FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

EFFECTS OF BLOOD FLOW RESTRICTION IMPLEMENTATION ON BONE MARROW EDEMA, CARTILAGE QUALITY RECOVERY AND BONE MINERAL DENSITY IN PATIENTS WITH KNEE OSTEOARTHRITIS. A RANDOMIZED CLINICAL TRIAL.

Wordcount: 3899

Noa Van Laethem (01808839)
Judith Vandepitte (01805057)
Theo Verdonck (01806573)

Promotor: Prof. Dr. Erik Witvrouw
Copromotors: Drs. Ewoud Jacobs, Drs. Sander Denolf

A Master's Thesis Submitted for the Attainment of the Master's Degree in Rehabilitation Sciences and Physiotherapy.

Academic Year: 2023-2024

UNIVERSITEIT GENT

FACULTEIT GENEESKUNDE EN
GEZONDHEIDSWETENSCHAPPEN

UNIVERSITEIT
GENT

FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

EFFECTS OF BLOOD FLOW RESTRICTION IMPLEMENTATION ON BONE MARROW EDEMA, CARTILAGE QUALITY RECOVERY AND BONE MINERAL DENSITY IN PATIENTS WITH KNEE OSTEOARTHRITIS. A RANDOMIZED CLINICAL TRIAL.

Wordcount: 3899

Noa Van Laethem (01808839)
Judith Vandepitte (01805057)
Theo Verdonck (01806573)

Promotor: Prof. Dr. Erik Witvrouw
Copromotors: Drs. Ewoud Jacobs, Dhs. Sander Denolf

A Master's Thesis Submitted for the Attainment of the Master's Degree in Rehabilitation Sciences and Physiotherapy.

Academic Year: 2023-2024

UNIVERSITEIT GENT

EXPRESSION OF GRATITUDE

We would like to express our deep gratitude to Prof. Dr. Erik Witvrouw, our promotor, for making this research possible.

Major thanks go out to Drs. Ewoud Jacobs and Drs. Sander Denolf, our copromotors, as well as Dr. Joke Schuermans for their feedback and for sharing their insights with us. This protocol would not have reached its full potential without their contributions.

We extend our gratitude to Prof. Dr. Jan Victor and Prof. Dr. Ruth Wittoek, for enabling patient recruitment at the Departments of Orthopaedics and Rheumatology, UZ Ghent.

Lastly, we would like to express our appreciation to each other for the excellent collaboration throughout this project.

TABLE OF CONTENT

LIST OF TABLES AND FIGURES

Tables

Figures

LIST OF ABBREVIATIONS

1RM	One Repetition Maximum
BFR(T)	Blood Flow Restriction (Therapy/Training)
BFR-RE	Blood Flow Restriction-Resistance Exercise
BMD	Bone Mineral Density
BME	Bone Marrow Edema
BML	Bone Marrow Lesions
CTX-1	Carboxy-Terminal Cross-Linked Telopeptide of Type 1 Collagen
DESS	Double Echo Steady State
DOT1	Histone Methyltransferase Disruptor of Telomeric Silencing 1-like
DVT	Deep Vein Thrombosis
EDTA	Ethylenediamine Tetraacetic Acid
HIF-1α	Hypoxia-Inducible Factor 1-Alpha
IFF	Interstitial Fluid Flow
IGF-1	Insuline-Like Growth Factor 1
ImP	Intramedullary Pressure
(K)OA	(Knee) Osteoarthritis
LL-BFR	Low Load Blood Flow Resistance
LL-RT	Low Load Resistance Training
LOP	Limb Occlusion Pressure
MMP13	Matrix Metallopeptidase 13
Nf-kB	Nuclear Factor Kappa B
P1NP	Procollagen Type I N-Terminal Propeptide
PE	Pulmonary Embolism
pQCT	Peripheral Quantitative Computed Tomography
RCT	Randomized Controlled Trial
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
VEGF	Vascular Endothelial Growth Factor

ABSTRACT

ENGLISH

Introduction/background:

Knee osteoarthritis (KOA) is a common chronic degenerative joint condition, characterized by degradation of articular cartilage and formation of subchondral bone marrow edema (BME), which causes pain, swelling and joint stiffness, leading to lowered levels of functioning and quality of life. Current treatment modalities are mainly focused on symptom control and support of functional status through behavioural and pharmacological interventions, combined with pain relief techniques, load management and specific strength training. However, strength training (i.e. high load exercises) is often not tolerable for KOA-patients due to a lowered load bearing capacity and pain threshold. Blood flow restriction therapy (BFRT) can bypass this problem, as this technique mimics the effect of high load training on muscles through metabolic stress instead of mechanical stress. Next to its muscular effects, this study aims to investigate the specific hypoxic effects of BFRT on damaged cartilage and bone tissue in KOA patients.

Methods/design:

This is a study protocol for a RCT including 25 participants under the age of 45. Individuals allocated to the control group will complete a twelve-week exercise program involving low load strength training combined with aerobic training (cycling). The same exercise protocol will be used for both the control as well as the intervention group, except the intervention group will apply a pressurized cuff. The use of BFR will be implemented to fully restrict venous blood flow and partially restrict arterial blood flow. Outcome measures will be taken before the start and at the end of the study period. Peripheral Quantitative Computed Tomography (pQCT) will provide a bone-mineral-density (BMD) analysis and evaluation of the functional 'muscle-bone unit'. Bone markers CTX-1 and P1NP will be assessed for bone resorption and formation using blood serum analysis. MRI imaging will map the presence and extent of subchondral edema, cartilage structure and composition.

Discussion:

Assuming this study shows significant findings on cartilage and bone level, the use of BFR in the treatment of knee osteoarthritis should be considered a useful intervention, especially for those individuals who are not eligible for any surgical procedures and cannot tolerate high loads.

Keywords:

Protocol; knee osteoarthritis; blood flow restriction; cartilage; subchondral bone marrow edema

NEDERLANDS

Introductie/achtergrond:

Knieartrose (KOA) is een veel voorkomende, chronische, degeneratieve gewrichtsaandoening die wordt gekenmerkt door slijtage van gewrichtskraakbeen en vorming van subchondraal beenmergoedeem. Het veroorzaakt pijn, zwelling en gewrichtsstijfheid en leidt tot lagere levels van functioneren en kwaliteit van leven. De huidige behandelingsmodaliteiten zijn voornamelijk gericht op symptoombeheersing en behoud van functionele capaciteiten door middel van gedrags- en farmacologische interventies, gecombineerd met pijndempende technieken, loadmanagement en specifieke krachttraining. Krachttraining (zijnde high-load-oefeningen) is echter vaak niet te verdragen voor KOA-patiënten vanwege een verminderde gewrichtsbelastbaarheid en een verlaagde pijngrens. Bloedstroombeperkingstherapie (BFRT) kan dit probleem omzeilen, aangezien deze therapie hetzelfde trainingseffect van high-load-krachttraining op spieren kan nabootsen door middel van metabole stress in de plaats van mechanische stress. Deze studie heeft het doel om, naast het effect op spierniveau, de specifieke hypoxische effecten van BFRT op aangetast kraakbeen- en botweefsel bij KOA-patiënten te onderzoeken.

Methode/design:

Dit is een onderzoeksprotocol voor een RCT met 25 participanten die jonger zijn dan 45 jaar. Individuen die aan de controlegroep worden toegewezen, zullen een oefenprogramma van twaalf weken volmaken, waarbij low-load-krachttraining wordt gecombineerd met fietsen als aerobe training. Voor zowel de controlegroep als de interventiegroep zal hetzelfde oefenprogramma gebruikt worden, al is dit bij de interventiegroep mét BFRT. Het gebruik van BFR zal geïmplementeerd worden om de veneuze bloedstroom volledig en de arteriële bloedstroom gedeeltelijk te beperken. Uitkomstparameters zullen vóór aanvang en na het einde van de interventieperiode afgenomen worden. Peripheral Quantitative Computed Tomography (pQCT) zal zorgen voor een analyse van de bot-mineralen-densiteit (BMD) en een evaluatie van de functionele 'spier-boteenheid'. Botmarkers CTX-1 en P1NP zullen beoordeeld worden op botresorptie en -vorming met behulp van bloedserumanalyse. MRI-beeldvorming zal de aanwezigheid en omvang van subchondraal oedeem, en de structuur en samenstelling van het kraakbeen in kaart brengen.

Discussie:

Wanneer deze studie significante resultaten op kraakbeen- en botniveau oplevert, zou het gebruik van BFR bij de behandeling van knieartrose als een nuttige interventie beschouwd moeten worden, zeker voor die personen die niet in aanmerking komen voor chirurgische ingrepen maar ook geen hoge belastingen kunnen verdragen.

