Credibility of Blood Flow Restriction Training in Patients With Knee Osteoarthritis

A Systematic Review and Meta-analysis

Jinrong He,[*] MSc, Lei Zhang,[*] MD, Quanshuo Wu,[†] MSc, and Jialin Zhang,[‡§] MD, Prof.
Investigation performed at the School of Physical Education, Shanghai University of Sport, Shanghai, China

Background: The effectiveness and practicality of blood flow restriction training (BFRT) as a nonsurgical intervention for treating patients with knee injuries are uncertain because of the small size of BFRT trials and inconsistent results.

Purpose: To conduct a meta-analysis comparing the effectiveness of BFRT versus traditional resistance training in patients with knee osteoarthritis (OA) in terms of pain, muscle strength, functional performance, self-reported function, muscle size, and adverse events during exercise.

Study Design: Systematic review; Level of evidence: 1.

Methods: Under the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, we searched the Web of Science, PubMed, EMBASE, and other databases for randomized controlled trials of BFRT interventions in patients with knee OA. Methodological and quality evaluations, heterogeneity analysis, and subgroup analysis of the included studies were conducted, and effect sizes were evaluated using mean differences or standardized mean differences (SMDs). Subgroup and sensitivity analyses were used to explore the sources of heterogeneity.

Results: Of 2826 initial studies, 6 studies (N = 228 patients) were included. The results of the meta-analysis indicated that compared with resistance training, BFRT did not significantly affect pain relief (SMD, −0.02 [95% CI, −0.30 to 0.26]; *P* = .88), muscle strength (SMD, 0.32 [95% CI, −0.33 to 0.96]; *P* = .33), functional performance (SMD, 0.25 [95% CI, −0.29 to 0.80]; *P* = .36), or self-reported function (SMD, −0.252 [95% CI, −0.88 to 0.45]; *P* = .52). However, BFRT reduced the risk of adverse events (risk ratio, 0.45 [95% CI, 0.20 to 1.01]; *P* = .05). Subgroup analysis revealed that compared with low-load resistance training, BFRT significantly increased muscle size (SMD, 0.88 [95% CI, 0.09 to 1.68]; *P* = .02). The quality-of-evidence assessment indicated that the evidence level for the above outcomes was low and that the strength of the recommendation was weak.

Conclusion: The results of our meta-analysis indicated that compared with resistance training, BFRT did not significantly improve symptom outcomes in patients with knee OA. It is important to acknowledge that the findings were limited by the small number of studies and sample sizes that were included.

Keywords: blood flow restriction training; exercise intervention; knee osteoarthritis; meta-analysis

Osteoarthritis (OA) is the most prevalent chronic degenerative bone and joint disease among middle-aged and elderly individuals globally, and the knee is particularly susceptible to OA.[31] In the United States, almost 40% of older adults suffer from symptomatic knee OA, which typically presents with pain, stiffness, decreased joint mobility, and muscle weakness.[10] The pathogenesis of knee OA is closely related to several factors.[45] Normal wear and tear, abnormal mechanical loading, injury, and aging are all common causes of damage to articular cartilage, subchondral bone, synovial tissue, and ligaments, leading to alterations in the extracellular matrix composition and

---

The Orthopaedic Journal of Sports Medicine, 13(2), 23259671241300145
DOI: 10.1177/23259671241300145

stimulating chondrocytes to produce more catabolic factors involved in cartilage degradation—such matrix metalloproteinases and a disintegrin and metalloproteinase with thrombospondin motifs—resulting in a progressive loss of proteoglycans, followed by degradation of type 2 collagen.[37] Continuation of this process disrupts cartilage integrity, increases the water content of hyaline cartilage, and induces apoptosis of articular chondrocytes, ultimately leading to knee OA symptoms.[57]

Rehabilitation training through exercise aims to enhance any aspect of a patient's body function either through the patient's strength or with the aid of specific equipment.[46] This approach is nonpharmacological and is recommended by the treatment guidelines of the Osteoarthritis Research Society International[2] and the American College of Rheumatology.[21] A systematic review of randomized trials of exercise-based therapies for patients with knee OA showed that exercise significantly reduced pain and improved physical function and quality of life.[13] In addition, exercise training improves cardiorespiratory fitness, muscle strength, joint balance, and mental health.[14]

Resistance training is a common rehabilitation option for patients with knee OA, usually combined with anaerobic, aerobic endurance, or aquatic exercise using a progressive loading strategy based on self-weight.[9,25,36] A study of patients with knee OA demonstrated significant improvements in function, strength, and joint mobility after 8 weeks of resistance training.[38] According to American Medical Association recommendations, the minimum mechanical load required to improve muscle strength and mass during resistance training is 60% and 70% of the 1-repetition maximum (1-RM; ie, the maximum weight that can be lifted only once), respectively.[1] However, in patients with knee OA, high-intensity resistance training can increase joint stress, leading to further escalation and worsening of pain and decreased patient compliance with training.[32] It has been shown that 40% of patients with knee OA (40-70 years old) who perform high-intensity resistance exercise with large muscle groups (70% of 1 RM) experience a significant increase in knee cartilage systolic blood pressure (up to 250 mm Hg), resulting in several orthopaedic injuries.[39]

In 2014, Scott et al[41] reported that low-intensity endurance exercise performed with blood flow restriction improved muscle strength and mass while minimizing adverse events, and a later study by Conceição et al[8] indicated that such training enhanced motor adaptions in patients. Blood flow restriction training (BFRT) is synonymous with terms such as *kaatsu*, occlusion training, and hypoxic training.[30] The purpose of BFRT is to reduce partial arterial blood inflow while blocking venous blood flow[7] of the limb during resistance training or exercise by using tourniquets,[47] inflatable cuffs,[50] or elastic knee pads,[29] thereby inducing local hypoxia environment during exercise. Reducing joint load by applying a lower resistance load achieves similar results as high-load resistance training (HLRT) ($\geq$70% of 1-RM) in terms of increasing muscle size and strength.[41] Although the American College of Sports Medicine recommends that resistance training loads should exceed 60% of the 1-RM to achieve muscle hypertrophy,[1] various studies have demonstrated that even low-intensity BFRT (20% of 1-RM) can result in substantial gains in muscle hypertrophy and muscle strength.[49,51]

There is yet to be a consensus on the effectiveness of BFRT owing to the limited sample sizes of BFRT trials in patients with knee OA and the variability of the results. Some studies have shown that resistance training that restricts blood flow in patients with knee OA reduces joint stress and pain, increases muscle strength, improves quadriceps mass, and increases joint motor function.[11] However, Teixeira et al[53] concluded by performing BFRT on 49 men that BFRT incorporated into HLRT during rest intervals or muscle contractions did not enhance muscle strength or hypertrophy. In addition, pain is an essential indicator of the effect of exercise interventions in patients with knee OA, but pain scores have yet to be evaluated in previous studies.[22] It is also essential to consider the safety of BFRT in patients with knee OA, as most of this population is elderly and has various complications. Therefore, the efficacy and feasibility of BFRT as a nonsurgical intervention for treating patients with knee injuries remain uncertain.

The purpose of this systematic review was to evaluate the efficacy of BFRT compared with traditional resistance training in patients with knee OA. As variability in subject populations, adverse events, training cycles, and outcome measures in previous studies may have contributed to inconsistencies in experimental results, we included only randomized controlled trials (RCT) and synthesized, generalized, and specified training effects of the included studies. We hypothesized that BFRT would be more effective in improving pain, muscle strength, functional performance, self-reported function, and muscle size while reducing adverse events in patients with knee OA compared with conventional resistance training.

METHODS

Search Strategy

The search strategy and reporting of this systematic review adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[35]

[§] Address correspondence to Jialin Zhang, MD, Prof, School of Physical Education and Sport Science, Fujian Normal University, 1 Keji Road, Minhou District, Fuzhou, Fujian 350117, China (email: zhangjialinx@126.com) .

[*] School of Physical Education, Shanghai University of Sport, Shanghai, China.

[†] School of Physical Education and Sport Science, South China Normal University, Canton, China.

[‡] School of Physical Education and Sport Science, Fujian Normal University, Fuzhou, China.

Final revision submitted September 27, 2024; accepted October 10, 2024.

and followed the recommendations of the Cochrane Handbook for Systematic Reviews.[20] The protocol of the review was prospectively registered in PROSPERO and submitted online in February 2024 (ID: CRD42024516481).

Two researchers (J.H. and Q.W.) searched for relevant studies in a systematic and double-masked manner using 4 sets of keywords in accordance with the PRISMA statement.[35] The databases that were searched included Web of Science, PubMed, EMBASE, and the Cochrane Library, and the search dates ranged from January 1, 2000, to April 13, 2024. The first set of keywords comprised synonyms for BFRT as follows: "KAATSU," "blood flow," "BFR," and "occlusion." The second set of keywords included synonyms for OA of the knee as follows: "KOA," "OA," "osteoarthritis," and "arthritis." The third set of keywords comprised synonyms for exercise intervention as follows: "exercise," "train," and "training." To ensure that at least 1 search term within each set of keywords was included in the results, the Boolean operator "OR" was used to connect all synonyms, and synonyms between sections were connected by "AND." Additionally, ClinicalTrials.gov and the International Clinical Trials Registry Platform were searched to identify unpublished records.

