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Review Article

Quadriceps strengthening with blood flow restriction for the rehabilitation of patients with knee conditions: A systematic review with meta-analysis

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Abstract.
OBJECTIVE: The purpose of this systematic review with meta-analysis was to compare the effects of low load resistance combined with blood flow restriction (BFR) versus conventional quadriceps strengthening on knee symptoms and function as well as knee extensor strength and muscle thickness in adults with knee conditions.
LITERATURE SURVEY: Guidelines based on the latest evidence highlight the importance of quadriceps strengthening to reduce pain and improve function in patients with knee conditions. Blood flow restriction is based on brief periods of vascular occlusion which cause muscle hypertrophy and increased strength. Before it can be recommended for individuals with knee conditions, quadriceps strengthening with low load resistance combined with BFR (LL-BFR) must show beneficial effects on clinical outcomes in addition to quadriceps strength and mass.
METHODS: A systematic review with meta-analysis was conducted to identify relevant studies through PubMed, PEDro, and ScienceDirect up to January 2019. The protocol was registered on PROSPERO (CRD42019121306). Differences in pre- and post-intervention means and standard deviations were extracted to calculate the standardized mean difference for each intervention in each included study.
SYNTHESIS: Eight studies were included. Limited evidence suggests that LL-BFR is more beneficial on quadriceps strength and thickness in patients with knee conditions than LL training alone or in addition to a rehabilitation program. Limited evidence indicates that LL-BFR training is equally effective in improving function and muscle thickness compared with a HL quadriceps strengthening program but elicits less knee pain, corresponding to additional benefits of 22 (95% confidence interval 1 to 43) mm on a 0–100 mm visual analogue scale.
CONCLUSIONS: BFR could be a useful option for patients with knee conditions where conventional quadriceps strengthening program exacerbate knee symptoms. Future investigations should compare different BFR protocols to help establish better guidelines for clinicians.

Keywords: Knee, quadriceps, strengthening, rehabilitation

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1. Introduction

Knee conditions such as patellofemoral pain and knee osteoarthritis can cause functional limitations at work, in sports, or activities of daily living and lead to decreased quality of life [1,2]. Guidelines based on the latest evidence highlight the importance of quadriceps strengthening to reduce pain and improve function in patients with knee conditions [3–5]. Nonetheless, quadriceps strengthening exercises can also exacerbate knee symptoms if exercises are not adapted to joint load capacities [6]. Thus, recommending sufficient resistance to increase muscle function without provoking or exacerbating knee symptoms can sometimes be challenging for clinicians.

Blood flow restriction (BFR) training is a muscle strengthening technique based on brief periods of partially limited arterial and venous flow [7]. The partial vascular occlusion during BFR strengthening exercises generates a greater anaerobic environment and more fatigue in the target muscle than the same exercise without BFR [8]. Moreover, BFR is characterized by its capacity to boost muscle improvements while using low resistance, typically 30% of the maximum load a person can lift once (1 repetition maximum [1RM]) [9]. Several systematic reviews concluded that BFR could represent an interesting rehabilitation tool for patients with physical limitations [10–14]. However, none of them focused on symptoms and function outcomes.

Before recommending quadriceps strengthening with low load resistance combined with BFR (LL-BFR) for individuals with knee conditions, this technique must show beneficial effects on clinical outcomes as well as on quadriceps strength and muscle mass. Despite concluding that LL-BFR improves lower limb muscle strength and cross-sectional area as well as symptoms in people with knee conditions, the most recent systematic review by Barber-Westin and Noyes [11] did not provide clinical recommendations based on meta-analyses and the level of evidence. Thus, the aim of this systematic review and meta-analysis was to compare the effects of LL-BFR training versus conventional quadriceps strengthening on knee symptoms and function as well as knee extensor strength and muscle thickness in adults with knee conditions. We also sought to provide recommendations based on the current level of evidence.

2. Methods

2.1. Search srategy

The protocol for this systematic review was registered on PROSPERO (Central Registration Depository: CRD42019121306). Studies were identified through PubMed, PEDro, and ScienceDirect up to January 2019. The search strategy combined the following keywords: 'blood flow restriction' OR 'vascular occlusion' OR 'resistance training associated with blood flow restriction' OR 'strength training associated with blood flow restriction' OR 'low-load resistance training' OR 'exercise training' AND 'knee extensor' OR 'muscle strength' AND 'knee conditions' OR 'patellofemoral pain' OR 'knee surgery' OR 'knee arthroscopy' OR 'knee' OR 'quadriceps' OR knee extensors' OR 'knee pain'. All systematic reviews, meta-analyses, case series, and case reports were excluded from our search. The search was complemented by hand searching the references of all articles selected for this review.

2.2. Study selection

Studies were included if they (1) investigated the effectiveness of LL-BFR quadriceps strengthening programs in adults with knee conditions; (2) included a control group with a knee condition; (3) were published in English; (4) reported effect of LL-BFR on quadriceps muscle strength, muscle thickness, knee function or knee symptoms. Knee conditions were defined as any knee injury, disorder or post-surgery; knee function was defined as the capacity of an individual to participate in activities of daily living including work; and knee symptoms included only knee pain. Studies were excluded if they (1) included participants under 18 years old; (2) included healthy participants or participants with conditions other than at the knee; (3) were systematic reviews, meta-analyses, case series or reports and editorials. All titles and abstracts were screened individually by two reviewers (EA, ADC). A third reviewer (JVC) was available when consensus on inclusion could not be reached.

2.3. Data extraction and analysis

Data from included articles were extracted using a standardized data extraction form: study design (author, date), clinical population characteristics (sample size, age, sex, knee conditions), rehabilitation protocol (equipment used, type of training, frequency, sets/repetitions, resting time and cuff parameters), variables of interest (knee symptoms, functional limitations, knee extensor strength, muscle thickness), follow-up duration, and results (mean difference and 95% confidence interval and P-values).

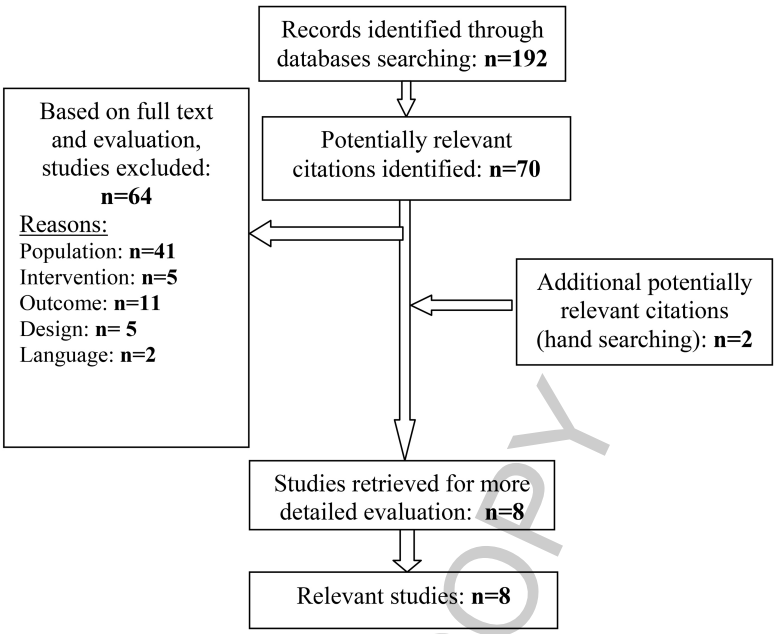

Fig. 1. Flowchart of study selection.

