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Effects of Blood-Flow Restricted Resistance Exercise Versus Neuromuscular Exercise on Mechanical Muscle Function in Adults With Chronic Knee Osteoarthritis—A Secondary Analysis From a Randomized Controlled Trial

Brian Sørensen[1,2,3] | S. Peter Magnusson[2,3,4] | Rene B. Svensson[2,5] | Mikkel H. Hjortshoej[2,3,6] | Sofie K. Hansen[7] | Charlotte Suetta[4,7] | Christian Couppé[2,3,4] | Finn E. Johannsen[2,8] | Per Aagaard[1]

[1]Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense M, Denmark | [2]Department of Orthopaedic Surgery, Institute of Sports Medicine Copenhagen (ISMC), Copenhagen University Hospital Bispebjerg-Frederiksberg, Copenhagen, NV, Denmark | [3]Department of Physical & Occupational Therapy, Copenhagen University Hospital Bispebjerg-Frederiksberg, Copenhagen, NV, Denmark | [4]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark | [5]Department of Health Technology, Center for Fast Ultrasound Imaging, Technical University of Denmark, Lyngby, Denmark | [6]Centre for Health and Rehabilitation, University College Absalon, Slagelse, Denmark | [7]Geriatric Research Unit, Department of Geriatric and Palliative Medicine, Copenhagen University Hospital Bispebjerg-Frederiksberg, Copenhagen, NV, Denmark | [8]Furesø-Reumatologerne, Rheumatology Clinic, Farum, Denmark

Correspondence: Brian Sørensen (bsoerensen@health.sdu.dk)

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Keywords: blood-flow restriction | exercise | knee | neuromuscular | osteoarthritis

ABSTRACT

Knee osteoarthritis (knee OA) is a prevalent condition worldwide. Globally recognized rehabilitation guidelines for knee OA include patient education and neuromuscular exercises (NEMEX). While heavy-load resistance exercise (70%–90% 1RM) often induces pain with knee OA, low-load exercise (20%–40% 1RM) combined with partial blood-flow restriction (BFR-RE) has been introduced without inducing excessive knee joint pain. The present study aimed to compare the effects of NEMEX and BFR-RE on mechanical muscle function in knee OA individuals. Ninety-six participants (age 56.7 ± 7.6; 47 males, 49 females) with symptomatic, radiographic knee OA were randomized to free-flow land-based NEMEX or unilateral machine-based BFR-RE. Both groups exercised biweekly for 12 weeks while also receiving patient education. Outcomes measured from baseline to 12 weeks included maximal isometric knee extensor strength (MVIC), rate of force development (RFD), maximal leg extensor power (LEP), and cross-sectional area (mCSA) of rectus femoris (RF) and vastus lateralis (VL). Significant ($p < 0.01$) within-group improvements from baseline to 12 weeks were observed in both groups for MVIC (BFR-RE: +0.4 vs. NEMEX: +0.1 Nm/kg), LEP (+0.6 vs. +0.2 W/kg), mCSA for RF (+1.8 vs. +0.6 cm^2), and VL (+3.7 vs. +1.0 cm^2). BFR-RE led to increases in RFD (+2.11 (50-ms), +4.48 (200-ms) Nm/s/kg) ($p < 0.01$), whereas NEMEX did not ($p > 0.05$). Between-group comparisons revealed greater improvements with BFR-RE for all outcomes ($p < 0.01$). BFR-RE appears superior to NEMEX in enhancing mechanical muscle function and knee extensor mCSA in knee OA individuals. The enhanced physiological responses observed with BFR-RE suggest that this exercise modality should be considered as an adjunct therapeutic tool in future treatment protocols for knee OA patients.

1 | Introduction

Osteoarthritis (OA) is a common musculoskeletal disorder affecting millions globally [1]. The prevalence of OA has increased by 132% from 1990 to 2020 [1]. The knee is the most frequently affected joint, with knee OA prevalence projected to rise 75% by 2050 due to population growth and a progressively increased proportion of aging adults [1]. Risk factors for the development and progression of knee OA include genetic predispositions, sex, age, obesity, malalignment, previous knee injuries, repetitive high-impact activities, and reduced lower limb muscle mass, strength, and power [2–4]. The latter factors (reduced mass, strength, power) have been linked to increased cartilage damage and worsening knee joint structural abnormalities, such as cartilage loss and bone marrow lesions, leading to pain, reduced mobility, and limitations in physical function [5–7]. Thus, increasing lower limb muscle mass, strength, and power is crucial in both early and late stages of knee OA rehabilitation.

Neuromuscular exercise (NEMEX), which also includes patient education and body weight counseling, is globally recognized as the first-line treatment for knee OA [8]. NEMEX is offered to Danish knee OA patients in the form of the standardized concept GLA:D (Good Life with osteoArthritis in Denmark) [9]. Launched in 2013, GLA:D has been adopted in several countries worldwide (i.e., Australia, Austria, Canada, China, New Zealand, and Switzerland) [10]. This program comprises an 8-week, twice-weekly supervised NEMEX exercise protocol, combined with 1–2 patient education sessions [9]. Research on the effects of the NEMEX program in knee OA patients has primarily focused on changes in self-perceived symptoms, functional performance, and quality of life (QOL) [9–15]. However, only a few studies have specifically examined the impact of NEMEX on lower limb muscle strength and muscle mass [13, 16, 17]. While improvements in muscle strength (10%–16%) and muscle mass (3%) were observed after 12 weeks of NEMEX [13, 16, 17], no significant changes were noted in maximal leg extensor power (LEP) [14]. Low levels of maximal muscle strength have been associated with high levels of knee pain [18] and low functional performance in knee OA patients [19]. However, recent literature suggests that LEP may be a stronger predictor of functional performance in this population [4, 20], underscoring the importance of enhancing this parameter in addition to maximal muscle mass and strength.