Inclusion and Exclusion Criteria

Inclusion Criteria. The selection and assessment of the literature were conducted according to the population, intervention, comparators, outcome[s], and study design principle[23]: (1) The population of interest was patients meeting the diagnostic criteria for knee OA as outlined in the Osteoarthritis Diagnostic Guidelines of the Orthopedic Branch of the Chinese Medical Association (2019 edition)[58] or the American College of Rheumatology.[12] No restrictions were placed on the age, sex, or clinical course[56] of the patients, and there were no racial or geographic limitations. (2) Regarding intervention and comparators, this study compared BFRT with other exercise interventions—including HLRT ($\geq$70% of 1-RM); moderate-intensity resistance training (40%-70% of 1-RM); low-load resistance training ($<$40% of 1-RM), stretching, and brisk walking. (3) For outcome indicators, studies were required to include at least 1 of the following outcomes: pain, muscle strength, muscle size, functional performance, self-reported function, or adverse events. Adverse events were defined as unintended or unexpected incidents that may result in temporary or permanent disability for the patient.[55] (4) Regarding study design, the included studies were all RCTs.

Exclusion Criteria. Excluded were (1) studies published in a language other than English, (2) literature reviews, (3) animal studies, (4) studies in which data could not be extracted or combined, and (5) studies in which participants underwent surgery—eg, total knee replacement or anterior cruciate ligament reconstruction—or experienced lower extremity trauma.

Data Extraction

Upon completion of the literature retrieval process, the collected sources were uniformly imported into the literature management software to eliminate any duplicates. Two researchers (J.H. and Q.W.) independently screened the literature according to the inclusion and exclusion criteria and extracted data using Excel (Microsoft Corp). Any discrepancies in judgment were discussed with a third researcher (L.Z.) to reach a consensus. The extracted data included information such as the study authors, year of publication, patient characteristics (sample size, age, and sex), intervention (intervention mode, intervention period, training intensity, cuff position, and pressure), and outcome metrics (pain, muscle strength, muscle size, functional performance, self-reported function, and adverse events).

Quality Assessment

The methodological evaluation of the 6 included papers was based on the Cochrane Handbook for Systematic Reviews (Version 5.1.0),[16] and the risk of bias was scored individually for each study by 2 authors (J.H. and Q.W.) independently. Disagreements were resolved through discussion with a third researcher (L.Z.). The Cochrane evaluation criteria consist of randomized sequence generation (selective bias), allocation concealment (particular bias), blinding of the subject investigators (implementation bias), blinding of the outcome assessment (measurement bias), incomplete outcome data (follow-up bias), selective reporting (reporting bias), and other biases. Each indicator is categorized as *low risk, unclear risk*, or *high risk* of bias, and an overall grade is then assigned: grade A ($\geq$4 items with low risk), grade B (2-3 items with low risk), and grade C (0-1 items with low risk; possibility of bias).[16]

Evaluation of the Quality of Evidence

The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system was used to evaluate the quality of evidence for meta-analysis.[17] The GRADE comprises 5 assessment categories—study limitations (risk of bias); inconsistency; indirectness; imprecision; and publication bias—each categorized as *none* (not downgraded), *severe* (downgraded by 1 level), or *very serious* (downgraded by 2 levels). The quality of evidence is categorized into 4 levels—*high, moderate, low*, or *very low*.

Statistical Analysis

Heterogeneity and subgroup analyses of the outcome indicators of the continuous variables included in the study were performed using Review Manager 5.4 software (The Cochrane Collaboration, 2020). The effect sizes were evaluated using the mean difference for consistent units of continuous data and the standardized mean difference (SMD) with 95% CI for units that were not consistently presented; for SMD, $<$0.5 indicated small effect size, $0.5 \leq \text{SMD} < 0.8$ indicated medium effect size, and $\geq$0.8 indicated large effect size. For comparison, the risk ratio (RR) with 95% CI was used to evaluate noncontinuous data. The degree of heterogeneity was quantitatively analyzed using the I^2 statistic, which represents the level of heterogeneity between studies and ranges from 0% to 100%. Heterogeneity among studies was classified as none (I^2 = 0%); small and negligible (I^2 = 0%-25%), low degree (I^2 = 25%-50%), medium (I^2 = 50%-75%), and high (I^2 = 75%-100%). Comparisons of studies with low heterogeneity were analyzed using a fixed-effects model, while those of studies with moderate and high heterogeneity were analyzed using a random-effects model. Subgroup and sensitivity analyses were used to explore the sources of heterogeneity and were performed using Stata/SE 15.1 (StataCorp).

RESULTS

Search Results

A total of 2826 studies were identified across the 4 databases, resulting in the elimination of 744 duplicates. After the initial screening, 2082 studies remained, but 2019 were deemed irrelevant after a review of their titles and abstracts. Subsequently, 63 studies underwent a second screening based on the exclusion criteria, of which 57 were excluded. Reasons for exclusion included wrong study design (not an RCT), missing pre- or posttest values, duplicate experiments, nonconformity to the indicator format, synergistic treatment with drugs, and documents reporting only study design protocols. Ultimately, 6 studies[4,11,19,42,43,44] were included in the present review. The screening process is illustrated in Figure 1.

Study Characteristics

The baseline information for the 6 included studies, published between 2015 and 2021, is shown in Table 1. The studies comprised 228 patients with knee OA (61 men and 167 women; mean age, 61.05 ± 7.75 years). Participants in 2 studies[4,44] (n = 64) had a previous diagnosis of knee OA, in 2 studies[11,19] (n = 83) the participants were screened using diagnostic criteria promulgated by the American College of Rheumatology, and in the remaining 2 studies[42,43] (n = 81) the participants were screened based on risk factors for knee OA. Of the studies involving BFRT, all described where the cuffs were worn, and 3 described the cuff size in detail,[11,42,43] but the blood flow occlusion protocol varied between studies. In 2 studies,[42,43] the cuff pressure was gradually increased from 30 to 40 mm pumping during the preparation phase to 160 to 200 mm pumping during individual training sessions; 1 study[11] set cuff pressure at 70% of the total arterial occlusion pressure; 2 studies[4,44] each used 200 mm pumping and pressures sufficient to block venous return but not completely block arteries (not explicitly stated); and 1 study[19] individualized each participant's cuff pressure using the equation *pressure* = 0.5 (*systolic blood pressure*) + 2 (*thigh circumference*) + 5 based on previous literature.

All studies included exercise protocols performed under blood flow restrictions (Table 2). Only 1 study[44] specified the intensity of the intervention; the remaining 5 studies used a 1-RM percentage system for BFRT combined with LLRT (20%-30% of 1-RM), and the control group received resistance training alone (30%-70% of 1-RM). Five studies measured changes in quadriceps strength: 4 of the studies[4,19,42,43] measured peak isometric knee extensor torque in the unilateral lower extremity using a Biodex System 3 dynamometer, and 1 study[19] used a hand-held dynamometer (Lafayette Instrument Co) to assess maximum isometric voluntary contraction of the quadriceps muscle. Three studies looked at the effect of muscle strength in patients with bilateral OA: 2 of the studies[42,43] used an instrumented pneumatic leg press (Keiser A420; Keiser) to measure the strength of isometric leg presses supported by each participant's legs, and 1 study[19] used isometric measurements of the quadriceps muscle using the unilateral limb with the higher level of self-reported pain. Only 1 study[11] reported the effect of BFRT on hamstring muscle strength. Although some exercises were not assessed as part of the BFRT training program, 1 study[4] also included individual proprioceptive training with medial and lateral hip extension exercises.