Sleutelwoorden:

Protocol; knieartrose; bloedstroombeperking, kraakbeen, subchondraal botoedeem

INTRODUCTION

Osteoarthritis (OA) is a common degenerative joint condition with an estimated prevalence of 528 million patients worldwide.[1] It's a progressive chronic disease characterized by degradation and loss of articular cartilage, hypertrophic bone changes with osteophyte formation, subchondral bone remodelling and eventually chronic inflammation of the synovial membrane.[2] This tissue damage can be caused by multiple contributing factors, ranging from joint overloading to systemic inflammation to metabolic or enzymatic derangements, resulting in pain, reduced range of motion, swelling and stiffness, ultimately leading to reduced levels of functioning and quality of life.[3,4]

Out of all OA-patients, almost 70% suffers at knee-level, due to its constant use and high mechanical stress.[1] This number will most likely expand within the upcoming years, considering unfavourable risk factors such as the continuous increase of obesity and the tendency of population to live longer and to practice more high load sports.[5] This is concerning given the functional impairment and disability associated with this condition and thus needs to be detected and treated as early as possible.[4]

Due to the degenerative character of knee-osteoarthritis (KOA) and the lack of blood vessels in cartilage tissue, its regenerative capacity is quite limited which makes spontaneous restoration of damaged cartilage rather unlikely.[6] Throughout the years, lots of research has been conducted to finetune KOA-treatment opportunities. Educational and behavioural approaches including lifestyle modifications, self-management and weight regulation have been proven to be supportive, but seem to be insufficient on their own.[7] Pharmacological approaches such as NSAID's and intra-articular corticosteroids (if not contra-indicated) are also beneficial and thus frequently subscribed, but their effects appear to be relatively short-term and are therefore not fully sustainable.[7] As to invasive techniques, the holy grail has yet to be found as well. Arthroscopic lavage and debridement involve a surgical clean-up of the joint, but it looks like it only relieves symptoms temporarily.[6,7] A more promising technique appears to be found in the system of 'microfracturing' or 'icepicking', in which little perforations are made through the subchondral bone to provoke bleeding and gain access to the bone marrow, thereby stimulating growth factors and stem cells to form new tissue. However, results are solely proven to be favourable in small lesions and are therefore not suitable for most KOA-patients.[6,8] Other alternative invasive procedures including mosaicplasty, autologous chondrocyte implantation or scaffold treatment are upcoming innovative options for treating isolated cartilage lesions, but they also don't seem to be the perfect fit for resolving substantial KOA-damage as well.[9] In case of severe injury, physicians dare to skip the steps mentioned

above and opt for unilateral or total joint replacement right away, although this option is kind of a last resort, especially in younger, more active patients.

Therefore, current treatment modalities in mild to moderate KOA-cases are mainly focused on symptom control and functional status through prior behavioural and pharmacological interventions, combined with specific physical therapy including pain relief techniques, load management and strengthening exercises.[7] As supervised exercise therapy has proven to be the first line treatment of preference in tackling pain and disability caused by KOA, it should be promoted and facilitated.[10] Definitely for those patients suffering from KOA, but lacking the extent of structural degradation to be considered for arthroplastic joint replacement, the need for customized physical exercise in order to strengthen the lower limb muscles and prevent the weakened joint structures from being loaded excessively, is indisputable. By improving muscle force and functional performance, and reducing joint loading, respective exercise therapy has the ability to improve the patient's physical capacity and quality of life substantially.[10] However, this purpose of strength gain may seem inconsistent with the restrictions of the disease, since the muscle needs to be stressed with resisted exercises between 60-100% of 1 repetition maximum (1RM) in order to efficiently gain muscle strength.[11] This level of load is often not tolerable for KOA-patients, due to their lowered load bearing capacity and pain threshold.[12]

Nevertheless, strength training remains a crucial element and must be incorporated in the treatment plan of KOA despite its restrictions, as it has been proven to reduce pain, improve joint homeostasis and lower limb function.[10] It has been a challenge for clinicians to provide suitable physical therapy conform to these conflicting conditions, as pain-free exercises (being low-load exercises, <60% 1RM) don't trigger the muscles enough for significant strength gain, while high-load exercises are often too difficult to persevere. This requires an alternative technique, which could be found in blood flow restriction therapy (BFRT).

BFRT is an exercise therapy in which a pressurized cuff is applied to the proximal portion of the involved limb, combined with relatively low load exercises and short intervals in between sets. The external pressure applied aims to reduce arterial inflow whilst fully occluding venous outflow distal to the occlusion site.[13] Besides venous pooling and thus metabolite accumulation, this technique enhances an anaerobic environment in the muscle through a limited arterial oxygen supply and therefore creates localized hypoxia distal to the cuff. Consequently, it generates an accelerated fatigue of type I muscle fibres due to the increase of intramuscular metabolite accumulation which leads to the necessary activation of type II muscle fibres and its associated gain in muscular strength, mass and endurance.[14,15] It mimics the effects of heavy load training through metabolic stress instead of mechanical stress, which offers a unique advantage for a patient with KOA to still obtain the required muscle hypertrophy

and strength. On top of that, Bryk et al. (2016) investigated the difference between a low-load BFRT-program and a high-load conventional program in a population with KOA, which resulted in similar benefits in pain, function and quadriceps strength between both groups, but the BFRT-group experienced less anterior knee pain during training sessions. In summary, the additional effect of BFRT on muscular level has previously been described in multiple studies, but little is known about its specific effect on cartilage and bone tissue.[12,16] This is an interesting area to explore, since recent literature has indicated that BFRT could be beneficial to cartilage and bone tissue as well.

Articular cartilage is an avascular tissue composed of chondrocytes dispersed within an extracellular matrix.[2] These chondrocytes synthesize cartilage matrix and are nurtured through diffusion of intra-articular fluid, which is facilitated by compression of the cartilage or joint loading. Next to this need of compression, overall cartilage homeostasis is assumed to be a product of joint mechanics, growth factors, hormones and aging.[17] In case of injury, cartilage has a very slow turnover due to the lack of blood vessels, which makes spontaneous repair fairly difficult.[2,17] However, due to the characteristics of BFRT, the addition of a cuff allows for the induction of an hypoxic environment and causes an increased accumulation of metabolites in the cartilage. This generates a stress response, which leads to a release of hormones, such as insulin-like growth factor (IGF-1). IGF-1 has shown profound effects on chondrocyte biological behaviour and fundamentally regulates cartilage matrix metabolism during cartilage repair.[18] Firstly, IGF-1 contributes to the activation of the pathway that releases Hypoxia-Inducible Factor 1 alpha (HIF-1α). HIF-1α protects cartilage from inflammatory factors and anti-catabolic effects through suppression of catabolic genes such as matrix metalloproteinases (MMP13) and nuclear factor kappa B – integrin-like metallopeptidase (Nf-κB), thus reducing the progress of OAs.[19] Furthermore, Histone Methyltransferase Disruptor of Telomeric Silencing 1-like (DOT1L) is a master protector of cartilage health and is proven to be supressed in patients with OA. However, recent research has showed that hypoxia (HIF-1α) enhances DOT1L-expression, thereby possibly upregulating its protective effects.[20] Lastly, this pathway leads to chondrogenic differentiation of mesenchymal stem cells, proteoglycan synthesis in chondrocytes and chondrocyte proliferation, offering the potential for chondral regeneration.[18]

Bone tissue on the other hand is more dynamic and undergoes constant remodelling, allowing to repair itself when damaged.[21] Multiple mechanisms have been suggested explaining the possible pathways of bone synthesis stimulation. Comparable to HIF-1α on chondrocytes in cartilage, one possible mechanism covers the hypoxia-induced activation of HIF-1α, which leads to increased expression of vascular endothelial growth factor (VEGF), resulting in blood vessel growth and increased bone deposition.[19,22] Another mechanism is that BFRT generates venous occlusion, causing higher intramedullary pressure (ImP) and interstitial fluid flow (IFF)

in the bone, which proves to be an effective trigger for bone adaptation.[22] This boost in osteoblast function may be favourable for KOA-patients, as its deficient cartilage-function could eventually lead to painful subchondral bone marrow edema (BME), also labelled as bone marrow lesions (BML).[23,24] In this case too, research on the direct effect of BFRT on subchondral BME resorption has yet to be conducted. Therefore, this study aims to investigate the effect of BFRT on cartilage quality and BME-resorption within KOA-patients.

Based on preliminary evidence and recent research, this trial hypothesizes that next to its muscular benefits, BFRT might be able to improve subchondral BME-resorption and cartilage quality. This study aims to investigate to what extent these specific effects of BFRT may contribute to the case of KOA-patients.

METHODS

Study Setting

This study will take place at Ghent University Hospital, Belgium. Patients who are in treatment at the orthopaedics or rheumatology department will be recruited during the period of April 2024 to June 2024. Twenty-five patients, complying to the eligibility criteria, which can be found below, will be included in this RCT. The exercise protocol will be supervised by physiotherapists employed by the Ghent University Hospital, where outcome parameters also will be examined by a specialised team of radiologists, endocrinologists, orthopaedic surgeons and researchers in the domain of (K)OA. This study received approval by the Ethical Committee of the Ghent University Hospital (ONZ-2023-0192 AM01). The Guidelines for Interventional Trials (SPIRIT) were followed for the writing of this study protocol.[25]

Inclusion criteria

Patients will be enrolled if they report knee pain attributed to cartilage degeneration of non-traumatic origin. Individuals suffering from cartilage damage ranging from grade 1 – 3 according to the Kellgren Lawrence Scale (Table 1) can be included. [26] Both male and female participants will be eligible.