When possible, meta-analyses were performed using RevMan (Review Manager Version 5.3, The Nordic Cochrane Centre, Copenhagen, Denmark). The difference in pre- and post-intervention mean and standard deviation (SD) values for all groups in each study were used to calculate the standardized mean difference (SMD). According to Centner et al. [14], in case of incomplete data, SD_{change} was calculated as $[(SD^2_{pre}/N_{pre}) + (SD^2_{post}/N_{post})]$. Meta-analyses were conducted using a random effects model.

Heterogeneity in meta-analysis refers to the variation in study outcomes between studies [15]. Two statistical methods were used to verify statistical heterogeneity, the chi-square test for heterogeneity and the I^2 test. When the chi-square test is significant, statistical heterogeneity is present [15]. The I^2 value represents the total percentage of variation across studies due to heterogeneity, which can be interpreted as low ($I^2 =$ 0–30%), medium ($I^2 =$ 30–60%) or high ($I^2 =$ 60–100%) [15]. Descriptive analyses were performed when data were not sufficient for meta-analysis.

2.4. Methodological quality assessment

Individual study quality was assessed using the Physiotherapy Evidence Database (PEDro) scale, based on de Morton's list [16]. This assessment of clinical trials' methodological quality is a valid measure consisting in 11 questions for which 10 points can be assigned when criteria are clearly satisfied. On the basis of the PEDro score, the methodological quality of included studies was considered high ($\geqslant$ 7/10), medium (4–6/10), or low (leq 3/10) [17]. Two independent reviewers scored each study. In case of disagreement, scores were discussed with a third reviewer (JVC) and final score was determined by consensus.

2.5. Level of evidence

The level of evidence supporting the effects of LL-BFR on knee pain, function, quadriceps strength and thickness in comparison with control was determined using predetermined criteria [18]. Strong evidence was defined as results derived from a minimum of two studies with PEDro score $\geqslant$ 7/10 and low heterogeneity. Moderate evidence was defined as results derived from a minimum of two studies with PEDro score $\geqslant$ 7/10 and medium or high heterogeneity or from multiple studies with PEDro score $\leqslant$ 3/10 and low heterogeneity. Limited evidence was defined as results from multiple studies with PEDro score $\leqslant$ 3/10 and medium or high heterogeneity or from one study with PEDro score $\geqslant$ 7/10. Very limited evidence was defined as results from one study with PEDro score $\leqslant$ 3/10. Conflicting evidence was defined as insignificant pooled results derived from multiple studies, of which some show statistical significance individually, regardless of quality which is statistically heterogeneous ($p < 0.05$).

Table 1
PEDro scale assessment

Study	1	2	3	4	5	6	7	8	9	10	11	Total	Quality of study
Bryk et al. [19]	−	+	+	+	−	−	+	−	−	+	+	6/10	Medium
Ferraz et al. [20]	−	+	−	+	−	−	+	−	+	+	+	6/10	Medium
Giles et al. [21]	+	+	+	+	+	+	−	+	−	+	+	9/10	High
Iversen et al. [22]	+	+	−	+	−	−	+	+	−	+	−	6/10	Medium
Ohta et al. [23]	−	−	−	+	−	−	−	−	−	+	+	3/10	Low
Segal and al. [24]	+	+	+	+	−	−	+	+	−	+	+	8/10	High
Segal et al. [25]	+	+	+	+	−	−	+	+	−	+	+	8/10	High
Tennent et al. [26]	−	+	+	+	−	−	+	+	−	+	+	7/10	High

1 = eligibility criteria were specified, 2 = subjects were randomly allocated to groups, 3 = allocation was concealed, 4 = the groups were similar at baseline regarding the most important prognostic indicators, 5 = there was blinding of all subjects, 6 = there was blinding of all therapists who administered the therapy, 7 = there was blinding of all assessors who measured at least one key outcome, 8 = measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups, 9 = all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat", 10 = the results of between-group statistical comparisons are reported for at least one key outcome, 11 = the study provides both point measures and measures of variability for at least one key outcome.

3. Results

3.1. Flow of study selection

The database search provided 192 articles. After initial title and abstract screening, 70 articles were identified as potentially relevant citations. After full-text screening, 64 articles were excluded for not meeting the inclusion criteria. Hand searching yielded 2 more studies [20,25]. Therefore, 8 articles were included in the systematic review [19–26]. Figure 1 provides more details about the flow of study selection.

3.2. Characteristics of the included studies

3.2.1. Quality assessment

An overview of the quality assessment list is reported in Table 1. The majority of clinical trials scored at least 7/10, reflecting high study quality and reporting. The lowest score was 3/10 [23]. All studies did have a random allocation, similar groups at baseline and a statistical comparison between groups. Giles et al. [21] was the only study reporting blinding of both subjects and therapists but did not clearly describe if the assessor was blinded. Two references did not conceal allocation or indicate point estimates and measures of variability [22,23]. All studies, except Bryk et al. [19], showed dropout rates lower than 15%. None of the studies performed intention to treat analyses.

3.2.2. Participants

The included studies involved a total of 335 participants (157 in BFR, 178 in control interventions). Sample sizes ranged between 24 [22] and 79 [21]. Three studies examined only women [19,20,25], one study analyzed only men [24] and four had mixed cohorts [21–23,26]. Average cohort age ranged between 24 [22] and 62 years [19]. Studies included participants with knee osteoarthritis ($n = 164$) [19,20,24,25], patellofemoral pain ($n = 79$) [21], post knee arthroscopy ($n = 24$) [26] and anterior cruciate ligament reconstruction using hamstring tendon graft ($n = 68$) [22,23]. Table 2 summarizes participants' characteristics and Appendix 1 describes inclusion and exclusion criteria for participants in each study.

3.3. Intervention

3.3.1. BFR group intervention protocol

LL-BFR training was used in combination with leg press [21,24–26], leg extension [19,21,22,26] and static straight leg raise exercises [22]. Resistance during BFR exercise was 30% of 1RM in all interventions except Iverson et al. [22] and Ohta et al. [23] who did not specify resistance parameters. In the included studies, BFR intervention's duration varied from 2 to 16 weeks, with a frequency of 2 [20] to 6 [23] sessions per week. Most studies based their training on 4 sets with 30 repetitions in the first set and 15 repetitions in the last three sets, with 30 seconds resting time between the sets [21,24–26]. One study used 3 sets of 30 repetitions without mentioning the resting time [19]. Participants in Iversen et al. [22] performed 100 repetitions twice per day and those in Ferraz et al. [20] performed five sets of 10 repetitions twice per week. Finally, in Ohta et al. [23], 2 sets of various exercises were performed