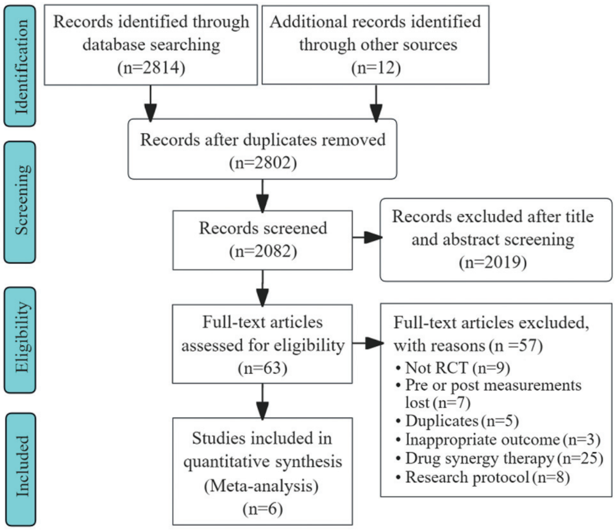


Figure 1. A PRISMA flow diagram of the literature search and selection process. RCT, randomized controlled trials; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Risk-of-Bias Assessment

The methodological evaluation of the included studies (Figure 2) revealed that 4 studies[4,11,19,42] had an evaluation grade of A and the remaining 2 studies[43,44] had an evaluation grade of B. None of the studies had an evaluation grade of C. All of the included trials used randomized sequence generation in their study design. Four mentioned allocation concealment, while the remaining 2 studies[11,19] were at moderate risk for selection bias. None of the studies successfully masked participants or staff. Regarding

TABLE 1
Baseline Characteristics of the Included Studies[a]

Lead Author (Year)	Sample Size; Sex	Age, Years	Basis of Diagnosis	Intervention	Frequency
Segal[42] (2015)	• EG: 19 • CG: 22 All men	• EG: 58.4 ± 8.7 • CG: 56.1 ± 7.7	Knee injury preventing walking (2 d), knee surgery, knee pain, overweight or obese	• EG: BFRT+LLRT (30% of 1-RM) • CG: LLRT (30% of 1-RM)	3 d/wk for 4 wk
Segal[43] (2015)	• EG: 19 • CG: 21 All women	• EG: 56.1 ± 5.9 • CG: 54.6 ± 6.9	BMI $\geq$25 kg/m^2, radiographic knee OA, knee joint injury or surgery, knee symptoms	• EG: BFRT+LLRT (30% of 1-RM) • CG: LLRT (30% of 1RM)	3 d/wk for 4 wk
Bryk[4] (2016)	• EG: 17 • CG: 17 All women	• EG: 62.3 ± 7 • CG: 60.4 ± 6.7	Fulfilled combined clinical and radiographic symptoms of knee OA	• EG: BFRT+LLRT (30% of 1-RM) • CG: HLRT (70% of 1-RM)	3 d/wk for 6 wk
Ferraz[11] (2018)	• EG: 16 • CG: 16 • CG2: 16 All women	• EG: 60.3 ± 3.0 • CG: 59.9 ± 4 • CG2: 60.7 ± 4	Diagnosed with K-L radiographic knee OA	• EG: BFRT+LLRT (30% of 1-RM) • CG: HLRT (80% of 1-RM) • CG2: LLRT(30% of 1-RM)	2 d/wk for 12 wk
Harper[19] (2019)	• EG: 16 • CG: 19 women/men	• EG: 67.2 ± 5.2 • CG: 69.1 ± 7.1	Radiographic evidence of osteophytes; Graded Chronic Pain Scale; K-L grade $\geq$2 knee OA	• EG: BFRT+LLRT (20%-30% of 1-RM) • CG: MIRT (60% of 1-RM)	3 d/wk for 12 wk
Shakeel[44] (2021)	• EG: 15 • CG: 15 women/men	• EG: 50-62 (n = 4), 63-75 (n = 11) • CG: 50-62 (n = 3), 63-75 (n = 12)	Knee pain diagnosed with knee OA, inability to perform ADL	• EG: BFRT • CG: No BFRT	4 d/wk for 4 wk

[a] ADL, activities of daily living; BFRT, blood flow restriction training; CG, control group; CG2, control group 2; EG, experimental group; HLRT, high-load resistance training; K-L, Kellgren-Lawrence; LLRT, low-load resistance training; MIRT, moderate-intensity resistance training; OA, osteoarthritis.

detection bias, 4 studies[4,19,42,43] used blinding for outcome assessment, and 2 studies[11,44] did not specify. Only 1 trial[43] was considered to have a high risk of incomplete bias, and all the articles had a low risk of selective reporting bias.[4,11,19,42,43,44] In addition, only 1 study[44] was assessed to be at a high risk of other biases because participants used stretching exercises in addition to BFRT and resistance training; the other trials were unclear about other biases.

Results of the Meta-analyses

Pain. All 6 included studies examined the effect of BFRT on pain outcomes in patients with knee OA, with sample sizes of 114 and 122 in the experimental and control groups, respectively (Figure 3). There was low heterogeneity between studies (I^2 = 12%; P = .34); thus, the effect sizes were combined using a fixed-effects model, and the results of the meta-analysis showed that BFRT did not improve the pain of knee OA patients compared with the control group (SMD, −0.02 [95% CI, −0.30 to 0.26]; P = .88).

Muscle Strength. Five studies[4,11,19,42,43] reported 11 effect sizes to investigate the effects of BFRT on muscle strength in patients with knee OA, with a sample size of 150 in the experimental group and 161 in the control group (Figure 4). The results showed high interstudy heterogeneity (I^2 = 86%; $P < .01$). Therefore, the effect sizes were combined using a random-effects model. The meta-analysis revealed no significant difference in muscle strength between patients with knee OA and controls in the BFRT group (SMD, 0.32 [95% CI, −0.33 to 0.96]; P = .33).

To investigate the factors contributing to the high rate of heterogeneity, researchers carried out subgroup analyses on training load, intervention cycle, and measurement mode (Table 3). Analysis of the training load was performed by categorizing the subgroups and comparing the relationship between BFRT and resistance training with different loads. The results demonstrated that none of the 3 factors served as sources of heterogeneity.

Functional Performance. The performance of physical function in patients with knee OA was examined in 4 studies,[4,11,19,43] which covered a total of 8 effect sizes. A sample size of 124 participants was included in the experimental group, while 132 were included in the control group (Figure 5). The results indicated high levels of interstudy heterogeneity (I^2 = 78%; $P < .01$). Consequently, the effect sizes were combined using a random-effects model. The findings of the meta-analysis revealed no statistically significant difference between the BFRT and control groups in promoting functional performance in patients with knee OA (SMD, 0.25 [95% CI, −0.29 to 0.80]; P = .36).

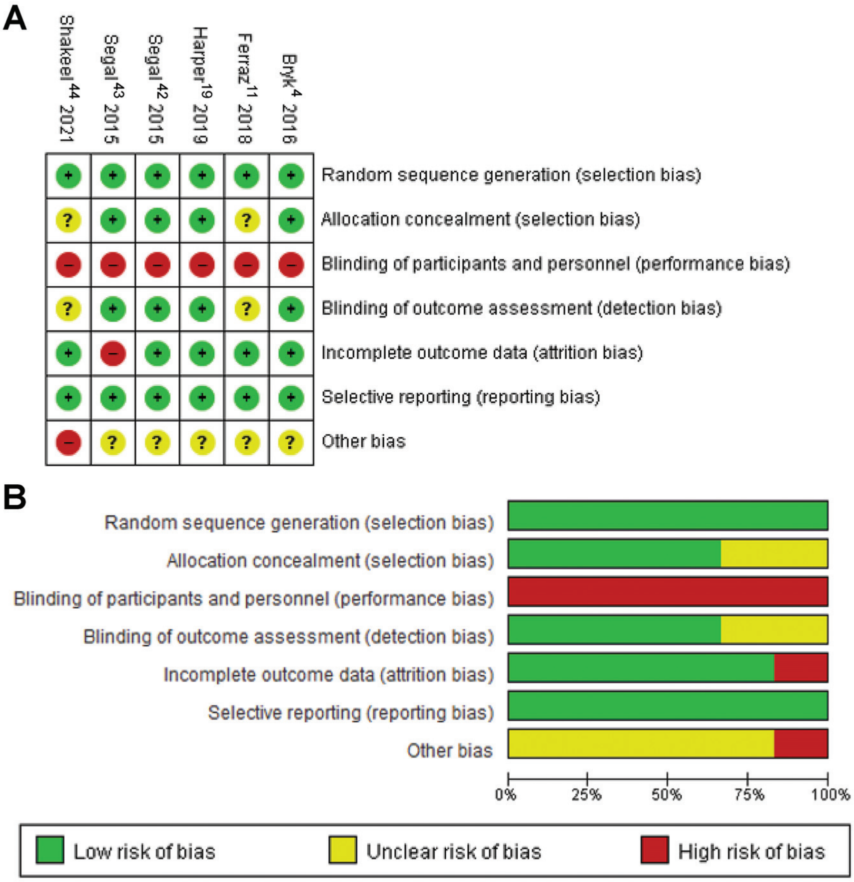
TABLE 2
Baseline Characteristics of the Included Studies[a]