Heavy-load resistance training (HIRT) is widely regarded as effective, potentially the gold standard, for enhancing lower limb muscle strength, muscle power, and muscle mass in knee OA [21]. HIRT involves lifting heavy loads (70%–90% of 1 repetition maximum: RM) with few repetitions (6–12) and long rest intervals (>45 s), which optimally stimulates muscle hypertrophy, neuromuscular adaptations, and maximal muscle power generation [22]. However, HIRT is not suitable for all individuals with knee OA due to exacerbation of knee pain, swelling, and inflammation (~25%) [23, 24]. An alternative exercise approach to HIRT is low-load resistance training (20%–40% 1RM) performed with restricted blood-flow to the muscles, also known as blood-flow restricted resistance exercise (BFR-RE) [25]. BFR-RE has been shown to be superior to conventional free-flow low-load resistance training [24, 26], and equally effective as HIRT [24, 27] for evoking increases in muscle mass and strength in individuals with knee OA, while also promoting gains in muscle power [28]. In a knee OA population, where heavy-load exercises can be challenging and in some cases, contraindicated due to excessive pain, BFR-RE could serve as a viable alternative training modality to NEMEX. However, no direct comparisons between these exercise modalities (BFR-RE vs. NEMEX) have yet been performed.

The aim of the present study, therefore, was to examine the effects of BFR-RE compared to NEMEX on maximal lower limb muscle power generation, quadriceps muscle strength, and muscle mass in females and males with symptomatic and radiographically verified knee OA. The hypothesis was that 12 weeks of BFR-RE would be superior to NEMEX in improving maximal muscle power, quadriceps muscle strength, and muscle mass.

2 | Materials and Methods

2.1 | Study Design

This study was performed as a secondary analysis of a randomized controlled trial with assessor blinding, involving two intervention groups [29]. The primary endpoint of the main analysis was self-reported pain following 12 weeks of either BFR-RE or NEMEX [29]. The present analysis focused on the effects on quadriceps muscle strength, rate of force development, muscle power, and muscle mass after 8- and 12-week training. The study was approved by the Scientific Ethics Committees for the Capital Region of Denmark (H-19079135) and the Danish Data Protection Agency (P-2019-814). The study was registered on ClinicalTrials.gov (NCT05437770), and a protocol article has been published elsewhere [29].

2.2 | Participants

From June 2022 to March 2024, participants were recruited from the Institute of Sports Medicine Copenhagen (ISMC) and the Department of Physical & Occupational Therapy at Bispebjerg-Frederiksberg Hospital, Copenhagen, Denmark. Participants were referred by general practitioners, rheumatologists, physical therapists, or through social media advertisements. Each potential participant was examined by both a physical therapist and a rheumatologist to ensure they met the inclusion and exclusion criteria (Table 1). All eligible participants provided their informed written consent. After baseline assessments, participants were randomly assigned to BFR-RE or NEMEX intervention, with stratification based on gender and BMI ≥27. The randomization process was managed using the REDCap software, version LTS 14.5.17, by two independent staff members from ISMC.

2.3 | Intervention Procedures

2.3.1 | Neuromuscular Exercise (NEMEX)

Participants assigned to the NEMEX group were enrolled in the Danish rehabilitation program for knee OA patients, also termed GLA:D (Good Life with osteoArthritis in Denmark) [9].

TABLE 1 | Inclusion and exclusion criteria.

Inclusion:
• Unilateral knee pain resulting in functional limitations for a minimum of 3 months
• Meeting the American College of Rheumatology (ACR) criteria for knee OA [30]
• Radiographic documented knee OA on ultrasound scanning (US), X-ray, or MRI scanning
• Understand and speak Danish
Exclusion:
• Unable to perform unassisted 90° flexion in the knee
• Unable to perform the strength training on the exercise machines
• Long-duration travel plans within the intervention period
• Bilateral knee OA symptoms
• Prior knee or hip alloplasty
• Glucocorticosteroid injection in the knee within the last 6 months
• Inflammatory arthritis
• Neurologic disease
• Prior myocardial infarct or apoplexy
• Chest pain during physical activity
• Diabetes 1
• Peripheral vascular disease
• Excessive varicose veins
• Prior history of deep venous thrombosis
• Venous insufficiency
• Systolic blood pressure over 160 mmHg or under 100 mmHg
• Other health-related or medical conditions hindering participation in the study

This program was offered at various certified physical therapy clinics in the greater Copenhagen area. GLA:D is an established 8-week program involving 16 supervised group-based NEMEX sessions and 1–2 patient education sessions, all conducted by certified GLA:D instructors [9].