Table 2
Characteristics of participants

Study	BFR group	Control group	Sex	Knee conditions
Bryk et al. [19]	$n = 17$ Age (y): 62.3 ± 7.0	$n = 17$ Age (y): 60.4 ± 6.7	BFR and control group: females (100%)	Knee osteoarthritis
Ferraz et al. [20]	$n = 16$ Age (y): 60.3 ± 3.0	$n = 32$ Age (y): 60.3 ± 4.0	BFR and control group: females (100%)	Knee osteoarthritis
Giles et al. [21]	$n = 40$ Age (y): 28.5 ± 5.2	$n = 39$ Age (y): 26.7 ± 5.5	BFR group (24 females/16 males) Control group (19 females/20 males)	Patellofemoral pain
Iversen et al. [22]	$n = 12$ Age (y): 29.8 ± 9.3	$n = 12$ Age (y): 24.9 ± 7.4	BFR group (5 females/7males) Control group (5 females/7 males)	Anterior cruciate ligament reconstruction
Ohta et al. [23]	$n = 22$ Age (y): 28.0 ± 9.7	$n = 22$ Age (y): 30.0 ± 9.7	BFR group (9 females/13males) Control group (10 females/12 males)	Anterior cruciate ligament reconstruction
Segal et al. [24]	$n = 20$ Age (y): 58.4 ± 8.7	$n = 22$ Age (y): 56.1 ± 7.7	BFR and Control groups: males (100%)	Knee osteoarthritis
Segal et al. [25]	$n = 19$ Age (y): 56.1 ± 5.9	$n = 21$ Age (y): 54.6 ± 6.9	BFR and Control groups: females (100%)	Knee osteoarthritis
Tennent et al. [26]	$n = 11$ Age (y): 37.0 (30–46.2)	$n = 13$ Age (y): 37.0 (32–47)	BFR (70% male) Control (71.43% male)	Knee arthroscopy

daily, 6 times per week during the first 16 weeks after anterior cruciate ligament reconstruction.

Pneumatic cuffs, hand pumped blood pressure cuffs and a size-specific tourniquet were used during BFR training interventions. Some studies placed the cuff on the most proximal part of the thigh [19–23,26], while others simply mentioned they used a consistent location without additional details [24,25]. Initial occlusive pressure in included studies ranged between 30 mmHg [24] and 100 mmHg [25]. The pneumatic cuff was then inflated until a desired exercise pressure ranged from 100 [24] to 200 mmHg [19]. Table 3 describes the different interventions used in the included studies.

3.3.2. Control group intervention

Control interventions were generally based on the same exercise protocols as BFR but without using vascular occlusion. The only exception was the study by Tennent et al. [26], in which both groups followed the same supervised accelerated physical therapy protocol but the BFR group performed three additional exercises under partial vascular occlusion.

Besides, three studies performed a low-load resistance training with 30% of 1 RM [22,24,25] during the treatment protocol. Bryk et al. [19] and Giles et al. [21] applied a high-load training with 70% of 1 RM. Finally, in Ferraz et al. [20], two control groups were formed: low-resistance training program (30% of 1 RM) and high-resistance training program (80% of 1 RM).

3.3.3. Outcome measures

Knee pain was measured using a numerical pain rating scale (NPRS) [19] and a visual analog scale (VAS) for worst pain in the last week [21]. In addition, Anterior Knee Pain Scale (AKPS), Knee Injury and Osteoarthritis Outcome Score (KOOS), Veterans general health questionnaire (VR-12), Lequesne questionnaire and Western Ontario and McMaster Universities Arthritis Index (WOMAC [19–21,24–26]) were used to assess knee symptoms and function. Studies that evaluated physical capacity used self-selected walking velocity (SSWV), sit-to-stand 5 times (STS5), 4 squares step test (FSST), timed stair ascent (TSA), timed-up and go (TUG) [19,20,24–26].

Muscle strength was evaluated in two studies by measuring maximum isotonic strength using a 1RM test [23–25]. Knee extensor strength was also assessed using a dynamometer [19–21,24–26]. Knee extensor strength was measured at baseline and 8-week and 6-month follow-up [21], 2 days before the initiation of treatment and 6 weeks after intervention [19], at base-

Table 3
Protocol intervention of the included studies

Study	Type of exercise training	BFR protocol	Control protocol	Cuff's parameters
Bryk et al. [19]	Leg extension	TOT: Low-load resistance (30% 1RM) T: 6 weeks F: 3 times/week TD: not specified R: 10-10-10 RT: not specified CTT: not specified	70% of 1RM without BFR for knee extension seated exercise	CF: upper third of the thigh TOF: pneumatic cuff ICPUA: N/A 1 min IIP: −200 mmhg
Ferraz et al. [20]	Leg press Leg extension	TOT: Low-load resistance (30% 1RM) T: 12 weeks F: 2 times/week TD: not specified R: 15-15-15-15-(15) RT: not specified CTT: not specified	80% of 1RM without BFR (high-intensity group) 30% of 1RM without BFR (low-intensity group)	CF: proximal thigh in supine position. TOF: Pneumatic cuff ICPUA: –N/A 1min IIP:70% of LOP
Giles et al. [21]	Leg press Leg extension	TOT: Low-load resistance (30% 1RM) T: 8 weeks F: 3 times/week with 2 weeks interval TD: 7 minutes R: 30-15-15-15 RT: 30 secs CTT: 5 minutes	70% of 1RM without BFR	CF: proximal thigh in standing position. TOF: Pneumatic cuff ICPUA: −N/A 1 min IIP: 60% of LOP
Iversen et al. [22]	Leg extension Straight leg raise	TOT: Low-load resistance T: 2 weeks F: Twice per day TD: not specified R: 200/day RT: not specified CTT: 5 minutes	Same protocol without using BFR	CF: most proximal part of the thigh. TOF: portable blood pressure ICPUA: –N/A 1 min IIP: –130–180 mmhg
Ohta et al. [23]	Straight-leg raises, half-squats, step-ups, knee-bending walking, elastic tube squat resistance	TOT: Low-load resistance T: 16 weeks F: 6times/week TD: variable R: variable RT: variable CTT: variable	Same protocol but without BFR	CF: most proximal part of the thigh. TOF: portable blood pressure ICPUA: –N/A 1 min IIP: 180 mmhg
Segal et al. [24]	Leg press	TOT: Low-load resistance (30% 1RM) T: 4 weeks F: 3 times/week TD:7 minutes R: 30-15-15-15 RT: 30 seconds CTT: 5 minutes	Same protocol but without BFR	CF: Same position but not determined TOF: Pneumatic cuff ICPUA: 100 mmhg 1 min IIP: –100–200 mmhg
Segal et al. [25]	Leg press	TOT: Low-load resistance (30% 1RM) T: 4 weeks F: 3 times/week TD: 7 minutes R: 30-15-15-15 RT: 30 seconds CTT: 5 minutes	Same protocol but without BFR	CF: Same position but not determined TOF: Pneumatic cuff ICPUA: 30–40 mmhg 1 min IIP: –100–200 mmhg
Tennent et al. [26]	Leg press Leg extension	TOT: Low-load resistance (30% 1RM) T: 4 weeks (12 sessions) F: not specified TD: 7 minutes R: 30-15-15-15 RT: 30 seconds CTT: 5 minutes	Same protocol without using BFR	CF: 6-cm and 16-cm measured proximal to the superior patellar pole TOF: Size-specific tourniquet ICPUA: N/A 1 min IIP: −80% of LOP

Abbreviations: ICPUA: Initial Cuff Pressure Upon Application, IIP: Incremental Inflation Pressures, CF: cuff placement, TOF: Type of cuff, TOT: type of training, T: Time, F: Frequency TD: Training duration, R: Repetitions, RT: Resting time, CTT: Cuff training time, LOP: limb occlusion pressure.