Study	Cuff Size/Site/Pressure	Occlusion	Exercise During Occlusion (BFRT)	Adverse Effects	Outcomes
Segal et al[42] (2015)	65 × 650 mm/proximal thigh and hip joint/ 160-200 mm Hg	Inflated for 6.5 min (5 min exercise, 1.5 min rest)	30% of 1-RM in both groups: leg press, knee extension, reverse press, 1 set 30 reps	One patient withdrew (intolerance of discomfort from pressure cuff)	• Pain: KOOS-Pain • Muscle strength: isokinetic knee extension strength, isotonic leg press strength
Segal et al[43] (2015)	65 × 650 mm/proximal thigh and hip joint/ 160-200 mm Hg	Inflated for 6.5 min (5 min exercise, 1.5 min rest)	Performed 4 sets of bilateral leg presses at 30% of 1 RM	One patient withdrew (intolerance of pain from pneumatic cuff)	• Pain: KOOS-Pain • Muscle strength: isokinetic knee extensor strength, isotonic leg press strength • Muscle size: quadriceps volume
Bryk et al[4] (2016)	Unknown/upper third of thigh/200 mm Hg	Inflated to 200 mm Hg during quadriceps exercises	Knee extension machine, 3 sets of 30 reps	No patients withdrew	• Pain: NPRS • Muscle strength: quadriceps strength • Self-reported function: Lequesne index • Functional performance: TUG
Ferraz et al[11] (2018)	175 × 920 mm/inguinal fold/97.4 ± 7.6 mm Hg	Continuous inflation during training (including intervals) and release at the end of the session	Bilateral leg press and knee extension exercises. At wk 0-2: 20% of 1-RM, 4 sets of 15 reps; at wk 2-5: 30% of 1-RM, 4 sets of 15 reps; at wk 5-12: 30% of 1-RM, 5 sets of 15 reps	Four patients from the HLRT group discontinued through the follow-up, exercise-induced knee pain	• Pain: WOMAC-Pain • Muscle strength: leg press strength, knee extension strength • Self-reported function: WOMAC • Functional performance: TS, TUG • Muscle size: quadriceps CSA
Harper et al[19] (2019)	Unknown/proximal thigh/ not specified	Breathing breaks between different exercise movements, continuous wear between the same sets	Leg press, leg extension, leg curl, and calf flexion	Fourteen patients reported adverse events of knee pain, of whom 1 patient from the BFR group deemed possibly related to the study	• Pain: WOMAC-Pain • Muscle strength: knee extensor strength • Self-reported function: LLFDI • Functional performance: gait speed, SPPB
Shakeel et al[44] (2021)	Unknown/femoral artery of thigh muscle and tibial artery of calf muscle/enough to cause a blocked venous return	Inflate during exercise, deflate at group rest (5 sec)	Received strengthening exercises of quadriceps, hamstrings, and calf muscles; 3 sets of 10 reps for each exercise	No patients withdrew	• Pain: VAS pain • Self-reported function: Kujala • Muscle size: thigh muscle dimension

[a] BFRT, blood flow restriction training; CSA, cross-sectional area; CG, control group; reps, repetitions; CG2, control group 2; EG, experimental group; KOOS, Knee injury and Osteoarthritis Outcome Score; LLFDI, Late Life Function and Disability Instrument; NPRS, numerical pain rating scale; RM, repetition maximum; SPPB, Short Physical Performance Battery; TS, timed stand-up test; TUG, timed up-and-go test; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

To explore the source of the heterogeneity, researchers conducted subgroup analyses regarding training load and intervention period, with results indicating that neither factor was the source of the heterogeneity (Table 4). Regarding training load, the HLRT group had a lower heterogeneity than the LLRT group (I^2 = 7% vs 93%), although there was no improvement in either group ($P > .05$). Regarding the intervention cycle, a long-cycle (≥8-week) intervention had a lower heterogeneity than short-cycle (<8-week) intervention (I^2 = 31% vs 93%), with no improvement in either group ($P > .05$).

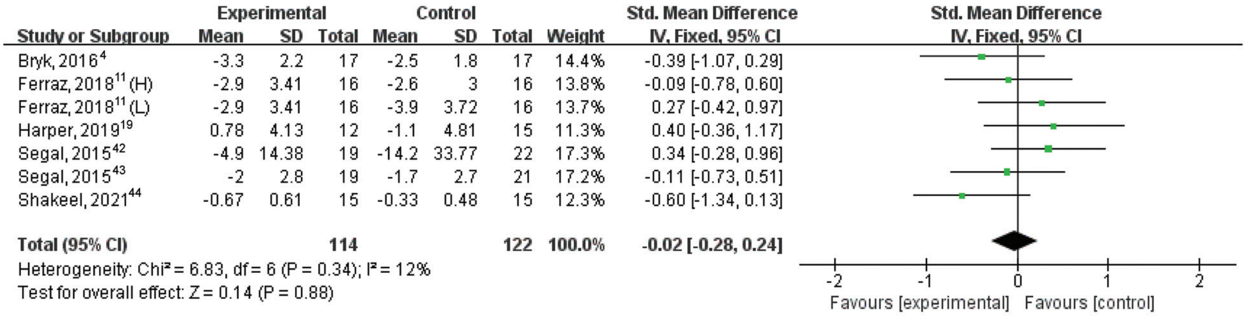
Sensitivity analyses were used to individually remove the included studies to further explore the sources of heterogeneity, assessing each study's effect on the overall effect size (Table 5). Heterogeneity was significantly lower after removing Segal et al[43] (I^2 = 20%; $P > .05$). After analyzing the study again, it was found that for the intervention approach, in addition to the same progressive increase



A

Shakeel[44] 2021	Segal[43] 2015	Segal[42] 2015	Harper[19] 2019	Ferraz[11] 2018	Bryk[4] 2016	
+	+	+	+	+	+	Random sequence generation (selection bias)
?	+	+	+	?	+	Allocation concealment (selection bias)
−	−	−	−	−	−	Blinding of participants and personnel (performance bias)
?	+	+	+	?	+	Blinding of outcome assessment (detection bias)
+	−	+	+	+	+	Incomplete outcome data (attrition bias)
+	+	+	+	+	+	Selective reporting (reporting bias)
−	?	?	?	?	?	Other bias

Figure 2. Summary of the risk of bias according to Cochrane criteria[16] (A) in each study and (B) as a percentage across all included studies.



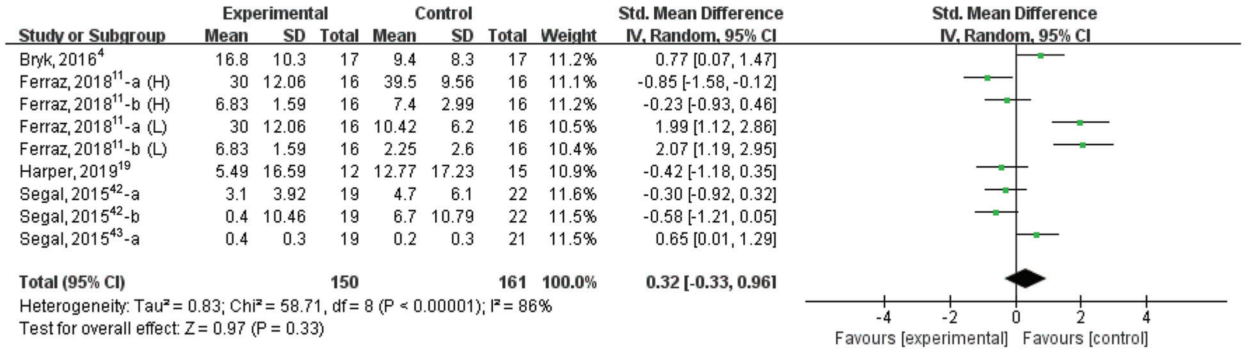
	Experimental			Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Bryk, 2016[4]	-3.3	2.2	17	-2.5	1.8	17	14.4%	-0.39 [-1.07, 0.29]
Ferraz, 2018[11] (H)	-2.9	3.41	16	-2.6	3	16	13.8%	-0.09 [-0.78, 0.60]
Ferraz, 2018[11] (L)	-2.9	3.41	16	-3.9	3.72	16	13.7%	0.27 [-0.42, 0.97]
Harper, 2019[19]	0.78	4.13	12	-1.1	4.81	15	11.3%	0.40 [-0.36, 1.17]
Segal, 2015[42]	-4.9	14.38	19	-14.2	33.77	22	17.3%	0.34 [-0.28, 0.96]
Segal, 2015[43]	-2	2.8	19	-1.7	2.7	21	17.2%	-0.11 [-0.73, 0.51]
Shakeel, 2021[44]	-0.67	0.61	15	-0.33	0.48	15	12.3%	-0.60 [-1.34, 0.13]
Total (95% CI)			**114**			**122**	**100.0%**	**-0.02 [-0.28, 0.24]**

Heterogeneity: Chi² = 6.83, df = 6 (P = 0.34); I² = 12%
Test for overall effect: Z = 0.14 (P = 0.88)

Figure 3. A meta-analysis forest plot of the effect of blood flow restriction training on pain in knee osteoarthritis patients. IV, inverse variance; H, high-load resistance training; L, low-load resistance training.

in cuff pressure on the training cycle as in other studies, the same progressive increase in cuff pressure was also used for the single training session, with the transition from the initial cuff pressure (30-40 mm Hg) to the 1-minute cuff pressure being applied (100-180 mm Hg) to ultimately reach the amount of load set for the single training session (160-200 mm Hg) for training.[43]

