Statistical Analysis Plan (SAP)

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

Trial registration

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1. Introduction

Osteoarthritis (OA) is 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 part of these people receive treatment to reduce the pain and improve 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) per 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, muscle weakness 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.

Representing the most widespread non-medical and non-operative treatment modality both internationally and in Denmark, knee-OA patients often are offered a combination of patient education, weight loss counseling and physical exercise program[3,7]. Physical exercise including conventional strength training, functional training (whole body exercises) and cardiovascular training all seem to have improving effects on knee pain, functional function and quality of life, respectively, 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 often 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[6,24]. 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 load on the involved muscles and joints because the exercises are performed using low exercise loads (≤30% of max) concurrently with a reduced blood flow to the working muscles, which is achieved by means of a 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 conventional heavy-resistance strength training[30,32,35,36,39,43]. Importantly, recent data indicate that BFR can have an acute pain-reducing effect[34,36] 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[31]. Based on these observations BFR exercise may represent an attractive alternative training modality in patients with knee-OA.

1. Study objective

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.

We hypothesise that 12 weeks of BFR training will lead to improved perceived joint pain and muscle function compared to GLA:D training.

2. Study design

Inclusion takes place via the Institute of Sportsmedicine (ISMC), and the Department of Physical and Occupational Therapy at Bispebjerg Hospital. 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, social media etc., as well as invitations to attend lectures with information about the study.

Participants will be invited to a preparatory examination by the attending rheumatology chief physician at Bispebjerg Hospital. At the consultation a standard clinical assessment will be performed and the participant will be examined for meeting the explicit inclusion or exclusion criteria of the study. For participants adhering to the inclusion criteria, an information document will be handed out and the participant will be invited into an in-depth interview about the study with the chief physician. If the participant after receiving all oral and written information wishes to participate in the study and also meets the objective X-ray criteria for OA, an informed consent will be obtained. Randomization procedures will take place following baseline testing, which will be performed at Bispebjerg Hospital by a blinded (to group allocation) assessor. Subsequently, training intervention procedures will be initiated.

2.1. Intervention procedures

All included patients will be randomized into two intervention groups, either standard rehabilitation (education and exercise) or BFR strength training. Each participant randomized to the education and exercise programme will be offered participation in the GLA:D programme[16]. GLA:D training will involve a circuit training program with four stations. Each station involves two to six exercises where the participants perform 10-15 repetitions over 2-3 sets, which depends on the participants pain- and functional level. The BFR group will perform unilateral training with the knee-OA diagnosed leg only. 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)[44-48]. The participant will afterwards 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)[45,46,48].

The intervention period will last 12 consecutive weeks with 2 weekly training sessions at selected physiotherapy clinics. The participants in the GLA:D group will attend a supervised group training with certified GLA:D instructors. Training in the BFR group will be conducted at Bispebjerg Hospital by trained supervisors (PT) who are experienced in BFR exercise intervention. Both intervention groups will attend a 2-hours GLA:D-lecture performed by the involved physiotherapists within the first 8 weeks of training. The lecture includes information about osteoarthritis, how to deal with the diagnosis, and presenting information about ergonomics, treatment and training related to OA[16].

2.2. Sample size calculation

The estimated number of participants in the study are based on the primary outcome variable, KOOS-Pain subscale[49], with the assumption that a change of 10 KOOS points may be considered of clinical relevance[49,50] as well as assuming a standard deviation (SD) averaging 15 KOOS points[11,50]. Assuming a statistical power of 80 %, a significance level of 0.05 and an expected within-group change in KOOS of 10 points magnitude with 12 weeks training (primary endpoint), was calculated to require 37 participants. To compensate for potential dropouts, a total of 90 participants are planned to be included in the study, divided equally and randomly into two intervention groups (45 participants in each group).

2.3. Blinding and randomization

The physician assessor conducting the pre and post testing of physical function, muscle mechanical function, ultrasonography and all statistical analysis will be blinded to participants' group allocation. The participants and the physiotherapists conducting both GLA:D- and BFR-training cannot be blinded for group allocation.

After baseline assessment, patients will be randomized (1:1) to either the GLA:D-training group or the BFR-training group using the Research Electronic Data Capture (REDCap) randomisation system.

3. Outcomes

3.1. Primary outcome

Primary outcome variable is KOOS (Knee injury and Osteoarthritis Outcome Score) Pain subscale. KOOS is an instrument to assess the patient's opinion about their knee

and associated problems. KOOS consists of 5 subscales; Pain, Symptoms, Function in daily living (ADL), Function in sport and recreation (Sport/Rec) and knee related quality of life (QOL).

3.2. Secondary outcomes

Secondary outcome variables at functional level includes:

- 4x10 m maximal horizontal fast-paced walking[51,52]
- 30-s chair-stand test[51-54]
- Stair Climb test (12 steps)[51,55-58]
- Pain Pressure Threshold on affected and non-affected side[59-64]
- Total KOOS score[49,50]
- Oxford Knee Score[49,65]

Secondary outcome parameters related to mechanical muscle function will be obtained as well, including:

- Maximal isometric knee extensor (KE) strength (KinCom, isokinetic dynamometer)[66-68]
- KE Rapid force capacity (Rate of Force Development, RFD) (KinCom, isokinetic dynamometer)[66,68,69]
- Maximal leg muscle power (Nottingham Power Rig)[11,69-71]
- Lower limb muscle mass (Ultrasonography)[72-79]
- Muscle biopsies will be obtained from the thigh muscle (vastus lateralis) for evaluation of myocellular properties (myofiber area, vascularization, muscular satellite cells, myonuclei content)[40,80-84]

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 be obtained before the intervention period and at 12 weeks (primary endpoint). Moreover, patient-reported questionnaires and functional performance will be assessed 6 months after the intervention period.

4. Inclusion and exclusion criteria

All people with symptoms of knee-OA or patients diagnosed with knee-OA are eligible. To be included in the study, participants must meet the following inclusion criteria:

- All participants must meet the American College of Rheumatology (ACR) criteria for OA[85]
- Visible OA on X-ray pictures (Kellgren & Lawrence grade 2-3)[86]
- 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 (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

Individuals will be excluded if meeting these exclusion criteria:

- Kellgren & Lawrence grade 1 and 4[86]
- 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 apoplexy, 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 exceeding 160 mmHg or below 100 mmHg

5. Analysis

All outcome variables will be presented using descriptive statistics such as numerical mean and standard deviation (SD) with 95% confidence interval. Binary and categorical variables will be presented using counts and percentages. SPSS will be used for all statistical analysis. Statistician will be blinded to group allocation.

The subsections below will describe the specific procedures of statistical analyses and related descriptive statistics.

5.1. Primary analysis

The change in the primary outcome (KOOS-Pain) from baseline to primary endpoint (12 weeks) will be calculated for both groups, and a mixed linear model will be used to examine if there is a systematic difference between the two intervention groups.

5.2. Secondary analyses

For all secondary outcomes, including the primary outcome, assessed at multiple time points (more than two) will be analysed using a mixed linear model approach. Secondary outcomes assessed at baseline and at one more time point will be analysed as described for the primary outcome above.

Explorative analysis will be conducted. The primary outcome will be correlated to the various secondary outcomes.

5.3. Intension-to-treat (ITT) analysis

Statistical ITT analysis will include all subjects who are randomized to the intervention procedures.

5.4. Per protocol (PP) analysis

Statistical PP analysis will include subjects who adhere to the major criteria in the protocol and completed the whole study period (i.e. all subjects with ≥85 % training adherence).

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