Table 4
Overview of the outcomes measure

Study	Knee functional capacities and knee pain	Knee extensor strength	Muscle thickness
Bryk et al. [19]	NPRS, Lequesne scale, TUG	Isometric dynamometer	N/A
Ferraz et al. [20]	TST, TUG, Self-reported quality of life, WOMAC	1RM measured in leg press and knee extension machine	Quadriceps cross-sectional area
Giles et al. [21]	Kujala Patellofemoral Score, VAS	Isometric dynamometer	Ultrasound
Iversen et al. [22]	N/A	N/A	MRI anatomical cross sectional area for muscle thickness (ACSA)
Ohta et al. [23]	N/A	Isokinetic dynamometer (60°/sec, 180°/sec)	MRI anatomical cross sectional area for muscle thickness (ACSA)
Segal et al. [24]	KOOS	1RM measured in leg press strength Isokinetic dynamometer (60°/sec)	N/A
Segal et al. [25]	KOOS	1RM measured in leg press strength Isokinetic dynamometer (60°/sec)	MRI (quadriceps volume)
Tennent et al. [26]	KOOS, VR-12, SSWV, STS5, FSST, and TSA	Isometric dynamometer	Thigh girth

Abbreviations: MRI: Magnetic resonance imaging, VAS: Visual Analogue Scale, NPRS: Numerical Pain Rating Scale, TUG: timed-up and go, KOOS: Knee Injury and Osteoarthritis Outcome Score, VR-12: general health questionnaire, SSWV: Self-selected walking velocity, STS5: sit-to-stand 5 times, FSST: 4 square step test, TSA: timed stair ascent, 1RM: one resistance maximal.

line and 4-week follow-up [24–26], 12-week follow-up [20] and 16-week follow-up [23].

Muscle thickness was evaluated by measuring cross-sectional area using CT-scan [20], MRI [22,23,25], thigh girth [26] and ultrasound [21]. Measurements were taken at the baseline and final visits, except Iverson et al. [22] who evaluated muscle thickness 2 days before and 16 days after surgery.

Table 4 reports an overview of the outcome measures.

3.4. Study results

Detailed study results can be found in Appendix 2. Figures 2 and 3 show forest plots for the studies comparing the effects of LL-BFR and control interventions on knee pain, function, quadriceps strength and thickness. Heterogeneity was generally high for these meta-analyses with I^2 ranging from 0% to 97%.

3.4.1. LL-BFR training versus LL quadriceps strengthening

Three studies [20,24,25] compared the effects of LL-BFR to conventional group using 30% of 1RM on knee pain. Overall, limited evidence indicates no superiority of LL-BFR for decreasing pain (SMD = −0.84, 95% CI −1.74 to 0.06). Similarly, two studies [20,25] with five outcome measures investigated the effects of LL-BFR and LL quadriceps strengthening on function. Limited evidence indicates that LL-BFR training is equally effective in improving function compared with an LL quadriceps strengthening program (SMD = −0.45, 95% CI–1.28 to 0.39).

As for quadriceps strength, 9 comparisons were included in the meta-analysis because the five studies that compared LL-BFR to control interventions using 30% of 1RM reported several outcome measures [20,22–25]. Overall, limited evidence indicates that LL-BFR is significantly more effective (SMD = 2.14, 95% CI 0.38 to 3.90). Finally, four studies [20,22,23,25] measured the effects of LL-BFR and LL quadriceps strengthening on muscle thickness and limited evidence indicate that LL-BFR is significantly more effective in improving quadriceps mass (SMD = 1.33, 95% CI 0.24 to 2.42).

3.4.2. LL-BFR training versus HL quadriceps strengthening

Three studies [19–21] with four comparisons compared the effects of LL-BFR to HL quadriceps training program on knee pain and limited evidence indicates superiority of LL-BFR in improving pain (SMD = 1.32, 95% CI 0.08 to 2.57). Limited evidence from three studies [19–21] with seven outcome measures indicate that LL-BFR and HL quadriceps strengthening are equally effective in improving function (SMD = −0.59, 95% CI −0.35 to 0.63). A total of three studies [19–21] and four outcome measures compared the effects of LL-BFR and HL control on quadriceps strength and conflicting evidence indicates no superiority of any method for increasing quadriceps strength (SMD = 0.16, 95% CI −0.64 to 0.96). Finally, on the basis of two studies [20,21], limited evidence indicates that LL-BFR training is equally effective in improving muscle thickness compared with an HL quadriceps strengthening program (SMD, 95% CI −0.31, −0.70 to 0.08).

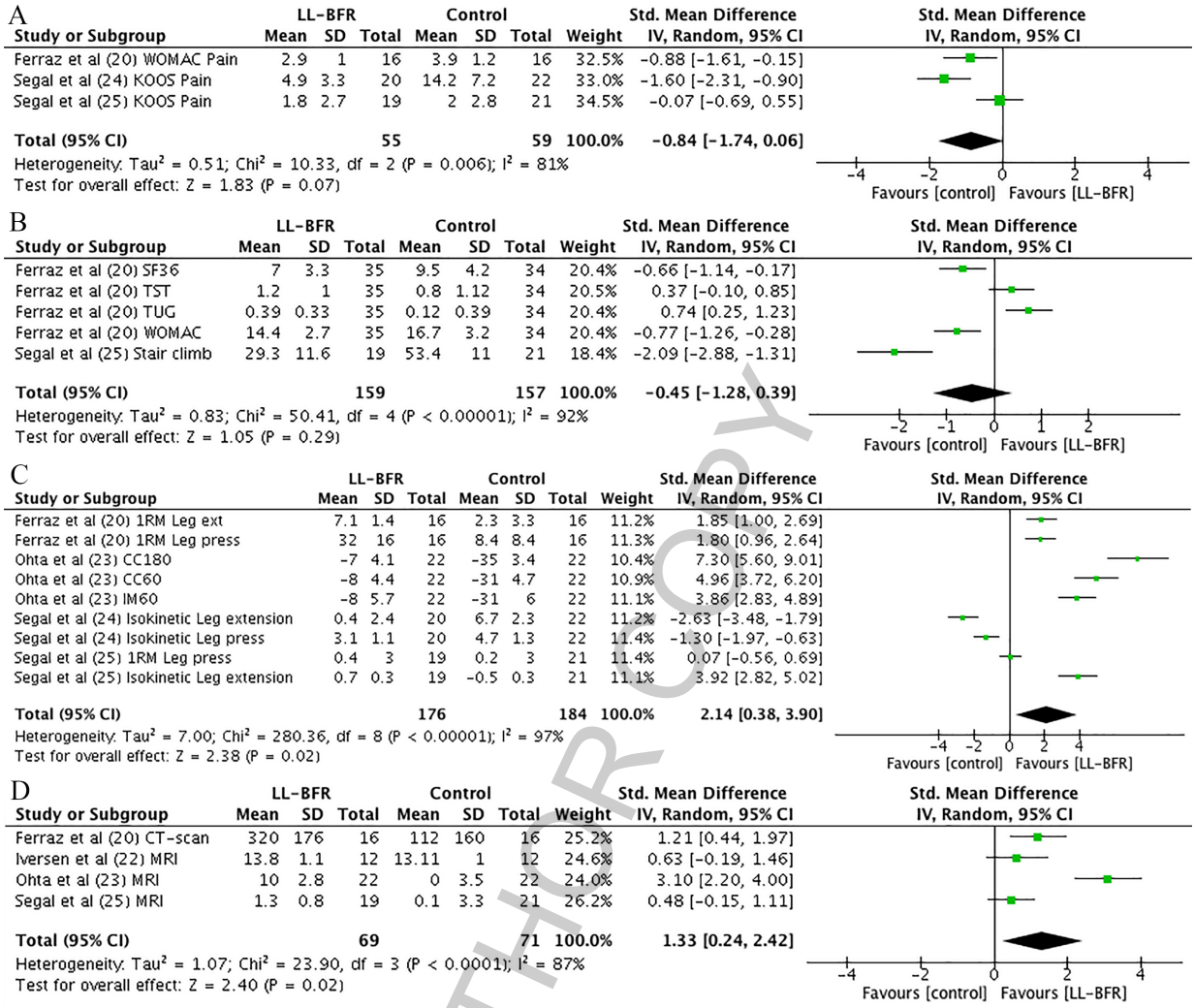

Fig. 2. Blood flow restriction combined with low-load program versus low-load comparison group: (A) pain, (B) function, (C) knee extensor strength, (D) muscle thickness.