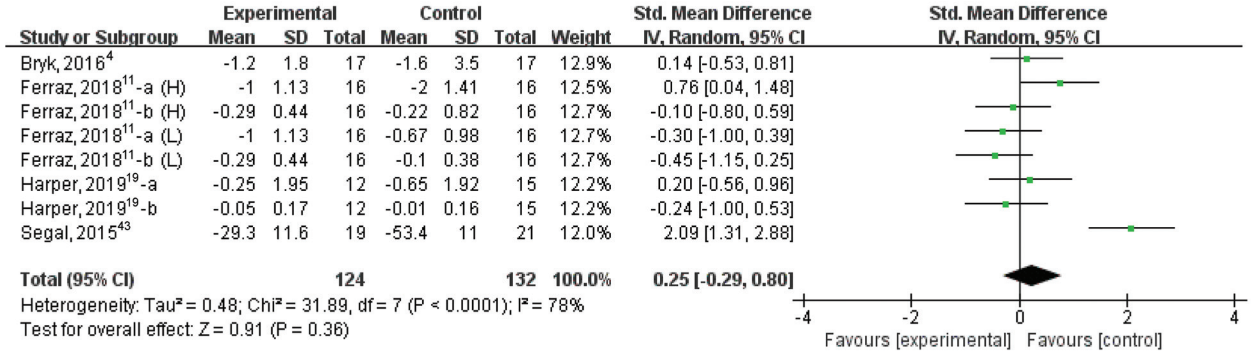
The effect of BFRT versus control on self-reported function in patients with knee OA was examined using 5 effect sizes,[4,11,19,44] with sample sizes of 76 and 79 in the experimental and control groups, respectively (Figure 6). The results indicated high between-study heterogeneity (I^2 = 76%; $P < .01$), necessitating the use of a random-effects model to combine the effect sizes. The meta-analysis



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bryk, 2016[4]	16.8	10.3	17	9.4	8.3	17	11.2%	0.77 [0.07, 1.47]
Ferraz, 2018[11]-a (H)	30	12.06	16	39.5	9.56	16	11.1%	-0.85 [-1.58, -0.12]
Ferraz, 2018[11]-b (H)	6.83	1.59	16	7.4	2.99	16	11.2%	-0.23 [-0.93, 0.46]
Ferraz, 2018[11]-a (L)	30	12.06	16	10.42	6.2	16	10.5%	1.99 [1.12, 2.86]
Ferraz, 2018[11]-b (L)	6.83	1.59	16	2.25	2.6	16	10.4%	2.07 [1.19, 2.95]
Harper, 2019[19]	5.49	16.59	12	12.77	17.23	15	10.9%	-0.42 [-1.18, 0.35]
Segal, 2015[42]-a	3.1	3.92	19	4.7	6.1	22	11.6%	-0.30 [-0.92, 0.32]
Segal, 2015[42]-b	0.4	10.46	19	6.7	10.79	22	11.5%	-0.58 [-1.21, 0.05]
Segal, 2015[43]-a	0.4	0.3	19	0.2	0.3	21	11.5%	0.65 [0.01, 1.29]
Total (95% CI)			**150**			**161**	**100.0%**	**0.32 [-0.33, 0.96]**

Heterogeneity: Tau^2 = 0.83; Chi^2 = 58.71, df = 8 (P < 0.00001); I^2 = 86%
Test for overall effect: Z = 0.97 (P = 0.33)

Figure 4. A forest plot of the effect of blood flow restriction training on muscle strength in patients with knee osteoarthritis. Ferraz 2018-a[11] (H and L) refers to leg press strength, while Ferraz 2018-b[11] (H and L) refers to knee extension strength. Segal 2015[42]-a refers to leg press strength, while Segal 2015[42] -b refers to knee extension strength; Segal 2015[43]-a refers to the scaled leg press 1RM, expressed in kg per kg body mass. IV, inverse variance; H, high-load resistance training; L, low-load resistance training.



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bryk, 2016[4]	-1.2	1.8	17	-1.6	3.5	17	12.9%	0.14 [-0.53, 0.81]
Ferraz, 2018[11]-a (H)	-1	1.13	16	-2	1.41	16	12.5%	0.76 [0.04, 1.48]
Ferraz, 2018[11]-b (H)	-0.29	0.44	16	-0.22	0.82	16	12.7%	-0.10 [-0.80, 0.59]
Ferraz, 2018[11]-a (L)	-1	1.13	16	-0.67	0.98	16	12.7%	-0.30 [-1.00, 0.39]
Ferraz, 2018[11]-b (L)	-0.29	0.44	16	-0.1	0.38	16	12.7%	-0.45 [-1.15, 0.25]
Harper, 2019[19]-a	-0.25	1.95	12	-0.65	1.92	15	12.2%	0.20 [-0.56, 0.96]
Harper, 2019[19]-b	-0.05	0.17	12	-0.01	0.16	15	12.2%	-0.24 [-1.00, 0.53]
Segal, 2015[43]	-29.3	11.6	19	-53.4	11	21	12.0%	2.09 [1.31, 2.88]
Total (95% CI)			**124**			**132**	**100.0%**	**0.25 [-0.29, 0.80]**

Heterogeneity: Tau^2 = 0.48; Chi^2 = 31.89, df = 7 (P < 0.0001); I^2 = 78%
Test for overall effect: Z = 0.91 (P = 0.36)

Figure 5. A forest plot of the effect of blood flow restriction training on functional performance in patients with knee osteoarthritis. Ferraz 2018-a (H and L) refers to the timed-stands test, while Ferraz 2018 -b (H and L) refers to the timed up-and-go test; Harper 2019-a refers to a 400-m gait speed, while Harper 2019-b refers to the short physical performance battery. H, high-load resistance training; IV, inverse variance; L, low-load resistance training.

TABLE 3
Subgroup Analysis of the Effect of Blood Flow Restriction Training on Muscle Strength in Knee Osteoarthritis Patients[a]

Subgroups	No. of Studies	Effect Size[b]	*P* (Effect Size)	Statistical Model	*I*^{2}, %
Load					
LLRT	5	0.73 (−0.29 to 1.75)	.16	Random-effects	90
HLRT	4	−0.18 (−0.86 to 0.51)	.62	Random-effects	72
Intervention cycle					
<8 weeks	4	0.13 (−0.53 to 0.79)	.71	Random-effects	76
≥8 weeks	5	0.49 (−0.68 to 1.67)	.41	Random-effects	91
Measurement mode					
Leg extension	5	0.30 (−0.59 to 1.18)	.51	Random-effects	87
Leg press	4	0.35 (−0.74 to 1.44)	.53	Random-effects	90

[a] HLRT, high-load resistance training; LLRT, low-load resistance training; SMD, standardized mean difference.
[b] Effect size is presented as SMD (95% CI).

TABLE 4

Subgroup Analysis of the Effect of Blood Flow Restriction Training on Functional Performance in Knee Osteoarthritis Patients[a]

Subgroups	No. of Studies	Effect Size[b]	*P* (Effect Size)	Statistical Model	I^2, %
Load					
LLRT	3	0.73 (−0.29 to 1.75)	.16	Random-effects	93
HLRT	5	−0.18 (−0.86 to 0.51)	.62	Fixed-effects	7
Intervention cycle					
<8 weeks	2	0.13 (−0.53 to 0.79)	.71	Random-effects	93
≥8 weeks	6	0.49 (−0.68 to 1.67)	.41	Random-effects	31

[a] HLRT, high-load resistance training; LLRT, low-load resistance training; SMD, standardized mean difference.

[b] Effect size is presented as SMD (95% CI).

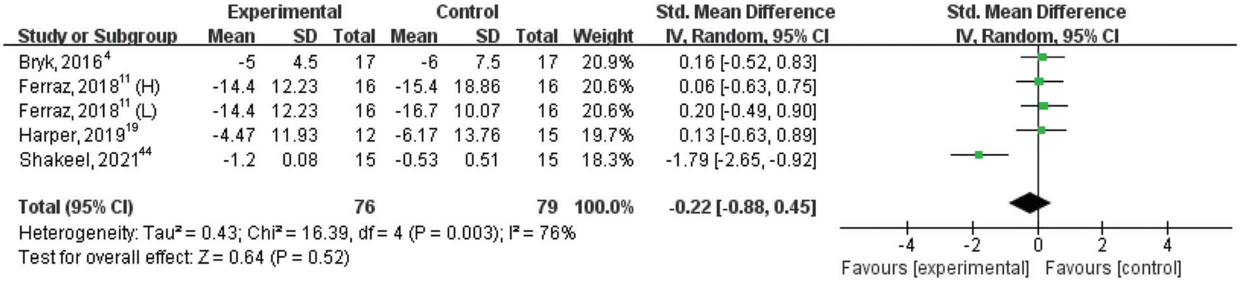
TABLE 5

Sensitivity Analysis of Blood Flow Restriction Training on Functional Performance in Patients With Knee Osteoarthritis[a]

Study or Study Subgroup (Year)	Elimination Effect Size[b]	*P* (Effect Size)	I^2, %	*P*
Bryk et al[4] (2016)	0.27 (−0.37 to 0.91)	.40	81%	<.0001
Ferraz et al[11] (2018)				
HLRT-a (TS)	0.18 (−0.43 to 0.78)	.56	80	<.0001
HLRT-b (TUG)	0.31 (−0.32 to 0.93)	.34	81	<.0001
LLRT-a (TS)	0.33 (−0.27 to 0.94)	.28	80	<.0001
LLRT-b (TUG)	0.35 (−0.24 to 0.95)	.24	78	<.0001
Harper et al[19] (2019)				
A (gait speed)	0.26 (−0.36 to 0.89)	.41	81	<.0001
B (SPPB)	0.32 (−0.29 to 0.93)	.30	80	<.0001
Segal et al[43] (2015)	0.01 (−0.29 to 0.30)	.99	20	.28

[a] HLRT, high-load resistance training; LLRT, low-load resistance training; SMD, standardized mean difference; SPPB, short physical performance battery; TST, timed-stands test; TUG, timed up-and-go test.

