Study Protocol

Effects of low-intensity blood-flow restricted exercise compared to standard rehabilitation in patients with knee osteoarthritis - a randomized controlled trial

Trial registration

ClinicalTrials.gov trial registration identifier:

Ethical Committee in Region Hovedstaden: H-19079135

Data Protection Agency: P-2019-814

Study Protocol Version and Date

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Background

Osteoarthritis (OA) is the second most common disease in Denmark and it is estimated that over 1 million danish people suffer from OA in one or multiple joints[1,2]. A significant number of these people have to receive treatment to reduce pain and maintain the ability to work, and the socioeconomic costs in Denmark as a direct consequence of OA is estimated to be approximately 11 billion Danish kroner (1,5 million EUR) each year[2].

Knee-OA is the most common OA-diagnosis and it is estimated that 60.000 Danish people with symptoms of knee-OA seek medical treatment each year[3]. The occurrence of knee-OA is related to overweight, inactivity, aging, earlier knee injuries and exposure to lifelong physical work[4-6]. The elderly population continuous to increase, and so does the numbers of inactive and overweight people and therefore the occurrence of knee-OA can be expected to increase in the coming decades.

Knee-OA patients often are offered a combination of patient education, weight loss counseling and physical exercise[3,7]. Physical exercise including conventional strength training, functional training (whole body exercises) and cardiovascular training all seem to have an beneficial effect on knee pain, functional function and quality of life in people with OA[8-13]. In Denmark, the GLA:D (Good Life with osteoArthritis in Denmark) concept is a nationwide exercise paradigm, which consists of eight weeks of designated and supervised multi-component training performed twice weekly[14-16]. The concept is a combination of education and supervised neuromuscular exercise (NEMEX) delivered by GLA:D-certified physiotherapists, with the purpose to improve lower limb muscle strength and increase muscular stability around the knee- and hip joints, respectively[14-16]. NEMEX has previously shown positive results on pain perception[11,15-20], functional capacity[11,15] and quality of life[15,16], however the effect of NEMEX (or GLA:D) on muscle strength and lower limb muscle mass has never been investigated to the best of our knowledge. Notably, deficits in maximal muscle strength is often a critical factor in people with knee-OA, and can reach of 20-40 % compared to healthy sex and age-matched individuals[21-23]. Furthermore, prior systematic reviews have indicated that reduced knee extensor muscle strength is an important risk factor for the incidence of KOA as well as for the severity of symptoms and the decline in functional performance[5,24]. As such, improving lower limb muscle strength, with a particular focus on knee extensor strength, may be a key factor in improving symptoms and function in KOA. People with OA, who are able to tolerate heavy strength training, typically experience a positive effect on maximal muscle strength and power[25,26]. Unfortunately however, a large proportion of OA patients are forced to refrain from this type of training due to excessive joint- and muscle pain during and following the training sessions[27].

In recent years strength training combined with concurrent blood flow restriction, i.e. occlusion training, has gained increasing acceptance and usage in athletes[28,29] as well as different patient groups[30-38]. This type of training, often referred as BFR (Blood Flow Restricted) exercise, imposes low levels of mechanical stress on the involved muscles and joints because the exercises are performed with low training load (≤30% of max) concurrently with a reduced blood flow to the working muscles, which is achieved by means of a modified pneumatic blood pressure cuff. BFR training has been documented to result in significant improvements in muscle mass and muscle strength even with just a few weeks of intense daily training[39-41]. Moreover, especially in the clinical setting, BFR exercise has been reported to effectively activate muscular satellite cells (stem cells), which are involved in muscle regeneration and myofiber growth[40,42]. The marked improvements in muscle mass and strength with BFR training seem to be comparable to that achieved by conventionel heavy-resistance strength training[31,34,37-39,43]. Importantly, recent data indicate that BFR training can have an acute pain-reducing effect[33,38] and result in greater strength gains and more pronounced reductions in pain with daily activities compared to heavy strength training in knee patients who experiences pain during training[30]. Based on these observations BFR exercise may represent an attractive alternative training modality in patients with knee-OA.

Study Purpose

To investigate whether an enhanced rehabilitating effect on muscle function and joint pain can be achieved by training with low-intensity BFR exercise compared to standard rehabilitation (education and exercise) in people with knee-OA.

Methods

Inclusion takes place via the Institute of Sports Medicine (ISMC), and the Department of Physical and Occupational Therapy at Bispebjerg Hospital, Copenhagen, Denmark. Assessment for inclusion is made after referral from general practitioner or after conversation with physician assessor at the ISMC. Recruitment will also include advertising through local newspapers, posters in public libraries etc., as well as invitations to attend lectures with information about the study.

Patients will be called in for an initial examination by the attending physicians. At the consultation a standard clinical assessment will be performed and the participant will be examined to ensure that they meet the explicit inclusion but have none of the exclusion criteria of the study. For participants that adhere to the inclusion criteria, an information document will be handed out and the participant will be invited to an in-depth interview regarding the study with a physician (FJ; clinical project leader and PI). Participants will be informed that they may bring a friend or family member to the information interview. Standard radiographs will be obtained. An informed consent will be obtained if the patients meet all of the criteria. Randomization procedures will take place following baseline testing, and will be performed at Bispebjerg Hospital by a blinded (to group allocation) assessor. Subsequently, training intervention procedures will be initiated.