Each NEMEX session lasted 60 min and consisted of three parts: warm-up, a circuit program, and cool-down [31]. The warm-up comprised ergometer cycling for 10 min at a perceived exertion level of "somewhat hard" (Modified Borg CR10 RPE scale: 4–5) [32]. The circuit program comprised four exercise circles, each containing two neuromuscular exercises targeting key elements: (1) core stability/postural function (exercises: pelvic lift and sit-ups); (2) postural orientation (exercises: forward, backward, and sideways sliding/lunges); (3) lower extremity muscle strength (exercises: hip adduction/abduction and knee extension/flexion); and (4) functional exercises (sit-to-stand and stair climbing/step-up). Each exercise was performed for 2–3 sets of 10–15 repetitions (reps), with a rest period of approximately 60 s between sets and exercises. The outlined exercises and training variables are representative of standard NEMEX sessions conducted in clinical practice. To facilitate progression, three levels of difficulty were provided for each exercise. For quadriceps-targeting exercises (sliding/lunges, knee extension, sit-to-stand, and step-up), progression was structured as follows: Sliding/lunges: (1) The exercising leg remains on an even surface while the contralateral leg slides backward, returns to the starting position, and slides sideways on a sliding surface. (2) The same movement is performed on an uneven surface (e.g., foam pillow). (3) The exercising leg takes a large step forward, returns to the starting position, and then steps sideways while the contralateral foot remains in contact with the floor. Knee extension: (1) Seated on a chair with an elastic band around the exercising foot, ensuring tension in the band at 90° knee flexion. The exercising leg is then fully extended and returns to 90°. (2) The same exercise is performed with increased resistance in the elastic band. (3) Further resistance is added by using a stronger elastic band (see later). Sit-to-stand: (1) Seated on a chair with feet parallel, the participant rises to full knee and hip extension before returning to a seated position, using hand support for balance. (2) The same movement is performed without hand support. (3) The movement is performed with one foot placed in front of the other. Further progression includes adding dumbbells. Step-up: (1) A controlled step-up followed by a step-down is performed on a low step board with hand support for balance. (2) The same movement is executed on a medium-height step board without hand support (alternatively with dumbbells). (3) The movement is performed on a high step board without hand support (alternatively with dumbbells) [31].

General progression in all exercises was achieved through modifying movement parameters (e.g., changing feet positioning, increasing hip/knee joint range of motion, exercise velocity or number of reps); using elastic bands with increased resistance (color-coded from light to heavy: green, blue, red, black); and/or reducing support surface stability. Progression occurred when a participant successfully completed three sets of 15 repetitions while maintaining good sensorimotor control and movement quality, as assessed through visual inspection by the physiotherapist. Proper control and quality included maintaining appropriate hip and knee alignment with minimal exertion, perceived by the participant as 3–4 on the Modified Borg CR10 RPE scale [29, 31]. Participants were instructed that exercise-induced knee joint pain up to 5 on the Visual Analog Scale (VAS) was allowed, provided that the pain subsided to the participant's baseline

level ("pain as usual," defined as the pre-exercise pain level) by the following day.

In the present study, the NEMEX program was extended by an additional 4 weeks, to comprise a total of 12 weeks, with participants continuing the same supervised group-based exercises during the final 4 weeks as performed in the initial 8 weeks. Depending on the clinic, participants attended either one extended patient educational session (2 h) or two shorter sessions (1 h each), which is an integral part of the GLA:D program.

2.3.2 | Blood-Flow Restricted Resistance Exercise (BFR-RE)

Participants in the BFR-RE group completed 24 exercise sessions over 12 weeks, with sessions held twice weekly under the supervision of experienced clinical BFR-RE instructors at the Department of Physical & Occupational Therapy, Bispebjerg-Frederiksberg Hospital, Copenhagen. The exercise regimen included two lower limb exercises: unilateral leg press and unilateral knee extension, performed using standard strength training machines (TechnoGym). The symptomatic knee with OA was always exercised first, using a pneumatic occlusion cuff placed around the upper thigh, followed by the contralateral asymptomatic leg. Occlusion pressure was determined individually for each participant, starting in the first week at 60% of total arterial occlusion pressure (AOP), increasing to 70% in the second week, and reaching 80% from the third week onward. If this pressure was not tolerated by the participant, cuff pressure was decreased to 70% AOP. The BFR-RE instructors manually inflated the occlusion cuff using a handheld sphygmomanometer equipped with a manual pump and pressure gauge (model 0123) to the estimated training pressure before the first exercise set and deflated it after the fourth set. Between sets, the instructors adjusted, monitored, and maintained the correct cuff pressure.

A detailed description of the AOP determination has been provided in the published protocol [29]. In brief, individual AOP was measured using a pneumatic, conically shaped cuff (12 cm wide, Occlude Aps, Denmark) attached to the participant's proximal thigh on the symptomatic knee OA leg, followed by application to the proximal thigh of the contralateral leg. In the present study, sizes L (45–61 cm) and XL (60–74 cm) were utilized based on the participants' thigh circumference. While seated in an upright position on an examination table with the ankle and one-third of the lower limb off the table (approximately 80° knee joint flexion, 0° = full extension), a vascular Doppler probe (EDAN Instruments, China) was placed posterior to the medial malleolus, over the posterior tibial artery, to detect the auscultatory pulse. The cuff was then gradually inflated in 20-mmHg increments until the auscultatory pulse was interrupted, indicating the AOP. This procedure was repeated twice, with a 1-min rest period between assessments. If the second AOP measurement was identical to the first (within 10-mmHg), it was considered the participant's AOP. A larger difference between measurements prompted a third assessment, and the AOP was defined as the mean of the two values within a 10 mmHg difference [29, 33]. Individual AOP was reassessed after 4 and 8 weeks of training. No participants increased or decreased by more than 10 mmHg compared to their pre-intervention assessment.

Training load intensity was set at 30% of the estimated one-repetition maximum (1RM) based on unilateral sub-maximal testing (5-10RM). Consequently, participants may have trained at load levels that were either lower or higher than the predefined levels during certain sessions. Load magnitudes were progressively modified according to the participant's ability to perform the designated repetitions: 30 in the first set, 15 in the second and third sets, and as many as possible in the fourth set. Load magnitudes were increased if more than 20 repetitions were performed in the final set for two consecutive sessions. Conversely, if fewer than 10 repetitions were completed in the fourth and final set, load magnitudes were decreased in the subsequent training session. Participants were instructed that exercise-induced knee joint pain up to VAS 5 was allowed, provided that the pain subsided to the baseline level by the following day. Additionally, participants were informed that thigh muscle discomfort during BFR-RE was expected to exceed VAS 5, but should resolve within minutes after cuff removal. Detailed information about the BFR-RE protocol has been published elsewhere [29]. Additionally, all participants joined a 2-h educational session at the Department of Physical & Occupational Therapy, Bispebjerg Hospital.