[b] Effect size is presented as SMD (95% CI).



	Experimental			Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Bryk, 2016[4]	-5	4.5	17	-6	7.5	17	20.9%	0.16 [-0.52, 0.83]
Ferraz, 2018[11] (H)	-14.4	12.23	16	-15.4	18.86	16	20.6%	0.06 [-0.63, 0.75]
Ferraz, 2018[11] (L)	-14.4	12.23	16	-16.7	10.07	16	20.6%	0.20 [-0.49, 0.90]
Harper, 2019[19]	-4.47	11.93	12	-6.17	13.76	15	19.7%	0.13 [-0.63, 0.89]
Shakeel, 2021[44]	-1.2	0.08	15	-0.53	0.51	15	18.3%	-1.79 [-2.65, -0.92]
Total (95% CI)			**76**			**79**	**100.0%**	**-0.22 [-0.88, 0.45]**

Heterogeneity: Tau² = 0.43; Chi² = 16.39, df = 4 (P = 0.003); I² = 76%

Test for overall effect: Z = 0.64 (P = 0.52)

Figure 6. A forest plot of the effect of blood flow restriction training on self-reported function in patients with knee osteoarthritis; IV, inverse variance; H, high-load resistance training; L, low-load resistance training.

revealed that patients with knee OA in the BFRT group did not experience a statistically significant improvement in self-reported functioning compared with patients in the control group (SMD, −0.252 [95% CI, −0.88 to 0.45]; $P = .52$).

Researchers typically perform subgroup analyses to investigate sources of heterogeneity. These analyses were conducted with regard to the training load and intervention period (Table 6). Within the training load, the HLRT subgroup showed minor heterogeneity ($I^2 = 0\%$), whereas the LLRT subgroup exhibited the most extreme heterogeneity ($I^2 = 92\%$). Additionally, no improvement was observed in either group ($P > .05$). In terms of the intervention cycle, the long-cycle intervention displayed minor heterogeneity ($I^2 = 0\%$), and the short-cycle intervention displayed the most extreme heterogeneity ($I^2 = 92\%$). Again, no improvement was observed in either group ($P > .05$).

TABLE 6
Subgroup Analysis of the Effect of Blood Flow Restriction Training on Self-reported Functioning in Patients With Knee Osteoarthritis[a]

Subgroups	No. of Studies	Effect Size[b]	*P* (Effect Size)	Statistical Model	I^2, %
Load					
LLRT	3	−0.78 (−2.72 to 1.17)	.43	Random effects	92
HLRT	2	0.12 (−0.29 to 0.52)	.58	Fixed effects	0
Intervention cycle					
<8 weeks	2	−0.79 (−2.70 to 1.11)	.41	Random effects	92
≥8 weeks	3	0.13 (−0.28 to 0.54)	.54	Fixed effects	0

[a] HLRT, high-load resistance training; LLRT, low-load resistance training; SMD, standardized mean difference.

[b] Effect size is presented as SMD (95% CI).

TABLE 7
Subgroup Analysis of the Effect of Blood Flow Restriction Training on Muscle Size in Patients With Knee Osteoarthritis[a]

Subgroups	No. of Studies	Effect Size[b]	*P* (Effect Size)	Statistical Model	I^2, %
Load					
LLRT	2	1.19 (0.26-2.11)	.01	Random-effects	68
HLRT	2	0.14 (−0.35 to 0.63)	.58	Fixed-effects	0
Intervention cycle					
<8 weeks	3	0.88 (0.46-1.92)	.03	Random-effects	72
≥8 weeks	1	0.02 (−0.71 to 0.68)	—	—	—

[a] Dashes indicate areas not applicable (independent samples cannot be analyzed in subgroups. HLRT, high-load resistance training; LLRT, low-load resistance training; SMD, standardized mean difference.

[b] Effect size is presented as SMD (95% CI).

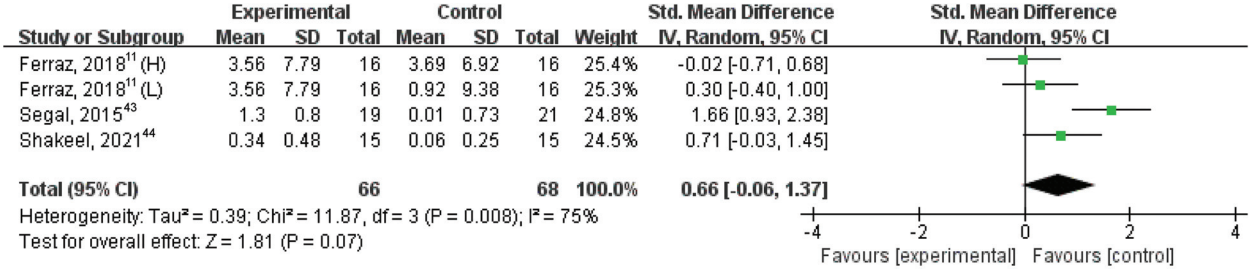


Figure 7. A forest plot of the effect of blood flow restriction training on muscle size in patients with knee osteoarthritis. IV, inverse variance; H, high-load resistance training; L, low-load resistance training.

Muscle Size. Three studies[11,43,44] examined the effect of BFRT on muscle size in patients with knee OA, with a - sample size of 66 in the experimental group and 68 in the control group (Figure 7). The results showed high heterogeneity between studies (I^2 = 75%; *P* < .01). Therefore, the effect sizes were combined using a random-effects model. The results of the meta-analysis showed no significant difference between the BFRT groups in terms of improving muscle size in patients with knee OA (SMD, 0.66 [95% CI, −0.06 to 1.37]; *P* = .07).

Results of Subgroup Analyses

Subgroup analyses were performed to investigate the source of heterogeneity, focusing on the intervention cycle and training load (Table 7). Subgroup analyses revealed that heterogeneity was minimal in the long-cycle intervention group (I^2 = 0%), while it was the most extensive in the short-cycle intervention group (I^2 = 68%). In addition, the short-cycle intervention increased muscle size in patients with knee OA (SMD, 1.19; *P* = .01). When examining low-load heterogeneity, training loads (I^2 = 72%) exhibited the most significant variation. Furthermore, BFRT was found to have an advantage over LLRT in terms of enhancing muscle size in patients with knee OA (SMD, 0.88; *P* = .03), although this could not be evaluated owing to the lack of documented high-load interventions in the control group.

Adverse Events. Four studies[11,19,42,43] reported that knee OA patients withdrew from treatment because of

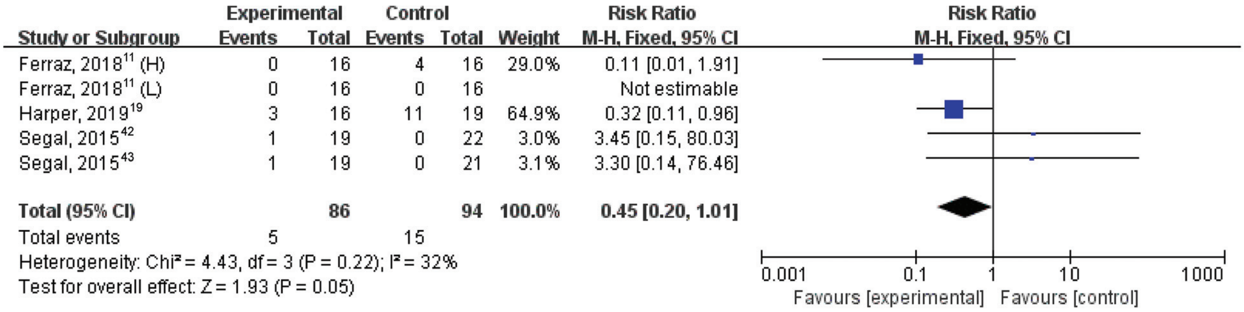


Figure 8. A forest plot of the effect of blood flow restriction training on adverse events in patients with knee osteoarthritis. H, high-load resistance training; L, low-load resistance training.

