; 0.7]	0.01 [-1.6; 1.6]
Per protocol 30-sec sit-to-stand (reps)	0.4 [-0.6; 1.4]	1.0 [-0.4; 2-4]	-0.0 [-1.1; 1.0]	1.5 [0.1;2.4]	-0.4 [-1.9; 1.0]	0.5 [-1.5; 2.4]
Timed Up & Go (sec)	-0.5 [-1.3; 0.2]	-0.6 [-1.3; 0.0]	0.01 [-0.8; 0.8]	-0.6 [-1.2; 0.1]	0.5 [-0.6; 1.6]	0.1 [-0.8; 1.0]
40 meter fast paced walk test (sec)	0.2 [-1.5; 1.9]	-0.9 [-2.6; 0.9]	0.2 [-1.6; 2.1]	-0.8 [-2.5; 0.9]	0.01 [-2.5; 2.5]	0.1 [-2.4; 2.5]
Knee joint range of motion, affected leg						
Knee flexion (°)	-2 [-4; 1]	-1 [-6; 5]	0 [-3; 3]	-2 [7; 3]	1 [-3; 5]	-1 [-9; 6]
Knee extension (°)	-4 [-8; 1]	-4 [-8; 1]	-1 [-5; 4]	-3 [-8; 1]	3 [-3; 9]	0 [-6; 7]
Patient-reported outcomes						
KOOS Pain (0-100)	3.4 [-1.4; 8.2]	23.1 [16.6; 29.7]*	3.7 [-1.6; 9.0]	29.4 [23.1; 35.8]*	0.3 [-6.9; 7.5]	6.3 [-2.8; 15.4]
KOOS Symptoms (0-100)	6.8 [2.0; 11.5]*	14.3 [8.1; 20.5]*	2.6 [-2.7; 8.0]	14.9 [9.1; 20.7]*	-4.1 [-11.3; 3.0]	0.6 [-7.9; 9.1]
KOOS ADL (0-100)	2.5 [-2.4; 7.5]	22.9 [17.2;28.6]*	1.7 [-3.8; 7.2]	22.7 [17.3; 28.1]*	-0.8 [-8.2; 6.5]	-0.2 [-8.1; 7.7]
KOOS Sport (0-100)	2.7 [-3.6; 9.0]	20.9 [11.7; 30.1]*	-1.6 [-8.6; 5.4]	19.7 [10.9; 28.5]*	-4.3 [-13.7; 5.1]	-1.2 [-13.9; 11.6]
KOOS QoL (0-100)	3.3 [-1.2; 7.8]	33.8 [26.0; 41.7]*	-0.5 [-5.6; 4.6]	28.9 [21.2; 36.6]*	-3.7 [-10.5; 3.0]	-4.9 [-15.9; 6.1]
EQ-5D-5_Index (-0,624-1.000)	0.02 [-0.01; 0.06]	0.13 [0.07; 0.18]*	0.04 [-0.00; 0.07]	0.16 [0.11; 0.21]*	0.01 [-0.04; 0.07]	0.04 [-0.03; 0.11]
EQ-VAS (0-100)	8.6 [0.3; 16.9]*	19.8 [12.6; 27.0]*	2.2 [-6.6; 10.9]	12.6 [5.9; 19.3]*	-6.4 [-18.5; 5.7]	-7.2 [-17.0; 2.6]
Lower limb strength, affected leg						
1RM Leg press (kg)	27 [20; 35]*	17 [10; 24]*	-2 [-10; 7]	0 [-7; 8]	-29 [-42; -18]*	-16 [-26; -6]*
1RM Knee extensor (kg)	7 [4; 10]*	1 [-2; 3]	2 [-1; 5]	-4 [-7; 1]	-5 [-9; -1]*	-5 [-8; -1]*
Knee extensor MVC (Nm kg $^{-1}$)	0.2 [-0.1; 0.4]	0.1 [-0.2; 0.4]	-0.1 [-0.4; 0.2]	-0.4 [-0.7; -0.1]*	-0.2 [-0.6; 0.1]	-0.5 [-0.9; -0.1]*
Knee flexor MVC (Nm kg $^{-1}$)	0.2 [-0.0; 20.3]	-0.2 [-0.4; -0.1]*	0.0 [-0.2; 0.2]	-0.3 [-0.5; -0.2]*	-0.1 [-0.4; 0.1]	-0.1 [-0.3; 0.1]
Lower limb strength, non-affected leg						
1RM Leg press (kg)	9. [1; 17]*	13 [4; 22]*	5 [-4; 13]	0 [-10; 9]	-5 [-17; 8]	-13 [-26; 0.00]
1RM Knee extensor (kg)	2 [-1; 4]	-1 [-4; 2]	2 [-1; 4]	-1 [-4; 2]	0.00 [-3; 3]	-0.1 [-4; 4]

Knee extensor MVC (Nm kg $^{-1}$)	0.2 [-0.1; 0.4]	0.2 [-0.1; 0.4]	-0.2 [-0.5; 0.1]	-0.2 [-0.5; 0.1]	-0.4 [-0.8; 0.0]	-0.4 [-0.8; 0.0]
Knee flexor MVC (Nm kg $^{-1}$)	0.1 [-0.1; 0.2]	0.1 [-0.1; 0.2]	-0.1 [-0.3; 0.1]	-0.2 [-0.2; -0.1]	-0.2 [-0.4; 0.6]	-0.1 [-0.3; 0.1]

BFR-RT = preoperative low-load blood flow restricted resistance training; CI = confidence interval; rep = repetition; KOOS = Knee Injury & Osteoarthritis Outcome Score; RM = repetition maximum; kg = kilo; knee extensor MVC = maximal isometric knee extensor torque; knee flexor MVC = maximal isometric knee flexor torque; Sport = Sport & Recreational activities; QoL = quality of life; VAS = Visual Analog Scale; T1 = pre-surgery; T2 = 3 months postoperative; Rep = repetitions; Sec = Seconds; Nm = newton meter. *$p<0.05$

Secondary outcomes

Physical function

The TUG and 40mFWT tests demonstrated no between-group differences pre-surgery or three months after surgery (Table 10). Both tests displayed no significant within-group changes at any time point in any of the groups (Table 10).

Knee joint range of motion

Knee joint flexion and extension revealed no significant between-group changes pre-surgery or three months after surgery (Table 10). Likewise, no within-group changes occurred in knee joint flexion or extension at any time point in both groups (Table 10).

Patient-reported outcomes

No between-group changes in any of the KOOS subscales were observed pre-surgery or three months after surgery (Table 10). Notably, the BFR-RT group demonstrated a significant within-group improvement in KOOS Symptoms pre-surgery, while both groups demonstrated significant within-group improvements three months after surgery in all KOOS subscales (Table 10).

The EQ-5D-L5 index score displayed no significant between-group changes pre-surgery or three months after surgery (Table 10). Both groups demonstrated significant within-group changes three months after surgery in the index score and EQ-VAS (Table 10).

Lower limb strength

1RM leg press strength (Kg)

1RM leg press strength in the affected leg differed significantly between groups pre-surgery and three months after surgery, favoring BFR-RT (Table 10). Only the BFR-RT group demonstrated significant within-group changes (increases) pre-surgery and after surgery (Table 10).

In the non-affected leg, 1RM leg press strength was different between groups at three months after surgery favoring BFR-RT, while no between-group difference was observed pre-surgery (Table 10). The BFR-RT group showed significant gains 1RM leg press strength in the non-affected leg pre-surgery and three months after surgery (Table 10).

1RM knee extensor strength (Kg)

Significant between-group changes in 1RM knee extensor strength were observed in the affected leg pre-surgery and three months after surgery favoring BFR-RT (Table 10). BFR-RT demonstrated significant within-group improvements in 1RM knee extensor strength in the affected leg pre-surgery but not three months after surgery (Table 10). No within-group changes in knee extensor strength were observed in CON at any time point (Table 10).

No between-group or within-group changes were observed in 1RM leg knee extensor strength in the non-affected leg at any time point (Table 10).

Knee extensor MVC

Significant between-group differences in isometric knee extensor MVC of the affected leg were observed three months after surgery favoring BFR-RT (Table 10), with no between-group differences pre-surgery (Table 10). BFR-RT demonstrated significant within-group improvements in knee extensor MVC in the affected leg pre-surgery but not three months after surgery (Table 10). The CON group displayed a significant within-group decrease in knee extensor MVC in the affected leg from baseline to three months after surgery (Table 10).

Knee extensor MVC in the non-affected leg showed no between-group differences pre-surgery or three months after surgery (Table 10), or any within-group changes at any time point in both group (Table 10).

Knee flexor MVC

Isometric knee flexor MVC in the affected leg revealed no significant between-group differences pre-surgery or three months after surgery (Table 10). Both groups demonstrated significant within-group decreases in knee flexor MVC in the affected leg three months after surgery (Table 10).

No between-group or within-group changes in knee flexor MVC were noted in the non-affected leg at any time point in any of the groups (Table 10).

Intervention-related outcomes

Paper III

Table 11 displays all exercise-related outcomes.

Ninety percent of the patients allocated to BFR-RT completed ≥80% of the exercise sessions. Excellent adherence to the exercise sessions was observed (>90%), and patients waited on average three weeks from the last exercise session and until surgery (Table 11). Five patients waited ≥4 weeks and seven patients received more than 24 exercise sessions because their surgery was postponed due to the COVID-19 pandemic (Table 11).

No within-session changes in knee joint pain before, during, or immediately after the exercise sessions appeared, while the loading intensity increased significantly in both the leg press exercise and the knee extension exercise from the first to last exercise session (Table 11).

The number of repetitions completed in each exercise set remained constant during the exercise period, while the number of repetitions decreased from sets 1 through 4 (Table 11).

Table 11. Exercise-related variables

		Mean [CI95%]	
Patients	n	41	
Patient with <80% adherence	n	4	
Exercise adherence	%	90.6 [83.5; 97.8]	
Days from last exercise session and until surgery		22.8 [8.3; 37.3]	
Waiting ≥4 weeks from last exercise session to surgery due to COVID-19	n	5	
Receiving >24 exercise sessions due to COVID-19	n	7	
Knee pain		1st sessions	Last session
Knee pain at rest before exercise	0-10	2.4 [2.3; 2.6]	2.9 [2.1; 3.7]
Knee pain after 1st set Leg press	0-10	3.3 [2.5; 4.0]	2.9 [1.9; 3.8]
Knee pain after 1st set Knee extension	0-10	3.3 [2.4; 4.1]	2.7 [1.7; 3.7]
Knee pain immediately after exercise	0-10	2.9 [2.1; 3.6]	2.5 [1.5; 3.4]
Leg press			
Load	Kg	16 [13; 18]	45 [36; 55]
Set 1	Rep	30 [29; 30]	29 [27; 30]
Set 2	Rep	15 [14; 15]	15 [14; 15]
Set 3	Rep	13 [12; 14]	13 [12; 15]
Set 4	Rep	12 [9; 16]	11 [9; 13]
Knee extension			
Load	Kg	5 [4.; 6]	8 [6; 10]
Set 1	Rep	28 [27; 30]	28 [27; 30]
Set 2	Rep	13 [11; 14]	12.7 [12; 14]
Set 3	Rep	11 [9; 12]	12 [10; 13]
Set 4	Rep	12 [8; 15]	10 [8; 13]

CI = confidence interval; NRS = numeric ranking scale; Kg = kilo; rep = repetition

A similar number of surgery-related adverse events was noted between BFR-RT and the CON group (12 vs. 13 adverse events). Seven and nine surgery-related adverse events occurred in the BFR-RT and CON group, respectively. Five and four adverse events unrelated to surgery occurred in the BFR-RT and CON group (Table 12).

In the BFR-RT, 54% of the patients were referred to supervised physical therapy rehabilitation, while 70% were referred to supervised physical therapy rehabilitation in the CON group within the first three months after surgery.

Two patients in each group declined TKA surgery. In the BFR-RT group both patients declined surgery due to self-perceived improvements in knee joint pain and symptoms. In the CON group, both declined surgery due to personal reasons.

Table 12. Adverse events related and un-related to surgery and requirement for supervised physiotherapy in the period following the total knee arthroplasty surgery

	BFR-RT	**Con**
Surgery-related adverse events		
Infection in the knee	1	1
Reoperation		1
Deep vein thrombosis	1	
Neuropathic pain or sensation in the limb following surgery	1	1
Severe postoperative knee effusion requiring further examination		4
Cicatrize (insufficient wound healing)	2	1
Severe knee pain requiring further examination at the hospital	2	
Severe pain during the night		1
Brissement force	1	
Adverse events unrelated to the surgery		
Experienced hip symptoms following surgery	1	1
Fall episode resulting in a fractured arm	2	
Severe pain in the operated limb		1
Shingles	2	
Ulster		1
Strain in the calf muscle during rehab		1
Additional rehabilitation following surgery		
Supervised municipal rehabilitation	24	31

BFR-RT = intervention group; Con = control group

DISCUSSION

Key findings

Paper II

- STS Power was associated with physical function in both genders. STS Power only associated with KOOS Pain, ADL, and Sport in the male patient-cohort.
- Knee extensor MVC demonstrated no correlation to physical function or patient-reported outcomes in the male- or female-patient cohort.
- The crude correlation coefficients of physical function and patient-reported outcomes correlated to a similar or greater extent with STS Power than the same correlations with knee extensor strength in our male- and female patient cohorts.

Paper III

- Preoperative BFR-RT for the affected leg yielded no superior effects on 30STS or the KOOS subscales compared with usual preoperative medical care three months postoperatively.
- The BFR-RT protocol yielded significant gains in unilateral 1RM leg press strength in both the affected- and non-affected leg pre-surgery and three months after surgery compared with the CON group.

Paper IV

- Preoperative BFR-RT protected against loss of knee extensor MVC in the exercised leg three months after TKA surgery.
- Knee joint ROM and physical function remained unchanged three months following surgery in both groups, while significant improvements in health status emerged in both groups three months postoperatively.

STS power versus knee extensor MVC in patients with knee OA

As a main finding in Paper II, STS power was significantly associated with TUG and 40m-FWT in both male- and female patients with advanced stages of knee OA, while knee extensor MVC showed no associations with TUG or 40mFWT in the male- or female patient cohorts (Paper II). In slight contrast, previous studies have found physical function to be correlated both with lower limb muscle power and knee extensor MVC in patients with mild-to-advanced stages of knee OA (Accettura et al. 2015; Holm et al. 2022; Murray et al. 2015; Davison et al. 2017; Skoffer et al. 2015).

Skoffer et al. (Skoffer et al. 2015) and Holm et al. (Holm et al. 2022) reported significant associations with 30STS (Holm et al. 2022; Skoffer et al. 2015), TUG (Skoffer et al. 2015), 40m-FWT (Holm et al. 2022), and 10 meters fast-paced walk test (Skoffer et al. 2015) to isometric and isokinetic knee extensor MVC (Skoffer et al. 2015). Accetura et al. (Accettura et al. 2015) found significant associations with 6-minute walking test, stair descent, and stair ascent to both knee extensor MVC and knee extensor power, respectively (Accettura et al. 2015). Holm et al. demonstrated that 40m-FWT, stair climbing, and 30STS were associated with leg extension power and knee extensor MVC (Holm et al. 2022). Thus, based on previous results both lower limb power and knee extensor strength would be expected to be associated with various measures of lower limb physical function, although muscle power would tend to be more strongly associated with physical function than knee extensor MVC (Holm et al. 2022; Accettura et al. 2015; Murray et al. 2015).

The apparent disparities between the present results and previous reports may rely at least in part on methodological differences. Skoffer (Skoffer et al. 2016), Accettura (Accettura et al. 2015), and Holm (Holm et al. 2021) all analyzed the association to the peak knee extensor MVC, while we analyzed the average knee extensor MVC of three trials.

Also, Skoffer (Skoffer et al. 2015) and Accettura (Accettura et al. 2015) assessed knee extensor MVC with sophisticated isokinetic dynamometry (Human Norm and Biodex, respectively). Holm et al. (Holm et al. 2022) used a standardized HHD setup, but in contrast to the present trial, Holm et al. (Holm et al. 2022) restricted vertical BCM displacement by stabilizing the patients at mid-thigh using a belt attached to a custom-built testing chair. This may increase the reliability of the HHD-testing setup as the knee joint angle is not affected by vertical unintentional BCM displacement (hip movement), securing all knee extensor MVCs to be measured at a 90-degree joint angle.

Table A-1, Appendix display a significant difference in the average MVC output of three trials and the peak MVC output exerted in one of the three trials in the present trial. Further, the associations to peak MVC in the affected leg with TUG (males: β=-0.46 [-1.39; 0.48], $p<0.05$; females: β=-0.92 [-2.03; 0.19], $p<0.05$) and 40mFWT (males: β=-1.89 [-5.27; 1.50], $p<0.05$; females: β=-2.38 [-4.97; 0.21], $p<0.05$) remained insignificant in both the male- and female patient cohorts.

Thus, based on the present results, STS power appears to be more strongly associated with ambulatory function including walking speed compared with knee extensor MVC of the affected leg.

Correlation coefficients based on STS power vs. knee extensor MVC strength

To our best knowledge, no previous studies have statistically compared correlations to physical function and patient-reported outcomes based on lower limb muscle power versus strength. The Pitman's test is a significance test of correlation coefficients (PITMAN 1939), and previously Skoffer et al. (Skoffer et al. 2015) reported statistically stronger correlations with TUG and 10-meter walking speed to 30STS test outcome compared with the relationships based on isolated knee extensor strength by applying the Pitman's test.

In Paper II we reported that when compared to MVC strength, STS Power was statistically more strongly or at least similarly correlated to physical function and all KOOS subscales. Thus, based on the present results STS muscle power appears to be a stronger determinant of physical function and patient-reported outcomes compared with knee extensor MVC, at least in males and females suffering from advanced stages of knee OA (Paper II) (Langgård Jørgensen et al. 2023).

Changes in physical function from baseline to three months after TKA

In Paper III and Paper IV, we observed no differences in the between-group changes in physical function (30STS, TUG, 40m-FWT) from baseline to pre-surgery, nor from baseline to three months after surgery. A recent systematic review and meta-analysis from our research group found improvements in physical function, isometric knee extensor strength, and self-reported pain in response to preoperative muscle strengthening exercise (HL-PRT), when evaluated three and 12 months after TKA and THA (Jørgensen et al. 2022). Thus, the present lack of improvements in physical function despite substantial increases in lower limb muscle strength at three months postoperatively seem in partial conflict with our previous meta-analysis findings (Jørgensen et al. 2022).

Based on a systematic PubMed literature search on December 7th, 2023 (Table A-2, Appendix), 17 systematic reviews were identified involving preoperative exercises in patients scheduled for TKA (of 206 hits in total), and we extracted 50 original studies from these reviews. Six of the systematic reviews recommended preoperative exercise before surgery (Wallis and Taylor 2011; Peer et al. 2017; Moyer et al. 2017; Chen et al. 2018; Wang et al. 2021; Gränicher et al. 2022) to improve postoperative outcomes of pain, length of stay, quality of life, quadriceps strength, physical function, and knee range of motion, whereas the remaining eleven reviews concluded that there were no postoperative effects of preoperative exercise compared with control-interventions (Silkman Baker and McKeon 2012; Gill and McBurney 2013; Jordan et al. 2014; Kwok, Paton, and Haddad 2015; Wang et al. 2016; Chesham and Shanmugam 2017; Ma et al. 2018; Husted et al. 2020; Blasco et al. 2021; Su et al. 2022; Vasileiadis et al. 2022).

Although improving knee extensor muscle strength before TKA is deemed important to improve postoperative physical function (Bade, Kohrt, and Stevens-Lapsley 2010; Bade and Stevens-Lapsley 2012), only four of the 50 trials extracted from the search in December 2023 (Table A-2, Appendix) reported sufficiently detailed exercise protocols (sets, repetitions, loading-intensity, frequency, duration) to assume that the intervention was able to induce gains in maximal muscle strength (Calatayud et al. 2016; Skoffer et al. 2016; McKay, Prapavessis, and Doherty 2012; Domínguez-Navarro et al. 2021) (A-3). Therefore, the discussion below will mainly focus on the comparison of the present observations with those of Skoffer et al. (Skoffer et al. 2016), Calatayud et al. (Calatayud et al. 2016), McKay et al. (McKay, Prapavessis, and Doherty 2012), and Dominguez-Navarro et al. (Domínguez-Navarro et al. 2021).

Improvements favoring preoperative lower limb strength training have been demonstrated for preoperative 30STS (Skoffer et al. 2016), TUG (Domínguez-Navarro et al. 2021; Skoffer et al. 2016; Calatayud et al. 2016), walking speed (McKay, Prapavessis, and Doherty 2012) and stair climbing (Calatayud et al. 2016), while positive postoperative effects in terms of enhanced 30STS (Skoffer et al. 2016), TUG (Skoffer et al. 2016;

Calatayud et al. 2016), and stair climbing performance (Calatayud et al. 2016) have been reported when assessed three months after surgery.