2.4 | Outcome Variables

Comprehensive details on all outcome measures, including their validity and reliability, have been addressed in the published protocol [29].

Outcomes related to mechanical muscle function included assessments of maximal isometric voluntary contraction (MVIC) knee extensor strength in the symptomatic knee OA leg obtained by isometric dynamometry (KinCom) while including the analysis of rapid force capacity (contractile rate of force development: RFD) from 0–50 and 0–200 ms and unilateral maximal leg extensor muscle power (LEP) for the symptomatic knee OA leg assessed by the Nottingham Power-Rig. The anatomical muscle cross-sectional area (mCSA) of the knee extensor muscles rectus femoris (RF) and vastus lateralis (VL) was obtained in the symptomatic knee OA leg by the use of panoramic extended field-of-view ultrasonography.

Assessment of outcome variables was performed at baseline (prior to randomization and before intervention onset), after 8 weeks of training, and after 12 weeks of training (primary endpoint). The first follow-up assessment was conducted 8 weeks +3–4 days after the first training session, while the final follow-up assessment took place 12 weeks +3–4 days after the first training session. All three assessment sessions (baseline, 8 weeks, and 12 weeks) for each participant were scheduled at approximately the same time of day (within 2-h) to ensure consistency. Participants were instructed to avoid vigorous exercise for 24 h prior to each session to minimize muscle water accumulation. Additionally, they were advised to use the same mode of transportation for all test occasions to reduce variability. Outcome variables were assessed at each test session in the following order: (1) mCSA of RF, (2) mCSA of VL, (3) maximal LEP, (4) knee extensor MVIC and RFD [29]. Upon completion of the final test, participants were informed that muscle discomfort might occur in the following days.

2.5 | Sample Size

The sample size calculation for the primary analysis of the RCT was based on the primary outcome variable KOOS-Pain subscale (Knee injury and Osteoarthritis Outcome Score), requiring 45 participants per intervention group, accounting for a 20% dropout rate. To ensure reaching the initial statistical power of 90 participants in total, an additional 6 participants were recruited to replace early dropouts [29].

2.6 | Statistical Analysis

This secondary analysis adhered to the same statistical analysis plan (SAP) as used for the primary analysis. The SAP was made publicly accessible in autumn 2022 on ClinicalTrials.gov, and a comprehensive description of the analysis has been published elsewhere [29].

Briefly, this secondary analysis utilized the intention-to-treat (ITT) population. Systematic mean differences between groups for all outcome measures were evaluated using a linear mixed model (LMM) analysis, with participants as a random factor and intervention groups (BFR-RE, NEMEX) and time points as fixed factors. Baseline to 8 weeks and baseline to 12 weeks comparisons were conducted using the same LMM approach in two separate models. Missing data in the ITT analysis were handled by the LMM [34]. Grubbs' Test [35] was employed to identify potential outliers in the dataset, but no outliers were found for any outcome measures. Effect sizes (ES) were calculated using Cohen's d and interpreted using the following benchmarks: small ($d = 0.2$), medium ($d = 0.5$), and large ($d = 0.8$) [36]. The significance level was set at $p < 0.05$ (two-tailed). All statistical analyses were carried out using JMP Pro version 16.0.0.

3 | Results

3.1 | Participants

Between June 2022 and March 2024, 194 individuals were screened for eligibility. Ninety-six participants met the inclusion and exclusion criteria and were assigned to baseline testing and randomization. Of these, 47 participants were assigned to BFR-RE, while 49 participants were assigned to the NEMEX group. No exercise-related adverse events during the intervention period were observed for either group. No participants except one from the NEMEX group withdrew from the study due to exercise-induced or test-related knee joint pain, knee joint effusion, muscle discomfort, or other side effects. The participant who withdrew reported exercise-induced knee joint pain after 3 weeks of training, which persisted throughout the intervention period. In the BFR-RE group, three participants were unable to perform BFR-RE at 80% AOP due to intense muscle discomfort and continued at 70% AOP. Some participants in both intervention groups experienced muscle soreness following baseline assessment and the initial training sessions, which gradually subsided. Mean maximal AOP used to determine training pressures in the BFR-RE group was 211.6 ± 24.4 mmHg. Mean training pressures at 70% and 80% AOP were 147.5 ± 16.6 and 168.5 ± 18.9 mmHg, respectively. Baseline characteristics are depicted in Table 2.

TABLE 2 | Demographics and characteristics in the intention-to-treat population.

Demographics	BFR-RE ($n = 47$)	NEMEX ($n = 49$)	
Female gender, *n* (%)	24 (51.1)	25 (51.0)	$p = 0.99$
Age, years	57.4 ± 7.4	56.1 ± 7.3	$p = 0.32$
Height, cm	173.0 ± 7.3	175.6 ± 9.3	$p = 0.13$
Weight, kg	86.2 ± 19.2	87.6 ± 19.1	$p = 0.72$
BMI, kg/m^2	28.7 ± 5.9	28.3 ± 5.4	$p = 0.70$
Tegner Activity Scale	3.8 ± 0.2	3.6 ± 0.2	$p = 0.69$
Recreationally physically active more than twice a week, *n* (%)	37 (78.7)	35 (71.4)	$p = 0.41$
Duration of symptoms, months	71.5 ± 71.9	79.8 ± 79.7	$p = 0.59$
Compliance, completed training sessions (%)	19.4 (80.7)	19.4 (80.9)	$p = 0.97$

Note: Group means ± standard deviation (SD).
Abbreviations: BFR-RE, Blood-Flow Restricted Resistance Exercise group; NEMEX: NEuroMuscular EXercise group; BMI: Body Mass Index; Tegner Activity Scale: An 11-point scale, ranging from 0 (sedentary/inactive) to 10 (elite competitive athlete); Compliance: Number of completed supervised training sessions out of possible 24 sessions.