TABLE 8
Subgroup Analysis of the Effect of Blood Flow Restriction Training on the Occurrence of Adverse Events in Patients With Knee Osteoarthritis[a]

Subgroups	No. of Studies	Effect Size[b]	P (Effect Size)	Statistical Model	I^2, %
Load					
LLRT	3	3.37 (0.37-31.15)	.28	Fixed-effects	0
HLRT	2	0.26 (0.09-0.72)	.009	Fixed-effects	0
Intervention cycle					
<8 weeks	2	3.37 (0.37-31.15)	.28	Fixed-effects	0
≥8 weeks	3	0.26 (0.09-0.72)	.009	Fixed-effects	0

[a] HLRT, high-load resistance training; LLRT, low-load resistance training; SMD, standardized mean difference.
[b] Effect size is presented as SMD (95% CI).

adverse events, with sample sizes of 86 and 94 in the experimental and control groups, respectively (Figure 8). Adverse events primarily included severe pain caused by high-intensity exercise (n = 4), knee pain induced by moderate-intensity exercise (n = 11), intolerance to the interventional compression cuff in BFRT (n = 2), and knee pain induced by exercise (n = 3). The RCTs were analyzed using the RR effect index, and the results showed a low degree of interstudy heterogeneity (I^2 = 32%; P = .22); therefore, the meta-analysis was performed using a fixed-effects model. The results showed that the difference between the BFRT and control groups was statistically significant in terms of overall adverse events (RR, 0.45 [95% CI, 0.20-1.01]; P = .05, with 95% CI above zero).

A subgroup analysis of adverse event outcome indicators was performed (Table 8). The results showed that in the HLRT subgroup, HLRT was associated with a greater risk of adverse events than was BFRT (RR, 0.26; P = .009), and the risk of adverse events was greater in the short-cycle intervention group (RR, 0.26; P = .009) than in the long-cycle intervention group (RR, 3.37; P = .28).

GRADE Quality of Evidence Evaluation

Although the included studies were RCTs, there were multiple downgrading factors in terms of the 5 GRADE categories—risk of bias, inconsistency, indirectness, imprecision, and publication bias. The quality of the evidence was downgraded because of specific design methodologies, incomplete characteristics, and mismatches, with the results of the determination as follows: (1) the pain outcome indicator was intermediate; (2) the outcome metrics for muscle strength, functional performance, muscle size, and adverse events were low grade; and (3) the self-reports of functioning were very low grade. The strength of the recommendations for each of the above outcomes was weak (Table 9).

DISCUSSION

The main findings of the present systematic review and meta-analysis were as follows: low-level deterministic evidence showed that patients with knee OA did not develop specific adverse events when performing BFRT, that BFRT was safer than HLRT (RR, 0.26; P = .009), that it improved patients' muscle size better than LLRT (SMD, 1.19; P = .01), and it showed benefits in building muscle size in interventions of <8 weeks (SMD, 0.88; P = .03). However, compared with traditional resistance training, evidence of low to intermediate certainty showed no advantage of BFRT in pain, functional performance, or self-reported function, consistent with previous studies.[15] In addition, inconsistencies were demonstrated in the effects of BFRT on muscle strength in the control intervention subgroup. Although a different methodology with

TABLE 9
Quality of Evidence for Outcome Indicators Using GRADE[17] Criteria[a]

	Outcome Indicator					
Variable	Pain (7 Studies)	Muscle Strength (9 Studies)	Functional Performance (8 Studies)	Self-Reported Function (5 Studies)	Muscle Size (4 Studies)	Adverse Effects (5 Studies)
GRADE category[b]						
Risk of bias	↓ 1 level[I]	↓ 1 level[I]	↓ 1 level[I]	↓ 1 level[I]	↓ 1 level[I]	↓ 1 level[I]
Inconsistency	No downgrade	↓ 1 level[II]	↓ 1 level[II]	↓ 1 level[II]	↓ 1 level[II]	No downgrade
Indirectness	No downgrade	No downgrade	No downgrade	No downgrade	No downgrade	No downgrade
Imprecision	No downgrade	No downgrade	No downgrade	No downgrade	No downgrade	↓ 1 level[III]
Publication bias	No downgrade	No downgrade	No downgrade	↓ 1 level[IV]	No downgrade	No downgrade
Sample size						
Experimental group	114	150	124	76	66	5
Control group	122	161	132	79	68	15
Effect size[c]	−0.02 (−0.30 to 0.26)	0.32 (−0.33 to 0.96)	0.25 (−0.29 to 0.80)	−0.252 (−0.88 to 0.45)	0.66 (−0.06 to 1.37)	0.45 (0.20-1.01)
Quality of evidence	Moderate	Low	Low	Very low	Low	Low

[a] GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; RR, risk ratio; SMD, standardized mean difference.

[b] Reasons for downgrade: [I] Some randomized controlled trials with random methods, assignment concealment, and blinding methods have defects; [II] large heterogeneity; [III] insufficient sample size; [IV] fewer negative results.

[c] Effect sizes are presented as SMD (95% CI) except for adverse event outcomes, which are presented as RR (95% CI).

measurement criteria was used in this study and this finding is limited by low-certainty evidence due to imprecision, the results are consistent with other studies that have shown no difference in the effects of BFRT and traditional resistance training on the improvement of muscle strength in patients with knee OA.[54]

Pain is a common concern in patients with knee OA, and our results showed no improvement in pain relief in patients with knee OA treated with BFRT, which is consistent with previous reviews on the effectiveness of BFRT in treating musculoskeletal disorders.[26] Although researchers usually focus more on improvements in pain in patients with knee OA, functional improvements play an equally important role in treatment.[24] The results of this study showed no advantage of BFRT over traditional resistance training either in terms of functional performance or self-reported function; this may be due to the nonsignificant potential differences between serum biomarkers while performing different forms of intervention. For example, TWEAK (serum tumor necrosis-like weak inducer of apoptosis) is associated with skeletal muscle hypertrophy and increased strength,[34] IGF-1 (insulin-like growth factor-1) is associated with increased protein synthesis and muscle mass,[18] and serum P3NP (a peptide of procollagen type 3) is associated with skeletal muscle growth, muscle repair, and fibrosis.[3] Harper et al[19] performed BFRT versus MIRT in patients with knee OA and found no significant differences between the 2 in serum TWEAK, IGF-1, or serum P3NP. Furthermore, due to the limited number of studies, we could not investigate the effect of BFRT on quality of life. Therefore, future clinical studies on BFRT may focus on patients' quality of life.

Improving muscle size and strength, which can relieve pain, reduce stiffness, improve functional performance, and increase the shock absorption capacity of the lower extremity muscles during walking, is considered the most crucial benefit of rehabilitation training for patients with knee OA.[57] Subgroup analysis of different training intensities for muscle size showed that BFRT demonstrated the advantage of being able to enhance muscle size in patients with knee OA compared with LLRT, which may be attributed to the ability of BFRT to put the limbs into a state of ischemia and hypoxia through the reduction of arterial blood flow and the aggregation of venous blood flow, causing a significant increase in metabolic stress through low-load training. This would result in the massive replenishment of fast-twitch muscle fibers and a significant increase in IGF-1, which ultimately leads to an improvement in muscle cross-sectional area.[49,52] Furthermore, the implementation of BFRT and HLRT interventions administered twice a week for 12 weeks in patients with knee OA[19] demonstrated similar outcomes in terms of enhancing muscle size. This may be attributed to the fact that both forms of exercise trigger perturbations in the myofibrils and the associated extracellular matrix, increasing the size and number of parallel muscle segments, as well as an increase in the diameter of individual fibers. As a result, the cross-sectional area of the muscle is increased, which ultimately leads to a greater muscle size.[40] This result is consistent with a previous review of BFRT performed in older adults to observe muscle strength and size.[5]

We further conducted a subgroup analysis of the muscle strength outcome metrics to explore the effects of different training intensities, intervention cycles, and measurement modalities on muscle strength in patients with knee OA. We found that heterogeneity was reduced by 14% in the HLRT subgroup and by 10% in the short-cycle subgroup, suggesting that the training intensity and intervention cycle may be potential sources of heterogeneity. Moreover, conflicting results were also demonstrated in the analysis of the intervention cycle subgroups, as a comprehensive study that simultaneously treated patients with knee OA with BFRT, LLRT, and HLRT for 12 weeks revealed that HLRT and BFRT produced similar improvements in strength and that both training methods outperformed traditional LLRT.[11] In contrast, another study that included an intervention cycle of 4 weeks showed no additional advantage of BFRT over LLRT.[42] Therefore, this may be related to the intervention cycle; that is, there was no difference between BFRT and HLRT regarding muscle strength enhancement in patients with knee OA. In contrast, the advantage of BFRT over LLRT in enhancing muscle strength in knee OA patients is gradually manifested by prolonging the intervention cycle.