Table 1*: Kellgren Lawrence Scale*

Grade	*Radiologic Findings*
0	No joint space narrowing or reactive changes
I	Doubtful narrowing of joint space and possible osteophytic lipping
II	Definite osteophytes and possible narrowing of joint space
III	Moderate osteophytes, definite narrowing of joint space, some sclerosis, possible bone-end deformity
IV	Large osteophytes, marked narrowing of joint space, severe sclerosis, and definite deformity of bone ends

Exclusion criteria

Patients will be excluded for the study if they show no pain; had previous knee surgery in the last 10 years; show grade 4 cartilage degeneration according to the Kellgren Lawrence Scale (Table 1); have a biomechanical axis deviation in the frontal plane >10°; have a knee-extension deficit >5°; have a BMI>30; have a history of DVT, lung embolism or rhabdomyolysis; suffer any metabolic or neurological condition; have rheumatoid arthritis or any other rheumatoid conditions; have chondrocalcinosis; are receiving hormone therapy; are <45 years old or take (anti-) bone resorbing medication.

Interventions

Eligible participants will be divided into two groups: a control group and an intervention group. The control group will complete a standard of care rehabilitation process, while the intervention group will complete the exact same rehabilitation protocol, but with an additional pressurized cuff, applied to the proximal thigh of the affected leg to initiate blood flow restriction. Limb Occlusion Pressure (LOP) is the needed pressure to fully occlude both arterial inflow and venous outflow. During the first week of the protocol, the cuff in this study will be inflated to the point of 60% of individual LOP, which fully occludes venous blood flow but only partially restricts arterial blood flow. Starting from week two until the end of the protocol, the cuff will be inflated to the point of 80% of individual LOP. This allows both the control leg within the intervention group and the control group itself to serve as comparators for the intervention applied to the affected leg. All participants will exercise twice a week over a twelve-week period resulting in a total of 24 sessions. These sessions will involve low load strength training and aerobic training (cycling). The used Exercise Protocol can be found in the additional file. This study aims to examine if BFR can also promote bone and cartilage tissue synthesis and load bearing capacity.

The intervention will be administered by physiotherapists affiliated with the Ghent University Hospital who are accustomed to work with study participants, given the institutions' frequent involvement in clinical trials. Profound briefing by the research team will establish thorough understanding about all details and guidelines of the trial. The physiotherapist present will instruct and guide the participants through the protocol providing feedback whenever relevant. Their continuous presence during the trial will ensure consistent follow up.

Outcomes

Peripheral Quantitative Computed Tomography (pQCT)

Peripheral Quantitative Computed Tomography provides an automatic scan analysis of trabecular and cortical bone compartments, calculating not only their bone mineral density (BMD), but also bone geometrical parameters, such as marrow and cortical Cross-Sectional Area (CSA), Cortical Thickness (CoTh), both periosteal and endosteal circumference, as well as biomechanical parameters like Cross Sectional Moment of Inertia (CSMI), a measure of bending, polar moment of inertia, indicating bone strength in torsion, and Strength Strain Index (SSI). Also, CSA of muscle and fat can be extracted. Muscles, which are thought to stimulate bones to adapt their geometry and mineral content, are determinant to preserve or increase bone strength; thus, pQCT provides an evaluation of the functional ‘muscle-bone unit’, defined as BMC/muscle CSA ratio.[27] This pQCT measurement will be conducted using the bone densitometry device of the department of endocrinology of the Ghent University Hospital, which will also carry out blood serum analysis for the evaluation of bone marker concentration.

Blood serum analysis

In order to objectify bone marker concentration, patients will be submitted to blood serum analysis. Both C-terminal telopeptide of type I collagen (CTX-1) and procollagen type I N-terminal propeptide (P1NP) will be assessed for bone resorption and bone formation, respectively. According to the study by Eastell et al. (2017), CTX-1 reflects the degradation of type I collagen, the main protein in bone matrix, providing a reliable indicator of bone resorption activity. Elevated levels of CTX-1 indicate increased bone resorption. On the other hand, P1NP reflects the synthesis of type I collagen, serving as a direct marker of bone formation activity. Higher P1NP levels suggest increased bone formation, which is important for maintaining bone health and density. Eastell et al. (2017) also stated that samples for CTX-I must be collected consistently in the morning hours in the fasted state. EDTA plasma – blood plasma that has been treated with the anticoagulant ethylenediaminetetraacetic acid (EDTA) – is preferred for CTX-I for its greater sample stability. Sample collection conditions for P1NP are less critical as P1NP has minimal circadian variability and is not affected by food intake. Measuring both CTX-1 and P1NP, will gain comprehensive insights into the dynamic balance between bone resorption and formation, allowing for more accurate assessment of the impact of Blood Flow Restriction training on bone turnover, as a surrogate for bone quality.

Multi-sequence Magnetic Resonance Imaging (MRI)

The intent of the MRI examination is to map the presence and extent of subchondral edema as well as cartilage structure and composition. During this procedure, Double Echo Steady State (DESS), Dixon and T2-weighted sequences will be run. DESS provides images with high contrast between cartilage and fluids. It has the advantage to combine morphological and quantitative analysis of cartilage from the same dataset with high resolution, and the imaging time is relatively short.[28] To evaluate subchondral bone marrow edema, Dixon sequences will be used. As seen in the study by Chen et al. (2022), these sequences highlight the fat-water separation. T2 mapping uses intrinsic cartilage water as a probe to study the structural integrity of the extracellular matrix. Because of its central role in the biomechanical properties of cartilage, water is an ideal biomarker of cartilage damage.[29]

The described outcome measures make it possible to evaluate bone and cartilage health and quality. These outcome measures will be collected prior to, and immediately after the 12-week rehabilitation period. (Figure 1) By comparing the differences in BMD, bone marker concentration, subchondral edema and cartilage quality (structure and composition) between groups, also taking time into account (differences between first and second scan), this study wants to verify whether BFR can do more than amplifying muscular responses to strength training by also promoting bone and cartilage tissue synthesis and load bearing capacity. If so,

BFR might be applied in various rehabilitation and prevention training settings looking to promote bone and cartilage health and to prevent lower limb osteoarthritis.

Participant timeline

Participants will be recruited in the period from April 2024 to June 2024 and, if meeting the inclusion criteria, will be included in the study. Starting in May 2024, at the beginning of the intervention, pQCT, blood serum analysis and an MRI scan will be conducted. The anticipated termination of the study is projected for August 2024, at which point the same outcome measures will be retaken. Afterwards, all collected data will be statistically analysed with the creation of the RCT article following, as is shown in Figure 1 below.