3.2 | Outcomes

No between-group differences at baseline were observed in the various measures of mechanical muscle function. Statistically significant within-group improvements were observed from baseline to 8- and 12 weeks for all mechanical outcomes in the BFR-RE group ($p < 0.01$). For the NEMEX group, significant changes from baseline to 8- and 12 weeks were observed for Nottingham LEP and MVIC ($p < 0.05$) as well as for RF- and VL mCSA ($p < 0.01$). Between-group Δ-changes at 12 weeks were 0.37 W/kg (95% CI: 0.21 to 0.52, ES = 0.95, $p < 0.01$) for Nottingham LEP (Figure 1A), 0.33 Nm/kg (95% CI: 0.24 to 0.42, ES = 1.47, $p < 0.01$) for MVIC (Figure 1B), 4.48 Nm/s/kg (95% CI: 2.90 to 6.07, ES = 1.15, $p < 0.01$) for RFD 50-ms (Figure 1C), 2.11 Nm/s/kg (95% CI: 1.30 to 2.92, ES = 1.07, $p < 0.01$) for RFD 200-ms (Figure 1D), 1.2 cm^2 (95% CI: 1.0 to 1.4, ES = 2.09, $p < 0.01$) for RF mCSA (Figure 1E), and 2.7 cm^2 (95% CI: 2.3 to 3.0, ES = 3.33, $p < 0.01$) for VL mCSA (Figure 1F), all in favor of BFR-RE ($p < 0.01$) (Table 3). Sex-stratified absolute- and percentage changes for all outcome measures are provided in Tables S1–S4).

4 | Discussion

The present study demonstrated that a 12-week low-load BFR-RE intervention elicited greater enhancements in LEP, MVIC, RFD, and mCSA compared to NEMEX in elderly adults with chronic,