In contrast to the above findings - suggesting significant postoperative benefits in physical function arising from prehabilitation - the present results are more in line with the results of McKay et al. (McKay, Prapavessis, and Doherty 2012) and Dominguez-Navarro et al. (Domínguez-Navarro et al. 2021). McKay (McKay, Prapavessis, and Doherty 2012) found no superior effect of preoperative lower limb resistance training compared with control intervention (engaging in upper body exercises) on walking speed or stair climbing three months after surgery. Dominguez-Navarro (Domínguez-Navarro et al. 2021) reported no differences between usual preoperative medical care compared with preoperative resistance training (Table A-3, Appendix) on TUG when assessed six weeks after surgery.

These contrasting findings may, at least in part, be explained by differences in exercise protocols (Table A-3, Appendix). Firstly, McKay (McKay, Prapavessis, and Doherty 2012) and Dominguez-Navarro (Domínguez-Navarro et al. 2021) employed fewer sets at repetition maximum in each exercise compared with Skoffer (Skoffer et al. 2016) and Calatayud (Calatayud et al. 2016) (Table A-3, Appendix). Thus, considering the relatively short exercise periods used by Mckay (McKay, Prapavessis, and Doherty 2012) and Dominguez-Navarro (Domínguez-Navarro et al. 2021), their total training volume exposure for the lower limbs (load x sets x frequency x weeks) might have been insufficient.

Skoffer et al. (Skoffer et al. 2016) elegantly provided a total of eight weeks of exercise to their intervention group: Four weeks of preoperative HL-PRT followed by four weeks of postoperative HL-PRT (Table A-3, Appendix), whereas CON participants received postoperative HL-PRT only. For comparison, the intervention group in Calatayud et al. (Calatayud et al. 2016) exercised for 12 weeks achieving a high total training volume.

Also, Skoffer and Calatayud included hamstring- and hip abduction exercises. High levels of hamstring and hip abductor strength are associated with better physical function in patients with advanced stages of knee OA and after TKA (Skoffer et al. 2015; Piva et al. 2011; Alnahdi, Zeni, and Snyder-Mackler 2014; Thomas et al. 2022). Therefore, future studies should include exercises targeting these muscle groups.

Changes in lower limb strength from baseline to three months after TKA

The present RCT demonstrated significant between-group changes in the gains in 1RM leg press strength on the affected and non-affected leg (Paper III) and in 1RM knee extensor strength (Paper IV), respectively, favoring preoperative BFR-RT. The observed increases in 1RM leg press strength and 1RM knee extensor strength observed at surgery (i.e. after preoperative training) and again three months after surgery were obviously expected. That is, gains in strength are typically more pronounced when tested in the exercises/machines that were used during training (training specificity) compared with measured in isokinetic or isometric test devices (Dankel et al. 2020; Mitchell et al. 2012).

Spitz et al. (Spitz et al. 2023) quantified the effect sizes of gains in specific and non-specific strength and specific strength to be 0.8 (cohen's *d*) and 1.8 (cohen's *d*) in healthy subjects relative to healthy non-exercising controls. The authors found 95% predictions intervals of the non-specific test to be -1.2 to 2.8, indicating that it may be difficult to detect (or at least expect) improvements in non-specific strength. Therefore, the present observations of significant between-group differences in the change in knee extensor MVC in the affected leg when assessed three months after surgery in the present trial are noteworthy (Paper IV).

Interestingly, these between-group differences were partly driven by decreases in knee extensor MVC strength three months after surgery in the CON, while the BFR-RT sustained knee extensor MVC outputs corresponding to baseline-levels. Thus, the present BFR-RT exercise protocol was effective of preventing postoperative impairments in knee extensor MVC. This in line with Calatayud et al. (Calatayud et al. 2016) and Skoffer et al. (Skoffer et al. 2016) who also found postoperative effects favoring preoperative muscle strengthening exercises when performing isokinetic knee extensor strength testing three months after surgery.

Knee flexor MVC decreased three months after surgery in all our trial participants irrespectively of group allocation. In contrast, Calatayud (Calatayud et al. 2016) and Skoffer (Skoffer et al. 2016) prevented decreases in isometric knee flexor MVC (Skoffer et al. 2016; Calatayud et al. 2016), and hip abductor strength (Calatayud et al. 2016) in the intervention groups, indicating that exposure to systematic (exercise-induced) overloading is necessary to prevent impairments in strength. Therefore, including exercise specifically targeting the hamstring muscles (i.e. the hamstring curl exercise) could potentially have prevented the decrease observed in hamstring muscle strength in the present trial. These protective effects of muscle strength in both the knee extensors, knee flexors, and hip abductors might also, at least in part, explain the better results on physical function reported by Calatayud et al. (Calatayud et al. 2016) and Skoffer et al. (Skoffer et al. 2016).

Changes in patient-reported outcome from baseline to three months after TKA

Both groups yielded significant and clinically relevant improvements in all KOOS subscales three months after surgery (Paper III). Likewise, both BFR-RT and CON demonstrated significant improvements in EQ-5D-L5 Index and EQ VAS when evaluated three months after surgery (Paper IV).

The baseline data on the KOOS subscales indicate that the patients were highly affected by their knee OA conditions. Fortunately, therefore, both groups experienced clinically relevant improvements three months following TKA surgery (Paper III).

In accordance with the present results, Skoffer (Skoffer et al. 2016) and Dominguez-Navarro (Domínguez-Navarro et al. 2021) demonstrated similar between-group changes in all KOOS subscales with preoperative muscle strengthening exercises and usual preoperative medical care three months and six weeks after surgery, respectively. Also, McKay (McKay, Prapavessis, and Doherty 2012) found no between-group differences in WOMAC pain and function three months after surgery. In contrast, Calatayud (Calatayud et al. 2016) found significant between-group changes in WOMAC pain and stiffness three months after surgery favoring the intervention group compared with the control group.

The present improvements in EQ-VAS scores in BFR-RT (20 points) and CON (13 points) following TKA (Paper IV) are in line with Skoffer et al. (Skoffer et al. 2016). Further, in the present trial EQ-5D-5L Index scores improved following TKA to reach 0.82 and 0.82 in the BFR-RT and CON, respectively. In comparison, healthy age-matched Danish peers are reported to have an EQ-5D-5L Index of 0.89 (Jensen et al. 2023).

Changes in knee joint range of motion from baseline to three months after TKA

The data from the present trial on changes in active knee joint flexion and extension from baseline to three months after surgery confer with those reported by Skoffer et al.(Skoffer et al. 2016). The high baseline levels in knee flexion and knee extension ROM observed in the present trial may have induced a ceiling effect in knee ROM hindering postoperative improvements with training.

Only Calatayud et al.(Calatayud et al. 2016) demonstrated significant between-group changes favoring the intervention group in terms of knee flexion ROM and knee extension ROM before and three months after surgery. However, the patients enrolled in Calatayud et al. (Calatayud et al. 2016) demonstrated more pronounced impairments in knee joint ROM compared with our patient population (~12° lower baseline levels), which may explain these between-trial differences.

Adherence, loading progression and adverse events

In the present trial, patients allocated to BFR-RT demonstrated a high exercise adherence (90.6%) without any gradual worsening of their knee joint pain or other major adverse effects during the exercise period. Thus, despite substantial progression in exercise loading during both the leg press exercise (184% increase) and the knee extensor exercise (57% increase), knee joint pain remained constant. Further, the present BFR-RT exercise protocol did not acutely lead to increases in within-session knee joint pain, suggesting that BFR-RT can be applied without expecting to provoke knee joint pain in patients with advanced stages of knee OA. These observations add new insights to the applicability of BFR-RT, supporting previous reports that patients with mild-to-moderate stages of knee

OA may engage safely in BFR-RT (Ferraz et al. 2018; Bryk et al. 2016; Segal, Davis, and Mikesky 2015; Segal et al. 2015).

Strengths and limitations

To be included in the present trial, the patients accepted (i) several extra hospital visits before and after surgery and (ii) agreed to participate in three weekly supervised exercise sessions for eight weeks before TKA surgery. These demands for participation may render the trial vulnerable to selection bias. Notably, transportation to exercise sessions was the most frequent reason for declining to participate.

All patients eligible for participation who declined to participate in the trial were invited to complete the questionnaires included in the RCT at baseline. As illustrated in Table A-4, Appendix, patients declining to participate indeed suffered from more severe knee joint pain and were more affected in ADL activities compared with patients volunteering to participate in the trial. These findings suggest that the patients included in the present trial may at least in part have been affected by selection bias.

The obvious limitation of trial II is the cross-sectional design implying that no conclusions can be drawn on causality. The relatively low sample sizes in each cohort (males: n=37; females: n=49) kept us from performing more extensive adjustments in the regression analysis (Green 1991). Nonetheless, the analyses may have benefitted from taking other potentially confounding factors into account such as pain levels.

Our comparisons of correlation coefficients based on STS Power and knee extensor MVC, respectively, versus physical function and patient-reported outcome were performed only on the crude data. Therefore, these data must be interpreted cautiously as confounding factors such as age, pain, BMI, etc. was not taking into account.

Due to the nature of the RCT design (intervention-group vs. no-intervention group), the present trial may have been affected by an attention bias favoring the intervention group. The BFR-RT group received 24 supervised exercise sessions, two testing sessions, and one information meeting before surgery, whereas the CON group received two testing sessions and one information meeting before surgery. Only the preoperative information meeting was designated for educating and mentally preparing the patients for surgery, while the testing sessions and exercise sessions focused on performance during physically demanding tests and exercises. Regardless, the present findings of similar between-group changes in postoperative physical function and patient-reported outcomes do not suggest that attention bias played any systematic role in the present trial.

Blinding of the assessors was successfully maintained by i) randomizing the patients after baseline testing and ii) stressing to the patients to withhold information about their group allocation at follow-up test sessions. Additionally, the assessors were informed (i) to remind the patients to withhold information about their allocation during the follow-up visits and, maybe most importantly, (ii) to treat all patients as first-time visitors to the testing facilities and procedures (i.e. leading the way to and thoroughly explaining each test).

We made multiple comparisons between the BFR-RT and CON group. This increases the risk of statistical type I errors, meaning that the significant differences found in our secondary outcomes must be interpreted with some caution.

During the trial period, 16 patients were not assessed pre-surgery and 16 patients were not assessed three months after surgery (Figure 6, Flow Chart). This was higher than the expected 10% dropout rate. Fourteen of the 16 unassessed patients at baseline were allocated to the CON group. This large number (~30%) of absent patients may have influenced the preoperative results. In contrast, the number of unassessed patients three months after surgery were similar between groups. Additionally, at the primary end-point, we did not achieve data on the desired 39 patients in each group (sample size). Thus, we cannot rule that our trial was slightly underpowered. Nonetheless, the results from the intention-to-treat analysis and per-protocol analysis on the primary outcome (30ST) at the primary end-point (3 months after surgery) were similar, indicating that present results were robust.

Methodological related limitation and considerations

In designing the trial, we decided to use 30STS – a test of lower limb function – as our primary outcome variable. In contrast, the exercise protocol solely focused on the single leg scheduled for surgery. TUG and 40mFWT performance also relies on bilateral lower limb performance. However, Skoffer et al. previously established that (i) the knee extensors of the affected leg is significantly weaker compared with the knee extensors of the non-affected leg (Skoffer et al. 2015) and (ii) performing four weeks of preoperative muscle strengthening exercises only for the affected leg improved physical function three months after surgery compared with receiving usual preoperative medical care (Skoffer et al. 2016). Thus, based on these results, and intending to reduce the magnitude of lower limb asymmetry in maximal knee extensor strength (Skoffer et al. 2015), we decided not to exercise the non-affected leg. Ultimately, the unilateral focus in the exercise protocol could potentially have limited the effectiveness of the preoperative intervention protocol on all the outcome variables related to physical function.

As mentioned above, muscle strengthening exercises for the hip abductors and knee flexors appears important to include in prehabilitation protocols to achieve improvements postoperative gains in postoperative physical function (Skoffer et al. 2016; Calatayud et al. 2016). However, only the leg press machine and knee extension machine were available at all three sites. Thus, from a pragmatic perspective to provide identical exercise protocols at each hospital site, we decided to only include these two exercises. Furthermore, at the time we designed our exercise protocol, little was known about the adaptations to BFR-RT in the exercising lower limb muscles proximal to the cuff (non-occluded muscles). Therefore, we considered that low-load BFR-RT exercises for the hip abductors would provide an insufficient physiological stimulus to promote positive adaptation in hip abductor muscle strength and size. Interestingly, more recent reports have suggested that positive effects may be attained for this muscle group with the use of lower leg BFR-RT intervention (Høgsholt et al. 2022; Bowman et al. 2019).

In the present trial, we compared BFR-RT with a non-exercising control group. This have obviously made it easier to detect between-group changes in strength pre-surgery and three months after surgery. Therefore, it remains unknown how our preoperative BFR-RT protocol would compare with other preoperative muscle strengthening protocols (i.e. HL-PRT). However, the present data suggest that patients scheduled for TKA who perceive other types of preoperative muscle strengthening exercises intolerable due to excessive knee pain can perform BFR-RT without experiencing exercise-related exacerbation of knee pain.

As a measure of lower limb muscle strength, we decided to use both estimated 1RM strength testing in the leg press exercise and the knee extensor exercise as well as isometric knee and flexor MVC. We assumed that the patients were unable to express their true 1RM strength due to knee OA-related pain and, thus, we decided to derive 1RM values from maximal 5-8RM testing. Despite using a standardized formula for deriving 1RM (Hansen 2012), this extrapolation may have skewed our 1RM data.

The hospitals were not equipped with isokinetic muscle strength dynamometers. Therefore, we used a standardized testing protocol with HDD to assess isometric lower limb strength (Koblbauer et al. 2011). As opposed to Holm et al. (Holm et al. 2021) we did not fixate the patients' thigh with straps to avoid hip movement during the test. This may have affected the data, as the strongest patients were able to lift their body center of mass horizontally, ultimately reducing the designated 90° knee flexion to a more favorable joint angle (closer to 70° knee flexion) for producing maximal knee extensor muscle forces.

AOP and 1RM were determined at baseline only. Blood pressure is dynamic and fluctuates constantly, which can be affect lower limb AOP (Parati et al. 2018; Ingram et al. 2017). Furthermore, thigh circumference influences on the AOP (Loenneke et al. 2012). Thus, longer periods of exercise (i.e. 24 sessions) some changes in AOP are expected to occur, especially if muscle mass has increased (Loenneke et al. 2012). Therefore, preferably we should have reassessed AOP every second week during the exercise period. However, we intended to use the same equipment as the clinicians in our department to increase the transferability of our exercise method. Also, the cuff pressure applied during sessions remained most likely within the recommended range of 40-80%AOP (Patterson et al. 2019).

Further, we did not reassess 1RM subsequent to the first exercise session. Thus, the loads applied in later exercise sessions may not reflect 30%1RM. To avoid excessive time spent on 1RM testing during exercise sessions and the potential risk of inducing knee joint pain exacerbation due to high loading intensities, we decided to progress the loading whenever a patient were able to perform more than 15 repetitions in the fourth set in one of the exercises.

As mentioned in the Background section, the most frequent radiographic grading system to determine knee OA severity is the Kellgren & Lawrence scale (Kellgren and Lawrence 1957). We included all patients scheduled for TKA due to advanced stages of knee OA regardless of the radiographic findings and grading. Therefore, it is possible that the patients included in our trial demonstrate various degrees of joint space narrowing, osteophytes, etc. Nonetheless, the patients included in the preset trial were deemed eligible for TKA due to symptoms of knee OA supplemented with a clinical and radiographic examination.

Generalizability

The patient cohort in this trial was selected based on a number of in- and exclusion criteria. A large number of the patients initially assessed for eligibility failed to meet the inclusion criteria which causes our results only to be generalizable to this particular group of patients. In addition, our trial participants reported systematically better on KOOS pain and KOOS ADL compared with eligible patients who declined to participate, which also impairs the generalizability of our results.

Patients accepting to participate in this trial may have been highly motivated towards training. Unfortunately, we did not collect data on self-reported activity levels or if patients allocated to the CON group engaged in other preoperative exercise interventions. However, although anecdotally, patients allocated to the CON group were usually dissatisfied with the allocation underlining that the patients were motivated and positive towards exercising.

Ethical precautions and consideration

The three primary ethical considerations of the trial were (i) the risk of inducing adverse events due to the blood-flow restriction during exercise; (ii) postponing surgery; (iii) and depriving participants of the treatment guarantee.

No adverse health-related events have been reported with previous BFR-RT protocols in subjects suffering from knee OA (Segal, Davis, and Mikesky 2015; Segal et al. 2015; Bryk et al. 2016; Ferraz et al. 2018). Also, we followed the recommendations outlined for BFR-RT (Patterson et al. 2019) with supervised training sessions and careful education of the physiotherapists in charge of training.

The patients were expected to benefit from three weekly BFR-RT sessions for eight weeks, which would justify postponing TKA surgery and depriving the treatment guarantee.

All patients volunteered and were entitled to withdraw from the trial at any time. All patients were insured by the national patient insurance in case of adverse events, in accordance with "Promulgation of the Danish Act on the Right to Complain and Receive Compensation within the Health Service". The Danish Act on Processing of Personal Data (DAPPD) was followed.

Collectively, we considered the overall benefits greater than the potential risks and possible adverse events.

CONCLUSIONS

Study II

- STS lower limb muscle Power demonstrated moderate-to-strong associations with physical function in both male and female patients with advanced stages of knee OA, while predicting KOOS Pain and ADL in male patients only.
- Knee extensor MVC revealed no associations with physical function or any patient-reported outcomes in the male- or female-patient cohort.
- STS power was significantly better correlated with physical function, KOOS pain, and ADL compared with the corresponding relationships based on knee extensor MVC.
- Simple on-site assessments of STS power can aid researchers and clinicians to rapidly obtain estimates of physical function, pain, and ADL in patients with advanced knee OA.

Study III

- Changes in 30STS and KOOS subscales were not increased in response to preoperative BFR-RT when assessed three months after surgery.
- Eight weeks of preoperative BFR-RT caused improvements in unilateral leg press strength for both the affected and the non-affected legs when assessed three months postoperatively, and when compared with usual preoperative medical care.

Study IV

- Eight weeks of preoperative BFR-RT was effective of protecting against decreases in knee extensor MVC in the affected leg three months after surgery. This may support the long-term postsurgical recovery of physical function in this patient population.

- Regardless of the intervention received, physical function and knee joint range of motion remained unaltered three months postoperatively compared to baseline.

PERSPECTIVES

The findings of the present PhD thesis have shown that the current usual preoperative medical care approach yields similar postoperative levels of physical function compared with eight weeks of preoperative BFR-RT. Thus, considering the existing focus on prioritizing (limited) healthcare resources optimally to i) optimize patient treatment algorithms and ii) protect the healthcare employees from work overload, it seems redundant to implement the specific prehabilitation program tested in this thesis.

Nonetheless, available observations from Calatayud et al. (Calatayud et al. 2016) and Skoffer et al. (Skoffer et al. 2016) are encouraging, suggesting that preoperative muscle strengthening exercises involving exercises for the knee extensor-, knee flexor, and hip abductor muscles improves physical function three months after TKA surgery. Additionally, a recent RCT from Franz et al. (Franz et al. 2022) demonstrated that six weeks of twice-weekly preoperative blood flow-restricted low-intensity cycling exercise led to significant gains in leg extensor and flexor strength, while also improving KOOS scores in ADL, Sport, and QoL compared with usual preoperative medical care three-to-six months postoperatively. These results call for future research on how to apply contemporary training principles (incl. BFR-RT) to real-world settings where 1-to-1 supervision often is less affordable.

On that note, our research group has demonstrated that home-based blood flow-restricted exercises with biweekly onsite or online supervision may be safe and feasible in various patient populations (Høgsholt et al. 2022; Bentzen et al. 2023; Mechlenburg et al. 2023; Mortensen, Mechlenburg, and Langgård Jørgensen 2023;

Petersson et al. 2020; Petersson et al. 2022; Jørgensen and Mechlenburg 2021; Bentzen 2024). Also, BFR-RT appears to induce similar gains in muscle strength, muscle size, and physical function compared with HL-PRT in patients with orthopedic disorders (Jørgensen et al. 2023). Therefore, home-based BFR-RT protocols inspired by the principles of Skoffer et al. or Calatayud et al. (in regards to exercise selection, combining pre- and postoperative exercises, and total training volume) may be relevant for providing home-based preoperative muscle strengthening exercises in patients scheduled for TKA that can be implemented into clinical practice.