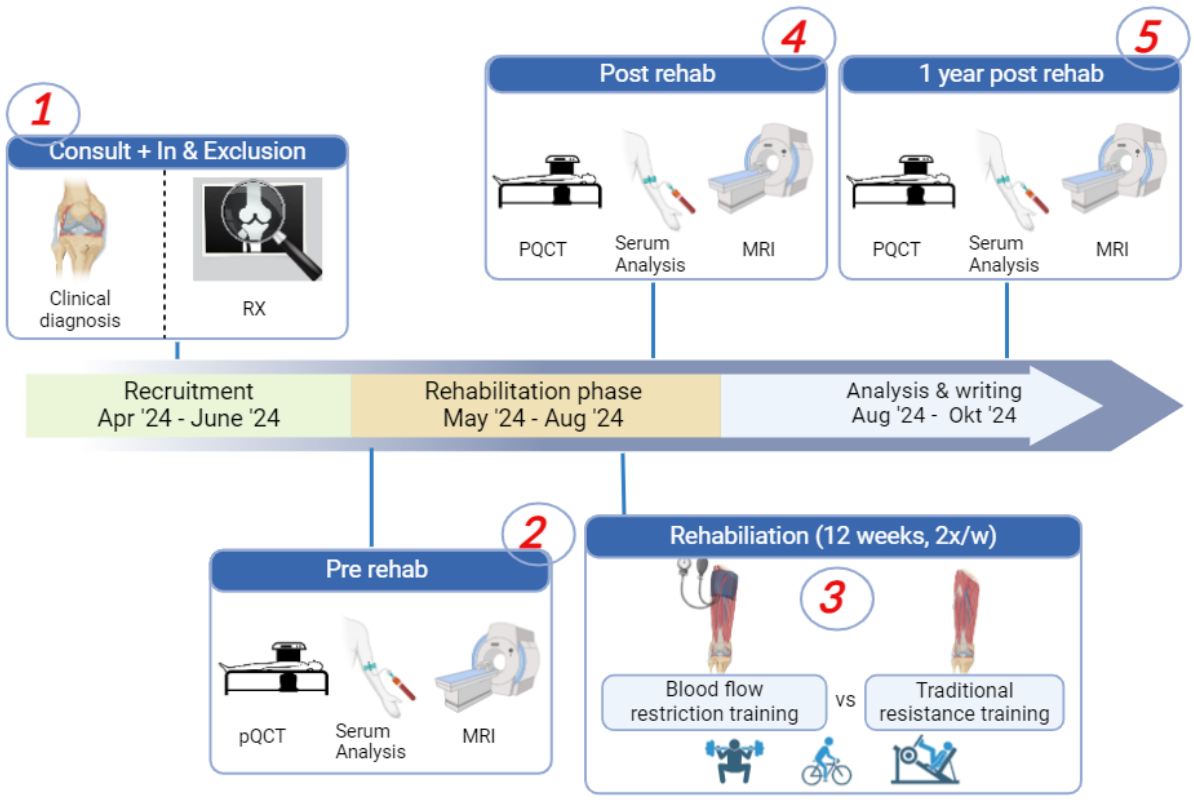


***Figure 1**: Participant Timeline*

Sample Size

Previous research conducting a twelve-week intervention of low load resistance training combined with BFR (LL-BFR) compared with low load resistance training without the use of BFR (LL-RT) found significant increases in bone turnover markers such as P1NP and CTX-1. That study enrolled 26 participants divided into four groups. Based on those findings, 25 patients divided over two groups would yield sufficient power to detect statistically significant differences between a control LLRT and experimental LL-BFR group for this RCT.[30]

Recruitment

Twenty-five patients will be recruited at the orthopaedics and/or rheumatology department of Ghent University Hospital. When a patient meets the eligibility criteria, according to the orthopaedist or rheumatologist, the informed consent will be presented for signature. If the patient agrees, the following imaging will be done: a bilateral full leg RX, FACE, profile and Schuss image. If the patient still meets the predetermined criteria after this, the patient will be definitively included in the study.

Allocation

Eligible participants will randomly be allocated in a 1:1 ratio, considering gender (female, male, X) and degree of knee osteoarthritis (grade 1-3), using computer-generated blocks ranging from 3-5. The randomization sequence is created by a biostatistician. Allocation will be concealed using password-protected software (REDCap, version 13.7.30), accessible only to the trial coordinator. Following randomization, the trial coordinator will disclose patient allocation to the treating physiotherapists, who conduct exercise sessions for both trial groups to maintain consistency in treatment quality. The study will employ single blinding, with outcome assessors unaware of the randomization process, although participant masking is not feasible due to the intervention's nature. However, patients remain unaware of the trial hypotheses. Participants will be randomized into either a control group receiving standard low-intensity strength training or an experimental group receiving the same training with the additional application of blood flow restriction via pressurized cuffs.

Statistical methods

Statistical analyses will be performed using the Statistical Package for the Social Sciences (SPSS V.28, IBM). Descriptive statistics will be utilized to present subject characteristics for both the control and experimental groups. Normality of the data will be assessed using the Shapiro-Wilk test, histograms, and Q-Q plots. The significance level will be set at $\alpha = 0.05$. Baseline characteristics will be assessed using linear mixed models analysis, which will subsequently be employed to examine the effects of the intervention with or without BFR and the progression over time (pre / post intervention) on P1NP, CTX-1, pQCT and MRI-imaging. In the models, participants will be included as a random factor, with time and randomization group serving as fixed predictors. Post hoc analyses, investigating differences in mean changes in P1NP, CTX-1, pQCT and MRI, will be conducted using Bonferroni corrections.

DISCUSSION

To the best of our knowledge, this RCT will be the first to investigate the potential benefits of BFRT on cartilage and bone tissue in KOA patients. This study aims to examine the contribution of BFRT to the treatment of KOA by comparing outcomes between a control group and a BFRT intervention group.

In line with existing literature suggesting the beneficial effects of a hypoxic environment on cartilage and bone tissue, this study is the first to hypothesize that BFRT may induce a similar hypoxic environment in the knee joint, leading to improved outcomes in cartilage and bone health among KOA patients. Additionally, BFRT induces hypertrophy and an increase in muscle strength, leading to improved joint relief. These physiological responses contribute to enhanced outcomes with BFRT.

Physical therapy utilizing BFRT may have a positive impact and simultaneously is unlikely to cause harm. Based on the available literature, BFRT appears to be a safe exercise modality when used according to evidence based guidelines. In their study in 2006, Nakajima and colleagues reported serious adverse event rates of 0.055%, 0.008% and 0.008% for deep vein thrombosis (DVT), pulmonary embolism (PE) and rhabdomyolysis, respectively. Furthermore, research investigating blood coagulation factors following BFR training in elderly individuals has not shown any adverse effects. Three studies, involving participants aged between 61 and 85 years, have examined both lower and upper extremities BFR training.[31,32,33] Additionally, a study focused on BFR-RE in an elderly clinical population with ischemic heart disease found no increase in blood coagulation factors.[34] Nevertheless, a thorough screening remains primordial to screen for possible risk factors for severe adverse events such as DVT's.

Based on preliminary evidence, this study hypothesises that the use of BFRT might be an innovational asset to optimize both functional outcome as well as more fundamental degenerative characteristics. This way of treatment might be suitable for those who are not (yet) eligible for invasive interventions but nonetheless experience significant symptoms and perceive conventional exercise therapy to be inadequate or too painful. Given the multifaceted nature of KOA, it remains important to recognize that BFRT should always be part of a broader treatment plan including other individual modalities such as pharmacotherapy, education, physical therapy and lifestyle modifications in order to optimize suitable outcomes in KOA patients.

This study has multiple strengths. The first one being the inclusion of pre- and post-intervention measurements which allows for a longitudinal study design, advantageous for observing changes over the twelve-week period, which is longer than other similar conducted studies on the use of BFR in rehabilitation settings and contributes to the evidence base supporting the

effectiveness of the intervention. The use of objective outcome parameters such as pQCT and bloodserum analysis reduces the likelihood of inducing any reporting bias. Objective outcome parameters lead to more reliable and correct data interpretation. These offer a broad range of measurements providing a thorough view of various aspects of the musculoskeletal system showing a detailed evaluation of the bone and cartilage health.

Opposed to the previous described parameters is the use of MRI interpretations a less objective data collection process as MRI findings are more subjective and reliant on the expertise of the radiologists, which may affect the reliability of those findings. This study may further have some limitations using a rather small sample size of twenty-five participants. This lowers the statistical power of the study and makes it more challenging to detect significant differences between the intervention and control groups. At last, it's not possible to blind the participants for group allocation since the intervention is rather obvious; individuals always know whether they'll need to use a cuff. This challenge is mitigated by their unawareness to the hypothesis of the study, which eliminates any possible performance bias. Participants' knowledge of their allocation doesn't prompt them to alter their expectations of- and adherence to the study, thereby minimizing the risk of augmenting or decreasing any possible findings during the trial.

This study will hopefully stimulate further investigation into the potential of BFRT in the management of KOA and inspire future studies to elucidate its mechanisms of action and optimize its clinical application.

REFERENCES

1. World Health Organization: WHO & World Health Organization: WHO. (2023, 14 July). *Osteoarthritis*. https://www.who.int/news-room/fact-sheets/detail/osteoarthritis#:~:text=With%20a%20prevalence%20of%20365,benefit%20from%20rehabilitation%20(3).
2. Martel-Pelletier, J., Boileau, C., Pelletier, J., & Roughley, P. J. (2008). Cartilage in normal and osteoarthritis conditions. *Best Practice & Research Clinical Rheumatology*, *22*(2), 351–384. https://doi.org/10.1016/j.berh.2008.02.001
3. Long, H., Liu, Q., Yin, H., Wang, K., Diao, N., Zhang, Y., Lin, J., & Ai, G. (2022b). Prevalence trends of Site-Specific osteoarthritis from 1990 to 2019: Findings from the Global Burden of Disease Study 2019. *Arthritis & Rheumatology*, *74*(7), 1172–1183. https://doi.org/10.1002/art.42089
4. Mora, J. C., Przkora, R., & Cruz-Almeida, Y. (2018). Knee osteoarthritis: Pathophysiology and current treatment modalities. *Journal of Pain Research*, *Volume 11*, 2189–2196. https://doi.org/10.2147/jpr.s154002
5. Durau, J., Diehl, S., & Terlutter, R. (2022). Motivate me to exercise with you: The effects of social media fitness influencers on users' intentions to engage in physical activity and the role of user gender. *DIGITAL HEALTH*, *8*, 205520762211027. https://doi.org/10.1177/20552076221102769
6. Vaquero, J., & Forriol, F. (2012). Knee chondral injuries: Clinical treatment strategies and experimental models. *Injury-International Journal Of The Care Of The Injured*, *43*(6), 694–705. https://doi.org/10.1016/j.injury.2011.06.033
7. American Academy of Orthopaedic Surgeons Management of Osteoarthritis of the Knee (NonArthroplasty) Evidence-Based Clinical Practice Guideline. https://www.aaos.org/globalassets/quality-and-practice-resources/osteoarthritis-of-the-knee/oak3cpg.pdf
8. Bekkers, J., Inklaar, M., & Saris, D. B. (2009). Treatment Selection in Articular Cartilage Lesions of the Knee. *The American Journal Of Sports Medicine*, *37*(1_suppl), 148–155. https://doi.org/10.1177/0363546509351143
9. Bedi, A., Feeley, B. T., & Williams, R. J. (2010). Management of Articular Cartilage Defects of the Knee. *Journal Of Bone And Joint Surgery. American Volume/The Journal Of Bone And Joint Surgery. American Volume*, *92*(4), 994–1009. https://doi.org/10.2106/jbjs.i.00895
10. Xu, C., Nie, Y., Tan, C., Zeng, Y., Si, H., Zhou, Z., Shen, B., Song, W., & Li, K. (2021). Role of lower limb muscle strength in knee osteoarthritis progression for patients with

mild and moderate knee osteoarthritis. *American Journal of Physical Medicine & Rehabilitation*, *101*(5), 433–438. https://doi.org/10.1097/phm.0000000000001843