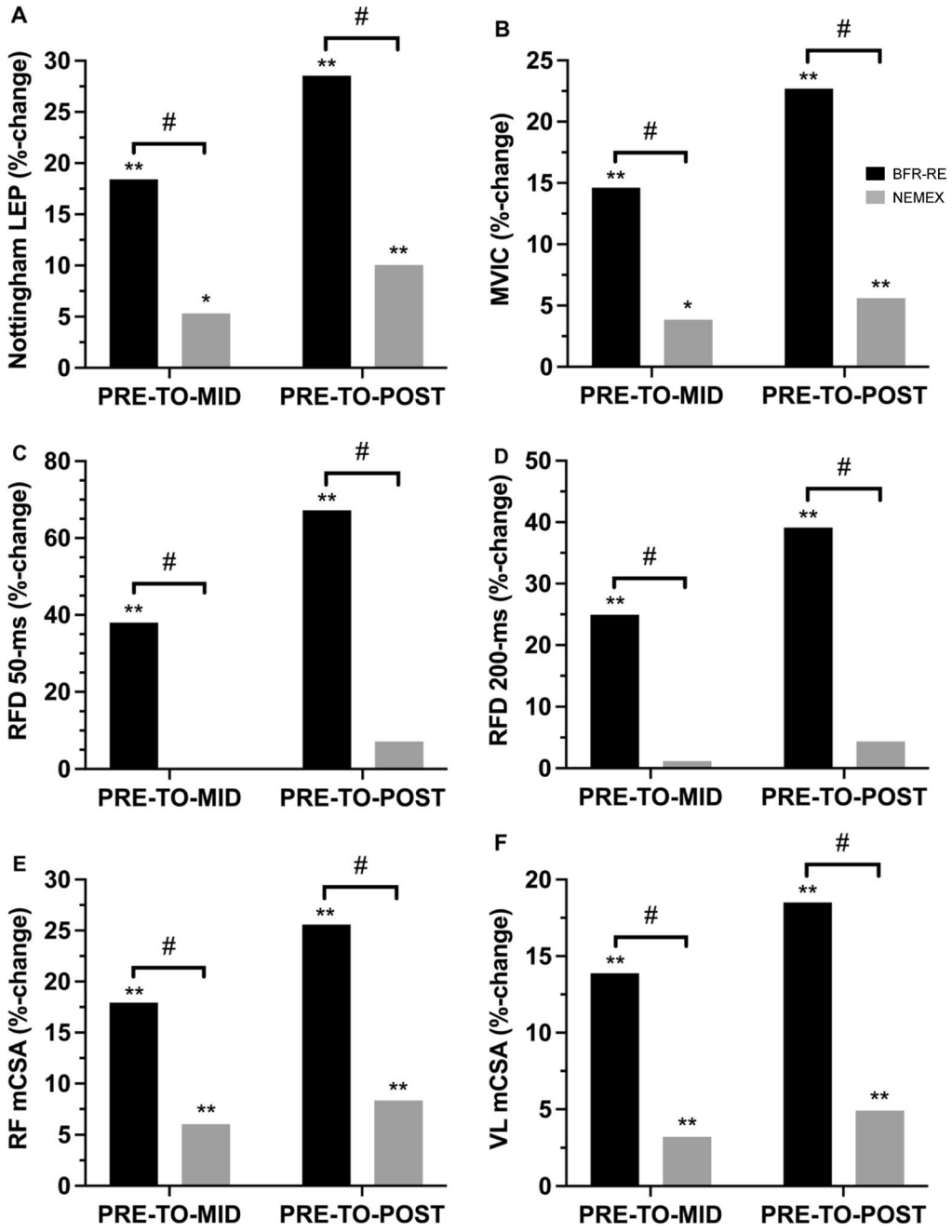

FIGURE 1 | Within- and between-group changes in percentage related to mechanical muscle function. Group mean %-changes from baseline to 8 weeks (PRE-TO-MID) and baseline to 12 weeks (PRE-TO-POST). *$p < 0.05$ for within-group change. **$p < 0.01$ for within-group change. #$p < 0.01$ for between-group difference in delta change (Δ). (A) Nottingham LEP: Leg Extensor Power for the symptomatic knee OA leg, Nottingham Power-Rig; (B) MVIC: Maximal Voluntary Isometric Contraction, KinCom; (C) RFD: Rate of Force Development at 50 ms, KinCom; (D) RFD: Rate of Force Development at 200 ms, KinCom; (E) RF mCSA: Rectus Femoris muscle Cross-Sectional Area; (F) VL mCSA: Vastus Lateralis muscle Cross-Sectional Area; BFR-RE: Blood-Flow Restricted Resistance Exercise group; NEMEX: NEuroMuscular EXercise group.

symptomatic knee OA. Notably the BFR-RE group also demonstrated superior improvements when assessed at 8 weeks of intervention for all outcome variables. While both NEMEX and BFR-RE were effective at improving given muscle mechanical outcomes, the greater increases seen with BFR-RE offer new insights that could optimize future knee OA treatment programs.

In Denmark and various other countries, NEMEX is implemented as the primary (first-in-line) choice of treatment [9]. However, the application of standardized training regimens to heterogeneous populations, such as individuals with knee OA, with different levels and stages of the disorder [37], may explain the marked discrepancies in treatment outcomes reported across the literature [14, 16, 38–41]. This underscores the necessity for patient stratification and more personalized treatment modalities to optimize knee OA rehabilitation [37]. The present observations demonstrate that BFR-RE is superior to NEMEX in enhancing mechanical muscle function measured as MVIC, LEP, and RFD, while also amplifying the gain in muscle mass (mCSA). Furthermore, these observations align with the

TABLE 3 | Outcomes related to mechanical muscle function.

				Within-group change from baseline to 8 weeks		Within-group change from baseline to 12 weeks		Between-group Δ-change from baseline to 8 weeks		Between-group Δ-change from baseline to 12 weeks	
	Baseline	8 weeks	12 weeks	Mean difference (95% CI)	Effect size	Mean difference (95% CI)	Effect size	Mean difference (95% CI)	Effect size	Mean difference (95% CI)	Effect size
LEP (W/kg)											
BFR-RE	2.10 ± 0.74	2.49 ± 0.75	2.70 ± 0.75	0.39 (0.27, 0.50)**	1.30	0.60 (0.46, 0.75)**	1.55	0.26 (0.14, 0.38)**	0.87	0.37 (0.21, 0.52)**	0.95
NEMEX	2.35 ± 0.74	2.47 ± 0.75	2.59 ± 0.76	0.12 (0.01, 0.24)*	0.47	0.24 (0.09, 0.38)**	0.78				
MVIC (Nm/kg)											
BFR-RE	1.97 ± 0.69	2.25 ± 0.68	2.41 ± 0.69	0.29 (0.22, 0.35)**	1.81	0.45 (0.36, 0.53)**	2.33	0.21 (0.14, 0.28)**	1.20	0.33 (0.24, 0.42)**	1.47
NEMEX	2.11 ± 0.70	2.19 ± 0.68	2.22 ± 0.70	0.08 (0.01, 0.15)*	0.50	0.12 (0.03, 0.20)**	0.55				
RFD 50-ms (Nm/s/kg)											
BFR-RE	7.79 ± 6.11	10.76 ± 6.26	13.04 ± 6.33	2.96 (1.81, 4.12)**	0.87	5.24 (3.75, 6.73)**	1.48	2.95 (1.72, 4.18)**	0.95	4.48 (2.90, 6.07)**	1.15
NEMEX	10.59 ± 6.11	10.60 ± 6.27	11.35 ± 6.34	0.01 (−1.13, 1.16)	0.03	0.76 (−0.71, 2.23)	0.19				
RFD 200-ms (Nm/s/kg)											
BFR-RE	6.23 ± 3.04	7.78 ± 3.13	8.66 ± 3.15	1.55 (0.99, 2.12)**	1.01	2.44 (1.68, 3.19)**	1.37	1.47 (0.87, 2.06)**	0.98	2.11 (1.30, 2.92)**	1.07
NEMEX	7.40 ± 3.04	7.48 ± 3.14	7.72 ± 3.16	0.09 (−0.47, 0.64)	0.02	0.32 (−0.43, 1.07)	0.15				
RF mCSA, cm^2											
BFR-RE	7.2 ± 2.6	8.5 ± 2.7	9.0 ± 2.7	1.3 (1.1, 1.5)**	2.56	1.8 (1.6, 2.1)**	2.78	0.8 (0.6, 1.0)**	1.82	1.2 (1.0, 1.4)**	2.09
NEMEX	7.6 ± 2.6	8.0 ± 2.7	8.2 ± 2.7	0.5 (0.3, 0.6)**	1.43	0.6 (0.4, 0.8)**	1.90				
VL mCSA, cm^2											
BFR-RE	20.0 ± 7.0	22.8 ± 7.0	23.7 ± 7.0	2.8 (2.5, 3.1)**	3.18	3.7 (3.4, 4.0)**	4.01	2.1 (1.8, 2.4)**	2.75	2.7 (2.3, 3.0)**	3.33
NEMEX	21.3 ± 7.0	22.0 ± 7.0	22.4 ± 7.0	0.7 (0.4, 1.0)**	1.61	1.0 (0.7, 1.3)**	2.18				