The present results demonstrate that the vast majority of knee OA patients undergoing TKA surgery are able to recover to reach baseline levels in terms of physical function and perceive clinically meaningful improvements in all KOOS subscales after surgery. Therefore, shifting focus to prioritize the subgroup of patients achieving poor postoperative outcomes (i.e. insufficient pain relief, persistent impairments in physical function, and those at risk of revision arthroplasties) may seem highly relevant.

As previously described, ~20% of the patients are dissatisfied with the outcome of the TKA surgery. This subpopulation, with poor postoperative outcomes are characterized by higher physiotherapy utilization and costs, however, with lower benefits of the interventions compared with patients achieving satisfying postoperative results (Orndahl et al. 2021). Thus, to improve QoL, and physical function, relieve pain, and also reduce the need for healthcare utilization, more effective pre- and rehabilitation protocols should be developed for this subgroup of patients.

To our best knowledge, only two previous studies have investigated the myocellular adaptation to TKA surgery without (Toth et al. 2022) or with postoperative muscle strengthening intervention (Neuromuscular Electrical Stimulation (NMES) (Cheuy et al. 2023). Toth et al. (Toth et al. 2022) observed a 24% decrease in muscle fiber size, and up to 50% decrease in single-muscle fiber force output of chemically skinned muscle fibers five weeks after surgery (Toth et al. 2022). Notably, two weeks of twice-daily NMES intervention initiated two days after TKA surgery attenuated muscle strength loss while concurrently offsetting postsurgical-induced muscle atrophy compared with controls receiving standard postoperative rehabilitation (Cheuy et al. 2023). Therefore, the protective effect on muscle strength with preoperative BFR-RT found in our intervention group is highly interesting and may be related to adaptations in muscle at the cellular level. Needle muscle biopsies using the Bergstrom technique (Aagaard et al. 2001; Bergstrom 1962; Ekblom 2017; Nielsen et al. 2012) of the vastus lateralis muscles on both legs were harvested from all patients scheduled for TKA at Horsens Regional Hospital at baseline, during surgery, and three months after surgery. These results (awaiting Lab analysis) may extend our understanding of how prehabilitation protocols can be used to sustain muscle strength under conditions (surgery) that usually involve excessive loss of maximal muscle strength and mass (Toth et al. 2022). Consequently, these results can potentially also be of interest to other populations planned for elective surgery.

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APPENDENCIES

Table A-1. Differences in average and peak knee extensor MVC of the affected leg at baseline

		Average (n=80)	**Peak** (n=80)
Knee extensor MVC	Nm kg^{-1}	2.5 [2.3; 2.7]	2.9 [2.7; 3.2]*

Knee extensor MVC = maximal isometric knee extensor torque; * = $p>0.05$

Table A-2. Search strategy
("Arthroplasty, Replacement, Knee"[Mesh]) AND ((prehabilitation OR "preoperative rehabilitation" OR "preoperative training*" OR "preoperative exercise*" OR "preoperative physiotherapy" OR "preoperative physical therapy") OR ("Preoperative Exercise"[Mesh]))

Table A-3. Key exercise variables for trials using muscle strengthening exercises

Trial	Exercises	Sets	Repetitions	Loading intensity	Progression model	Frequency Duration Supervision
McKay (McKay, Prapavessis, and Doherty 2012)	Calf raises Leg Press Leg Curl Leg Extension *Exercises were performed bilaterally*	2	8	60% 1RMSets at 100%RM: none	Adding 1-2 kilos per week	3/week 6 weeks All sessions
Dominguez-Navarro (Domínguez-Navarro et al. 2021)	Leg Raise Knee extension Hamstring Curl Isotonic hamstring activation *Both legs were exercised*	3	10	Knee extension and Hamstring Curl: Initial load: 50% 10 RM (1st set) 2nd set: 75%RM 3rd set: 100% RM (if possible)** Leg raise and isotonic hamstring activation: Load: 50%10RM*. No progression Sets at 100%RM: 1 in two exercises, respectively	Based on 10RM testing at each exercise session	3/week 4 weeks All sessions
Skoffer (Skoffer et al. 2016)	Leg press Knee extension Knee flexion Hip extension Hip abduction Hip adduction *Exercises were performed on the affect leg only*	3	12-8	12-8RM Sets at 100% RM: 3 in each exercise	12RM progressing towards 8RM	3/week 4 weeks All sessions
Calatayud (Calatayud et al. 2016)	Leg Press Knee Extension Leg Curl Hip Abduction *Exercises were performed on each leg*	5	10	10RM Sets at 100% RM: 5 in each exercise		3/week 12 weeks All sessions

RM = repetition maximum; * = The 10RM calculation was performed each session, after the warm-up phase. It is understood by 10RM the maximum weight that a subject could lift correctly for 10 repetitions. **= Progression from 50% 10RM to 75% 10RM and 10RM was performed if possible. Otherwise, the load applied was the maximum the participants could stand (Domínguez-Navarro et al. 2021).

Table A-4. Patient characteristics of the patients included in the trial versus the observational cohort

	All (n=86)	**Cohort** (n=66)
	Mean [CI]	Mean [CI]
Age (years)	66.6 [64.9; 67.7]	68.4 [66.4; 70.4]
KOOS Pain (0-100)	50.5 [45.7; 55.3]	41.4 [37.3; 45.5]
KOOS Symptoms (0-100)	52.8 [47.3; 68.4]	49.2 [43.6; 54.8]
KOOS Activities of daily living (0-100)	54.3 [49.4; 59.1]	45.2 [41.2; 49.1]
KOOS Sport & Recreational Activities (0-100)	17.1 [11.8; 22.4]	16.3 [12.0; 20.6]
KOOS Quality of Life (0-100)	31.0 [26.9; 35.1]	27.5 [23.9; 31.2]

All = BFR-RT and controls; BFR-RT = intervention group; Cohort = eligible patients declining to participate in the trial; cm = centimetre; kg = kilo; CI = confidence interval

Open access Protocol

BMJ Open

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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To cite: Jørgensen SL, Bohn MB, Aagaard P, *et al*. 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. *BMJ Open* 2020;**10**:e034376. doi:10.1136/bmjopen-2019-034376

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-034376).

Received 17 September 2019
Revised 13 August 2020
Accepted 20 August 2020

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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.

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.

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

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.

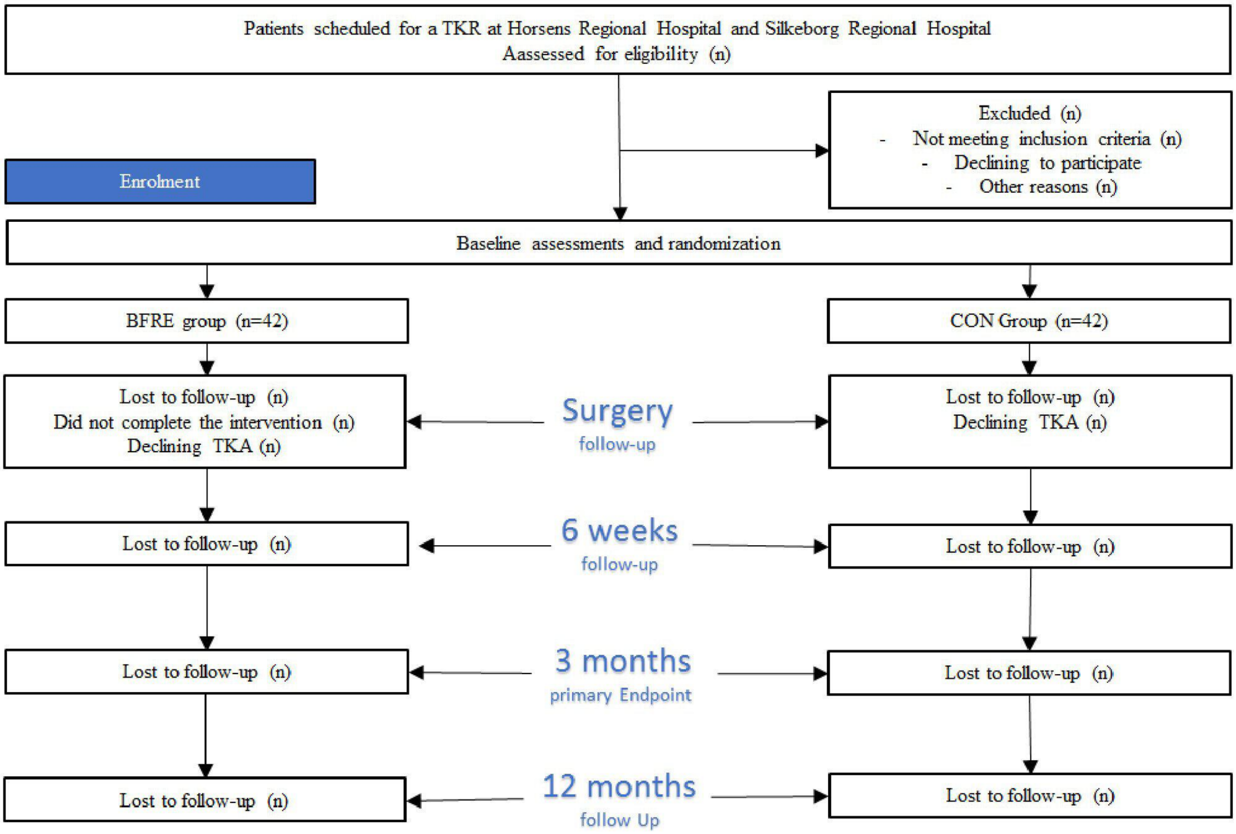

Figure 1 Flow chart of the enrolment, treatment and follow-up phases. BFRE, low-load blood flow restricted exercise; CON, control; TKR, total knee replacement.

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-post-training 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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Funding This work trial is supported by Aase og Ejnar Danielsen's Foundation (100,000 dkk), Nis-Hanssen's Mindeslegat (163,883 dkk) and the Health Research Foundation of Central Denmark Region (99,658 dkk), Hede-Nielsen Foundation (8,000 dkk).

Competing interests None declared.

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.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Stian Langgård Jørgensen

This declaration concerns the following article/manuscript:

Title:	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.
Authors:	Stian Langgård Jørgensen, Marie Bagger Bohn, Per Aagaard, Inger Mechlenburg

The article/manuscript is: Published ☒ Accepted ☐ Submitted ☐ In preperation ☐

If published, state full reference: Jørgensen SL, Bohn MB, Aagaard P, et al. 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. BMJ Open 2020;10:e034376. doi:10.1136/bmjopen-2019-034376

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A. Has essentially done all the work (>90%)
B. Has done most of the work (67-90 %)
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D. Has contributed (10-33 %)
E. No or little contribution (<10%)
F. N/A

Category of contribution	Extent (A-F)
The conception or design of the work:	C
Free text description of PhD student's contribution ***(mandatory)*** The PhD student, Stian Langgård Jørgensen, has contributed significantly and was responsible for the process of designing the study.	
The acquisition, analysis, or interpretation of data:	B
Free text description of PhD student's contribution ***(mandatory)*** There is no data in this manuscript.	
Drafting the manuscript:	A
Free text description of PhD student's contribution ***(mandatory)*** The PhD student, Stian Langgård Jørgensen, wrote the first draft of the manuscript and was responsible for most of the amendsments as well.	

Submission process including revisions:	A
Free text description of PhD student's contribution ***(mandatory)*** The PhD student, Stian Langgård Jørgensen, performed the submission and lead the work on the revisions.	

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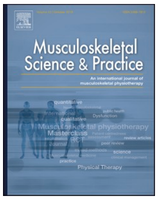
Musculoskeletal Science and Practice 69 (2024) 102899

Contents lists available at ScienceDirect

Musculoskeletal Science and Practice

journal homepage: www.elsevier.com/locate/msksp



Original article

Sit-to-stand power predicts functional performance and patient-reported outcomes in patients with advanced knee osteoarthritis. A cross-sectional study

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ARTICLE INFO

Keywords:
Knee osteoarthritis
Muscle power
Functional performance
Patient-reported outcome
Knee

ABSTRACT

Background: Lower limb muscle power is positively associated with functional performance and patient-reported outcomes (PROMs) and suggested as an important variable to evaluate in patients with advanced knee osteoarthritis (OA).
Objectives: To explore the association between muscle power derived from the 30-sec sit-to-stand test (STS power) with functional performance and PROMs compared to maximal isometric knee extensor strength (KE MVC) in male- and female patients with advanced OA.
Study design: Cross-sectional design.
Methods: Eighty-six patients (66.6 [64.9–67.7]years) with advanced knee OA were included. Dependent variables were STS power and KE MVC. Independent variables were Timed Up&Go (TUG), 40-m fast-paced walk test (40mFWT), Knee injury and Osteoarthritis Outcome Score (KOOS) subscales.
Covariate: Age.
Analyses: Simple linear- and multiple regression analyses with and without adjusting for age. Pitman's test was used to evaluate differences in correlation strength among dependent variables.
Results: STS power demonstrated a statistical relationship with TUG and 40mFWT for both sexes (β coefficients -1.11 to -4.36 ($p < 0.05$), $r2 = 0.47–0.55$ ($p < 0.05$)), and with KOOS Pain, ADL, and Sport for male patients (β coefficients 6.53 to 7.17 ($p < 0.05$), $r2 = 0.29–0.33$ ($p < 0.05$)). Knee extensor MVC demonstrated no relationship with any outcomes for male patients or female patients. STS power displayed statistically stronger correlation to functional performance.
Conclusion: STS power was associated with functional performance in both male patients and female patients suffering from advanced knee OA. Moreover, STS power was associated with KOOS Pain, Sport, and ADLin male patients. The assessment of STS power should be considered in the evaluation of patients with advanced knee OA.
Trial registration number: NCT04081493.

1. Introduction

Osteoarthritis (OA) is among the world's most prevalent and disabling musculoskeletal diseases and has been ranked as a major contributor to disability (March et al., 2014; Murray et al., 2010). The knee has previously been identified as the joint most prevalently affected by OA with an 113% increase in prevalence since 1990 (Covinsky et al., 2008; Global, 2019). Ultimately, around 528 million people worldwide are currently suffering from knee OA (Global, 2019).

Persons affected by knee OA typically experience impaired functional performance, reduced lower limb strength and impaired quality of life compared to asymptomatic healthy peers (Skoffer et al., 2015a; Bade et al., 2010; Alkan et al., 2014). Reduced knee extensor strength has been associated with reduced functional performance in patients with

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https://doi.org/10.1016/j.msksp.2023.102899
Received 23 May 2023; Received in revised form 11 December 2023; Accepted 12 December 2023

knee OA (Chun et al., 2013; Skoffer et al., 2015b). However, some studies have suggested muscle power as a stronger determinant of functional performance than knee extensor strength in patients with OA (Accettura et al., 2015; Murray et al., 2015; Davison et al., 2017). Muscle power is a unique parameter distinct from muscle strength, reflecting the product of contractile force and instantaneous contraction velocity (force · velocity = power (W)) (Cormie et al., 2011a, 2011b; Bean et al., 2002, 2003; Caserotti et al., 2001, 2008). Maximal leg extensor power is known to affect activities of daily living such as rising from a chair, ascending stairs, and brisk walking (Alcazar et al., 2020/10; Rittweger et al., 2004; Larsen et al., 2009; Bassey et al., 1992; Elam et al., 2021). Specifically, muscle power has been observed to be positively associated with objective measures of functional performance, lean muscle mass, pain, and quality of life, respectively, in patients with knee OA (Accettura et al., 2015; Murray et al., 2015; Davison et al., 2017; Reid et al., 2015). Collectively, this highlights the relevance of monitoring lower limb muscle power in patients with advanced knee OA. In addition, the onset of age-related decline in maximal muscle power occurs earlier and with a steeper rate of decline than muscle strength (3.5% per year vs. 1.5–2% per year from 65 years of age), and with different trajectories for males and females (Skelton et al., 1994; Edwen et al., 2013). Also, previous studies in frail older subject have observed associations of different strength between lower limb muscle power and functional performance in males and females (Bassey et al., 1992; Rantanen and Avela, 1997). Thus, measuring lower limb muscle power in male and female patients with knee OA, respectively, may aid the evaluation of knee and OA disease progression in this population. Also, previous studies in frail older subject have observed associations of different strength between lower limb muscle power and functional performance in males and females (Bassey et al., 1992; Rantanen and Avela, 1997). Thus, measuring lower limb muscle power in male and female patients with knee OA, respectively, may aid the evaluation of knee and OA disease progression in this population.

Lower limb muscle power has been obtained in subjects with knee OA using various dynamometer-based methodologies (i.e. isokinetic dynamometry, Nottingham Power Rig, pneumatic leg press machines) (Accettura et al., 2015; Murray et al., 2015; Davison et al., 2017; Reid et al., 2015; Calder et al., 2014; Barker et al., 2004; Tevald et al., 2016), which unfortunately only rarely are available in clinical settings. Interestingly, recent reports have demonstrated that mechanical lower limb muscle power can be derived from a simple sit-to-stand test (STS power) (Alcazar et al., 2020/10) in older healthy adults with good correlation to functional performance in both males and females, respectively (Alcazar et al., 2020/10; Alcazar et al., 2018; Alcazar et al., 2021). Therefore, the STS power test could potentially aid clinicians with an easy-to-use and validated assessment tool to assess leg extensor muscle power in subjects suffering from advanced knee OA.

The aim of the present study was twofold: Firstly, to examine the relationship of STS muscle power and maximal isometric knee extensor strength (knee extensor MVC) on objective measures of functional performance and selected patient-reported outcomes in a cohort of male and female patients with advanced (end-stage) knee OA. Secondly, we aimed to determine if STS muscle power was more strongly correlated than knee extensor MVC with given objective and subjective measures of functional performance, knee function, pain and quality of life, respectively.

2. Material & methods

The present cross-sectional study was part of a larger randomized controlled trial (RCT) that investigated the effect of preoperative low-load blood flow restricted resistance exercise (LL-BFRE) compared to usual preoperative care on postoperative measures of: functional performance, muscle strength, muscle morphology, and patient-reported outcomes subsequent to TKR surgery (Jørgensen et al., 2020). To reduce the risk of motivational bias due to group allocation, baseline assessments were conducted prior to randomization into either LL-BFRE or standard (usual) preoperative care. The detailed study protocol has been published elsewhere (Jørgensen et al., 2020). In the present study, baseline data from all 86 patients (i.e. assessed prior to intervention) were harvested from the RCT trial. The original sample size was determined for the RCT study to allow detection of a significant between-group difference in the training-induced change in the 30-s sit-to-stand test three months post surgery.

In brief, the study participants were included from the Orthopedic Departments at Regional Hospital Horsens, Denmark and Regional Hospital Silkeborg, Denmark from September 2nd 2019 and until October 30th 2022. Patients aged $\geq$50 years scheduled for Total Knee Replacement (TKR) due to knee OA were included in the present study. Patients were excluded from the trial if suffering from severe cardiovascular diseases (New York Heart Association class III and IV); previously suffered from a stroke incident or thrombosis incident; suffered from a traumatic nerve injury in affected limb; were living with unregulated hypertension (systolic $\geq$180 or diastolic$\geq$110 mm Hg); affected by spinal cord injury; had planned other lower limb surgery within 12 months; diagnosed with cancer and currently undergoing chemotherapy, immunotherapy or radiotherapy; unable to understand or write in Danish; had an existing prosthesis in the index limb; were living more than 45 min from either Horsens Regional Hospital, Silkeborg Regional Hospital or Aarhus University Hospital; or were pregnant.

The study adhered to the Declaration of Helsinki and was approved by Central Denmark Region Committee on Biomedical Research Ethics (Journal No 10-72-19-19) and the Danish Data Protection Agency (Journal No 652164). All participants gave informed consent and signed a form for participation. The study was registered at ClinicalTrials.gov (NCT04081493).

2.1. Outcome measures

The present data included standardized measures of functional performance, maximal lower limb muscle strength and power, and patient-reported outcomes. All outcomes variables are elaborated in detail in elsewhere (Jørgensen et al., 2020).

2.2. Dependent variables

STS power was derived from the 30-s chair stand test (30STS) as described by Alcazar et al. (2021). During 30STS testing we recorded the maximal number of full sit-to-stands (i.e. from sitting to standing with full hip- and knee extension) completed within 30 s when rising from a 44 cm (seat height) chair without armrests. The patients were instructed to perform the test with their arms across the chest (Jørgensen et al., 2020; Høgsholt et al., 2022; Petersson et al., 2020, 2022). Prior to actual testing the patients performed 3–5 repetitions to practice and become familiarized to the test. Subsequently, participants performed a single trial.

Subsequently, STS mean power (W) was calculated as described by Alcazar et al. (2021):

$$STS\ \ power = \frac{Body\ mass \bullet 0.9 \bullet [Height \bullet 0.5 - Chair\ height]}{\left[\frac{Time}{number\ of\ repetitions}\right] \bullet 0.5}$$

In this equation, body mass was expressed in kg, body height and chair height in m, and time in seconds (30 s). 0.9 is the fraction of body mass that is vertically displaced during the STS movement, 0.5 in the numerator denotes the estimated ratio of leg length relative to body height, and 0.5 in the denominator denotes the relative duration (ratio) of the concentric movement phase relative to each cyclic STS repetition (Alcazar et al., 2021).