11. Stand, P. (2009). Progression Models in Resistance Training for Healthy Adults. Medicine and Science in Sports and Exercise, 41(3), 687–708. https://doi.org/10.1249/mss.0b013e3181915670
12. Bryk, F. F., Reis, A. C. D., Fingerhut, D., Araujo, T., Schutzer, M., De Paula Leite Cury, R., Duarte, A., & Fukuda, T. Y. (2016). Exercises with partial vascular occlusion in patients with knee osteoarthritis: a randomized clinical trial. *Knee Surgery, Sports Traumatology, Arthroscopy*, *24*(5), 1580–1586. https://doi.org/10.1007/s00167-016-4064-7
13. Pope, Z., Willardson, J. M., & Schoenfeld, B. J. (2013). Exercise and Blood Flow Restriction. Journal of Strength and Conditioning Research, 27(10), 2914–2926. https://doi.org/10.1519/jsc.0b013e3182874721
14. Wernbom, M., Augustsson, J., & Raastad, T. (2008). Ischemic strength training: a lowload alternative to heavy resistance exercise? Scandinavian Journal of Medicine & Science in Sports, 18(4), 401–416. https://doi.org/10.1111/j.1600-0838.2008.00788.x
15. DePhillipo, N. N., Kennedy, M. I., Aman, Z. M., Bernhardson, A. S., O'Brien, L., & LaPrade, R. F. (2018). Blood Flow Restriction Therapy After Knee Surgery: Indications, Safety Considerations, and Postoperative Protocol. Arthroscopy techniques, 7(10), e1037–e1043. https://doi.org/10.1016/j.eats.2018.06.010
16. Cohen, M., Komatsu, W. R., De Freitas, M. S., De Melo, M. E. V., & De Melo, R. F. V. (2022). Comparison of quadriceps and hamstring muscle strength after exercises with and without blood flow restriction following anterior cruciate ligament surgery: a randomized controlled trial. *Journal of Rehabilitation Medicine*, *54*, jrm00337. https://doi.org/10.2340/jrm.v54.2550
17. Mollon, B., Kandel, R., Chahal, J., & Theodoropoulos, J. (2013). The clinical status of cartilage tissue regeneration in humans. *Osteoarthritis And Cartilage*, *21*(12), 1824–1833. https://doi.org/10.1016/j.joca.2013.08.024
18. Wen, C., Xu, L., Xu, X., Wang, D., Liang, Y., & Duan, L. (2021). Insulin-like growth factor-1 in articular cartilage repair for osteoarthritis treatment. *Arthritis Research & Therapy, 23*(1), 277. https://doi.org/10.1186/s13075-021-02662-0
19. Fu, L., Zhang, L., Zhang, X., Chen, L., Cai, Q., & Yang, X. (2021). Roles of oxygen level and hypoxia-inducible factor signaling pathway in cartilage, bone and osteochondral tissue engineering. *Biomedical Materials, 16*(2), 022006. https://doi.org/10.1088/1748-605X/abdb73

20. A, D. R., Núñez, A. E., Cornelis, F., Cherifi, C., Casas-Fraile, L., Sermon, A., Cailotto, F., Lories, R., & Monteagudo, S. (2021). Hypoxia induces DOT1L in articular cartilage to protect against osteoarthritis. *JCI Insight*, *6*(24). https://doi.org/10.1172/jci.insight.150451
21. Florêncio-Silva, R., Da Silva Sasso, G. R., Sasso-Cerri, E., De Jesus Simões, M., & Cerri, P. S. (2015). Biology of Bone Tissue: Structure, Function, and Factors That Influence Bone Cells. *BioMed Research International*, *2015*, 1–17. https://doi.org/10.1155/2015/421746
22. Bittar, S. T., Pfeiffer, P., De Pontes Santos, H. B., & Cirilo-Sousa, M. D. S. (2018). Effects of blood flow restriction exercises on bone Metabolism: A Systematic review. *Clinical Physiology and Functional Imaging*, *38*(6), 930–935. https://doi.org/10.1111/cpf.12512
23. Felson, D. T., McLaughlin, S., Goggins, J., LaValley, M. P., Gale, M. E., Tötterman, S., Li, W., Hill, C., & Gale, D. (2003). Bone marrow edema and its relation to progression of knee osteoarthritis. *Annals of Internal Medicine*, *139*(5_Part_1), 330. https://doi.org/10.7326/0003-4819-139-5_part_1-200309020-00008
24. Manara, M. C., & Varenna, M. (2014). A clinical overview of bone marrow edema. *Reumatismo*, *66*(2), 184–196. https://doi.org/10.4081/reumatismo.2014.790
25. Chan, A. W., Tetzlaff, J. M., Gøtzsche, P. C., Altman, D. G., Mann, H., Berlin, J. A., et al. (2013). SPIRIT 2013 explanation and elaboration: Guidance for protocols of clinical trials. BMJ. https://www.bmj.com/content/346/bmj.e7586
26. Kohn, M. D., Sassoon, A. A., & Fernando, N. D. (2016). Classifications in Brief: Kellgren-Lawrence Classification of Osteoarthritis. Clinical orthopaedics and related research, 474(8), 1886–1893. https://doi.org/10.1007/s11999-016-4732-4
27. Stagi, S., Cavalli, L., Cavalli, T., de Martino, M., & Brandi, M. L. (2016). Peripheral quantitative computed tomography (pQCT) for the assessment of bone strength in most of bone affecting conditions in developmental age: a review. *Italian Journal of Pediatrics*, 42(1), 88. https://doi.org/10.1186/s13052-016-0297-9.
28. Väärälä, A., Casula, V., Peuna, A., Panfilov, E., Mobasheri, A., Haapea, M., Lammentausta, E., & Nieminen, M. T. (2022). Predicting osteoarthritis onset and progression with 3D texture analysis of cartilage MRI DESS: 6-Year data from osteoarthritis initiative. *Journal of Orthopaedic Research*. Advance online publication. https://doi.org/10.1002/jor.25293
29. Mosher TJ, Dardzinski BJ. Cartilage MRI T2 relaxation time mapping: overview and applications. *Semin Musculoskelet Radiol.* 2004 Dec;8(4):355-68. https://doi: 10.1055/s-2004-861764. PMID: 15643574.
30. Linero, C., & Choi, S. J. (2021). Effect of blood flow restriction during low-intensity resistance training on bone markers and physical functions in postmenopausal

women. Journal of exercise science and fitness, 19(1), 57–65. https://doi.org/10.1016/j.jesf.2020.09.001

31. Fry CS, Glynn EL, Drummond MJ, et al. Blood flow restriction exercise stimulates mTORC1 signaling and muscle protein synthesis in older men. *Journal of applied physiology* (Bethesda, Md: 1985). May 2010;108(5):1199-209. https://doi:10.1152/japplphysiol.01266.2009
32. Yasuda T, Fukumura K, Iida H, Nakajima T. Effects of detraining after blood flow-restricted low-load elastic band training on muscle size and arterial stiffness in older women. Springerplus. 2015; 4:348. https://doi:10.1186/s40064-015-1132-2
33. Yasuda T, Fukumura K, Uchida Y, et al. Effects of Low-Load, Elastic Band Resistance Training Combined With Blood Flow Restriction on Muscle Size and Arterial Stiffness in Older Adults. J Gerontol A Biol Sci Med Sci. Aug 2015;70(8):950-8. https://doi:10.1093/gerona/glu084
34. Madarame H, Kurano M, Takano H, et al. Effects of low-intensity resistance exercise with blood flow restriction on coagulation system in healthy subjects. Clinical physiology and functional imaging. May 2010;30(3):210-3. https://doi:10.1111/j.1475-097X.2010.00927

ABSTRACT IN LEKENTAAL

Introductie/achtergrond:

Knieartrose (KOA) is een veel voorkomende, chronische, degeneratieve gewrichtsaandoening die wordt gekenmerkt door slijtage van gewrichtskraakbeen en onderliggend bot. Het veroorzaakt pijn, zwelling en gewrichtsstijfheid en leidt tot minder goed functioneren en een lagere kwaliteit van leven. De huidige behandeling is voornamelijk gericht op symptoombeheersing en behoud van functionele capaciteiten door middel van medicatie en levensstijladvies, gecombineerd met specifieke krachttraining. Deze krachttraining (zijnde oefeningen met hoge belasting) is echter in sommige gevallen niet te verdragen voor KOA-patiënten vanwege een verminderde gewrichtsbelastbaarheid en een verlaagde pijngrens. Blood flow restriction therapie (BFRT: hierbij plaatst men een opgeblazen manchet rond een lidmaat en voert men terwijl oefeningen met lage belasting uit) kan dit probleem omzeilen, aangezien deze therapie hetzelfde trainingseffect van oefeningen met hoge belasting op de spieren kan nabootsen, zonder het gewricht te overbelasten. Deze studie heeft het doel om, naast het effect op spierniveau, de specifieke effecten van BFRT op aangetast kraakbeen- en botweefsel bij KOA-patiënten te onderzoeken.