3.4.3. BFR as an adjunct to conventional rehabilitation

One study was identified comparing the effects of LL-BFR as an adjunct to postoperative rehabilitation after knee arthroscopy [26]. Tennent et al. [26] found a significant increase in thigh girth at both 6-cm ($p = 0.01$) and 16-cm ($p < 0.01$) proximal to the patellar pole. In comparison, no changes were observed in controls. The VR-12 and KOOS subscales and all physical performance outcome measures significantly improved in the LL-BFR group ($p < 0.05$). The LL-BFR group displayed approximately 2-fold greater improvements in quadriceps strength compared with control (74.59% vs 33.5%, $p = 0.034$).

4. Discussion

The aim of this systematic review with meta-analysis was to compare the effectiveness of BFR training with low-load resistance and control interventions on knee pain and function, knee extensor strength and muscle thickness in individuals with knee conditions. While conflicting evidence indicates no superiority of an HL quadriceps strengthening program compared with LL-BFR interventions for increasing quadriceps strength, limited evidence indicates that LL-BFR training is equally effective in improving function. However, LL-BFR elicited less pain than HL quadriceps strengthening. Limited evidence indicates that, in comparison with a LL training, LL-BFR is significantly more effec-

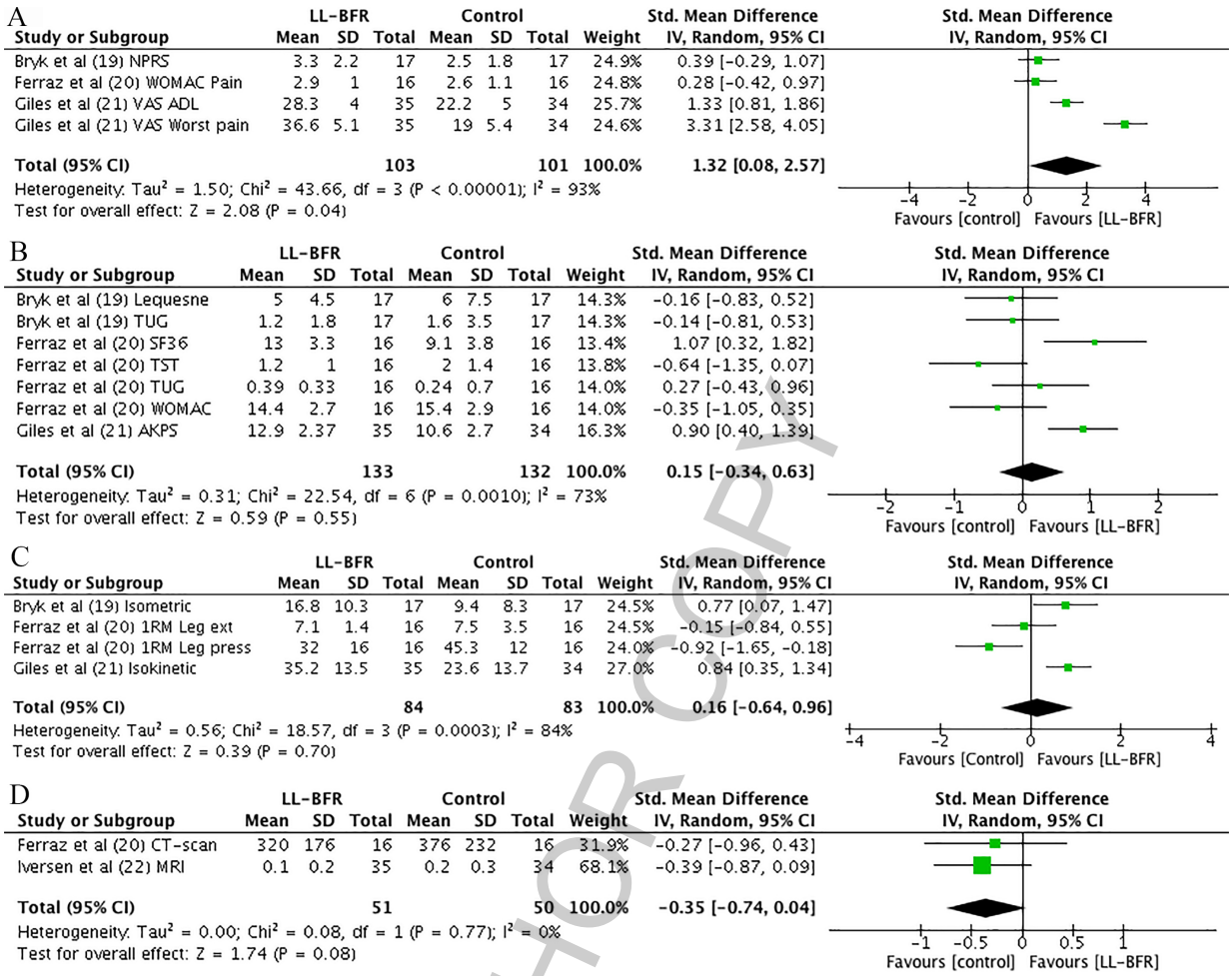

Fig. 3. Blood flow restriction combined with low-load program versus high-load comparison group: (A) pain, (B) function, (C) knee extensor strength, (D) muscle thickness.

tive in improving quadriceps strength and mass without eliciting more pain response. Moreover, limited evidence indicates that the addition of LL-BFR interventions to a postoperative therapy program can induce improvements in function, patient-reported outcome measures and quadriceps strength and thickness after knee arthroscopy.

Although our results do not suggest that LL-BFR can induce hypoalgesia in all patients with knee conditions, several studies included in this review reported pain reductions after BFR training. Bryk et al. [19] and Giles et al. [21] both reported significantly greater improvements in symptoms after 8 weeks of BFR compared with the control intervention. Specifically, participants in Giles et al. [21] reported 93% greater reduction in pain during activities of daily living, while Bryk et al. [19] noticed lower NPRS values during a quadriceps exercise. These results are in line with recent research. Korakakis et al. [27] reported that even a single acute LL-BFR exercise session induced clinically meaningful pain reductions for at least 45 minutes in subjects with anterior knee pain. Such reduction in pain allowed participants to perform exercises with increased knee loading, similarly to the results of Bryk et al. [19]. Therefore, acute pain reductions may allow clinical populations to benefit from exercises which would otherwise be associated with symptoms.

Because treatment effect in meta-analysis is calculated as the SMD, it could be difficult for the clinician to interpret the potential benefits of LL-BFR on pain. Bliddal and Christensen [28] presented an algorithm able to transform the SMD into a visual analogue scale ranging from 0 to 100 mm (VAS) by multiplying it by a standard deviation equal to 16.9 mm for pain. The

standard deviations used for conversion of SMD to millimetres were based on a cohort of 914 subjects with knee osteoarthritis [29]. In the present study, limited evidence indicated that LL-BFR elicited less pain than HL quadriceps strengthening (SMD = 1.32, 95% CI 0.08 to 2.57). Using these methods, this corresponds to a difference of 22 (95% CI, 1 to 43) mm between treatment groups on a VAS, enough to surpass the commonly suggested threshold of 15–20 mm for a clinically relevant difference in pain [30]. Therefore, despite showing no benefits of LL-BFR on function, results from this meta-analysis could provide a clinical rationale for the use of LL-BFR in individuals with knee conditions based on pain reductions. In comparison, knee arthroscopic surgery in middle aged and older patients with knee pain provided statistically significant but non clinically-relevant benefits of only 2.4 mm [31].