Maximal isometric knee extensor strength (MVC knee extensor) was measured with a stabilized handheld dynamometer (HHD) fixed to the examination bed with rigid adjustable straps (Jørgensen et al., 2020; Høgsholt et al., 2022). The patient was seated on the examination table without back rest with knees and hips positioned at 90° flexion and with the HDD attached with a rigid strap around the ankle 5 cm above the medial malleolus. The distance from the HHD to the knee axis of rotation (medial femur condyle) was measured (external lever arm). The patients were instructed to remain seated in an upright position and place both hands on the shoulder to avoid compensation. Patients were instructed to produce as much knee extensor force as possible in four separate trials of 3–4 s duration, separated by 30-s rest. For analysis, peak knee extensor torque (HDD peak force · external lever arm length) was averaged for the second, third and fourth trial, and subsequently normalized to bodyweight (Nm/kg) (Jørgensen et al., 2020).

2.3. *Functional performance*

The Timed Up & Go test (TUG) measures the time required for patients to stand up from a chair (seat height 44 cm), and walk as fast as possible to a mark on the floor 3 m away and subsequently return back to sit on the chair. Use of armrests was allowed. The faster of two trials was selected for analysis. One minute of rest was allowed between trials (Wright et al., 2011).

The 4 × 10 m walk test (40FWT) was performed as a measure the total time required to cover 4 × 10 m excluding turns (m/s). Patients were instructed to walk as fast as possible without running to a visible mark 10 m away, return and repeat for a total distance of 40 m. Prior to the test, one submaximal practice trial was performed to familiarize participants to the specific test procedure (Wright et al., 2011).

2.4. *Patient-reported outcomes (PROMS)*

Patient-reported outcomes were obtained using the Knee Injury and Osteoarthritis Outcome Score (KOOS) based on the subscales: pain, symptoms, sport and recreational activities (Sport), activities of daily living (ADL), quality of life (QoL). Each subscale consists of multiple items scored from 0 to 4 using Likert type scale boxes. The raw score for each of the five subscales is the total sum of the associated item scores ranging from 0 (worst) to 100 (best). KOOS is considered a valid, reliable, and responsive assessment tool for measuring patient-perceived outcomes during long-term and short-term follow-up for knee OA and TKA (Collins and Roos, 2012).

2.5. *Covariates*

Age was chosen as the only covariate factor since (i) STS power and knee extensor MVC were normalized to body mass and (ii) analyses were performed separately for male and female patients, respectively (Accettura et al., 2015; Holm et al., 2022).

2.6. *Statistical analysis*

Descriptive statistics were presented as group means and 95% CI in Table 1. Continuous data were evaluated for normality using histograms and QQ plots. Dependent variables comprised objective measures of mechanical muscle function: Sit-to-stand mean power and maximal knee extensor strength, while independent variables were TUG, 40mFWT, and KOOS subscales Pain, Symptoms, Sport, ADL, QOL. Correlation analysis was performed between STS power versus each of the individual independent variables using linear regression analysis (Pearson product-moment method) adjusted for age. Similar analysis was performed for knee extensor MVC strength (peak torque) as the dependent

Table 1

Characteristics of study participants (n = 86).

Outcome	Males (n = 37)				Females (n = 49)			
	Mean	[95%]			Mean	[95%CI]		
Height (cm)	178.2	[172.9	to	183.6]*	165.6	[162.9	to	166.3]
Weight (kg)	94.5	[89.5	to	99.5]*	86.6	[81.1	to	92.1]
Age (years)	65.9	[63.2	to	68.6]*	67.2	[64.9	to	69.4]
BMI	30.8	[27.2	to	34.4]	31.9	[30.1	to	33.8]
Knee Osteoarthritis Outcome Score								
Pain (0–100)	47.6	[42.3	to	53.0]	47.5	[43.1	to	51.9]
Symptoms (0–100)	53.8	[47.5	to	60.0]	51.8	[46.6	to	57.0]
Activities of daily living (0–100)	54.7	[49.3	to	60.1]	53.4	[49.0	to	57.9]
Sport & Recreational (0–100)	23.7	[17.6	to	29.8]#	16.8	[12.1	to	21.4]
Quality of life (0–100)	30.7	[26.2	to	35.2]	29.2	[25.3	to	33.1]
Functional Performance Measures								
Sit to stand (repetitions)	12.4	[11.1	to	13.6]	12.3	[11.3	to	13.4]
Timed Up & Go (seconds)	6.6	[5.8	to	7.4]*	7.8	[6.9	to	8.6]
40 m fast paced walk test (meter)	25.8	[23.4	to	28.3]	28.8	[26.8	to	30.9]#
STS power production (W/kg)	3.22	[2.81	to	3.63]	2.72	[2.46	to	2.97]
Maximal isometric knee extensor strength, affected leg (Nm/kg)	2.99	[2.67	to	3.31]**	2.03	[1.83	to	2.23]
Sex								
Male/female (n)*								
Knee scheduled for surgery (n)	Counts				Counts			
Right	18				26			
Left	19				23			
Existing total knee replacement in the contralateral knee (n)								
Yes/No	5/32				11/38			
Existing total hip replacement in the contralateral leg (n)								
Yes/No	3/34				2/47			
Symptoms duration (n)								
0–6 months	0				2			
6–12 months	4				3			
1–3 years	5				11			
>3 years	28				33			

*Male/female are presented as the absolute number of males and females, respectively.

Cm = centimeter; kg = kilo; CI = confidence interval.

*: $p < 0.05$, **=<0.01; #: $p < 0.07$.

variable. The assumption of the multiple regression analyses was verified using plots of observed versus predicted values, residual plots, histograms, and QQ plots. β coefficients with 95%CI were calculated (representing the change in the independent variable per unit change in the dependent variable) along with r-values as well as crude (unadjusted) and adjusted coefficients of determination (r^2) (Foldager et al., 2022). Pitman's test was performed to determine statistically significant differences in correlational strength (numeric r-values) between relationships based on STS power versus knee extensor strength (Skoffer et al., 2015b).

3. Results

A total of 2805 patients scheduled for a TKA were assessed for eligibility (Fig. 1). From these, 86 patients were included in the present study, as detailed in Fig. 1. Anthropometrics, patient-reported outcomes, measures of functional performance, STS power, knee range of motion and strength measures are presented in Table 1. Males were on average heavier and taller than female patients ($p < 0.05$) (Table 1), while also demonstrating faster TUG performance and higher knee extensor MVC torques normalized to body mass ($p < 0.05$) (Table 1). All other outcome variables were similar between male and female patients (Table 1).

3.1. Associations between STS power vs. functional performance and PROMS

3.1.1. Male patients

After adjusting for age, STS power was found to be negatively associated with TUG performance ($p=<0.01$) and 40mFPW ($p=<0.01$) (Table 2). Likewise, after adjusting for age, STS power was positively associated with KOOS Pain and ADL ($p < 0.01$) (Table 2).

3.1.2. Female patients

After adjusting the model, TUG and 40mFWT was negatively associated with STS power ($p < 0.05$), while none of the KOOS subscales demonstrated any statistical association (Table 3).

4. Associations between knee extensor MVC vs. functional performance and PROMS

4.1. Male patients

When adjusting for age, none of the outcome variables revealed a statistically significant β coefficient (Table 4).

4.2. Female patients

After adjusting for age none of the outcome variables revealed a statistically significant β coefficient (Table 5).

4.3. Comparison of the crude correlations based on STS power and knee extensor MVC

Table 6 compares the correlation coefficients based on STS power and knee extensor MVC strength for all outcome variables examined. A stronger correlation with STS power were observed for TUG in both male and female patients, respectively ($p < 0.05$), along with a stronger relationship for 40mFWT in male ($p < 0.01$) but not female patients ($p = 0.38$). Further, equal or stronger correlations with STS power were observed for all KOOS subscales (Table 6).

5. Discussion

The present study demonstrated that STS power but not knee extensor strength was associated with functional performance in male patients and female patients suffering from advanced knee OA. Additionally, patient reported outcomes (PROMs) KOOS Pain, ADL and Sport were associated with STS power. Notably also, functional performance (TUG and 40mFWT) and PROMs were correlated with STS power to a similar or greater extent than knee extensor strength in male and female patients.

The present assessments of sit-to-stand leg extensor power appear to provide a time efficient low-cost test tool that predict overall ambulatory function, horizontal walking speed and selected PROMs in female and male patients suffering from advanced knee OA. Further, the regression coefficients observed in the present study provide an estimate of the predicted improvement in these outcome parameters for given improvements in STS power (cf. Table 7), which may be useful information in the clinical practice.

5.1. Relationships between mechanical muscle function (STS power, MVC strength) and functional performance

The present study demonstrated moderate-to-strong linear relationships between STS power and functional performance (TUG, 40-m maximal walking speed) in male and female knee OA patients, respectively, in the absence of any relationships with knee extensor MVC strength, in overall support of previous reports (Accettura et al., 2015; Murray et al., 2015; Tevald et al., 2016; Holm et al., 2022). In line with the present observations, Accettura et al. (2015) found that knee extensor muscle power was significantly associated with functional performance (stair walking, 6-min walking distance) in persons aged

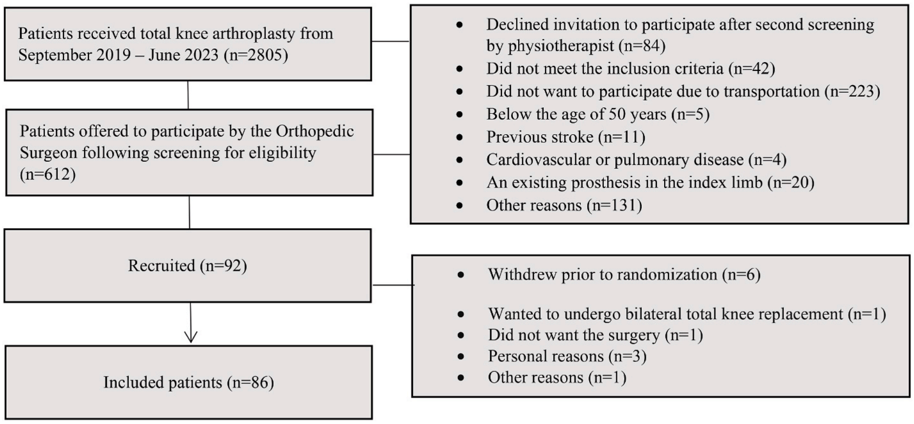

Fig. 1. Flow chart.

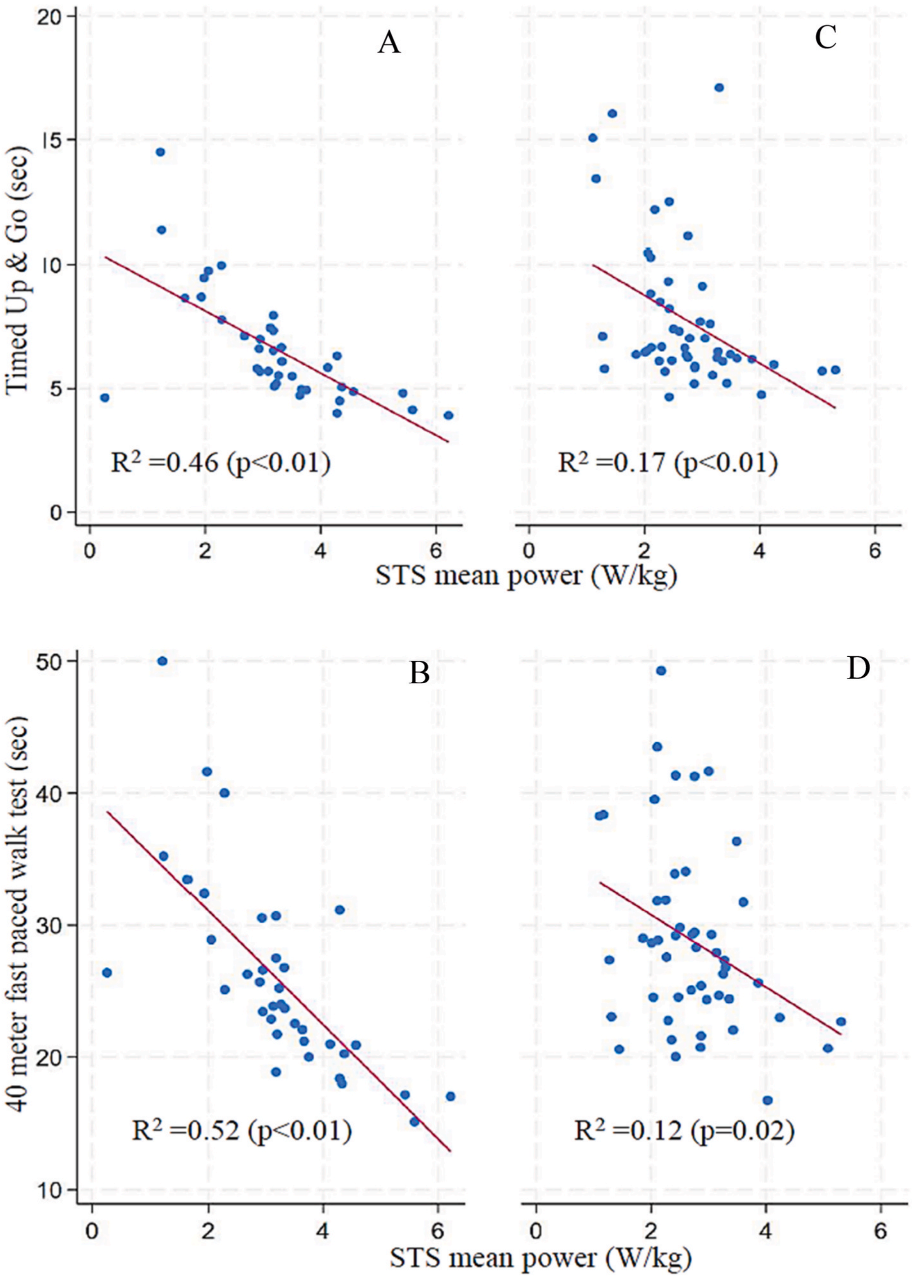

Fig. 2. Relationships (crude) between STS Power and Functional performance (top panels: TUG, bottom panels (40-m paced walk) in male (A, B) and female (C, D) knee OA patients. For regression slopes, see β-coefficients listed in Table 3 (males) and 4 Females).

40–70 years with clinically verified knee OA (Accettura et al., 2015). Likewise, Holm et al. (2022) reported moderate-to-strong associations between maximal leg extensor power vs. TUG and Stair ascent speed in patients with knee OA scheduled for TKR while less strong correlations were observed based on maximal knee extensor strength. Nonetheless, sit-to-stand function and PROM (KOOS physical function) was better predicted by knee extensor strength than maximal leg extensor power (Holm et al., 2022). The correlation between STS power and maximal 40-m walking speed observed in the present group of male knee OA patients was identical to previous relationships reported in healthy males aged 60–93 years of age (present study: r = 0.49 versus 0.53) (Alcazar et al., 2021). In contrast, markedly weaker relationship were observed between STS power and 40-m walking speed in the present group of female OA patients compared to previous observations in healthy females aged 60–93 years (present study: r = 0.33 versus 0.51) (Alcazar et al., 2021). This apparent disparity between healthy females and the present cohort of female knee OA patients may, at least in part, be explained by more severe impairments in walking ability in the present female OA patients due to their advanced state of OA disease progression.

5.2. Relationships between mechanical muscle function (STS power, MVC strength) and patients-reported outcomes

Moderate-to-strong correlations were observed in the present cohort of male knee OA patients between STS power vs. KOOS Pain and ADL function, respectively, whereas no correlations could be observed in female participants. Notably also, no relationships could be observed between maximal knee extensor MVC strength and any of the patient-reported outcome variables examined in the present study. The data obtained in the present male knee OA patients are in accordance with previous reports of associations between maximal leg muscle strength or

Table 2
Crude and adjusted associations between Sit-to-stand Power (Watt/body mass) and functional performance and PROMS in male knee OA patients.

	Crude	Adjusted for Age
Timed Up & Go (sec)		
β coefficient	−1.26**	−1.11**
95% CI	[-1.27; −0.79]	[-1.62; −0.60]
r	0.68	0.68
r^2 (Murray et al., 2010)	0.46	0.47
P value for r^2	<0.01	<0.01
Observations (n)	37	36
40 m fast paced walk test (sec)		
β coefficient	−4.32**	−4.36**
95% CI	[-5.76; −2.88]	[-5.99; −2.73]
r	0.72	0.74
r^2 (Murray et al., 2010)	0.52	0.55
P value for r^2	<0.01	<0.01
Observations (n)	37	36
KOOS Pain		
β coefficient	5.17*	6.53 **
95% CI	[1.19; 9.15]	[2.23; 10.82]
r	0.42	0.50
r^2 (Murray et al., 2010)	0.18	0.25
P value for r^2	0.01	<0.01
Observations (n)	34	33
KOOS Symptoms		
β coefficient	1.14	3.52
95% CI	[-3.96; 6.24]	[-1.44; 8.49]
r	0.08	0.49
r^2 (Murray et al., 2010)	>0.00	0.24
P value for r^2	0.65	0.17
Observations (n)	34	33
KOOS Sport & Recreation		
β coefficient	2.23	4.61*
95% CI	[-2.67; 7.14]	[0.02 9.20]
r	0.18	0.55
r^2 (Murray et al., 2010)	0.03	0.29
P value for r^2	0.36	<0.01
Observations (n)	34	33
KOOS Activities of daily living		
β coefficient	7.12**	7.17**
95% CI	[3.55; 10.70]	[3.31; 11.04]
r	0.58	0.58
r^2 (Murray et al., 2010)	0.34	0.33
P value for r^2	<0.01	<0.01
Observations (n)	34	33
KOOS Quality of life		
β coefficient	1.44	2.12
95% CI	[-2.23; 5.11]	[-1.61; 5.88]
r	0.15	0.32
r^2 (Murray et al., 2010)	0.02	0.10
P value for r^2	0.43	0.12
Observations (n)	34	33

$^{**}p < 0.01$, $^{*}p < 0.05$.

Table 3
Crude (unadjusted) and adjusted associations between Sit-to-stand Power (Watt/body mass) and functional performance and PROMS in female knee OA patients.

	Crude	Adjusted for Age
Timed Up & Go (sec)		
β coefficient	−1.38**	−1.35**
95% CI	[-2.27; −0.48]	[-2.25; −0.46]
r	0.41	0.43
r^2	0.17	0.19
P value for r^2	<0.01	<0.01
Observations (n)	49	49
40 m fast paced walk test (sec)		
β coefficient	−2.74*	−2.64*
95% CI	[-4.96; −0.51]	[-4.81; −0.48]
r	0.34	0.43
r^2	0.12	0.18
P value for r^2	0.02	0.01
Observations (n)	49	49
KOOS Pain		
β coefficient	3.47	3.53
95% CI	[-1.38; 8.32]	[-1.29; 8.35]
r	0.22	0.28
r^2	0.05	0.08
P value for r^2	0.16	0.17
Observations (n)	45	45
KOOS Symptoms		
β coefficient	−0.68	−0.63
95% CI	[-6.59; 5.22]	[-6.58; 5.31]
r	0.03	0.11
r^2	<0.00	0.01
P value for r^2	0.82	0.77
Observations (n)	46	46
KOOS Sport & Recreation		
β coefficient	3.24	3.34
95% CI	[-1.89; 8.38]	[-1.63; 8.32]
r	0.19	0.35
r^2	0.03	0.12
P value for r^2	0.21	0.07
Observations (n)	45	45
KOOS Activities of daily living		
β coefficient	2.74	2.75
95% CI	[-2.23; 7.72]	[-2.29; 7.79]
r	0.17	0.17
r^2	0.03	0.03
P value for r^2	0.27	0.54
Observations (n)	45	45
KOOS Quality of life		
β coefficient	3.09	3.20
95% CI	[-1.22; 7.40]	[-0.94; 7.33]
r	0.21	0.37
r^2	0.05	0.14
P value for r^2	0.16	0.04
Observations (n)	46	46

$^{**}p < 0.01$, $^{*}p < 0.05$.

knee extensor muscle power versus various patient-reported outcomes (Tevald et al., 2016; Holm et al., 2022; Berger et al., 1985). Notably, Reid et al. (2015) found a negative relationship between maximal knee extensor peak power and WOMAC pain (r2 = 0.26) while knee extensor power was positively correlated to health-related quality of life (r2 = 0.26) in a combined cohort of male and female patients suffering from symptomatic knee OA. Also, Berger et al. (1985) reported that knee extensor power had a low-to-moderately strong relationship to self-reported physical function (r^2 = 0.28-0.14, <0.05) (Berger et al., 1985), supporting the present findings of a positive relationship between STS power and KOOS ADL, although stronger relationships were observed in the present study. In contrast, no such associations could be identified by Holm et al. (2022).