Methode/design:

Dit is een onderzoeksprotocol voor een studie met 25 participanten die jonger zijn dan 45 jaar. Individuen die aan de controlegroep worden toegewezen, zullen een oefenprogramma van twaalf weken volmaken, waarbij oefeningen met lage belasting worden gecombineerd met fietsen. Voor zowel de controlegroep als de interventiegroep zal hetzelfde oefenprogramma gebruikt worden, al is dit bij de interventiegroep mét BFRT.

Uitkomstparameters zullen via verschillende scans en een bloedanalyse gemeten worden en zullen vóór aanvang en na het einde van de interventieperiode afgenomen worden om zo het verschil in kraakbeen- en botkwaliteit in kaart te brengen.

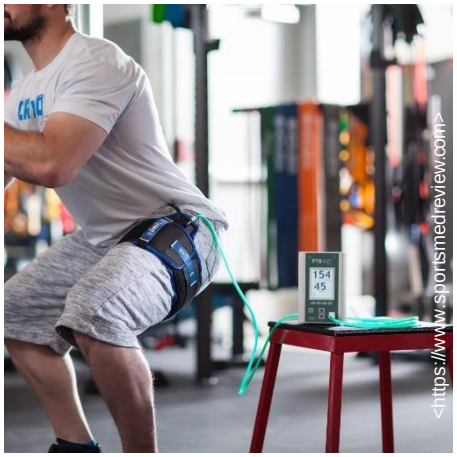
Discussie:

Wanneer deze studie significante resultaten op kraakbeen- en botniveau oplevert, zou het gebruik van BFR bij de behandeling van knieartrose als een nuttige interventie beschouwd moeten worden, zeker voor die personen die niet in aanmerking komen voor chirurgische ingrepen maar ook geen hoge belastingen kunnen verdragen.

Sleutelwoorden:

Protocol; knieartrose; bloedstroombeperking; kraakbeen; subchondraal botoedeem

POPULARISERENDE SAMENVATTING VAN HET ONDERZOEK



Knieartrose is een vaak voorkomende, chronische aandoening die wereldwijd miljoenen mensen treft. Ze wordt gekenmerkt door een aftakelingsproces van kraakbeen en onderliggend bot in het kniegewricht. Ze veroorzaakt pijn, zwelling en gewrichtsstijfheid, wat bijgevolg een negatieve invloed heeft op het dagelijks functioneren en de kwaliteit van leven van patiënten. De huidige behandeling is voornamelijk gericht op het bestrijden van bovengenoemde symptomen. Dit gebeurt enerzijds via educatie en levensstijladvies, om de patiënt te begeleiden in het leren omgaan met klachten, en anderzijds door middel van pijnstillende medicatie en specifieke krachttraining om klachten te verminderen. In het geval van ernstige schade kan geopteerd worden voor operatieve ingrepen (vb. knieprothese), maar lang niet elke knieartrose-patiënt met klachten komt hiervoor in aanmerking. Daarom wordt er vooral ingezet op conservatieve interventies, maar ondanks ze in de internationale behandelingsrichtlijnen van knie-artrose aangeraden worden, blijken ze niet voor iedere patiënt te werken of lijken de effecten eerder van korte duur. Ook het luik van krachttraining is geen evidentie voor patiënten, aangezien oefentherapie regelmatig ervaren wordt als te belastend voor het pijnlijk gewricht. Kortom, er is nog ruimte voor verbetering in het behandelingsprotocol van knieartrose.

Een innovatieve behandelingsoptie die de laatste jaren steeds vaker in de belangstelling staat, is Blood Flow Restriction Training (BFRT). Bij deze trainingsvorm wordt er een manchet bovenaan het te behandelen lidmaat bevestigd, die opgeblazen wordt tot een bepaald punt waarop de bloedtoevoer naar de spieren tijdelijk deels verminderd wordt. Hierdoor kan men oefeningen uitvoeren met lichtere gewichten, maar worden de spieren even hard geprikkeld alsof je met zware gewichten zou werken. Het immense voordeel van BFRT is dat trainen met deze lichtere gewichten een veel kleinere belasting op het gewricht met zich meebrengt, en tegelijkertijd toch voor een winst aan spierkracht kan zorgen. Dit wil zeggen dat BFRT een uitstekende behandeloptie kan zijn in die gevallen waarin het gewricht versterkt moet worden, maar niet goed reageert op te hoge belastingen, net zoals bij knie-artrose.

De hypothese van dit onderzoek stelt dat BFRT, naast het positief effect op spieropbouw, ook een positieve invloed heeft op de kwaliteit van gewrichtskraakbeen en bot. In dit onderzoek zal een groep van 25 personen met knieartrose opgesplitst worden in twee deelgroepen. Beide groepen zullen twaalf weken lang hetzelfde krachtschema met lage belasting uitvoeren, al dan niet met BFRT. Zo hopen wij, na vergelijking van bloedanalyses, MRI- en CT-scans voor en na de interventie, een positief effect van BFRT op kraakbeen en bot te kunnen aantonen.

MAATSCHAPPELIJKE MEERWAARDE/IMPACT VAN HET ONDERZOEK

Aangezien BFRT naast de voordelen op spierniveau ook positieve effecten kan hebben op kraakbeen en bot, draagt dit onderzoek in grote mate bij tot het efficiënter aanbieden van geschikte behandelopties bij patiënten met KOA. BFRT kan op deze manier leiden tot een verbeterde levenskwaliteit door o.a. het verminderen van pijn, het bevorderen van de zelfstandigheid en een algemene functionele optimalisatie van de patiënt. Dankzij de nieuwe inzichten van deze innovatieve behandeloptie kunnen heel wat medicatie- en ziekenhuiskosten vermeden worden en vormt dit onderzoek een belangrijk onderdeel in de kostenbesparing binnen onze gezondheidszorg. Verder kunnen vroegtijdige interventies met BFRT ertoe bijdragen de progressie van KOA te vertragen en zo mogelijke invaliditeit te voorkomen. Dit leidt op zijn beurt tot een kleinere populatie aan arbeidsongeschikte patiënten en een hogere tewerkstelling van patiënten in behandeling. KOA is een veelvoorkomende aandoening, deels omwille van de vergrijzende bevolking. Mede dankzij deze behandelmogelijkheid kan er getimmerd worden aan een kwaliteitsvolle zorg voor onze ouderen. Om deze redenen is het van groot belang het bewustzijn rond KOA en haar behandelopties bij zowel (para)medici als patiënten te verhogen. Dit interventiegebied biedt nog tal van opties voor verder onderzoek. Deze studie kan alvast bijdragen tot een betere en completere zorg binnen de wereld van KOA.

BEWIJS GOEDKEURING VAN HET ETHISCH COMITÉ

Afzender: Commissie voor medische ethiek

Prof. dr. Jan Victor
Orthopedie en Traumatologie
UZ Gent

contact	telefoon	e-mail
Commissie voor medische ethiek	+32 (0)9 332 33 36	Ethisch.comite@uzgent.be
Aanvrager	**datum**	**pagina**
Ewoud Jacobs	27/03/2024	1/6
Referentie hoofdstudie	**EudraCT-nr:**	**Belg. Regnr:**
ONZ-2023-0192		B6702023000776

Betreft:
Effecten van implementatie van partiele vasculaire occlusie voor herstel van botoedeem, kraakbeenkwaliteit en botdensiteit in functie van preventie van gonartrose. Een gerandomiseerde klinische studie.
Effects of blood flow restriction implementation on bone marrow edema, cartilage quality recovery and bone mineral density in patients with knee osteoarthritis. A randomized clinical trial.

Wijziging / toevoegen studiedocumenten
Amendement nr: #ONZ-2023-0192 AM01 dd. 14-Feb-2024

Beste collega

De Commissie Medische Ethiek (CME) verbonden aan de Universiteit Gent (Ugent) en het Universitair Ziekenhuis Gent (UZ Gent) heeft op 30/01/2024in eerste instantie een positief advies gegeven voor bovenvermeld protocol.