Note: Group means ± standard deviation (SD). Within- and between-group Δ-changes are expressed as group mean differences with 95% confidence interval.
Abbreviations: BFR-RE, Blood-Flow Restricted Resistance Exercise group; LEP, Leg Extensor Power for the symptomatic knee OA leg, Nottingham Power-Rig; MVIC, Maximal Voluntary Isometric Contraction, KinCom; NEMEX, NEuroMuscular EXercise group; RF mCSA, Rectus Femoris muscle Cross-Sectional Area; RFD, Rate of Force Development at 50 and 200 ms, KinCom; VL mCSA, Vastus Lateralis muscle Cross-Sectional Area.
*$p < 0.05$, **$p < 0.01$.

superior improvements in functional performance (sit-to-stand performance, stair climbing ability, and gait speed) observed with BFR-RE compared to NEMEX in the main study, which are intended for publication elsewhere. This highlights the critical importance of developing individualized rehabilitation regimens based on BFR-RE to better accommodate the specific needs of the single patient.

A number of studies have investigated the impact of BFR-RE and NEMEX on mechanical muscle function and morphology in individuals with knee OA by evaluating training-induced changes in MVIC, LEP, RFD, and mCSA [13, 14, 16, 27]. Improvements in MVIC between 10%–16% and 21%–25% were reported for NEMEX [13, 14, 16, 17, 27] and BFR-RE [13, 14, 16, 27], respectively. For BFR-RE, this aligns with the present observation of a 22.7% increase in MVIC at 12 weeks. However, an increase of 5.6% was observed with NEMEX at 12 weeks, which is lower than previously reported in NEMEX studies (10%–16%) [13, 16, 17]. This difference may be explained by baseline differences across study participants with lower levels of perceived knee pain and symptoms (~19%) in the present study.

Knee extensor (quadriceps femoris) weakness is considered a risk factor for accelerated knee OA disease progression [42]. Notably, knee OA patients appear to have 20%–40% reduced knee extensor strength compared to healthy-matched individuals [43]. Based on findings from the present study, an additional 20%-points increase in knee extensor muscle strength seems achievable with BFR-RE (+22.7%) compared to NEMEX (+5.6%), suggesting that BFR-RE is substantially more effective in reducing this strength deficiency, thereby potentially offering increased protection and unloading of the knee cartilage, as well as enhanced joint stability [43].

Along with reduced knee extensor muscle strength, low levels of maximal LEP and RFD have been identified as equally, if not more important risk factors in the development of knee OA [6, 20]. Research indicates that LEP, which is the ability to generate high muscle forces during fast muscle contractions, is a stronger determinant of functional performance, such as walking and stair climbing, compared to maximal muscle strength alone [20]. This is because muscle power reflects both the strength and speed of muscle contractions, which are both crucial parameters for performing dynamic movements and maintaining mobility [4, 44]. Similar to muscle strength, maximal LEP is reduced in knee OA patients [6]. Nonetheless, only limited research efforts have been directed to examine changes in LEP and/or RFD in response to BFR-RE or NEMEX intervention in knee OA patients. A single study investigated the change in LEP with 12 weeks of NEMEX intervention also using the Nottingham Power-Rig, without observing any improvements in LEP [14]. In the present study, strength exercises in the BFR-RE group were performed with a 2-s concentric and 2-s eccentric phase, thus with no emphasis on fast concentric contraction velocities. Despite this, improvements in LEP (28.5%) and RFD (39.1%–67.2%) for BFR-RE at 12 weeks were greater than the corresponding improvements of 10.0% and 4.4%–7.2% for LEP and RFD, respectively, were observed with NEMEX. This marked difference between groups may be attributed to both muscular and neural adaptations including the 3-4-fold greater gains in knee extensor mCSA (RF + VL) observed with BFR-RE (20.3%) compared to NEMEX (5.8%) at 12 weeks. Previous research has suggested that during BFR-RE, recruitment of type II muscle fibers (fast-twitch) occurs even at very low contraction intensities (~20% 1RM), due to the low oxygen levels and metabolite accumulation induced by vascular occlusion, causing the type I fibers to fatigue more rapidly [45, 46]. Consequently, type II myofibers are recruited to a large extent during BFR-RE, resulting in marked hypertrophy of type II fibers (as well as type I slow-twitch fibers) following BFR-RE in healthy adults [47, 48]. In particular, the proposed increase in type II muscle fiber CSA with BFR-RE is clinically attractive given that these fibers intrinsically produce high levels of contractile force, RFD, and power [49, 50], resulting in larger, stronger, and more powerful lower limb muscles. The significant gains in muscle power and strength following BFR-RE could also account for the notable improvements in functional performance (gait speed, stair climbing ability, and sit-to-stand performance) in this study, as observed in the main study.