5.3. Comparing relationships based on STS power vs. knee extensor MVC strength

The present study is the first to assess STS power in patients with knee OA. Correlations of STS power to functional performance and PROMs were compared to correlations based on knee extensor MVC strength by means of the Pitman's test (Skoffer et al., 2015b). To our best knowledge, the present data are the first to statistically verify the presence of stronger (for males) or comparable (40mFWT for females) relationships to functional performance when based on lower limb STS power than MVC strength. Likewise, all KOOS subscales were similarly or stronger correlated with STS power compared to knee extensor MVC strength. Also using the Pitman test, Skoffer et al. (2015b) observed that 30-s STS test outcome was more strongly correlated with TUG performance and 10-m fast paced walking test outcome compared to the relationships based on knee extensor strength. Thus, the present findings support and expand previous observations in patients suffering from various degrees of knee OA (Accettura et al., 2015; Calder et al., 2014; Tevald et al., 2016; Holm et al., 2022; Berger et al., 1985) by demonstrating STS muscle power to be a stronger determinant of functional performance and patient-reported outcomes than maximal knee

Table 4
Crude (unadjusted) and adjusted associations between maximal knee extensor strength in the affected limb (Nm/kg) versus functional performance and PROMS in male knee OA patients.

	Crude	Adjusted for Age
Timed Up & Go		
β coefficient	−0.90*	−0.60
95% CI	[-1.66; −0.15]	[-1.51; 0.31]
r	0.39	0.39
r^2	0.15	0.15
P value for r^2	0.02	0.08
Observations (n)	35	34
40 m fast paced walk test (sec)		
β coefficient	−2.93*	−2.70
95% CI	[-5.54; −0.33]	[-5.95; 0.54]
r	0.37	0.37
r^2	0.14	0.14
P value for r	0.03	0.08
Observations (n)	35	34
KOOS Pain		
β coefficient	−2.85	−1.99
95% CI	[-8.65; 2.95]	[-9.09; 5.11]
R	0.18	0.23
r^2	0.03	0.05
P value for r^2	0.32	0.45
Observations (n)	32	31
KOOS Symptoms		
β coefficient	−4.42	−2.25
95% CI	[-11.15; 2.30]	[-0.02; 0.01]
R	0.24	0.38
r^2	0.06	0.14
P value for r^2	0.19	0.11
Observations (n)	32	31
KOOS Sport & Recreation		
β coefficient	0.34	3.64
95% CI	[-6.11; 6.80]	[-3.51; 10.78]
R	0.02	0.39
r^2	<0.00	0.15
P value for r^2	0.91	0.10
Observations (n)	32	31
KOOS Activities of daily living		
β coefficient>	1.44	−0.10
95% CI	[-4.57; 7.44]	[-7.15; 6.95]
r	0.09	0.07
r^2	0.01	<0.01
P value for r^2	0.63	0.94
Observations (n)	32	31
KOOS Quality of life		
β coefficient	−0.65	0.32
95% CI	[-5.92; 4.61]	[-5.65; 6.29]
R	0.05	0.25
r^2	>0.00	0.06
P value for r^2	0.80	0.41
Observations	32	31

$^{**}p < 0.01$ $^{*}p < 0.05$.

Table 5
Crude (unadjusted) and adjusted associations between maximal knee extensor strength in the affected limb (Nm/kg) vs. functional performance and PROMS in female knee OA patients.

	Crude	Adjusted for Age
Timed Up & Go		
β coefficient	−1.02	−0.95
95% CI	[-2.26; 0.22]	[-2.20; 0.31]
r	0.24	0.26
r^2	0.06	0.07
P value for r^2	0.10	0.20
Observations (n)	48	48
40 m fast paced walk test (sec)		
β coefficient	−2.95*	−2.60$
95% CI	[-2.95; −0.02]	[-5.51; 0.31]
r	0.29	0.36
r^2	0.08	0.13
P value for r^2	<0.05	0.04
Observations (n)	48	48
KOOS Pain		
β coefficient	−0.03	0.32
95% CI	[-6.60; 6.54]	[-6.27; 6.91]
R	>0.00	0.17
r^2	>0.00	0.03
P value for r^2	0.99	0.54
Observations (n)	44	44
KOOS Symptoms		
β coefficient	−1.05	1.38
95% CI	[-6.28; 8.38]	[-6.10; 8.85]
R	0.04	0.10
r^2	>0.00	0.01
P value for r^2	0.77	0.81
Observations (n)	45	45
KOOS Sport & Recreation		
β coefficient	1.90	2.49
95% CI	[-4.98; 8.78]	[-4.23; 9.21]
R	0.09	0.29
r^2	0.01	0.09
P value for r^2	0.58	0.16
Observations (n)	44	44
KOOS Activities of daily living		
β coefficient>	1.87	1.89
95% CI	[-4.78; 8.52]	[-4.87; 8.66]
r	0.09	0.09
r^2	<0.01	<0.01
P value for r^2	0.57	0.16
Observations (n)	44	44
KOOS Quality of life		
β coefficient	−1.44	−0.63
95% CI	[-7.11; 4.23]	[-6.19; 4.92]
R	0.08	0.30
r^2	0.01	0.09
P value for r^2	0.61	0.61
Observations	45	45

$^{**}p < 0.01$ $^{*}p < 0.05$.

extensor strength in this patient cohort.

5.4. Limitations

A number of limitations may be mentioned with the present study. First, as this is a cross-sectional study, any causal relationships may not be inferred, and further the direction of any potential cause-effects also would be speculative, for which reasons the present associations must be interpreted with caution 40. Also, the present sample size did not allow for more extensive adjustments in the regression analysis (Green, 1991), which may have left the analyses unadjusted for other potentially confounding factors (i.e. pain).

5.5. Perspectives

From a clinical perspective the present STS power test offers a simple tool to evaluate lower limb mechanical power during a closed kinetic chain-activity, which resembles a multitude of ADL tasks (i.e. rising from a chair, ascending stairs, brisk walking) (Cormie et al., 2011b; Tevald et al., 2016). The current data suggest that STS power can be used as a low-cost assessment method for clinicians to monitor functional performance related to ambulatory function and walking speed in elderly knee OA patients (Fig. 2), while at the same time reflecting selected patient reported outcomes (PROMs) such as KOOS pain and KOOS ADL. The associations observed in the present study suggest that exercise protocols designed to improve STS power in knee OA patients may translate into parallel improvements in functional performance and PROMs in this patient population. However, this hypothesis awaits to be tested in future experimental studies.

6. Conclusion

In male and female patients with advanced knee OA, STS power was found to be a moderate-to-strong determinant of functional

Table 6
Comparison of sit-to-stand power vs. maximal knee extensor strength as crude predictors of functional performance and PROMs.

	Sex	STS Power		Knee extensor MVC
Timed Up & Go	Male	$r = 0.68$	$> p < 0.01$	$r = 0.39$
	Female	$r = 0.41$	$> p = 0.01$	$r = 0.24$
40 m fast paced waling	Male	$r = 0.72$	$> p < 0.01$	$r = 0.37$
	Female	$r = 0.34$	$= p = 0.48$	$r = 0.29$
KOOS Pain	Male	$r = 0.42$	$> p < 0.01$	$r = 0.18$
	Female	$r = 0.22$	$> p = 0.01$	$r = 0.00$
KOOS Symptoms	Male	$r = 0.08$	$< p = 0.03$	$r = 0.24$
	Female	$r = 0.03$	$= p = 0.01$	$r = 0.04$
KOOS Sport & Recreation	Male	$r = 0.18$	$> p < 0.01$	$r = 0.02$
	Female	$r = 0.19$	$> p = 0.05$	$r = 0.09$
KOOS Activities of daily living	Male	$r = 0.58$	$> p < 0.01$	$r = 0.09$
	Female	$r = 0.17$	$> p = 0.01$	$r = 0.09$
KOOS Quality of life	Male	$r = 0.15$	$> p = 0.01$	$r = 0.05$
	Female	$r = 0.21$	$> p = 0.01$	$r = 0.08$

> favors STS power, < favors knee extensor MVC strength, = no significant difference between STS power and knee extensor MVC strength.
STS power: mean 30-s sit-to stand power; MVC knee extensor MVC strength: maximal isometric knee extensor torque; KOOS=Knee Injury & Osteoarthritis Outcome Score.

Table 7
Expected mean improvements in STS Power required to produced relevant changes in functional performance.

FUNCTIONAL PERFORMANCE STS POWER		
Outcomes	Relevant change	Required to achieve clinically relevant change
Timed Up & Go	1.1–2.3 sec[43]	Males: 1.0–2.1 W/kg Females: 0.8–1.7 W/kg
40 m fast paced walking	$+0.3$ m/s[37] = 6.4 s faster*	Males: 1.5 W/kg Females: 2.4 W/kg

40-m paced walking averaged for the present cohort = 1.54 m/s [1.47; 1.63]. All data adjusted for age.

performance, while also predicting KOOS subscales Pain and ADL in male patients. Maximal isometric knee extensor strength did not show any associations with functional performance or any of the KOOS subscales. Importantly, STS power was more strongly correlated with measures of functional performance and KOOS Pain and ADL-scores than the corresponding relationships based on maximal knee extensor strength.

In conclusion, STS power testing may provide researchers and clinicians with a time- and cost efficient tool to evaluate overall ambulatory function (TUG, maximal horizontal walking speed), and self-reported pain and ADL-function in elderly patients with advanced knee OA.

Author contributions

All authors contributed significantly to all aspects of this manuscript.

Funding

This study was a part of PhD project funded by Health Research Foundation of Central Denmark Region, Aase & Ejnar Danielsens Foundation, Nis-Hanssens Mindeslegat, The Family Hede Nielsen, Brd. Hartmann's Foundation, The Danish Association of Physiotherapists Foundation.

Declaration of competing interest

The authors declare no competing interests.

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Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Stian Langgård Jørgensen

This declaration concerns the following article/manuscript:

Title:	Sit-to-stand power predicts functional performance and patient-reported outcomes in patients with advanced knee osteoarthritis. A cross-sectional study .
Authors:	Stian Langgård Jørgensen, Inger Mechlenburg, Marie Bagger Bohn, Per Aagaard

The article/manuscript is: Published ☒ Accepted ☐ Submitted ☐ In preperation ☐

If published, state full reference: Langgård Jørgensen, S., et al. (2023). "Sit-to-stand power predicts functional performance and patient-reported outcomes in patients with advanced knee osteoarthritis. A cross-sectional study." Musculoskelet Sci Pract 69: 102899.

If accepted or submitted, state journal: Musculoskeltal Science & Practice

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Category of contribution	Extent (A-F)
The conception or design of the work:	C
Free text description of PhD student's contribution ***(mandatory)*** The PhD student, Stian Langgård Jørgensen, has contributed significantly and was responsible for the process of designing the study.	
The acquisition, analysis, or interpretation of data:	B
Free text description of PhD student's contribution ***(mandatory)*** The PhD student, Stian Langgård Jørgensen, has contributed significantly and was responsible for leading the acquisition, analysis and interpretation of data.	
Drafting the manuscript:	A
Free text description of PhD student's contribution ***(mandatory)*** The PhD student, Stian Langgård Jørgensen, wrote the first draft of the manuscript and was responsible for most of the amendsments as well.	
Submission process including revisions:	A

Free text description of PhD student's contribution ***(mandatory)***
The PhD student, Stian Langgård Jørgensen, performed the submission and lead the work on the revisions.

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The efficacy of blood flow restriction EXercise prior to total Knee arthroplasty on sit-to-stand function 3 months postoperatively (EXKnee):
A randomized controlled trial

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Financial support: This work was supported by grants from the Health Research Foundation of Central Denmark Region, Aase & Ejnar Danielsens Foundation, Nis-Hanssens Mindeslegat, The Family Hede Nielsen Foundation, Brother's Hartmann Foundation, Augustinus Foundation, William Demant Foundation, The Danish Association of Physiotherapy Foundation.

Word count: 2913

Ethical Committee Approval: The trial was approved by the Central Denmark Region Committee on Biomedical Research Ethics (Journal No 10-72-19-19)

Conflicts of interests: The Authors have no conflicts of interest to disclose.

Role of funding sources: The funders of the study had no role in study design, data collection, data analysis, data interpretation, or conclusions of this trial.

ABSTRACT

Objective: To compare eight weeks of preoperative low-load blood flow restricted resistance training (BFR-RT) with preoperative standard care before total knee arthroplasty (TKA) on changes in the 30 seconds chair stand test (30STS) from baseline to three months after TKA as the primary outcome.

Design: Randomized controlled trial

Methods: Eighty-six patients scheduled for TKA were randomized to 8 weeks preoperative BFR-RT 3x/week or preoperative usual care. The 30-s sit-to-stand test was the primary outcome, while secondary outcomes consisted of the Knee injury and Osteoarthritis Outcome Score (KOOS) subscales Pain, Symptoms, Activities of Daily Living, Sport & Recreation, and Quality of Life, 1repetition maximum (RM) leg press strength on the affected and unaffected leg, exercise adherence and surgery-related complications.

Results: Intention-to-treat analysis of 86 patients did not reveal significant between-group changes from baseline to three months after surgery on 30STS performance 0.01(95%CI -1.7;1.7). No between-group changes were observed for KOOS subscales. Significant between-group changes in 1RM leg press strength were observed before surgery and three months after surgery for both legs favouring BFR-RT. Exercise adherence was 90.6%, and 36 patients completed >80% of the sessions. No differences were observed in surgery-related complication. Two patients declined TKA after engaging in BFR-RT.

Conclusion: Eight weeks of preoperative BFR-RT yielded no superior effects compared with usual care on functional performance and patient-reported outcomes three months after surgery. BFR-RT elicited significant gains in leg press strength persisting up to three months after surgery.

Keywords: Occlusion training, prehabilitation, physical function, exercise medicine

INTRODUCTION

Total Knee Arthroplasty (TKA) is considered highly effective in reducing pain and improving quality of life in patients suffering from advanced knee osteoarthritis (OA)[4, 14]. Unfortunately, ~20% of TKA patients are dissatisfied with the postoperative outcome, due to persistent pain and impairments in physical activity[4, 11]. Even in satisfied patients, the postsurgical physical function- and activity-level remains below that of age-matched healthy adults[1, 2]

Preoperative maximal knee extensor muscle strength and physical function are two key modifiable factors in the recovery of physical function following TKA[13, 26, 30, 35]. Engaging in preoperative rehabilitation exercises (prehabilitation) before TKA can potentially improve maximal knee extensor strength, physical function and patient-reported outcomes up to twelve months after surgery compared with usual preoperative care[14, 25, 34]. Thus, implementing prehabilitation efforts involving muscle strengthening exercises prior to TKA surgery seems highly relevant in this patient population.

Resistance training using low loading intensities (10-30% 1 repetition maximum (1RM)) combined with partial blood flow restriction (BFR-RT) induces gains in maximal muscle strength and physical function comparable to that achieved by heavy-load resistance training (HL-RT) in both clinical and healthy populations[15, 19, 20, 24] and alleviates knee pain and symptoms more than HL-RT in knee patients[9]. Recent study reports have suggested BFR-RT as an attractive prehabilitation-method in patients with knee OA awaiting TKA, specifically to counteract skeletal muscle atrophy induce preoperative gains in knee extensor muscle strength to enhance the postoperative recovery of physical function[11, 27]. To our best knowledge the efficacy of preoperative BFR-RT compared with usual preoperative care on the postoperative recovery in physical function remains unknown.

Therefore, the present study aimed to investigate the efficacy of eight weeks of preoperative BFR-RT compared with usual preoperative care on the postoperative recovery in physical function assessed by 30-s chair stand testing (30STS) at baseline and three months after TKA. As a secondary aim, we examined the temporal change in patient-reported outcomes and leg muscle strength from baseline to three months after TKA.

MATERIALS AND METHODS

Trial design

The trial was designed as a multicentre, randomised, assessor-blinded, controlled trial[29], pre-registered at Clinicaltrials.gov (NCT 04081493), approved 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). A detailed trial protocol was published 20th August 2020[23]. All participants provided signed informed consent and their rights were protected. Reporting coheres with the Consolidated Standards of Reporting Trials (CONSORT) statement[29].

Inclusion statement

Neither patients nor members of the public were involved in the design or conduct of this trial. All patients eligible for inclusion were invited to participate regardless of gender, race/ethnicity or socioeconomic status.

Participants

Patients were included from September 2019 to October 2022. Six experienced orthopaedic surgeons at XXX Regional Hospital (n=2) and YYY Regional Hospital (n=4) performed the initial screening and referred eligible patients to the local physiotherapist in charge of the patient enrolment procedures[23].

Patients aged ≥50 years scheduled for TKA due to knee OA at one of two orthopaedic departments in Denmark were considered eligible for enrolment. Exclusion criteria were: cardiovascular disease (New York Heart Association class III and IV); previous stroke or thrombosis incidents; traumatic nerve injury in the affected limb; unregulated hypertension (systolic ≥180 or diastolic≥110 mm Hg); spinal cord injury; planned lower limb surgery in the following 12 months, pregnancy; cancer and current chemotherapy; immunotherapy or radiotherapy; unable to understand or write Danish; an existing prosthesis in the affected limb; or living ≥45 min from one of three physiotherapy departments clinics (XXX, YYY, ZZZ).

Intervention procedures

All patients were tested at baseline by a blinded (to group allocation) assessor and subsequently randomised (stratified for sites) in a 1:1 ratio using the Research Electronic Data Capture (REDCap) randomization system[17, 18] to either preoperative exercise (BFR-RT) or adhering to the preoperative usual care-treatment (Con)[23]. Randomization was performed by the physiotherapists responsible for the BFR-RT at the local sites.

The preoperative BFR-RT exercise protocol consisted of three weekly exercise sessions performed for eight weeks (Table 1). BFR-RT was performed using pneumatic cuffs (Occlude APS, Denmark) inflated to 60% of total limb occlusion pressure (LOP)[21, 23] and supervised by physiotherapists educated in the BFR-RT protocol. The physiotherapists were aware of the intervention allocation. Each session was initiated with a 10-minute warm-up on an ergometer bike followed by i) leg press (Technogym Element Leg Press) and ii) knee extension

(SportArt Fitness Leg Extension). The exercises were performed in four sets: set one: 30 repetitions (reps); set two-three: 15 reps; set four: until volitional contraction failure. Exercise loads was 30% 1RM and was progressed when a participant was able to complete more than 15 reps in set 4. Thirty seconds rest was provided between sets[23] and five minutes without blood flow restriction between exercises. The Con group were encouraged to continue their lifestyle as usual.

Individual LOP was determined using a pneumatic, conically shaped cuff, 11.7 cm wide (Occlude Aps, Denmark) attached to the proximal thigh of the affected leg[32]. Sitting on an examination table with 2/3 of the lower limb resting on the table and the knee extended, a vascular Doppler probe (EDAN Instruments, inc., China) was placed posterior to the medial malleolus over the posterior tibial artery to measure the auscultatory pulse. The thigh cuff was gradually inflated until the distal auscultatory pulse was fully interrupted (defined as total leg occlusion pressure: LOP). The procedure was repeated until two consecutive identical LOPs were obtained. In case the auscultatory pulse was not interrupted at 300 mmHg, the procedure was interrupted for safety reasons and 300 mmHg was defined as LOP.

On the day of the surgical procedure or the day after, all patients were introduced to a home-based rehabilitation program by a physiotherapist in the hospital (care-as-usual)[23].

Insert table 1 about here

Due to COVID-19 restrictions, elective surgery was partially suspended at the two hospitals from March 2020 to June 2022. Consequently, patients were rescheduled for surgery with a delay of several months compared to their original date of surgery. Patients allocated to BFR-RT who had their surgery postponed were offered to continue the training protocol 1-3 times per week until the time of surgery, regardless of exceeding the pre-planned exercise protocol.

Assessments and outcome variables

Data for the present trial were collected on three separate test days: at baseline typically; in the week before surgery (pre-surgery); and three months following surgery. The pre-specified primary outcome was the between-group difference in the change in 30STS performance assessed from baseline to three months following surgery.

The **30STS** test was used to measure the number of completed sit-to-stands from a 44 cm (seat height) chair without armrests in 30 seconds [7, 12, 22, 36].

The **Knee Injury and Osteoarthritis Outcome Score (KOOS)** questionnaire was used to assess patient-reported measures of knee function; pain, symptoms, activities of daily living (ADL), sport & recreational activities (sport), and quality of life (QoL). Each subscale consists of multiple items scored from 0 to 4 using Likert-type scale boxes. The raw score for each of the five subscales is the total sum of the associated item scores ranging from 0 (worst) to 100 (best)[6].