Een gunstig advies voor deze wijziging werd gegeven op 27/03/2024.

Ingediende documenten: zie bijlage 1
Ledenlijst: zie Bijlage 2
Aandachtspunten: zie Bijlage 3a

Met vriendelijke groeten,

Prof. dr. Renaat Peleman
Voorzitter
Commissie voor Medische Ethiek U(Z) Gent

ALGEMENE DIRECTIE
Commissie voor Medische Ethiek

VOORZITTER:
Prof. dr. R. Peleman

SECRETARIS:
Dr. L. Goossens

INGANG 75
ROUTE 7522

CC: FAGG
Cc: HIRUZ_CTU (Clinical Trial Center UZ Gent)

Unofficial translation in English:

Modification/additional study documents

Amendment-id: ONZ-2023-0192 AM01 dd. 14-Feb-2024

The Ethics committee (EC) of Ghent University Hospital (UZ Gent) has initially given a positive advice for the above mentioned protocol on 30/01/2024.

A favorable advice for this modification was given on 27/03/2024.

Submitted documents: see Annex 1
List of members: see appendix 2
Points of concern: see appendix 3b

Bijlage 1: Documenten

Categorie: Informatie- en toestemmingsformulier
- clean versie, versie 4.0 dd. 14/02/2024 (NL)
- track changes versie, versie 4.0 dd. 14/02/2024 (NL)

Categorie: Protocol
- schema procedures, versie 1.0 dd. 14/02/2024 (NL)

Bijlage 2: Overzicht leden CME U(Z) Gent

voorzitter: Prof. dr. R. Peleman
Secretaris: Dr. L. Goossens

Effectief lid	Plaatsvervangend lid
Prof. dr. G. Van Lancker UZ Gent - klinisch farmacoloog, ♀	Prof. dr. S. Rottey UZ Gent - klinisch farmacoloog, ♀
Prof. dr. D. De Bacquer Ugent - statisticus, ♂	Prof. dr. P. Coorevits Ugent - statisticus, ♂
Dr. M. Cosyns Extern - huisarts, ♂	Dr. J. Matthys Extern - huisarts, ♂
Dr. J. Van Elsen Extern – huisarts ♂	Dr. J. Matthys Extern – huisarts, , ♂
Prof. dr. K. De Groote UZ Gent - kindercardioloog, ♀	Dr. P. De Bruyne UZ Gent - kinder gastro-enteroloog, ♀
Prof. dr. W. Notebaert UGent - psycholoog, ♂	Dhr. W. Schrauwen UGent - psycholoog, ♂
Mevr. R. Vrielynck UZ Gent - verpleegkundige, ♀	Mevr. A. Charles UZ Gent - verpleegkundige, ♀
Dhr. C. Demeestere UZ Gent - verpleegkundige, ♂	Dhr. G. De Smet UZ Gent - verpleegkundige, ♂
Apr. K. Kint UZ Gent - apotheker, ♀	Apr. L. Huys UZ Gent - apotheker, ♀
Dhr. B. Vanderhaegen UZ Gent - Ethicus, ♂	Dhr. K. Raus UZ Gent - Ethicus, ♂
Prof. dr. T. Goffin UGent - jurist, ♂	Mevr. V. Vanscheewijck UGent - jurist, ♀
Mevr. C. Van Caeneghem extern - patiëntvertegenwoordiger, ♀	Mevr. S. Degroote extern - patiëntvertegenwoordiger, ♀
Prof. dr. W. Van Biesen UZ Gent - nefroloog, ♂	Dr. A. Beyens UZ Gent - geneticus, ♀
Prof. dr. R. Peleman UZ Gent - internist en pneumoloog, ♂	Dr. L. Goossens UZ Gent - neonatoloog, ♀
Dr. T. Martens UZ Gent - hartchirurg, ♂	Dr. H. Eker UZ Gent - algemene en hepatobiliaire chirurg, ♂
Dr. L. Dhaenens UZ Gent - fertiliteitsarts, ♀	Dr. I. Dehaene UZ Gent - verloskunde, ♀
Dr. R. Van Der Looven UZ Gent - kinderrevalidatie, ♀	Dr. M. Neckebroek UZ Gent - anesthesist, ♀
Dr. E. Schoentjes UZ Gent - [kinder - jeugd]psychiater, ♂	Prof. dr. K. Dhondt UZ Gent - [kinder - jeugd]psychiater, ♀

Appendix 3a: Aandachtspunten (indien van toepassing)

De wijzigingen in de ICF moeten duidelijk aan de patiënt worden gecommuniceerd.
Wij willen u erop wijzen dat het bij wijzigingen aan de ICF ten zeerste wordt aangeraden om een ICF-addendum te gebruiken voor lopende deelnemers. Het ICF-addendum vermeldt alleen de wijzigingen of nieuwe informatie die voor de deelnemer duidelijker zijn dan een gewijzigde ICF waar wijzigingen worden gemarkeerd. Wanneer de inclusie nog gaande is, is een aangepaste ICF vereist voor nieuwe deelnemers.

De CME benadrukt de verantwoordelijkheid van de PI/promotor van dit onderzoek ten aanzien van de privacy van de persoons-/patiëntgegevens in contacten met patiënten, of bij het inzien van patiëntgegevens, inclusief de juiste uitvoering daarvan door collega's en studenten. De PI/promotor is verantwoordelijk voor de uitvoering van het projectvoorstel in overeenstemming met de toepasselijke wet- en regelgeving waaronder, maar niet beperkt tot, de EU-verordening 2016/679 (Algemene Verordening Gegevensbescherming), de Belgische Wet op de patiëntenrechten van 22/ 8/2002, en het beleid van de instelling waar het onderzoek wordt uitgevoerd.

De CME verwijst op haar website naar de ICH/GCP-richtlijnen en bevestigt dat van elke onderzoeker een GCP-training vereist is. Het is de verantwoordelijkheid van de hoofdonderzoeker dat elk lid van het onderzoeksteam een geldig GCP-certificaat heeft. De conformiteit van vertaalde documenten ten opzichte van de Nederlandse documenten is de verantwoordelijkheid van de opdrachtgever.

Wij vestigen uw aandacht op het feit dat de CME verwacht dat haar eerste opmerkingen ab initio in aanmerking worden genomen bij de volgende indiening door dezelfde sponsor.

Mits er een Clinical Trial Agreement is, kan de studie pas starten wanneer de Clinical Trial Agreement werd goedgekeurd en ondertekend door de CEO van het UZ Gent (en/of door een gemachtigde vertegenwoordiger van de UGent).

Studies met geneesmiddelen voor onderzoek en bepaalde studies met "medical devices" dienen door de klant (PI of sponsor) te worden ingediend bij het FAGG (Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten).

Studies met geneesmiddelen voor onderzoek mogen enkel uitgevoerd worden op voorwaarde dat de minister (FAGG) geen bezwaar maakt binnen de wettelijke termijnen zoals beschreven in art. 13 van de Belgische wet van 7/5/2004 betreffende experimenten op de menselijke persoon en in art. 21 van de Belgische wet van 7/05/2017 betreffende klinische proeven met geneesmiddelen voor menselijk gebruik.

Bepaalde onderzoeken met medische hulpmiddelen vallen ook onder wettelijke termijnen (KB van 17/3/2009). Raadpleeg de website van het FAGG voor meer informatie: www.fagg-afmps.be .

Onderzoek op embryo's in vitro valt onder de wet van 11 mei 2003. Alvorens het onderzoeksproject kan starten, vereist dergelijk onderzoek ook een positief advies van het Federaal Comité voor medisch en wetenschappelijk onderzoek op embryo's in vitro.

Gelieve rekening te houden met de reglementen van het ziekenhuis inzake weefselbeheer en de reglementen van de wet van 19 december 2008.

Dit gunstige advies van de CME houdt niet in dat zij de geplande studie op zich neemt. U blijft verantwoordelijk voor het onderzoek. Daarnaast dient u ervoor te zorgen dat uw mening als betrokken onderzoeker wordt weergegeven in publicaties, rapporten voor de overheid etc. die het resultaat zijn van dit onderzoek. U wordt eraan herinnerd dat met betrekking tot klinische onderzoeken elke waargenomen ernstige gebeurtenis onmiddellijk moet worden gemeld aan de sponsor en de ethische commissie, zelfs als het oorzakelijk verband met de studie onduidelijk is.

De CME-goedkeuring die voor een specifiek project wordt gegeven, is één jaar geldig. Wij verzoeken u ons te informeren als het onderzoek niet wordt gestart of als het onderzoek niet binnen 1 jaar na goedkeuring start.

De CME bevestigt dat - in geval van belangenverstrengeling - betrokken leden niet deelnemen aan de stemming over het onderzoek.

Indien het onderzoek niet binnen een jaar wordt beëindigd, eist de ICH-GCP dat jaarlijks een voortgangsrapportage aan de CME wordt verstrekt.

Tot slot verzoeken wij u de (voortijdige of geplande) beëindiging van het onderzoek binnen de wettelijke termijnen te melden en het Clinical Study Report (CSR) aan de CME te bezorgen.