Muscle weakness is frequently linked to decreases in mCSA. A recent MRI publication [51] reported that a decrease in quadriceps mCSA and an increase in intramuscular adipose tissue correlated with increased knee OA symptoms, altogether resulting in a higher likelihood of knee replacement [51]. Previous research has indicated that quadriceps mCSA in the affected limb is up to 12% smaller compared to the unaffected limb in patients with knee OA [52]. In the present study, a 20.3% increase in knee extensor mCSA (RF + VL) was found following 12 weeks of BFR-RE, which is higher than the 7%–10% improvements that have previously been reported following BFR-RE in comparable knee OA cohorts [24, 53]. This difference in muscle hypertrophy could be due to exercise execution. Unlike previous studies [24, 53], all exercises in the BFR-RE group were executed unilaterally. Exercises performed unilaterally have been shown to be better at improving maximal strength and muscle coordination, as well as correcting for muscle imbalances (e.g., side-to-side asymmetry in mCSA) compared to bilaterally executed exercises [54]. For NEMEX, a single study reported a 4% increase in quadriceps mCSA after 12 weeks of intervention, which is consistent with the 5.8% increase (RF + VL) observed in the present study [13]. The substantial increases in maximal muscle strength and mCSA observed after 8–12 weeks of BFR-RE in the present study suggest this exercise modality to be an effective adjunct tool in the treatment of knee OA patients.

4.1 | Limitations

This study has a number of limitations. Firstly, the dropout rate was higher than anticipated, necessitating the inclusion of six additional participants, bringing the total number of study participants to reach 96. The main reasons for the observed dropouts included logistical difficulties due to transportation and scheduling conflicts, along with personal reasons. Despite receiving reminders that group allocation was randomized, 6 participants withdrew due to dissatisfaction with their group allocation, which was distributed evenly between groups. Secondly, although efforts were made to blind the primary assessor to group allocation before 8- and 12-week assessment sessions, two participants in each group inadvertently revealed their group allocation at the 12-week assessment session. Thirdly, participants

in both groups engaged in dynamic knee extension exercises. While the BFR-RE group performed machine-based knee extensions, the NEMEX group executed similar exercises using elastic bands. To minimize any learning effects, we chose to assess participants' maximal isometric knee extensor strength [55]. Fourth, this study compared two low-load exercise modalities with different approaches. The BFR-RE group performed machine-based exercises, whereas the NEMEX group engaged in land-based, weight-bearing exercises with the option of incorporating elastic bands for additional resistance. However, key training variables, such as loading intensity (%1RM), repetitions, number of sets, and total training volume per session, were not matched between the intervention groups. This lack of standardization makes it difficult to determine whether the observed superior outcomes would be attributable to the blood-flow restriction mechanism itself or simply result from differences in the overall training stimulus. However, considering the overall exercise prescription, it is anticipated that the total training load volume per session would be higher in the NEMEX group, as five out of eight exercises involved quadriceps activation, compared to two exercises in the BFRE group. This is further supported by estimating active exercise time as a proxy measure of overall loading of the knee extensors, which revealed a more prolonged loading per session with NEMEX (15 min) compared to BFR-RE (10 min), suggesting that training exposure was not higher in BFR-RE compared to NEMEX. Additionally, the level of exertion and the extent to which the most resistant elastic bands provided a sufficient stimulus for some participants in the NEMEX group represent a limitation. This factor may, to some degree, contribute to the inadequate physiological progression observed. Fifth, the present study exclusively investigated the mCSA of RF and VL, omitting the vastus medialis (VM) and vastus intermedius (VI). This decision was based on preliminary panoramic ultrasonographic mCSA imaging of middle-aged to older adults, conducted prior to the study's initiation, which indicated potential difficulties in delineating the borders of VM and VI, particularly in individuals with increased subcutaneous adipose tissue. However, this exclusion represents a study limitation, as hypertrophic adaptations may not be uniformly distributed across the quadriceps muscles (RF, VL, VM, and VI), and different training modalities may elicit varying degrees of growth among these muscle heads [56]. Finally, the present study design did not allow for blinding of participants and instructors of the intervention programs regarding group allocation. To reduce potential bias, other personnel, including the statistician and assessor were blinded to group assignments and allocation.

5 | Conclusion

In agreement with the original hypothesis, 12 weeks of BFR-RE was superior to NEMEX in increasing lower limb muscle strength, rate of force development, leg extensor muscle power, and muscle mass in individuals with chronic symptomatic knee OA. Notably, BFR-RE also demonstrated superior effects compared to NEMEX after 8 weeks of intervention. The marked improvements in mechanical muscle function and knee extensor muscle mass seen with BFR-RE suggest that this training modality should be incorporated in the future rehabilitation of knee OA patients.

6 | Perspective

The findings in the present study suggest that BFR-RE is a valuable and promising addition to the current rehabilitation methods. Both intervention groups showed improvements in various muscle mechanical outcomes, highlighting the importance of exercise as medicine in the rehabilitation of knee OA patients. These novel findings indicate that BFR-RE is substantially more effective than the current first-in-line treatment used in clinical practice. Importantly, BFR-RE significantly improved muscle strength, muscle power, and muscle mass to clinically meaningful extents. Findings in the present study are relevant to clinical practice, demonstrating that BFR-RE can be used as a stand-alone method to either reduce the exercise load of some exercises or increase their intensity.

Author Contributions

Brian Sørensen, S. Peter Magnusson, Per Aagaard, Sofie K. Hansen, Charlotte Suetta, Christian Couppé, and Finn E. Johannsen were responsible for the conception and design of the study. Brian Sørensen, Sofie K. Hansen, and Finn E. Johannsen obtained funding. Finn E. Johannsen, Per Aagaard, Rene B. Svensson, S. Peter Magnusson, and Mikkel H. Hjortshoej provided administrative and technical support throughout the intervention period. Brian Sørensen collected and assembled all data. Brian Sørensen, S. Peter Magnusson, and Rene B. Svensson performed the statistical data analyses and quality assessment. All authors made substantial contributions to the interpretation of the results. Brian Sørensen drafted the article, and all authors revised it critically for important intellectual content. All authors approved the final submitted version.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.