1RM leg press strength was estimated based on the measurement of 5-RM leg press strength. Patients performed three low-load warm-up sets. The first and second warm-up sets consisted of 12 repetitions, and the third warm-up set consisted of eight repetitions. The load of each warm-up set was increased by 10 kilos. After the warm-up, the load was increased to determine the 5-RM load. If the 5-RM load could not be determined within three trials, a fourth all-out trial was performed. 1RM strength was calculated based on previously reported equations [1RM = load (kg)/1.0278-0.0278·number of repetitions)][16].

Sample size

No data were available in the literature on the change in 30STS following BFR-RT and subsequently undergoing TKA. Likewise, no data exist on the minimal clinically relevant change in

30STS in OA patients. We decided to apply the result of Skoffer et al.[33] to - a 3-4-rep (SD 4.7 chair stands) improvement in 30 three months after TKA with four weeks of preoperative HL-RT - in our calculation[33]. With a statistical power of 0.80 and a significance level of 0.05, 39 patients was required in each group, giving a total of 78 patients. Assuming a dropout rate of 10%, a total sample size of 84 patients was required.

Statistical analysis

Recommendations listed in the "Enhancing the QUAlity and Transparency Of health Research" (EQUATOR) network[5], the CONSORT statement[29], and a Checklist for statistical Assessment of Medical Papers[28] were followed using the *intention-to-treat* principle including all 86 knee OA patients. In addition, a pre-specified *per protocol* analysis on the primary outcome variable were performed. The *per protocol* population included patients in the intervention group attending ≥80% of the supervised exercise sessions (≥19 sessions), and all control subjects. A one-way analysis of variance (one-way ANOVA) model was used to analyse between-group mean changes in continuous outcome measures[31] including changes from baseline to 3-month follow-up. Between-group comparison from baseline to 3 months after surgery was analysed using a mixed linear model with patient ID as a random effect and time, hospital site, and subject group as fixed effects. Student t-testing was applied to compare the pre-to-post-training differences within the respective training or control groups. The level of statistical significance was set at P≤0.05. All statistical analysis was performed in Stata (Statacorp, College Station, Texas, USA).

RESULTS

A total of 2805 patients were assessed for eligibility from September 2019 through June 2023. Of these, 86 patients were randomly allocated to the two subject groups, with 42 in the BFR-RT group and 44 in the CON Group (Figure 1). Baseline characteristics did not differ between the two groups (Table 2). Two patients in CON decided to retract from surgery due to personal reasons, while two patients in BFR-RT decided to refrain from surgery after completing the BFR-RT protocol.

Insert Figure 1 about here

Insert Table 2 about here

Physical function

Baseline data and raw data for each follow-up assessment is presented in Table 3. Mean improvements for each group and between group differences are presented in Table 4. The mean improvement (95% CI) in the 30STS performance from baseline to three months after surgery was 1.2 (0.03; 2.4) chair stands in BFR-RT and 1.2 (0.03; 2.4) in CON, with a mean difference between the two groups of 0.01 (-1.7; 1.7) (Table 4). Also, no difference was observed in the between-group improvements assessed from baseline to pre-surgery (Table 4). *Per protocol* analysis on the primary outcome revealed no significant between-group differences at any time point (data not shown).

Significant within-group improvements in the 30STS performance were observed in both BFR-RT and CON from baseline to three months after surgery (Table 4).

Insert Table 3 and 4 about here

Patient-reported outcomes

No between-group differences in the magnitude of improvement from baseline to pre-surgery or three months post surgery were observed for any of the KOOS subscales (Table 4). However, significant within-group improvements were observed for all KOOS subscales three months after surgery in both groups (Table 4) while only BFR-RT experienced a significant within-group improvement in KOOS symptoms from baseline to pre-surgery (Table 4).

One repetition maximum leg press strength

A significant between-group increase in 1RM leg press strength for the affected leg was observed favouring BFR-RT from baseline to pre-surgery and at three months post-surgery (Table 4). Moreover, BFR-RT showed significant within-group increases in 1RM leg press strength for the affected limb from baseline to pre-surgery and when assessed at three months after surgery (Table 4). In the non-affected leg no between-group differences could be observed between the improvements from baseline pre-surgery or three months after surgery (Table 4). Finally, BFR-RT demonstrated a significant within-group increase in 1RM leg press strength for the non-affected leg pre-surgery as well as three months after surgery (Table 4).

BFR-RT adherence, pain, and exercise load progression

A total of 37 (90%) patients in the BFR-RT group demonstrated high adherence (≥ 80%) to the training protocol, while four (10%) patients completed less than 80% of the planned exercise sessions. Mean adherence in BFR-RT was 90.6% (CI 95% 83.5; 97.8) (Table 5).

No significant changes in knee joint pain were observed from the first exercise session to the last session whether assessed before, during or immediately post exercise.

Insert Table 4 about here

Due to COVID-19 restrictions, 6 patients were delayed ≥28 days from the last exercise session until admitted into surgery. Three patients waited more than 100 days (106, 120, and 216 days), while three waited 43, 44, and 34 days. Seven patients in BFR-RT received additional exercise sessions (1-24 sessions) because their surgery was delayed.

Postoperative complications

The incidence of postoperative complications was similar between the two groups (Table 6). In BFR-RT, 55% of the participants (n=23) and in CON 70% (n=31) were referred to supervised physiotherapy following surgery.

Insert Table 5 about here

DISCUSSION

The main finding of the present study was that eight weeks of preoperative BFR-RT yielded no superior effects compared with usual preoperative care on functional sit-to-stand performance or on any self-reported measures (KOOS subscales) when assessed three months postoperatively.

Notably, BFR-RT yielded significant gains in unilateral 1RM leg press strength in both the affected leg and the non-affected leg pre-surgery that were sustained and elevated compared to non-exercising controls at three months after surgery.

Physical function

As elaborated in a recent meta-analysis from our Lab, muscle strengthening prehabilitation can induce improvements in sit-to-stand performance 3-12 months after TKA and total hip arthroplasty compared with usual preoperative care[25]. The present results on 30STS performance refuted these observations, and also appeared to conflict with previous trials applying prehabilitation in patients scheduled for TKA[3, 33]. Skoffer et al.[33] observed significant between-group differences three months after TKA when combining four weeks of preoperative progressive HL-RT (8-12 RM, 3x/week, leg press, knee extension, knee flexion, hip abduction) with four weeks of postoperative progressive HL-RT compared with a control group receiving usual preoperative care followed by four weeks of postoperative progressive HL-RT. Calatayud et al. reported superior Timed Up & Go- and stair climbing performance three months after TKA with 12 weeks of preoperative HL-RT (10RM 3x/week, leg press, knee extension, knee flexion, hip abduction for both legs) compared with usual care[3].

More aligned with the present results, Franz et al.[10] found similar changes in 30STS and 6-min walking distance at three and six months following TKA when six weeks of preoperative, twice-weekly low-intensity cycling exercise at 40% LOP was compared with an active control group (sham-BFR) and a control group receiving preoperative usual care. Dominguez-Navarro et al. [8] reported that four weeks of preoperative HL-RT (50-100% 10RM, 3x/week, knee extensor, knee flexor exercises) produced improvements in Timed Up & Go at 2-12 months following TKA that did not differ from usual preoperative care.

The disparate observations in the literature (including the present data) may arise from methodological differences between the individual studies where Skoffer et al.[33] utilized both pre- and posteoperative HL-RT; Calatatyud et al.[3] applied 12 weeks of HL-RT; both Skoffer[33] and Calatayud[3] applied maximal effort-exercises (10RM) for the hamstring- and hip abductors, whereas lower loading intensities, fewer exercises and sets with maximal effort were applied in Dominguez-Navarro et al.[8] and the present trial

Patient-reported outcomes (PROMs)

Our KOOS data at baseline underline that the present patients were severely affected by knee OA, which may explain the marked improvements in all KOOS subscales observed following TKA surgery regardless of group allocation. Pre-surgery, we noted an improvements in KOOS Symptoms following BFR-RT only, supporting previous findings[3, 8, 33]. Skoffer et al.[33] observed preoperative HL-RT to improve KOOS symptoms pre-surgery although no statistical differences with usual preoperative care was observed. Domiguez-Navarro et al.[8] reported that HL-RT resulted in superior improvements in KOOS symptoms and pain pre-surgery compared with usual preoperative care. Calatayud et al. [3] demonstrated that twelve weeks of HL-RT resulted in improved WOMAC pain scores pre-surgery compared with usual preoperative care. Thus, designating knee extensor muscle-strengthening exercises can potentially reduce joint pain and disability in patients with knee OA.

Lower limb muscle strength

In the present trial, BFR-RT yielded significant improvements in 1RM leg press strength both pre- and three months after surgery compared with usual preoperative care. Somewhat unexpectedly, the training-induced gains in 1RM leg press strength were not translated into improvements in postoperative physical function[10, 33], which most likely arise from the same methodological between-trial differences as mentioned above.

Exercise adherence

The patients engaging in BFR-RT demonstrated a high adherence to the present BFR-RT exercise protocol (90.6%) with without exacerbating knee joint pain or other adverse effects. These observations are in line with previous reports that patients with knee OA can engage safely in muscle-strengthening exercises involving BFR-RT without experiencing increases in joint pain[9].

Limitations

A number of potential limitations may be mentioned with the present trial. Firstly, while assessors were blinded to group allocation, it was impossible to blind participants and physiotherapists supervising the BFR-RT sessions. Secondly, unilateral exercise was performed for the affected limb only, while our primary outcome parameter was a bilateral STS test. Thirdly, due to concurrent COVID19 restrictions not all pre-defined specifications in the pre-registered exercise protocol could be adhered. Specifically, several trial patients had their scheduled TKA postponed, which may have affected the effectiveness of the BFR-RT protocol.

Conclusions

Improvements compared to baseline in 30STS performance and KOOS subscales observed three months after TKA did not differ between patients engaging in eight weeks of preoperative unilateral BFR-RT or allocated to usual preoperative care. Nonetheless, superior gains in unilateral leg press strength were observed in both the affected and the non-affected legs three months post-surgery in response to eight weeks of preoperative BFR-RT compared with usual preoperative care.

Key Points

Findings: Eight weeks of preoperative muscle strengthening exercises, by means of low-load blood flow restricted resistance training did not improve physical function and patient-reported outcomes three months after surgery compared with usual preoperative care (no preoperative exercise).

Implications: The indications for applying supervised muscle strengthening prehabilitation to improve postoperative physical function and patient-reported outcomes with advanced knee OA scheduled for TKA appear vague.

Caution: Due to concurrent COVID19 restrictions not all pre-defined specifications in the pre-registered exercise protocol could be adhered.

Conflicts of interest

All authors have completed the ICMJE uniform disclosure form. All authors declare no support from any organization for the submitted work; no financial relationship with any organizations that might have an interest in the submitted work, no other relationships or activities that could appear to have influenced the submitted work.

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TABLES

Table 1. Exercise variables

Exercise variable		
Duration	(weeks)	8
Sessions per week	(no)	3
Load	(%)	30% 1RM
Limb occlusion pressure (%)	(%)	60
Cuff size (cm)	(cm)	11.7
Cuff material		Rigid nylon cuff
Repetition, first round	(rep)	30
Repetitions, second round	(rep)	15
Repetitions, third round	(rep)	15
Repetitions, fourth round	(rep)	To volitional failure
Contraction speed, the con phase	(sec)	2
Contraction speed, the ecc phase	(sec)	2
Contraction speed, the isometric phase	(sec)	0
Rest between sets	(min)	0.5
Rest without cuff compression between exercises	(mi)	5
Rest between sessions	(h)	≤36
Progression, leg press		>15 reps in round 4 = add 10 kg next session
Progression, knee extension		>15 reps in round 4 = add 1.6 kg next session

No = number; cm = centimetre; rep = repetition; sec = seconds; min = minutes; h = hours; RM = repetition maximum; con = concentric; ecc = eccentric

Table 2. Patient characteristics

	All (n=86)	BFR-RT (n=42)	CON (n=44)
	Mean (CI)	Mean (CI)	
Age (years)	66.6 (64.9; 67.7)	67.1 (64.6; 69.7)	66.1 (63.8; 68.5)
Height (cm)	170.5 (167.6; 173.3)	169.1 (164.2; 174.1)	171.7 (168.7; 174.8)
Weight (kg)	90.0 (86.2; 93.8)	90.3 (85.1; 95.6)	89.7 (83.9; 95.5)
Body mass index (weight (kg) • height (cm)^2)	31.4 (29.6; 33.3)	32.5 (29.2; 35.7)	30.5 (28.6; 32.4)
	Count	Count	Count
Males/females	37/49	16/26	21/23
Knee scheduled for surgery (n)			
Right	44	23	21
Left	42	19	23
Existing total knee replacement in the contralateral knee (n)			
No	70	33	37
Yes	16	9	7
Existing total hip replacement in the contralateral leg (n)			
No	81	40	43
Yes	5	2	3
Civil status			
Married/in a relationship	69	33	36
Single/divorced/widow/widower	17	9	8
Smoking			
Never smoked	43	21	22
Former smoker	23	16	17
Occasional smoker	3	1	2
Smoking	5	4	1

Duration of knee symptoms			
0-6 months	2	1	1
6-12 months	7	3	4
12-36 months	16	9	7
More than 36 months	61	29	32
Pain medication			
Paracetamol	65	33	32
Ibuprofen	34	17	17
Morphine	6	3	3
Did not use pain medication	15	6	9

BFR-RT = intervention group; Con = control group; cm = centimetre; kg = kilo; CI = confidence interval

Table 3. Raw data on 30 second sit-to-stand performance, patient-reported outcomes, and leg press strength intention-to-treat analysis

		BFR-RT			CON		
Outcome		Baseline (CI)	Pre (CI)	3 months (CI)	Baseline (CI)	Pre (CI)	3 months (CI)
Physical function							
30-sec sit-to-stand	Rep	12.8 (11.4; 14.1)	13.2 (12.0; 14.4)	13.9 (12.8; 15.1)	12.0 (10.9; 13.1)	11.8 (10.6; 13.1)	13.2 (12.0; 14.3)
Patient-reported							
KOOS Pain	0-100	50.5 (45.7; 55.3)	53.9 (48.3; 59.4)	72.8 (67.2; 78.3)	45.0 (40.5; 59.4)	48.5 (42.6; 54.5)	75.4 (69.9; 81.0)
KOOS Symptoms	0-100	52.8 (47.3; 68.4)	59.7 (53.6; 65.8)	66.1 (59.9; 72.4)	52.5 (47.2; 57.8)	55.3 (48.8; 61.8)	67.6 (61.4; 73.7)
KOOS ADL	0-100	54.3 (49.4; 59.1)	56.8 (51.2; 62.5)	76.4 (71.7; 81.1)	53.0 (48.5; 57.6)	54.7 (48.5; 60.8)	76.6 (71.9; 81.3)
KOOS Sport/recreation	0-100	17.1 (11.8; 22.4)	19.8 (13.0; 26.5)	37.7 (28.0; 47.4)	21.1 (16.1; 26.1)	20.6 (13.1; 28.0)	41.5 (32.0; 51.1)
KOOS Quality of Life	0-100	31.0 (26.9; 35.1)	34.3 (29.1; 39.5)	64.7 (57.1; 72.3)	28.3 (24.5; 32.2)	28.0 (22.3; 33.6)	58.2 (50.6; 65.7)
Strength							
1RM Leg press, affected	Kg	56 (48; 65)	84 (73; 94)	73 (65; 81)	57 (49; 65)	55 (44; 66)	57 (49; 65)
1RM Leg press, nonaffected	Kg	77 (66; 87)	86 (74; 98)	90 (74; 98)	75 (64; 85)	79 (67; 92)	75 (62; 88)

CI = confidence interval; rep = repetition; KOOS = Knee Injury & Osteoarthritis Outcome Score; RM = repetition maximum; kg = kilo; pre = pre-surgery; pre = prior to surgery; 3 months = 3 months postoperative

Table 4. Outcomes, intention-to-treat analysis

		BFR-RT		CON		Between-group	
Outcome		Change pre (CI)	Change 3 months (CI)	Change pre (CI)	Change 3 months (CI)	Pres (CI)	3 months (CI)
Physical function							
30-sec sit-to-stand	Rep	0.4 (-0.4; 1.3)	1.2 (0.03; 2.3)*	-0.1 (-1.1;0.8)	1.2 (0.03;2.4)*	-0.6 (-1.9; 0.7)	0.01 (-1.6; 1.6)
Patient-reported							
KOOS Pain	0-100	3.4 (-1.4; 8.2)	23.1 (16.6; 29.7)*	3.7 (-1.6; 9.0)	29.4 (23.1; 35.8)*	0.3 (-6.9; 7.5)	6.3 (-2.8; 15.4)
KOOS Symptoms	0-100	6.8 (2.0; 11.5)*	14.3 (8.1; 20.5)*	2.6 (-2.7; 8.0)	14.9 (9.1; 20.7)*	-4.1 (-11.3; 3.0)	0.6 (-7.9; 9.1)
KOOS ADL	0-100	2.5 (-2.4; 7.5)	22.9 (17.2;28.6)*	1.7 (-3.8; 7.2)	22.7 (17.3; 28.1)*	-0.8 (-8.2; 6.5)	-0.2 (-8.1; 7.7)
KOOS Sport/recreation	0-100	2.7 (-3.6; 9.0)	20.9 (11.7; 30.1)*	-1.6 (-8.6; 5.4)	19.7 (10.9; 28.5)*	-4.3 (-13.7; 5.1)	-1.2 (-13.9; 11.6)
KOOS Quality of Life	0-100	3.3 (-1.2; 7.8)	33.8 (26.0; 41.7)*	-0.5 (-5.6; 4.6)	28.9 (21.2; 36.6)*	-3.7 (-10.5; 3.0)	-4.9 (-15.9; 6.1)
Strength							
1RM Leg press, affected	Kg	27.3 (19.6; 35.0)*	16.7 * (9.7; 23.7)	-1.9 (-10.4; 6.6)	0.4 (-6.6; 7.5)	-29.2 (-40.7; -17.7)*	-16.3 (-26.2; -6.4)*
1RM Leg press, nonaffected	Kg	9.2 (0.9; 17.4)*	13.1 (4.0; 22.3)*	4.5 (-4.4; 13.4)	-0.04 (-9.5; 9.4)	-4.6 (-16.8; 7.5)	-13.2 (-26.3; 0.00)

CI = confidence interval; rep = repetition; KOOS = Knee Injury & Osteoarthritis Outcome Score; RM = repetition maximum; kg = kilo; pre = pre-surgery; pre = prior to surgery; 3 months = 3 months postoperative

Table 5. Exercise-related variables

		Mean (CI)	
Patients	n	41	
Exercise adherence	%	90.6 (83.5; 97.8)	
Days from last exercise session and until surgery		22.8 (8.3; 37.3)	
Patients waiting ≥4 weeks from last exercise session to surgery due to COVID-19	n	5	
Patients receiving >24 exercise sessions due to COVID-19	n	7	
Knee pain			
		1st sessions	Last session
Knee pain at rest before exercise	0-10	2.4 (2.3; 2.6)	2.9 (2.1; 3.7)
Knee pain after 1st set Leg press	0-10	3.3 (2.5; 4.0)	2.9 (1.9; 3.8)
Knee pain after 1st set Knee extension	0-10	3.3 (2.4; 4.1)	2.7 (1.7; 3.7)
Knee pain immediately after exercise	0-10	2.9 (2.1; 3.6)	2.5 (1.5; 3.4)
Leg press			
Load	Kg	16 (13; 18)	45 (36; 55)
Set 1	Rep	30 (29; 30)	29 (27; 30)
Set 2	Rep	15 (14; 15)	15 (14; 15)
Set 3	Rep	13 (12; 14)	13 (12; 15)
Set 4	Rep	12 (9; 16)	11 (9; 13)
Knee extension			
Load	Kg	5 (4; 6)	8 (6; 10)
Set 1	Rep	28 (27; 30)	28 (27; 30)
Set 2	Rep	13 (11; 14)	13 (12; 14)
Set 3	Rep	12 (9; 12)	12 (10; 13)
Set 4	Rep	12 (8; 15)	10 (8; 13)

CI = confidence interval; NRS = numeric ranking scale; Kg = kilo; rep = repetition

Table 6. Adverse events related and un-related to surgery and requirement for supervised physiotherapy in the period following the total knee arthroplasty surgery

	BFR-RT	Con
Surgery-related adverse events		
Infection in the knee	1	1
Reoperation		1
Deep vein thrombosis	1	
Neuropathic pain or sensation in the limb following surgery	1	1
Severe postoperative knee effusion requiring further examination		4
Cicatrize (insufficient wound healing)	2	1
Severe knee pain requiring further examination at the hospital	2	
Severe pain during the night		1
Brissement force	1	
Adverse events unrelated to the surgery		
Experienced hip symptoms following surgery	1	1
Fall episode resulting in a fractured arm	2	
Severe pain in the operated limb		1
Shingles	2	
Ulster		1
Strain in the calf muscle during rehab		1
Additional rehabilitation following surgery		
Supervised municipal rehabilitation	24	31