The mechanisms of action for BFR-induced pain reduction remain unclear. It has previously been hypothesized that decreased pain may be attributed to LL-exercise, arterial occlusion or the combination of both [27]. Acute exercise is believed to reduce sensitivity to painful stimuli in subjects with musculoskeletal conditions [32]. Thus, it is possible that low load quadriceps strengthening exercises simply induce better exercise-induced analgesia than HL-exercise, which can exacerbate knee symptoms. These assumptions are confirmed by the fact that, in the present meta-analysis, no significant between-group differences were found in studies comparing the effects of LL-BFR to conventional group using 30% of 1RM. Nevertheless, evidence suggest that hypoxia-induced analgesia could affect concentration of biochemical mediators that affect inhibition of nociceptive pathway [33]. Assuming that the mechanisms of action for BFR-induced pain reduction are a combination of exercise-induced and hypoxia-induced analgesia, it is likely that different combinations of arterial occlusion percentage and low-load may produce different pain responses [27].

The results of our meta-analysis suggest that LL-BFR program maximizes the effects of LL training on quadriceps strength and thickness in subjects with knee conditions. As for the mechanisms of action of LL-BFR training, the partial occlusion maintained by the cuff pressure likely induces anaerobic environment in the muscle during exercise. Therefore, type II muscle fibers could be better targeted [34,35], which could lead to muscle hypertrophy and increased strength. Moreover, other studies have suggested that BFR training can stimulate physiological mechanisms which can boost muscle strength [36,37]. Our results also suggest that LL-BFR training is equally effective in increasing quadriceps thickness compared with a conventional HL quadriceps training program. Conflicting results were found for muscle strength. Bryk et al. [19] and Giles et al. [21] reported no between-group differences for gains in knee extensor strength. However, a 49% greater improvement in the LL-BFR group compared to HL conventional group approached significance. Moreover, participants reporting pain during baseline resisted knee extension at 60° had greater increases in knee extensor torque with BFR. Similarly, in women with knee osteoarthritis, Ferraz et al. [20] reported that leg press and knee extension 1RM were increased to a similar extent in BFR group and HL-control.

Optimal BFR protocols remain unknown, mostly because of suboptimal reporting on parameters such as percentage load dose, training duration and cuff pressure. Some studies suggested that, since 4 weeks of LL-BFR are necessary to improve quadriceps strength [25, 37,38], interventions may have to be at least 8 weeks in order to detect any improvements in muscle size [39]. This could explain why Iverson et al. [22] did not observe any changes in muscle thickness with BFR during the first 16 days after ACL reconstruction. As for BFR training time, studies that showed significant changes in muscle strength used 30, 15, 15 and 15 repetitions per minute with 30 seconds rest between sets [24,25]. Fujita et al. [38] argued that LL-BFR at a 15 reps/min pace can increase muscle strength and that resting 1.5 minutes between sets can minimize fatigue levels. All studies from this systematic review used LL-BFR protocols of 30% of 1RM for each set. A recent review supported that LL-BFR training with progressive load is adequate to improve greater strength muscle [10]. Finally, it has been suggested that a frequency of two to three weekly sessions of LL-BFR could be enough to improve muscle strength [40].

Studies included in the present systematic review did not report any adverse effects of LL-BFR. Some authors have suggested that cuff pressure ranging between 120 and 200 mmHg is safe since it is insufficient to induce an entire arterial occlusion [23,41,42]. Nevertheless, Iverson et al. [22] reported rhabdomyolysis in less than 1/10,000 cases (0.008%), a proportion that could potentially be higher in symptomatic populations [12]. Therefore, clinicians should keep safety in mind when using BFR.

A major strength of this review is the synthesis of results through meta-analyses. Unlike previous reviews, this work allows for better interpretation and clearer messages for clinicians wishing to implement BFR in

their practice. This review also has limitations. Given that BFR is a relatively recent rehabilitation technique, only a few clinical trials including individuals with various knee conditions were identified in the current literature. Small samples (range: 24–79) recruited in these studies and high heterogeneity limit the ability to make definitive conclusions regarding the effect of BFR in people with knee conditions. Furthermore, meta-analyses considering multiple outcome measures from a same study could have influenced the homogeneity of the results and overestimated the effectiveness of BFR. Finally, the results of the different studies need to be interpreted with caution, because most of them did not report appropriate blinding of participants' assessor.

5. Conclusion

Limited evidence suggests that LL-BFR can induce benefits on knee pain, functional capacities and quadriceps strength and thickness in patients with knee conditions in comparison with a LL training program or in addition to a postoperative rehabilitation program. Furthermore, limited evidence indicates that LL-BFR training is equally effective in improving function and muscle thickness compared with a HL quadriceps strengthening program but elicits less knee pain. Therefore, BFR could potentially represent an interesting option for patients with knee conditions where conventional quadriceps strengthening program exacerbate knee symptoms. More research is needed to provide stronger recommendations and future investigations should compare different BFR protocols to help establish better guidelines for clinicians.

Conflict of interest

The authors confirm that there are no known conflicts of interest associated with this publication and there has been no financial support that could have influenced the outcomes of this work.

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Appendix 1. Inclusion and exclusion criteria

Study	Inclusion criteria	Exclusion criteria
Bryk et al. [16]	Scores of 2 or 3 in one of the knees based on the Kellgren and Lawrence scale.	Surgery of the affected knee; physical therapy; strengthening program for knee injuries; medication changed in the last 3 months; neurological disorder; heart condition.
Ferraz et al. [17]	Women (age between 50 and 65 yr) diagnosed with knee OA according to the American College of Rheumatology criteria.	Participation in physical exercise training over the past year; cardiovas- cular diseases and/or musculoskeletal disturbances which precluded exercise participation; Kellgren-Lawrence radiographic grade of 1 or 4; knee pain numeric Visual Analog Score less than 1 or greater than 8; use of non- steroidal anti-inflammatory drugs over the past three months; intra-articular infiltration with hyaluronic acid and cortico- steroids infiltration over the past 6 months.
Giles et al. [18]	Age between 18 and 40 years; atraumatic onset of anterior knee pain for more than 8 weeks; pain with two or more activities, including running, jumping, squatting, kneeling, stair ascent/descent or prolonged sitting; pain with any two of patellar compression; palpation of the peripatellar region and resisted isometric knee extension when sitting.	Patellar subluxation or dislocation; bursa; fat pad; knee surgery; participation in weight training of the legs in the past 6 months; patellar tendinopathy, increased symptoms with dynamic loads and pain reduction with sustained isometric contraction; elevated risk of venous thrombosis; lower limb surgery in the past 6 months; cardiovascular conditions; diabetes; unexplained chest pain or heart condition; fainting or dizzy spells during physical activity; exercise that causes loss of balance; pregnancy; or if exercise was contraindicated.
Iversen et al. [19]	Age between 18 and 40 years; physically active; no prior knee injuries, sport injury while; ACL injury not more than 6 months before surgery; reconstruction using hamstring tendon graft.	Not specified.
Ohta et al. [20]	Not specified.	Not specified.
Segal et al. [21]	At least one of the following risk factors symptomatic knee OA: Body Mass Index greater than or equal to 25 kg/m^2; knee joint injury or surgery, knee symptoms on most of last 30 days; radiographic knee OA.	Resistance training in the last 3 months; bilateral knee replacements; lower limb surgery in the last six months; back, hip or knee problems; inflammatory joint; or muscle disease; neurologic diagnoses; history of cancer, peripheral vascular disease or deep venous thrombosis; history of myocardial infarction or stroke in the last year; chest pain during exercise or at rest.
Segal et al. [22]	Radiographic knee OA without symptoms or had at least 1 of the following risk factors for symptomatic knee OA: knee injury with inability to walk without assistance for at least 2 days; knee surgery; knee pain, aching, or stiffness on most of the prior 30 days; body mass index over 25 kg/m^2.	Resistance training in the last 3 months; bilateral knee replacements; lower limb surgery in the last six months; back, hip or knee problems; inflammatory joint; or muscle disease; neurologic diagnoses; history of cancer, peripheral vascular disease or deep venous thrombosis; history of myocardial infarction or stroke in the last year; chest pain during exercise or at rest.
Tennent et al. [23]	Age between 18 and 65 years; nonreconstructive knee arthroscopy.	Inability to consent; any ligamentous, bony or soft tissue reconstruction; history of deep venous thrombosis; history of endothelial dysfunction; peripheral vascular disease; diabetes; easy bruising; contralateral extremity surgery; active infection; cancer; and pregnancy.