Inclusion criteria

- All participants must meet the American College of Rheumatology (ACR) criteria for OA[44]
- Visible OA on X-ray imaging (Kellgren & Lawrence grade 2-3)
- Pain and functional limited for a minimum of 3 months.
- Be able to voluntarily (i.e. unassisted) perform a 90 degrees flexion in the knee while standing
- Be able to perform loaded machine exercise (leg press and knee extension) planned for the BFR training.
- Be able to understand written and spoken Danish
- Be able to complete the intervention period without extensive time away.

Exclusion criteria

- Kellgren & Lawrence grade 1 and 4
- Bilateral OA-symptoms.
- Prior knee- or hip alloplasty.
- Glucocorticosteroid injection in the knee within the last 6 months.
- Inflammatory arthritis.
- Known neurotic disease such as multiple sclerosis or peripheral neuropathy.
- Prior myocardial infarct or stroke, or chest pain during physical activity.
- Other health related or medical conditions which makes it challenging to participate in the study.

Furthermore, it is an exclusion criterium in the following conditions where use of pneumatic occlusion would be considered contraindicated:

- Type I Diabetes
- Peripheral vascular disease
- Excessive varicose veins
- Prior history of deep venous thrombosis
- Venous insufficiens causing edema in the lower legs

- Systolic blood pressure over 160 mmHg or under 100 mmHg

All the included patients will be randomized into one of two intervention groups; education and neuromuscular exercise (GLA:D) or BFR training. Participants in the education and exercise group will be offered participation in the GLA:D programme[16]. The GLA:D training involve a circuit training program with four stations. Each station involves two to six exercises that the participants perform 10-15 repetitions over 2-3 sets, which depends on the participants pain- and functional level. The BFR group performs training with the knee-OA diagnosed leg. BFR training is performed with the BFR cuff placed at the top of the thigh on the leg being trained. The cuff will be inflated to 60-80 % of the total arterial occlusion pressure (AOP)[45-49]. The participant will then perform training of the knee extensors in a leg press exercise machine and a leg extension exercise machine with a load corresponding to 30 % of the maximal load (1RM = Repetition Maximum)[46,47,49].

The intervention period will last 12 consecutive weeks with 2 weekly training sessions. The participants in the GLA:D group will attend a supervised group training with educated physiotherapy GLA:D instructors at several chosen physiotherapy clinics. Training in the BFR group will be conducted at Bispebjerg Hospital by trained supervisors who are experienced in BFR exercise intervention.

Outcome measures

Before the intervention period, all participants will be tested for a number of different outcome measures. The primary outcome variable is KOOS (Knee injury and Osteoarthritis Outcome Score) [50,51]. Secondary outcome variables at the functional level include maximal and habitual timed up-and-go test (TUG)[52], balance test of postural sway[53], 30-s chair-stand test[52] and stair-climbing test[52,54]. Additional secondary outcome parameters related to mechanical muscle function and includes assessment of maximal knee extensor strength (KinCom, isokinetic dynamometer)[55], explosive muscle strength (rate of force development, RFD) (KinCom, isokinetic dynamometer) [55,56], maximal muscle power (Nottingham Power Rig) [57] and muscle mass (Ultrasonography and DXA-scan). Furthermore, muscle biopsies from the front thigh muscle (m. quadriceps) will be obtained in a sub-group (n=30) of patients for determination of selected myocellular parameters (fiber area, vascularization, muscular satellite cells, nuclei content)[40,58,59]. Testing will take place before the intervention period, after 8 weeks of training and at the end of the intervention (12 weeks) except for the muscle biopsies, which will take place before the intervention period and at the end (12 weeks).

Statistical power analysis

The estimated number of participants in the study are based on the primary outcome variable, KOOS, with the assumption that a chance of 10 KOOS points would be of clinical relevance as well as assuming a standard deviation (SD) of 15 points. With a statistical power of 80 %, a significance level of 0.05 and an expected change in KOOS of 10 point magnitude after 12 weeks of training, was calculated to require 37 participants. To account for drop outs, a total of 90 participants are planned to be included in the study.

Ethical considerations

The study has been accepted by the Committees on Health Research Ethics in Region Hovedstaden (H-19079135). The study will be carried out in accordance with international, standardized research ethics considerations and has been approved by the Danish Data Protection Agency.

All outlined experimental methods have previously been used by the involved researchers at Bispebjerg Hospital (Institute of Sports Medicine and Geriatric Research Unit), Herlev Hospital (Geriatric Research Unit, Department of Internal Medicine) and University of Southern Denmark (Research Unit of Muscle Physiology and Biomechanics at the Department of Sport and Biomechanics), respectively. At no time previously have any serious incidents taken place in our facility that may contraindicate the usage of these methods involved in the present research study. Furthermore, there is no indications in the literature that patients with knee-OA cannot complete 12 weeks of BFR training[25,26]. Due to the low load and the controlled movements when using exercise machines in connection with BFR training, this form of exercise is generally well tolerated by OA patients, who also demonstrate a high training compliance to this training modality [25,38]. Finally, BFR training is not associated with risks of uncontrolled or pain-triggering movement patterns.

Practical conditions

The project will be completed at the Institute of Sports Medicine Copenhagen (ISMC) at Bispebjerg Hospital (BBH) where recruitment, testing, biopsy will be performed. Project activities (data analyses etc) will also be performed at the Institute of Sports Science and Clinical Biomechanics at the University of Southern Denmark, where all muscle biopsy laboratory analysis will be performed.

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