BFR-RT = intervention group; Con = control group

FIGURE LEGENDS

FIGURE 1. Flow chart

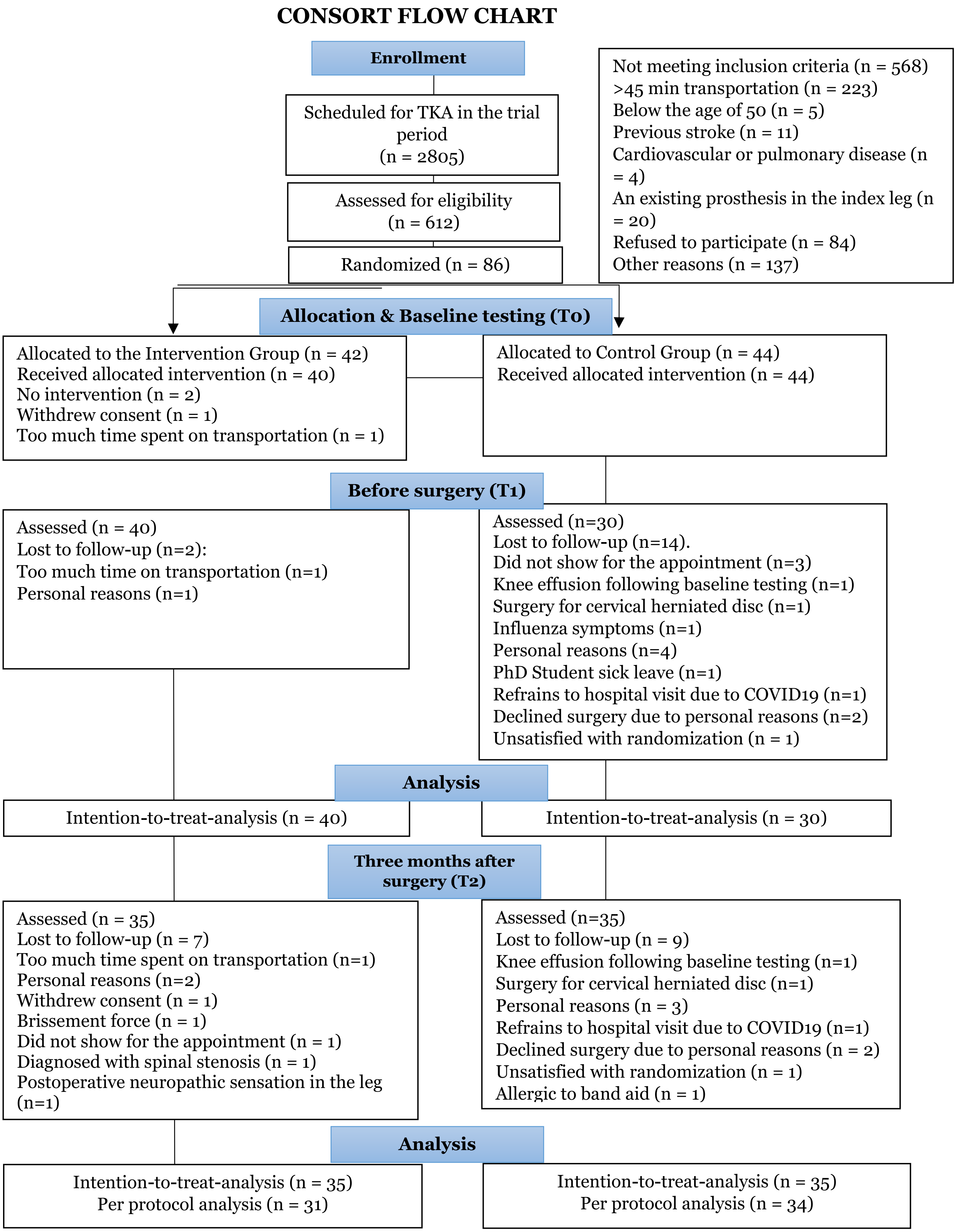

Figure 1. Consort study flow chart until three months follow-up. N represent the number of patients who was assessed for the primary outcome.

Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Stian Langgård Jørgensen

This declaration concerns the following article/manuscript:

Title:	The efficacy of blood flow restriction EXercise prior to total Knee arthroplasty on sit-to-stand function 3 months postoperatively (EXKnee): A randomized ontrolled trial
Authors:	Stian Langgård Jørgensen, Per Aagaard, Marie Bagger Bohn,Peter Hansen, Per Møller Hansen, Carsten Holm, Louise Mortensen, Mette Garval, Lisa Urup Tønning, Inger Mechlenburg

The article/manuscript is: Published ☐ Accepted ☐ Submitted ☒ In preperation ☐

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F. N/A

Category of contribution	Extent (A-F)
The conception or design of the work:	C
Free text description of PhD student's contribution ***(mandatory)*** The PhD student, Stian Langgård Jørgensen, has contributed significantly and was responsible for the process of designing the study.	
The acquisition, analysis, or interpretation of data:	B
Free text description of PhD student's contribution ***(mandatory)*** The PhD student, Stian Langgård Jørgensen, has contributed significantly and was responsible for leading the acquisition, analysis and interpretation of data.	
Drafting the manuscript:	A
Free text description of PhD student's contribution ***(mandatory)*** The PhD student, Stian Langgård Jørgensen, wrote the first draft of the manuscript and was responsible for most of the amendsments as well.	
Submission process including revisions:	A

Free text description of PhD student's contribution ***(mandatory)***
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Preoperative low-load blood flow restricted exercise prevents loss in knee extensor muscle strength after total knee arthroplasty:

Secondary analysis of a randomized controlled trial

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Financial support: This work was supported by grants from the Health Research Foundation of Central Denmark Region, Aase & Ejnar Danielsens Foundation, Nis-Hanssens Mindeslegat, The Family Hede Nielsen Foundation, Brother's Hartmann Foundation, Augustinus Foundation, William Demant Foundation, The Danish Association of Physiotherapy Foundation.

Conflicts of interests: The Authors have no conflicts of interest to disclose.

Authors' Contributions statement: Conception and design: SLJ, PA, MBB, IM. Data acquisition: SLJ. PH, PMH, CH, LM. Analysis and interpretation of the data: All authors. Writing/review/editing of manuscript: All authors. Final approval of the manuscript: All authors

Patient involvement statement: Study participants were not involved in the design, conduct, interpretation, or translation of the current research.

Data sharing statement: Data are available upon request (contact us via stiajo@rm.dk).

Acknowledgements

We like to thank research assistants and physiotherapists supervising the exercise sessions at Horsens Regional Hospital, Silkeborg Regional Hospital, and Aarhus University Hospital: Anette Borch, Trine Vestergaard, Line Jespersen, Cecilie Anée Langgård Jørgensen, Jonas Corneliussen, Karen Svidt, Mette Garval, Jeanette Trøstrup, Louise Mortensen, and Lisa Urup Tønning. Also, thanks are directed to Orthopedic surgeons, nurses and secretaries at the Orthopedic Departments, Horsens Regional Hospital and the Elective Surgery Center, Silkeborg Regional Hospital for the initial recruitment of participants and coordinating the treatments. We also wish to thank all the study participants for volunteering to participate in the study. This work was supported by grants from the Health Research Foundation of Central Denmark Region, Aase & Ejnar Danielsens Foundation, Nis-Hanssens Mindeslegat, The Family Hede Nielsen Foundation, Brother's Hartmann Foundation, Augustinus Foundation, William Demant Foundation, The Danish Association of Physiotherapy Foundation.

ABSTRACT

Objective: To compare eight weeks of preoperative low-load blood flow restricted resistance training (BFR-RT) with preoperative standard medical care on changes in maximal isometric knee extensor and flexor strength (MVIC), knee joint range of motion (ROM), physical function and health status from baseline to pre-surgery and three months after total knee arthroplasty (TKA).

Design: Secondary analysis of Randomized controlled trial.

Methods: Eighty-six patients scheduled for TKA were randomized to 8 weeks preoperative BFR-RT 3x/week or preoperative standard medical care (i.e. no exercise intervention). Data were collected at baseline, before surgery, and three months after surgery on unilateral estimated 1 repetition maximum (1RM) knee extensor strength, knee extensor and flexor MVIC, knee ROM, Timed Up&Go, 40-m fast-paced walking speed, and health status measured with EQ-5D-L5. Data were analyzed using intention-to-treat method.

Results: The trial comprised of 37 males and 49 females. Intention-to-treat analysis of the 86 patients revealed significant between-group changes from baseline to pre-surgery in estimated 1RM knee extensor strength (-4.9[95%CI -9.0;-0.9]) in the affected leg favoring BFR-RT. Three months postoperatively, estimated 1RM knee extensor strength and knee extensor MVIC was higher in patients receiving BFR-RT compared with usual preoperative medical care(-4.7[-8.4;-1.0] and -0.5[-0.9; -0.1], respectively) . No significant between-group changes were observed for physical function, knee ROM, or health status.

Conclusion: BFR-RT performed prior to TKA surgery was effective in preventing loss of maximal knee extensor strength three months postoperatively of the affected leg.

Keywords: Occlusion training, physical function, exercise medicine, orthopaedics, isometric strength

INTRODUCTION

Knee osteoarthritis (OA) is a highly prevalent and disabling disease[17], and a total knee arthroplasty (TKA) is offered when conservative treatments fail to reduce pain and improve physical function, and quality of life[33]. Knee OA and the TKA procedure, independently, impairs knee extensor muscle strength and size[1, 15, 17], ultimately affecting postoperative physical function[28, 36]. Interestingly, higher preoperative knee extensor muscle strength correlates positively with postoperative physical function and is considered an important modifiable factor (i.e. inducing gains in quadriceps strength) before surgery[1].

Preoperative heavy-load progressive resistance training (HL-PRT) (60-100% 1 repetition maximum (1RM)) is known to improve postoperative outcomes in patients scheduled for TKA[3, 16, 24, 35]. But for some patients with knee OA, the exposure to HL-PRT exacerbates knee joint pain[8]. These patients might prefer exercises with lower loading intensities to reduce knee joint discomfort. Low-load resistance training (10-30% 1RM) combined with blood flow restriction to the exercising limb (BFR-RT) induces gains in muscle strength and size and physical function comparable with HL-PRT in both healthy subjects and patients [10, 23]. Due to the low loading intensities applied with BFR-RT, it has been suggested as a relevant preoperative rehabilitation (prehabilitation) tool in patients with advanced knee OA scheduled for TKA [9, 26].

Our primary analysis found no differences in 30-second sit-to-stand function or any of the Knee Injury & Osteoarthritis Outcome Score subscales (pain, symptoms, activities of daily living, sport & recreational activities, or quality of life) with eight weeks of preoperative BFR-RT compared with no preoperative exercise intervention three months after receiving TKA surgery (Jørgensen et al. 2024, in review). In this secondary analysis of a randomized controlled trial (RCT), we examined the effect of eight weeks of preoperative BFR-RT compared with usual preoperative medical care on maximal knee extensor and flexor muscle strength, knee range of motion function, physical function, and patient-reported health-related quality of life before and three months after TKA.

MATERIALS AND METHODS

Trial design

The present study reports on secondary outcomes from an RCT investigating the efficacy of preoperative BFR-RT on 30 second sit-to-stand test performance (primary outcome) compared with usual preoperative medical care in patients scheduled for TKA[22].. Recommendations from the "Enhancing the QUAlity and Transparency Of health Research" (EQUATOR) network[4] and the CONSORT statement[29] were followed. The trial was accepted by the Central Denmark Region Committee on Biomedical Research Ethics (10-72-19-19) and by The Danish Data Protection Agency (652164). The trial was conducted in accordance with the *Declaration of Helsinki.* The trial was registered at Clinicaltrials.gov (NCT 04081493).

Participants were tested at (i) baseline (~10 weeks before surgery), (ii) three to five days before surgery (pre-surgery), and (iii) three months after surgery for various measures of physical function, lower limb muscle strength, and self-perceived health status[22]. The recruitment and randomization process has been described in detail elsewhere[22]. All patients provided informed signed consent to participate in the trial and were assured that their rights were protected.

Inclusion statement

Neither patients nor members of the public were involved in the design or conduct of this trial.

Participants

Patients were included from September 2019 to October 2022. All patients scheduled for TKA at the Orthopedic departments at two regional hospitals (XXX Regional Hospital, YYY Regional Hospital) were assessed for eligibility. Eligible patients were recruited by six orthopedic surgeons and project physiotherapists at the two sites. The main inclusion criteria were: ≥50 years of age scheduled for primary unilateral TKA due to knee OA. Exclusion criteria were:

- Cardiovascular disease classified as New York Heart Association class III-IV [6]
- Former stroke- or thrombosis event
- Systolic blood pressure ≥180 or diastolic blood pressure ≥110 mmHg
- Traumatic nerve injury in leg scheduled for surgery
- Spinal cord injury
- Pregnancy
- Living with an existing arthroplasty in the leg scheduled for surgery
- Other planned lower extremity surgery within 12 months
- Currently receiving chemo-, immuno-, or radiotherapy treatment due to cancer
- Other reasons for exclusion (i.e. inadequacy in written and spoken Danish, mental unable to participate, etc.). .

Intervention procedures

All patients were tested at baseline by a blinded (to group allocation) assessor and subsequently randomised (stratified for sites) in a 1:1 ratio using the Research Electronic Data Capture (REDCap) randomization system[12, 13] to either preoperative exercise (BFR-RT) or adhering to the preoperative usual medical care (CON)[22]. Randomization was performed by the physiotherapists responsible for the BFR-RT at the local sites. CON participants were instructed to "live their lives as usual" and follow the current standard care which involved a preoperative information meeting about pain management, nutrition, the surgical procedure, physical activity, postoperative home-based rehabilitation, and postoperative load management[22]. BFR-RT participants exercised three times per week for eight weeks with 1:1 supervision by physiotherapists trained in the present BFR-RT protocol. Each BFR-RT session consisted of; i) a 10-min warm-up (self-paced low-intensity ergometer cycling); ii) a unilateral leg press exercise; and iii) a unilateral knee extension exercise (Technogym Leg press, SportArt P-700 Leg Extension). Only the affected leg was trained. Before starting the exercises, a pneumatic cuff (Occlude APS, Denmark) was placed around the proximal part of the exercising thigh and inflated to 60% of the total limb occlusion pressure (LOP)[18, 22]. Each exercise was performed in 4 sets separated by 30-second rest involving 30-15-15 reps in sets 1-3, respectively, followed by repetitions to failure in the 4th (final) set. The concentric and eccentric contractions phases were performed in a slow controlled manner (lasting 2-s each)[22]. The initial load was 30% of 1RM. If patients were able to perform more than 15 repetitions in the 4th set, the exercise load was increased with the minimum extra load possible in the subsequent session (leg press: 10 kg; knee extension: 0.5 kg.). Failure in the fourth set was defined as the inability to complete the final concentric contraction phase in 2 seconds. The pneumatic cuff was released upon completion of the 4th set in each exercise, while kept inflated between successive sets in each exercise. Patients rested 5 minutes between exercises. LOP was determined with ultrasound Doppler at baseline assessment[18, 22, 31]. For safety reasons, 180 mmHg (LOP=300 mmHg) was decided as the maximum cuff pressure allowed during exercise.

The training adherence was reported in Jørgensen et al. 2024 (in review). In brief, mean exercise adherence was 91% where 36 patients completed at least 80% of the planned exercise session (Jørgensen et al. 2024, in review). The mean leg press load increased from 16 kg in the first session to 45 kg in the last exercise session, and mean knee extensor load increased from five kg to eight kilos. Knee pain did not increase during exercises and did not change from first session to last session (Numeric Ranking Scale for Pain after exercise, first session: 2.9; last session 2.5)

Assessments and outcome variables

All assessments were performed at baseline, in the week of surgery (pre-surgery), and 3 months postoperative.

Estimated 1RM knee extension strength was derived from a 5-8RM knee extensor test. Patients performed three low-load warm-up sets. The first and second warm-up sets consisted of 12 repetitions, and the third warm-up set consisted of eight repetitions. After the warm-up, the load was increased to determine the 5RM. If the 5RM was not determined within three trials, a fourth all-out trial (as many repetitions as possible) was performed. The estimation of 1RM load was calculated using a linear regression equation [estimated 1RM = load (kg)/1.0278-0.0278·number of repetitions)][11].

Maximum voluntary isometric knee extensor strength (knee extensor MVIC) was measured using stabilized dynamometry with the participant seated upright on a rigid examination bed with the hands crossed above the chest to avoid compensation, and knees and hips positioned at 90° flexion. The hand-held dynamometer (HHD) was positioned distally at the tibia (5 cm above the medial malleolus) and fixed with an adjustable rigid strap to the legs of the examination bed[25]. Patients completed four trials. For analysis, the average peak force (converted into torque) of the second, third, and fourth trials was calculated and normalized to bodyweight[25].

Maximal voluntary isometric knee flexor strength (knee flexor MVIC) was assessed also using stabilized HHD with patients seated as described for the knee extensor MVIC. In this test, the HHD was positioned on the posterior aspect of the calcaneus and fixed with an adjustable rigid strap to a wall-mounted rib[25]. Patients completed four trials. For analysis, the average peak force (converted into torque) of the second, third, and fourth trials was calculated and normalized to bodyweight[25].

Active knee joint range of motion (ROM) was measured with the patient lying supine on the examination bed with a 360° plastic goniometer with the fulcrum of the goniometer visually aligned to the medial epicondyle of the knee joint. The moveable arms of the goniometer were aligned towards the greater trochanter and the lateral malleolus[19]. First, the patients performed a maximal active flexion of the knee joint. Subsequently, the patients performed a maximal active extension of the knee. To allow hyperextension of the knee, the heel was placed on a firm square box (height:5 cm,width:8 cm;length:15 cm).

Timed Up & Go (TUG) testing was performed using a chair with a seat height of 46 cm. Patients were instructed to rise from the chair and walk as fast as possible to a tape mark 3 meters away and return to sitting in the chair. Use of the armrests was allowed. The fastest of the two trials was selected for further analysis. One minute of rest was allowed between trials[37].

40-m fast-paced walk testing (40m-FWT) excluding turns[37] was performed in a quiet hallway. Patients were instructed to walk as fast as possible between two visible marks on the floor 10 meters apart with 2 meters of space to turn safely around in each end [5]. The patients started behind the 10-m mark. Time was recorded within the 10-meter track[37]. The usage of assistive walking devices was allowed. Before the test, a practice trial was provided to familiarize the participants with the specific experimental procedure.

The **EQ-5D-5L** is a standardized, generic instrument for describing and assessing health status[20, 27]. The questionnaire generates two overall values: the *EQ-5D-5L Index* and the EQ Visual Analogue scale (VAS) ("Current state of health"). The EQ-5L-5D Index was calculated based on 5 separate dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression having five response categories (no problems, slight problems, moderate problems, severe problems, and extreme problems). This produced a five-digit code. Through an index calculator, these codes were converted into a numerical value (EQ-5D-5L index) ranging from -0.757 (worse than death) to 1.00 (best possible health)[20, 27]. EQ VAS was used to rate overall current health status by stating scores between 0 (worst imaginable health) to 100 (best imaginable health) (EQ-VAS)[20, 27].

Sample size calculations

The present data analysis was based on secondary data obtained from a randomized controlled trial, where the 30-s sit-to-stand test (30STS) performance was chosen as the primary outcome[22]. The sample size calculation did not account for the secondary outcomes. Therefore, all outcomes presented in the present study should be considered exploratory.

Statistical analysis

Our pre-specified analysis followed an intention-to-treat principle. Between-group comparisons of change from baseline to three months after surgery were analyzed using a linear mixed model with patients as a random effect and time and group as fixed effects [30]. Paired student t-tests were performed to gain insights into potential within-group changes from baseline to pre-surgery and 3 months post TKA, respectively. The level of statistical significance was set at P<0.05. Patients with missing values were excluded from the specific analyses (complete case-analysis CCA)[14]. All statistical analysis was performed using STATA (StataCorp LP, College Station, Texas) version 18.

RESULTS

All 86 patients were included in the analysis. Two patients in CON retracted from surgery due to personal reasons, while two patients in BFR-RT decided to refrain from surgery after completing the BFR-RT protocol due to improvements in self-perceived knee pain and knee symptoms. Demographic characteristics at baseline for patients in BFR-RT and CON are listed in Table 1.

insert Table 1 about here

Estimated 1RM knee extensor strength

Significant between-group differences in estimated 1RM knee extensor strength change favoring BFR-RT were observed in the affected leg from baseline to pre-surgery (-4.9 [-9.0; -0.9]) and from baseline to three months after TKA surgery (-4.7 [-8.4; -1.0]) (Table 2). No between-group differences in estimated 1RM knee extensor strength were observed for the contralateral non-affected leg at any time points (Table 2).