Appendix 2. Overview of the study results

Study	Knee functional capacities and knee pain	Knee extensor strength	Muscle thickness
Bryk et al. [16]	6 wk, preintervention and postintervention scores: *Lequesne Scale*: BFR grp pre, 11.5 ± 2.9; BFR grp post, 6.5 ± 3.4; C grp pre, 13.0 ± 8.3; C grp post, 7.0 ± 3.6. *TUG*: BFR grp pre, 7.5 ± 1.2; BFR grp post, 6.3 ± 1.6; C grp pre, 7.9 ± 2.7; C grp post, 6.3 ± 1.7. *NPRS*: BFR grp pre, 6.5 ± 2.5; BFR grp post, 3.2 ±1.9; C grp pre, 6.0 ± 2.6; C grp post, 3.5 ± 2.3. **No significant difference in Lequesne scale, NPRS and in TUG between groups (p =N/A). Significant increase in BFR group for NPRS while performing the quadriceps exercise ($p = 0.001$)**	6 wk, preintervention and postintervention scores: *Isometric dynamometer:* BFR grp pre, 23.2 kg ± 8.4; BFR grp post, 40.0 kg ± 9.2; C grp pre, 24.1 kg ± 10.1; C grp post, 33.5 kg ± 12.9. **No significant difference in quadriceps strength between groups (p = N/A)**	N/A
Ferraz et al [17]	12 wk, changes in outcomes : *WOMAC pain* : BFR grp, −45% C grp, −39% (LI-RT) −31% (HI-RT). *WOMAC stiffness*: BFR grp, −44% C grp, −41% (LI-RT) −32% (HI-RT). *WOMAC physical function*: BFR grp, −49% C grp, −42% (LI-RT) −49% (HI-RT). *WOMAC total*: BFR grp, −46% C grp, −42% (LI-RT) −39% (HI-RT). **Between groups comparison non provided**	12 wk, changes in outcomes: *1-RM leg press and knee extension*: Within-group increases in 1-RM leg press and 1-RM knee extension in HI-RT (+33%, ES = 0.82, $P < 0.0001$; +22%, ES = 0.83, $P < 0.0001$, respectively) and BFRT (+26%, ES = 1.01, $P < 0.0001$; +23%, ES: 0.86, $P < 0.0001$). 1-RM leg press (+8%, ES = 0.23, $P = 0.22$) and 1-RM knee extension (+7%, ES = 0.21, $P = 0.23$) after the intervention in LI-RT. HI-RT ($P < 0.0001$) and BFRT ($P = 0.0004$) significantly greater increases in 1-RM leg press when compared with LI-RT. HI-RT and BFRT greater increases in 1-RM knee extension ($P = 0.0004$ and $P = 0.0005$, respectively) when compared with LI-RT. **No significant differences between HI-RT and BFRT were observed ($P > 0.05$)**	12 wk, changes in outcomes: no significant differences between groups at PRE ($P = 0.77$). significant within-group increases in CSA were in HI-RT (+8%, ES = 0.54, $P < 0.0001$) and BFRT (+7%, ES = 0.39, $P < 0.0001$), but not in LI-RT (+2%, ES = 0.12, $P = 0.52$). **Significant difference in CSA in HI-RT and BFRT when compared with LI-RT ($P = 0.007$ and $P = 0.02$). No significant difference between HI-RT and BFRT ($P > 0.05$)**
Giles et al [18]	8 wk, preintervention and postintervention scores: All subjects: – *VAS worst pain*: BFR grp pre, 55.7 ± 13.9; BFR grp post, 27.4 ± .20.1; C grp pre, 51.4 ± 15.3; C grp post, 29.2 ± 25.6. *Kujula score*: BFR grp pre, 73.6 ± 9.9; BFR grp post, 86.5 ± 10.5; C grp pre, 72.6 ± 10.5; C grp post, 83.2 ± 12.3. *VAS ADL*: BFR grp pre, 58.2 ± 17.5; BFR grp post, 21.6 ± 25; C grp pre, 42.5 ± 22.8; C grp post, 23.5 ± 24.1. **No significant difference between groups in VAS worst pain (p = 0.237), Kujula score ($p = 0.308$). Significant differences between groups in VAS ADL ($p = 0.022$)** – Subjects with pain with resisted knee extension: *VAS worst pain*: BFR grp pre, 57.7 ± 13.4; BFR grp post, 25.0 ±15.8; C grp pre, 52.3 ± 15.6; C grp post, 27.4 ± 22.2. **No Significant differences between groups ($p = 0.2666$)**	8 wk, preintervention and postintervention scores: *Isokinetic dynamometer:* All subjects: BFR grp pre, 166.4 Nm ± 59.4; BFR grp post, 161.0 Nm ± 53.3; C grp pre, 135.1 Nm ± 55.1; C grp post, 158.7. Nm ± 57.04. **No significant difference between groups ($p = 0.073$)** Subjects with pain with resisted knee extension BFR grp pre, 117.5 Nm ± 54.9; BFR grp post, 161.0 Nm ± 53.3; C grp pre, 129.8 Nm ± 62.6; C grp post, 149.2. Nm ± 58.11. **Significant differences between groups (p = 0.003)**	8 wk, preintervention and postintervention scores: *Quadriceps size:* BFR grp pre, 7.9 cm ± 1.3; BFR grp post, 8.0 cm ± 1.1; C grp pre, 7.7 cm ± 1.4; C grp post, 7.9 cm ± 1.2. **No significant difference between groups ($p = 0.195$)**