Houd er in het geval van een klinische proef (EudraCT) rekening mee dat de resultaten moeten worden gepubliceerd in het European Clinical Trial Register. Het rapport van deze resultaten kan als CSR naar de EC worden gestuurd.

Appendix 3b: Points of concern (if applicable)

The changes in the ICF should be clearly communicated to the patient.
We would like to point out that in case of amendments to the ICF, it is strongly advised to use an ICF addendum for ongoing participants. The ICF addendum lists only the changes or new information which is more clear to the participant than an amended ICF where changes are highlighted. When inclusion is still ongoing, an amended ICF is required for new participants.

The EC emphasizes the responsibility of the PI/promotor of this study concerning the privacy of the person/patient data in contacts with patients, or when viewing patient data, including the correct implementation thereof by coworkers and students. The PI/promotor is responsible for the implementation of the project proposal in accordance with applicable laws and regulations including, but not limited to, the EU regulation 2016/679 (General Data Protection Regulation), the Belgian Law on patients' rights of 22/8/2002, and the policy of the institution where the research will be carried out.

The EC refers to the ICH/GCP guidelines on its website, and confirms that a GCP-training is required from each investigator. It is the responsibility of the principal investigator that each member of the study team has a valid GCP-certificate.

The conformity of translated documents compared to the Dutch documents, is the responsibility of the sponsor.
We would like to draw your attention to the fact that the EC expects her initial comments to be taken into account ab initio at the next submission by the same sponsor.

*Provided that there is a **Clinical Trial Agreement**, the study can only start when the Clinical Trial Agreement has been approved and signed by the CEO of UZ Gent (and/or by an authorized representative of UGent).*

Studies with investigational medicinal products and certain studies with "medical devices" should be submitted by the client (PI or sponsor) to the FAMHP (Federal Agency for Medicines and Health Products).
Studies with investigational medicinal products are only allowed to be conducted, provided that the minister (FAMHP) does not state objections within legal deadlines as described in art. 13 of the Belgian law of 7/5/2004 concerning experiments on the human person and art. 21 of the Belgian law of 7/5/2017 concerning clinical trials with medicines for human use.

Certain studies using medical devices are also covered by legal deadlines (KB of 17/3/2009). Please consult the FAMHP website for more information: www.fagg-afmps.be.

Research on embryos in vitro is covered by the law of May 11, 2003. Before the research project can start, such research also requires a positive advice of the Federal Committee for medical and scientific research on embryos in vitro.

Please take into account the regulations of the hospital concerning tissue management and the regulations of the law of December 19, 2008.

This favorable advice of the EC does not imply that it will assume responsibility for the planned study. You will remain responsible for the study. In addition, you should ensure that your opinion as an involved researcher is reproduced in publications, reports for the government, etc. which are the result of this study. You are reminded that concerning clinical studies, any observed serious event needs to be reported immediately to the sponsor and the ethics committee, even if the causal relationship with the study is unclear.

The EC approval given for a specific project, is valid for one year. We request you to inform us if the study will not be initiated or if the study does not start within 1 year after approval.

The EC confirms that - in case of conflict of interest - involved members do not take part in the vote concerning the study.

*If the study will not be terminated within a year, the ICH-GCP demands that an **annual progress report** will be provided to the EC.*

*Finally, we request you to report the termination (early or planned) of the study within the legal deadlines and provide the **Clinical Study Report** (CSR) to the EC.*

In case of a clinical trial (EudraCT), please be informed that the results must be published in the European Clinical Trial Register. The report of these results can be sent to the EC as the CSR.

ADDITIONAL FILE

Exercise Protocol

BFR-GROUP	WEEK 1	WEEK 2-6	WEEK 7-12*
WARM UP	10 min cycling - *1W/Kg*	10 min cycling - *1W/Kg*	10 min cycling - *1W/Kg*
Exercise 1 BFR + Quadriceps	leg extension, both legs train separately - 20% 1RM - 15-15-15 reps	Bipodal leg extension - 20% 1RM - 30-15-15-maximal fatigue	Bipodal leg extension - 20% 1RM - 30-15-15-maximal fatigue
Exercise 2 Calves	Bipodal seated calf raises - 20% 1RM - 15-15-15 reps	Bipodal seated calf raises - 20% 1RM - 30-15-15-maximal fatigue	Bipodal seated calf raises - 20% 1RM - 30-15-15-maximal fatigue
Exercise 3 BFR + Quadriceps	Leg press, both legs train separately - 20% 1RM - 15-15-15 reps	Bipodal leg press - 20% 1RM - 30-15-15-maximal fatigue	Bipodal leg press - 20% 1RM - 30-15-15-maximal fatigue
Exercise 4 Abductors	Bipodal leg abductor - 20% 1RM - 15-15-15 reps	Bipodal leg abductor - 20% 1RM - 30-15-15-maximal fatigue	Bipodal leg abductor - 20% 1RM - 30-15-15-maximal fatigue
Exercise 5 BFR + Hamstrings	Bipodal glute bridge with heels on ground - 20% 1RM - 15-15-15 reps	Bipodal leg curl - 20% 1RM - 30-15-15-maximal fatigue	Bipodal leg curl - 20% 1RM - 30-15-15-maximal fatigue
Stretching	Quadriceps, Hamstrings, Calves, Glutes - 3x30s	Quadriceps, Hamstrings, Calves, Glutes - 3x30s	Quadriceps, Hamstrings, Calves, Glutes - 3x30s
Exercise 6 BFR + bike	2x 5 min cycling - 40% HRR - 1 min deflated rest	Build up to 1x 5 min + 1x 10 min cycling - 45% HRR - 1 min deflated rest	Build up to 2x 10 min cycling - 50% HRR - 1 min deflated rest

Blood Flow Occlusion	60% LOP week 1, 80% week 2-12 (**BFR IS APPLIED UNILATERALLY**)
1RM	Maximum load with which the exercise can be performed pain free once
Progression*	Starting from week 6: add extra weight if maximal fatigue rep exceeds >15
Rest	30s in between sets, 5min in between different exercises

The **resistance exercises** used in this protocol are based on:

- Bryk, F. F., Reis, A. C. D., Fingerhut, D., Araujo, T., Schutzer, M., De Paula Leite Cury, R., Duarte, A., & Fukuda, T. Y. (2016). Exercises with partial vascular occlusion in patients with knee osteoarthritis: a randomized clinical trial. *Knee Surgery, Sports Traumatology, Arthroscopy*, *24*(5), 1580–1586. https://doi.org/10.1007/s00167-016-4064-7
- Ferraz, R. B., Gualano, B., Rodrigues, R., Kurimori, C. O., Fuller, R., Lima, F. R., De Sá-Pinto, A. L., & Roschel, H. (2018). Benefits of Resistance Training with Blood Flow Restriction in Knee Osteoarthritis. *Medicine And Science in Sports And Exercise*, *50*(5), 897–905. https://doi.org/10.1249/mss.0000000000001530
- Grantham, B., Korakakis, V., & O'Sullivan, K. (2021). Does blood flow restriction training enhance clinical outcomes in knee osteoarthritis: A systematic review and meta-analysis. *Physical Therapy in Sport*, *49*, 37–49. https://doi.org/10.1016/j.ptsp.2021.01.014

The **aerobic exercises** used in this protocol are based on:

- Beak, H. J., Park, W., Yang, J. H., & Kim, J. (2022). Effect of Low-Intensity Aerobic Training Combined with Blood Flow Restriction on Body Composition, Physical Fitness, and Vascular Responses in Recreational Runners. *Healthcare*, *10*(9), 1789. https://doi.org/10.3390/healthcare10091789
- Abe, T., Fujita, S., Nakajima, T., Sakamaki, M., Ozaki, H., Ogasawara, R., Sugaya, M., Kudo, M., Kurano, M., Yasuda, T., Sato, Y., Ohshima, H., Mukai, C., & Ishii, N. (2010). Effects of Low-Intensity Cycle Training with Restricted Leg Blood Flow on Thigh Muscle Volume and VO2MAX in Young Men. *DOAJ (DOAJ: Directory Of Open Access Journals)*. https://doaj.org/article/c067557f85ab4aa8a367aa96ee41ce3b
- Kim, D., Singh, H., Loenneke, J. P., Thiebaud, R. S., Fahs, C. A., Rossow, L. M., Young, K., Seo, D., Bemben, D. A., & Bemben, M. G. (2016). Comparative Effects of Vigorous-Intensity and Low-Intensity Blood Flow Restricted Cycle Training and Detraining on Muscle Mass, Strength, and Aerobic Capacity. *Journal Of Strength And Conditioning Research*, *30*(5), 1453–1461. https://doi.org/10.1519/jsc.0000000000001218
- Vanwye, W. R., Weatherholt, A. M., & Mikesky, A. E. (2017). Blood Flow Restriction Training: Implementation into Clinical Practice. *PubMed*, *10*(5), 649–654. https://pubmed.ncbi.nlm.nih.gov/28966705