BFR-RT, but not CON, demonstrated significant within-group improvements (~50% increase) (6.9 [4.1; 9.6]) in estimated 1RM knee extensor strength in the affected limb from baseline to pre-surgery (Table 2). No within-group changes in estimated 1RM knee extensor strength emerged for the non-affected leg at any time points (Table 2).

insert Table 2 about here

Maximal isometric knee extensor and knee flexor strength (MVIC)

There was no significant between-group change in knee extensor MVIC in the affected leg from baseline to pre-surgery (Table 2). A significant between-group difference favoring BFR-RT was observed in postoperative knee extensor MVIC for the affected leg from baseline to three months after surgery (-0.5 [-0.9; -0.1]) (Table 2).

Knee extensor MVIC showed no within-group changes between time points for the affected leg in BFR-RT, while decreasing in CON (-0.4 [-0.7; -0.1]) from baseline to three months after surgery (Table 2).

For the non-affected leg, no significant between-group changes or within-group changes occurred in knee extensor MVIC at any time point (Table 2).

Knee flexor MVIC showed no between-group changes for any of the legs at any time point (Table 2). Both BFR-RT and CON Group showed reduced knee flexor MVIC on the affected side from baseline to three months after surgery (Table 2). For the unaffected leg, no within-group changes emerged at any time point (Table 2).

Knee joint range of motion

No between-group differences in active knee joint ROM (flexion and extension) were observed at any time point (Table 2). Likewise, no within-group changes in knee joint ROM were observed at any time point for both knees (Table 2).

Physical function

TUG and 40mFWT performance remained unaltered in both groups at all time points (Table 3).

insert Table 3 about here

Patient-reported outcomes

No significant between-group differences emerged in the EQ-5D-5L Index pre-surgery or three months after surgery (Table 3). Both groups demonstrated significant within-group improvements (BFR-RT: 0.13 [0.07; 0.18]; CON: 0.16 [0.11; 0.21]) in EQ-5D-5L Index from baseline to three months after surgery (BFR-RT: 0.13 [0.07; 0.18]; CON: 0.16 [0.11; 0.21]) (Table 3).

No significant between-group differences in EQ-VAS occurred at any time point (Table 3). BFR-RT demonstrated within-group improvements in EQ-VAS from baseline to pre-surgery (8.6 [0.3; 16.9] and from baseline to three months after surgery (19.8 [12,6; 27.0]). Likewise, CON demonstrated an improvement ($p<0.05$) in EQ-VAS from baseline to three months after surgery (12.6 [5.9; 19.3]) (Table 3).

DISCUSSION

As the main study finding, BFR-RT performed before surgery in patients with advanced knee OA scheduled for TKA appeared effective in protecting against a loss in knee extensor muscle strength in the operated leg when assessed three months after surgery. This observation suggests a sustained effect of preoperative BFR-RT that persists at least three months into the postoperative rehabilitation phase. In contrast, patients receiving usual preoperative medical care involving no exercise intervention demonstrated a significant decrease in knee extensor MVIC when assessed three months following TKA surgery. Knee joint ROM and physical function remained unchanged three months following surgery in both groups, although we noted a tendency (p=0.08) towards improved active knee ROM in the BFR-RT group pre-surgery. Significant improvements in health status were seen in both groups three months postoperatively.

Maximal muscle strength

The present data show that engaging in preoperative BFT-RT preserves lower limb muscle strength in the operated limb following knee TKA surgery, which may help to enhance the long-term postoperative recovery in physical function. In support of this notion, combating knee extensor strength deficits typically is recommended as a main rehabilitation target following TKA, because reduced knee extensor strength leads to increased risks of falling and adopting aberrant movement patterns[2].

The present muscle strength data support previous reports by Skoffer et al.[35] and Calatayud et al.[3], who observed that preoperative muscle strengthening exercises (Calatayud: 8 wks of HL-PRT in 3x/wk 5 sets @10RM, leg press, knee extension, leg curl, and hip abduction performed for both legs; Skoffer: 4 wks of HL-PRT 3x/wk, 3 sets @8-12RM, leg press, knee extension, knee flexion, hip extension, hip abduction, hip adduction on the affected leg) led to sustained levels of knee extensor MVIC when assessed three months after TKA. Interestingly, the preoperative HL-PRT protocols discussed above[3, 35] also effectively prevented the loss in maximal knee flexor strength[3, 35], and hip abductor strength [3]. These disparities may reflect differences in exercise selection, where Skoffer[35] and Calatayud[3] included designated knee flexor- and hip abductor exercises. Both maximal knee flexor- and hip abductor strength are associated with physical function in patients undergoing TKA[32, 36]. Thus, exercise(s) targeting the knee flexor- and hip abductor muscles seems reasonable to implement in prehabilitation protocols for this patient population.

Knee Joint Range of Motion

The present ROM findings of no changes in active knee joint flexion and extension are in line with Skoffer et al.[35]. The high baseline levels in knee flexion and knee extension ROM observed in the present trial, suggest the potential presence of a ceiling effect hindering further improvements with training. In contrast, Calatayud et al.[3] reported much more impaired (~12° lower baseline levels) knee joint flexion and extension ROM compared with the present patient cohort. Consequently, they were better able to demonstrate significant between-group changes favoring prehabilitation in terms of improvements in knee flexion ROM and extension ROM before and three months after surgery[3].

Physical function

The lack of improvements in TUG and 40mFWT contrasts with previous findings[3, 35]. Calatayud et al.[3] demonstrated that eight weeks of HL-PRT was superior to preoperative standard care in improving TUG performance three months after surgery. Skoffer et al.[35] found that preoperative HL-PRT (4 wk) combined with early postoperative PRT (4 wk) resulted in better TUG-performance and 10-m maximal walking speed three months after TKA compared with only performing postoperative HL-PRT.

In line with our results, however, Dominguez-Navarro et al.[7] were unable to detect changes in TUG performance 6 weeks after TKA, when preceded by four weeks of preoperative

HL-PRT (3 sessions/wk,3 sets of 10 repetitions @50-100% 10RM in knee extensor and flexor exercises). These disparities between different studies may arise, at least in part, from methodological differences: (i) Patients included in Calatayud.[3] exercised both the affected and non-affected limb (Calatayud, personal communication); (ii) Skoffer[35] combined preoperative and postoperative HL-PRT; (iii) both Calatayud[3] and Skoffer[35] included exercises specifically targeting the knee flexors and hip abductor muscles, (iv) Navarro[7] used preoperative exercise of limited duration (4 wk). Thus, from a clinical perspective when prescribing preoperative muscle strengthening exercises to improve postoperative physical function, it seems important to exercise both limbs, provide a high total training volume, and include exercises for the hamstring muscles and hip abductor muscles.

Health status

The present observations of improved EQ-VAS scores in both BFR-RT (20 points) and CON (13 points) following TKA are in line with Skoffer et al.[35]. Further, EQ-5D-5L Index scores improved following TKA to 0.82 and 0.82 in the BFR-RT and CON, respectively. In comparison, healthy Danish peers (aged 60-69 yr) have an EQ-5D-5L Index of 0.89 [21].

Limitations

A number of potential limitations may be mentioned. First due to the secondary analysis approach, the present analysis may have been insufficiently powered to detect longitudinal changes in some of the presented outcome parameters. Second, EQ-5D-L5 is a generic questionnaire, which may mask the true change in health status in patients with advanced knee OA undergoing TKA surgery. Third, the present BFR-RT group and physiotherapists supervising their exercise sessions were unblinded to the group allocation. Thus, the BFR-RT group may have received additional (unintended) counseling from the physiotherapists during the preoperative exercise sessions. Fourth, we only exercised the affected leg which potentially could have limited the effectiveness of our intervention. However, (i) significant asymmetries in knee extensor strength between the affected- and non-affected leg have been demonstrated [34] and (ii) performing four weeks of preoperative HL-PRT (followed by four weeks of post-operative HL-PRT) for the affected leg only has been proven effective in improving postoperative physical function [35]. Therefore, based on previous results [34, 35], and to reduce the lower limb asymmetry in maximal knee extensor strength, we decided not to exercise the non-affected leg. Fifth, we compared BFR-RT with non-exercising control group. This have obviously made it easier to detect between-group changes in strength before surgery and three months after surgery. Therefore, it remains unknown how our intervention would compare with other preoperative muscle strengthening protocols. However, patients scheduled for TKA who perceive HL-PRT intolerable due to excessive knee pain would benefit from preoperative BFR-RT.

Some strengths may be mentioned as well for the present analysis: the use of an experimental RCT design; blinding of all assessors; education of the physiotherapists performing the supervised exercise sessions; 1:1-supervision in all exercise sessions; and selection of outcome measures relevant for this patient population[5].

Conclusion

Eight weeks of preoperative BFR-RT were observed to protect against a decrease in maximal knee extensor strength in the affected leg when evaluated three months following TKA. These observations may be clinically important for the long-term postsurgical recovery in physical function in this patient population. Regardless of the intervention received, physical function and knee joint range of motion were unchanged three months postoperatively compared to baseline.

Key Points

Findings: Eight weeks of preoperative BFR-RT prevented decrements in maximal knee extensor strength three months after TKA compared with usual preoperative medical care.

TKA induced similar changes in physical function and patient-reported outcomes when assessed three months after TKA regardless of receiving preoperative BFR-RT or usual preoperative medical care.

Implications: Low-load BFR-RT may be a useful training modality in patients with knee OA to preserve maximal knee extensor muscle strength following TKA, which can be important for the long-term retention in physical function in this patient population.

Caution: The control group received usual preoperative medical care which contained no exercise interventions.

Conflicts of interest

All authors have completed the ICMJE uniform disclosure form. All authors declare to have no financial relationship with any organizations that may have an interest in the submitted work, or to be influenced by any other relationships or activities that could have affected the submitted work.

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Table 1. Patient demographics

	All (n=86)	BFR-RT (n=42)	CON (n=44)
	Mean (SD)	Mean (SD)	Mean (SD)
Males/Females	37/49	16/26	21/23
Age (years)	66.6	67.1	66.1
	(8.4)	(9.1)	(7.6)
Height (cm)	171	169	172
	(168; 173)	(164; 174)	(169; 175)
Weight (kg)	90	90	90
	(86; 94)	(85; 96)	(84; 96)
Body mass index (weight (kg) • height (cm)^2)	31.4	32.5	30.5
	(29.6; 33.3)	(29.2; 35.7)	(28.6; 32.4)

BFR-RT = intervention group performing BFR-RT; Con = non-exercising control group

Table 2. Raw data on maximal thigh muscle strength and knee range of motion, intention-to-treat analysis

	BFR-RT			CON		
Outcome	Baseline (CI)	Pre (CI)	3 months (CI)	Baseline (CI)	Change pre (CI)	Change 3 months (CI)
Muscle Strength						
1RM Knee extensor, affected leg (Kg)	17 (14; 20)	24 (20; 29)	18 (15; 20)	21 (19; 24)	23 (19; 27)	17 (14; 20)
1RM Knee extensor, nonaffected leg (Kg)	24 (20; 28)	26 (21; 30)	23 (19; 28)	25 (22; 29)	27 (23; 31)	25 (20; 29)
Isometric knee extensor torque, affected leg (Nm kg $^{-1}$)	2.3 (2.0; 2.6)	2.5 (2.1; 2.8)	2.4 (2.1; 2.7)	2.6 (2.3; 2.8)	2.5 (2.2; 2.8)	2.2 (1.9; 2.4)
Isometric knee extensor torque, non-affected leg (Nm kg $^{-1}$)	2.4 (2.1; 2.7)	2.6 (2.3; 2.9)	2.6 (2.3; 2.9)	2.7 (2.4; 3.0)	2.5 (2.1; 2.9)	2.5 (2.2; 2.9)
Isometric knee flexor torque, affected leg (Nm kg $^{-1}$)	1.3 (1.2; 1.5)	1.5 (1.3; 1.7)	1.1 (0.9; 1.2)	1.3 (1.2; 1.5)	1.4 (1.1; 1.6)	1.0 (0.9; 1.1)
Isometric knee flexor torque, non-affected leg (Nm kg $^{-1}$)	1.5 (1.3; 1.6)	1.5 (1.4; 1.7)	1.5 (1.3; 1.7)	1.4 (1.3; 1.6)	1.4 (1.2; 1.5)	1.4 (1.3; 1.6)
Knee joint range of motion						
Knee flexion, affected limb Deg	115 (111; 120)	114 (109; 118)	114 (111; 118)	116 (111; 120)	116 (111; 120)	114 (110; 117)
Knee extension, affected limb Deg	7 (2; 11)	3 (1; 4)	3 (2; 4)	6 (1; 10)	5 (3; 7)	2 (1; 4)
Physical Function						
Timed Up & Go (Sec)	6.9 (6.1; 7.7)	6.3 (5.5; 7.2)	6.2 (5.6; 6.8)	7.7 (6.9; 8.5)	7.7 (6.7; 8.6)	7.1 (6.5; 7.7)
40 meter fast paced walk test (Sec)	26.4 (24.2; 28.6)	26.6 (24.2; 29.0)	25.5 (23.8; 27.2)	28.7 (26.6; 30.8)	28.9 (26.5; 31.4)	27.9 (26.2; 29.6)
Patient-reported variables (EQ-5D-5L)						
EQ-5D-5_Index (-0.0.624-1)	0.69 (0.65; 0.73)	0.71 (0.67; 0.75)	0.81 (0.77; 0.85)	0.65 (0.61; 0.69)	0.68 (0.64; 0.72)	0.81 (0.78; 0.85)
EQ-VAS (0-100)	61.9 (54.8; 69.9)	70.4 (631; 77.8)	81.6 (76.9; 86.4)	64.5 (57.8; 71.2)	66.6 (58.8; 74.5)	77.1 (72.6; 81.6)

Sec = seconds; Deg = degrees; Kg = kilo; Nm = Newton meter; RM = repetition maximum; Change pre = change form baseline to pre-surgery; Change 3 months = change from baseline to three months after surgery; BFR-RT = intervention group performing BFR-RT; Con = non-exercising control group

*<0.05

Table 3. Maximal thigh muscle strength and knee range of motion, intention-to-treat analysis

	BFR-RT		CON		Between-group difference in Change scores	
Outcome	Change pre (CI)	Change 3 months (CI)	Change pre (CI)	Change 3 months (CI)	Pre (CI)	3 months (CI)
Muscle Strength						
Estimated 1RM Knee extensor, affected leg (Kg)	6.9 (4.1; 9.6)*	0.7 (-1.9; 3.3)	2.0 (-1.0; 5.0)	-4.0 (-6.6; 1.4)	-4.9 (-9.0; -0.9)*	-4.7 (-8.4; -1.0)*
Estimated 1RM Knee extensor, nonaffected leg (Kg)	1.6 (-0.5; 3.6)	-0.8 (-3.5; 1.9)	1.6 (-0.6; 3.7)	-0.9 (-3.6; 1.7)	0.00 (-3.0; 3.0)	-0.1 (-3.9; 3.7)
Isometric knee extensor torque, affected leg (Nm kg $^{-1}$)	0.2 (-0.1; 0.4)	0.1 (-0.2; 0.4)	-0.1 (-0.4; 0.2)	-0.4 (-0.7; -0.1)*	-0.2 (-0.6; 0.1)	-0.5 (-0.9; -0.1)*
Isometric knee extensor torque, non-affected leg (Nm kg $^{-1}$)	0.2 (-0.1; 0.4)	0.2 (-0.1; 0.4)	-0.2 (-0.5; 0.1)	-0.2 (-0.5; 0.1)	-0.4 (-0.8; 0.0)	-0.4 (-0.8; 0.0)
Isometric knee flexor torque, affected leg (Nm kg $^{-1}$)	0.2 (-0.0; 0.3)	-0.2 (-0.4; -0.1)*	0.0 (-0.2; 0.2)	-0.3 (-0.5; -0.2)*	-0.1 (-0.4; 0.1)	-0.1 (-0.3; 0.1)
Isometric knee flexor torque, non-affected leg (Nm kg $^{-1}$)	0.1 (-0.1; 0.2)	0.1 (-0.1; 0.2)	-0.1 (-0.3; 0.1)	-0.2 (-0.2; -0.1)	-0.2 (-0.4; 0.1)	-0.1 (-0.3; 0.1)
Knee joint range of motion						
Knee flexion, affected limb Deg	-1.5 (-4.0; 1.0)	-0.8 (-6.2; 4.5)	-0.4 (-3.3; 2.5)	-2.2 (7.4; 3.1)	1.1 (-2.7; 4.9)	-1.3 (-8.8; 6.2)
Knee extension, affected limb Deg	-3.8 (-8.1; 0.5)	-3.6 (-8.2; 1.0)	-0.6 (-4.9; 3.8)	-3.3 (-7.8; 1.2)	3.2 (-2.9; 9.4)	0.3 (-6.2; 6.7)

Sec = seconds; Deg = degrees; Kg = kilo; Nm = Newton meter; RM = repetition maximum; Change pre = change form baseline to pre-surgery; Change 3 months = change from baseline to three months after surgery; BFR-RT = intervention group performing BFR-RT; Con = non-exercising control group

*<0.05

Table 4. Physical function and patient-reported outcomes, intention-to-treat analysis

	BFR-RT		CON		Between-group difference in Change scores	
Outcome	Change pre (CI)	Change 3 months (CI)	Change pre (CI)	Change 3 months (CI)	Pre (CI)	3 months (CI)
Physical Function						
Timed Up & Go (Sec)	-0.5 (-1.3; 0.2)	-0.6 (-1.3; 0.00)	0.01 (-0.8; 0.8)	-0.6 (-1.2; 0.1)	0.5 (-0.6; 1.6)	0.1 (-0.8; 1.0)
40 meter fast paced walk test (Sec)	0.2 (-1.5; 1.9)	-0.9 (-2.6; 0.9)	0.2 (-1.6; 2.1)	-0.8 (-2.5; 0.9)	0.01 (-2.5; 2.5)	0.1 (-2.4; 2.5)
Patient-reported variables (EQ-5D-5L)						
EQ-5D-5_Index (-0.0.624-1)	0.02 (-0.01; 0.06)	0.13 (0.07; 0.18)*	0.04 (-0.00; 0.07)	0.16 (0.11; 0.21)*	0.01 (-0.04; 0.07)	0.04 (-0.03; 0.11)
EQ-VAS (0-100)	8.6 (0.3; 16.9)*	19.8 (12.6; 27.0)*	2.2 (-6.6; 10.9)	12.6 (5.9; 19.3)*	-6.4 (-18.5; 5.7)	-7.2 (-17.0; 2.6)

Sec = seconds; Kg = kilo; Pre = change form baseline to pre-surgery; 3 months = change from baseline to three months after surgery; BFR-RT = intervention group performing BFR-RT; Con = non-exercising control group; W=watt

*<0.05

Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Stian Langgård Jørgensen

This declaration concerns the following article/manuscript:

Title:	Preoperative low-load blood flow restricted exercise prevents loss in knee extensor muscle strength after total knee arthroplasty: Secondary analysis of a randomized controlled triall
Authors:	Stian Langgård Jørgensen, Per Aagaard, Inger Mechlenburg, Peter Hansen, Per Møller Hansen, Marie Bagger Bohn

The article/manuscript is: Published ☐ Accepted ☐ Submitted ☒ In preperation ☐

If published, state full reference:

If accepted or submitted, state journal:

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

No ☒ Yes ☐ If yes, give details:

Your contribution

Please rate (A-F) your contribution to the elements of this article/manuscript, **and** elaborate on your rating in the free text section below.

A. Has essentially done all the work (>90%)
B. Has done most of the work (67-90 %)
C. Has contributed considerably (34-66 %)
D. Has contributed (10-33 %)
E. No or little contribution (<10%)
F. N/A

Category of contribution	Extent (A-F)
The conception or design of the work:	C
Free text description of PhD student's contribution ***(mandatory)*** The PhD student, Stian Langgård Jørgensen, has contributed significantly and was responsible for the process of designing the study.	
The acquisition, analysis, or interpretation of data:	B
Free text description of PhD student's contribution ***(mandatory)*** The PhD student, Stian Langgård Jørgensen, has contributed significantly and was responsible for leading the acquisition, analysis and interpretation of data.	
Drafting the manuscript:	A
Free text description of PhD student's contribution ***(mandatory)*** The PhD student, Stian Langgård Jørgensen, wrote the first draft of the manuscript and was responsible for most of the amendsments as well.	
Submission process including revisions:	A

Free text description of PhD student's contribution ***(mandatory)*** The PhD student, Stian Langgård Jørgensen, performed the submission and lead the work on the revisions.

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