Study	Knee functional capacities and knee pain	Knee extensor strength	Muscle thickness
	6 mo, preintervention and postintervention scores: – All subjects: *VAS worst pain*: BFR grp pre, 55.7 ± 13.9; BFR grp post, 28.1 ± 25.5; C grp pre, 51.4 ± 15.3; C grp post, 25.8 ± 27.1. *Kujula score*: BFR grp pre, 73.6 ± 9.9; BFR grp post, 84.4 ± 12.0; C grp pre, 72.6 ± 10.5; C grp post, 85.9 ± 13.3. *VAS ADL*: BFR grp pre, 58.2 ± 17.5; BFR grp post, 31.7 ± 26.6; C grp pre, 42.5 ± 22.8; C grp post, 23.9 ± 25.4. **No significant difference between groups in VAS worst pain ($p = 0.752$), Kujula score ($p = 0.351$) and VAS ADL ($p = 0.175$)** – Subjects with pain with resisted knee extension: *VAS worst pain*: BFR grp pre, 57.7 ± 13.4; BFR grp post, 29.8 ± 26.6; C grp pre, 52.3 ± 15.6; C grp post, 28.0 ± 27.1. **No significant differences between groups ($p = 0.708$)**		
Iversen et al. [19]	N/A	N/A	16 da, preintervention and postintervention scores: *Anatomical cross sectional area:* Mean change % BFR grp −13.8 ± 1.1; C grp, 13.1 ± 1.0; **No significant difference between groups ($p = 0.6265$)**
Ohta et al. [20]	N/A	16 wk, preintervention and postintervention scores: *Isokinetic dynamometer* (operated/healthy ratio): – Concentric 60°/sec: BFR grp pre, 84 ± 13; BFR grp post, 76 ± 16; C grp pre, 86 ± 14; C grp post, 55 ± 17. **Significant difference between groups ($p < 0.001$)** – Concentric 180°/sec: BFR grp pre, 84 ± 14; BFR grp post, 77 ± 13; C grp pre, 90 ± 9; C grp post, 65 ± 13. **Significant difference between groups ($p = 0.004$)** – Isometric 60° knee flexion: BFR grp pre, 92 ± 19; BFR grp post, 84 ± 19; C grp pre, 94 ± 21; C grp post, 63 ± 19. **Significant difference between groups ($p < 0.001$)**	16 wk, preintervention and postintervention scores: *Cross-sectional areas:* BFR grp pre, 9.1 cm ± 0.7; BFR grp post, 10.1 cm ± 11; C grp pre, 9.2 cm ± 1.1; C grp post, 9.2 cm ± 1.2. **Significant difference between groups ($p < 0.005$)**
Segal et al. [21]	4 wk, percentage of change in outcomes: *KOOS pain score:* BFR grp, 4.9 ± 3.3; C grp, 4.2 ± 7.2. **No significant difference between groups ($p = 0.254$)**	4 wk, percentage of change in outcomes: *Isotonic leg press strength:* BFR grp, 3.1 ± 0.9; C grp, 4.7 ± 1.3. *Isokinetic knee extensor strength:* BFR grp, 0.4 ± 2.4; C grp, 6.7 ± 2.3. **No significant difference between groups in isotonic leg press strength ($p = 0.322$) and isokinetic knee extensor strength ($p = 0.066$)**	N/A

Study	Knee functional capacities and knee pain	Knee extensor strength	Muscle thickness
Segal et al. [22]	4 wk, preintervention and postintervention scores: *KOOS*: BFR grp , 1.8 ± 2.7; C grp, 2.0 ± 2.8. **No significant difference between groups ($p = 0.9574$)**	4 wk, preintervention and postintervention scores: *Scaled leg press 1RM (kg/kg body mass):* BFR grp pre, 2.1 ± 0.5; BFR grp post, +0.4 ± 0.3; C grp pre, 2.3 ± 0.6; C grp post, +0.2 ± 0.3. *Scaled 40% 1RM Leg press power (Watts):* BFR grp pre, 12.6 ± 2.5; BFR grp post, +0.62 ± 0.27; C grp pre, 11.3 ± 2.9; C grp post, +0.42 ± 0.26. *Scaled isokinetic knee extensor (Nm/kg):* BFR grp pre, 1.3 ± 0.4; BFR grp post, +0.07 ± 0.3; C grp pre, 1.3 ± 0.3; C grp post, −0.05 ± 0.3. *Stair climb power (Watts):* BFR grp pre, 364.3 ± 71.2; BFR grp post, +29.3 ± 11.6; C grp pre, 404.3 ± 118.4; C grp post, +53.4 ± 11.0. No significant difference between groups in scaled 40% 1RM Leg press power ($p = 0.6173$) and isokinetic knee extensor Stair climb power ($p = 0.1520$). **Significant difference between groups in scaled leg press 1RM ($p = 0385$) and isokinetic knee extensor stair climb power ($p = 0.048$)**	4 wk, preintervention and postintervention scores: *Quadriceps volume:* BFR grp pre, 948.0 cm [3] ± 71.4; BFR grp post, +0.01% ± 0.73; C grp pre, 1030.8 cm [3] ± 65.2; C grp post, +1.3% ± 0.80. **No significant difference between groups ($p = 0.2604$)**
Tennent et al. [23]	12 ss, change in outcomes: *KOOS Pain*: BFR grp, 22.22 (7.64 to 30.56) C grp, 8.33 (5.6 to 19.4). *KOOS Symptoms*: BFR grp, 25.00 (7.1 to 33.00) C grp, 7.14 (0 to 21.4). *KOOS ADL*: BFR grp, 23.52 (4.8 to 34.2) C grp, 5.88 (1.5 to 25.0). *KOOS QOL*: BFR grp, 15.63 (0 to 50.0) C grp, 18.75 (-6.3 to 31.25). *KOOS Sport*: BFR grp, 40.00 (6.3 to 52.5) C grp, 15.00 (0.0 to 45.0). *VR-12 PCS*: BFR grp, 10.92 (−1.1 to 22.2) C grp, 8.32 (1.4 to 21.9). *VR12 MCS*: BFR grp, 13.05 (3.4 to 14.8) C grp, −1.77 (−5.7 to 2.4). *Physical outcome SSWV*: BFR grp, 0.49 (0.15 to 0.75) C grp, 0.45 (0.27 to 0.78). *Physical outcome Stair climb*: BFR grp, 3.77 (1.3 to 7.3) C grp, 0.78 (0.5 to 1.5). *Physical outcome FSST*: BFR grp, 2.07 (0.2 to 2.7) C grp, 1.30 (0.9 to 2.1). *Physical outcome Sit-Stand*: BFR grp, 2.8 (1.0 to 4.9) C grp, 3.13 (2.1 to 4.7). **No significant difference between groups (p = N/A), except for VR12 MCS (,$p = 0.0149$)**	12 ss, percentage of change in outcomes: *Isokinetic dynamometer:* BFR grp, 77.92 (42.4–129.6) C grp, 40.80 (3.6–74.6). **No significant difference between groups ($p = 0.0969$)**	12 ss, change in outcomes: *Thigh girth (cm) 6 cm proximal patella:* BFR grp, 1.75 (1 to 4.6) C grp, 0 (−1 to 0.5). *Thigh girth (cm) 16 cm proximal patella:* BFR grp, 2.25 (0.75 to 3) C grp, 0.5 (0 to 1.5). **Significant difference between groups ($p = 0.0069$)**

Abbreviations: VAS, Visual Analogue Scale; NPRS, Numerical Pain Rating Scale; TUG: timed-up and go; KOOS: Knee Injury and Osteoarthritis Outcome Score; VR-12, general health questionnaire; SSWV, Self-selected walking velocity; STS5, sit-to-stand 5 times; FSST, 4 square step test; 1RM, one resistance maximal; ADL, activity daily life; TSA, stair climb ascent; N/A: not available.