Knee OA is a leading cause of disability in the elderly and is often associated with metabolic syndromes. With the overall population aging, the incidence of knee OA is expected to rise significantly.[31] Therefore, safety is a critical concern in exercise rehabilitation. Previous reviews[28,33] indicate that BFRT may be a safe exercise intervention for patients with knee orthopaedic disorders, showing a lower risk of adverse events in treating musculoskeletal disorders and knee OA compared with traditional resistance training. However, since the authors did not perform a meta-analysis, the presented results require a more comprehensive analysis. In contrast, in our meta-analysis, adverse events in patients with knee OA were mainly due to cuff discomfort while performing BFRT and knee pain while performing regular resistance training. Our results showed a lower risk of adverse events with BFRT than with HLRT. Although a recent systematic review found no evidence suggesting that patients with musculoskeletal pain disorders achieve better outcomes from pain-free exercise compared with long-term painful exercise,[27] some studies suggest that experiencing pain during rehabilitation does not always indicate physical harm, according to a review by Smith et al.[48] We do not believe that this type of rehabilitation with pain experience is irrelevant to the patient, as we want to ensure that the patient is comfortable when performing the rehabilitation and maximizes the patient's compliance during the exercise. BFRT may serve as an alternative to reduce adverse events during exercise for patients with knee OA who are unable to complete traditional exercise programs due to pain, aligning with previous research by Kristensen and Franklyn-Miller.[25] However, a 20-year-old man was reported to have experienced rhabdomyolysis after 3 sets of knee extension and flexion exercises with BFRT, and studies have shown that BFRT induces a more intense cardiorespiratory response during exercise.[6,8] Although some of these studies were based on single-subject pathology, the side effects of BFRT should not be marginalized. Therefore, practitioners should closely monitor the patient's physical status (eg, oxygen saturation, heart rate, rate of perceived movement, and pain scores) during exercise to minimize adverse events.

Limitations

This study has several limitations. Only 6 publications had combined effect sizes and a relatively small sample size, and none of the studies were able to use a double-masked research methodology with participants and staff, which may be due to the challenges faced when inflatable pressurized blood pressure cuffs are used covertly during BFRT. The quality of evidence was rated low when analyzing the effects of BFRT on muscle strength and functional performance in patients with knee OA. All trials had an intervention period of $\leq$12 weeks and therefore did not assess the impact of BFRT on patients with intermediate (6-12 months) to long-term ($\geq$12 months) knee OA. In addition, only studies in English were included in this review, which may have resulted in more potential studies not being included. Hopefully, more studies will investigate the effects of BFRT on patients with knee OA in the mid- and long-term and the occurrence of adverse events during exercise. Future studies should pay close attention to BFR combined with LLRT since 5 of the 6 selected papers investigated BFR combined with LLRT and the optimal intervention protocol for BFRT has not yet been determined, especially the different cuff widths and pressures used when performing BFRT, and more outcomes—such as quality of life, patient adherence, and adjuvant efficiency—should be reported in BFRT studies.

CONCLUSION

Our review and meta-analysis demonstrated that compared with resistance training, BFRT did not significantly improve symptom outcomes in patients with knee OA. However, it may be a viable alternative for individuals who are unable to complete their prescribed training program within the expected time frame because of pain severity. It is important to acknowledge that the findings of this study were limited by the small number of studies and the sample size. Further high-quality research is needed to better understand the use of BFRT in patients with knee OA.

REFERENCES

1. American College of Sports Medicine. American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. *Med Sci Sports Exerc*. 2009;41(3):687-708.
2. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage*. 2019;27(11):1578-1589.
3. Berry SD, Ramachandran VS, Cawthon PM, et al. Procollagen type III N-terminal peptide (P3NP) and lean mass: a cross-sectional study. *J Frailty Aging*. 2013;2(3):129-134.
4. Bryk FF, Dos Reis AC, Fingerhut D, et al. Exercises with partial vascular occlusion in patients with knee osteoarthritis: a randomized clinical trial. *Knee Surg Sports Traumatol Arthrosc*. 2016;24(5):1580-1586.

5. Centner C, Wiegel P, Gollhofer A, König D. Effects of blood flow restriction training on muscular strength and hypertrophy in older individuals: a systematic review and meta-analysis. *Sports Med*. 2019;49(1):95-108.
6. Clark BC, Manini TM. Can KAATSU exercise cause rhabdomyolysis? *Clin J Sport Med*. 2017;27(1):e1-e2.
7. Cognetti DJ, Sheean AJ, Owens JG. Blood flow restriction therapy and its use for rehabilitation and return to sport: physiology, application, and guidelines for implementation. *Orthop Traumatol Surg Res*. 2022;4(1):e71-e76.
8. Conceição MS, Gáspari AF, Ramkrapes APB, et al. Anaerobic metabolism induces greater total energy expenditure during exercise with blood flow restriction. *PLoS One*. 2018;13(3):e0194776.
9. Coudeyre E, Jegu AG, Giustanini M, Marrel JP, Edouard P, Pereira B. Isokinetic muscle strengthening for knee osteoarthritis: a systematic review of randomized controlled trials with meta-analysis. *Ann Phys Rehabil Med*. 2016;59(3):207-215.
10. Dillon CF, Rasch EK, Gu Q, Hirsch R. Prevalence of knee osteoarthritis in the United States: arthritis data from the Third National Health and Nutrition Examination Survey 1991-94. *J Rheumatol*. 2006;33(11):2271-2279.
11. Ferraz RB, Gualano B, Rodrigues R, et al. Benefits of resistance training with blood flow restriction in knee osteoarthritis. *Med Sci Sports Exerc*. 2018;50(5):897-905.
12. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis & Rheumatol*. 2021;73(7):1108-1123.
13. Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee: a Cochrane systematic review. *Br J Sports Med*. 2015;49(24):1554-1557.
14. Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc*. 2011;43(7):1334-1359.
15. Grantham B, Korakakis V, O'Sullivan K. Does blood flow restriction training enhance clinical outcomes in knee osteoarthritis: a systematic review and meta-analysis. *Phys Ther Sport*. 2021;49:37-49.
16. Green S, Higgins P, Alderson P, Clarke M, Mulrow D, Oxman D. Chapter 8: assessing risk of bias in included studies. In Higgins JP, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* (updated March 2011). https://handbook-5-1.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm
17. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.
18. Hamarneh SR, Murphy CA, Shih CW, et al. Relationship between serum IGF-1 and skeletal muscle IGF-1 mRNA expression to phosphocreatine recovery after exercise in obese men with reduced GH. *J Clin Endocrinol Metab*. 2015;100(2):617-625.
19. Harper SA, Roberts LM, Layne AS, et al. Blood-flow restriction resistance exercise for older adults with knee osteoarthritis: a pilot randomized clinical trial. *J Clin Med*. 2019;8(2):265.
20. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester, UK: The Cochrane Collaboration and John Wiley & Sons Ltd. 2008.
21. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res* (Hoboken). 2012;64(4):465-474.
22. Hughes L, Paton B, Rosenblatt B, Gissane C, Patterson SD. Blood flow restriction training in clinical musculoskeletal rehabilitation: a systematic review and meta-analysis. *Br J Sports Med*. 2017;51(13):1003-1011.
23. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med*. 2015;162(11):777-784.
24. Javed S, Riaz H, Saeed A, Begum R. Effects of Biodex balance training on symptomatic knee osteoarthritis in Rawalpindi: a randomized control trial. *J Pak Med Assoc*. 2021;71(2(A)):402-405.
25. Kristensen J, Franklyn-Miller A. Resistance training in musculoskeletal rehabilitation: a systematic review. *Br J Sports Med*. 2012; 46(10):719-726.
26. Ladlow P, Coppack RJ, Dharm-Datta S, et al. Low-load resistance training with blood flow restriction improves clinical outcomes in musculoskeletal rehabilitation: a single-blind randomized controlled trial. *Front Physiol*. 2018;9:1269.
27. Liaghat B, Skou ST, Søndergaard J, Boyle E, Søgaard K, Juul-Kristensen B. Short-term effectiveness of high-load compared with low-load strengthening exercise on self-reported function in patients with hypermobile shoulders: a randomised controlled trial. *British Journal of Sports Medicine*. 2022;56(22):1269-1276.
28. Li S, Shaharudin S, Abdul Kadir MR. Effects of blood flow restriction training on muscle strength and pain in patients with knee injuries: a meta-analysis. *Am J Phys Med Rehabil*. 2021; 100(4):337-344.
29. Loenneke JP, Kearney ML, Thrower AD, et al. The acute response of practical occlusion in the knee extensors. *J Strength Cond Res*. 2010;24(10):2831-2834.
30. Lorenz DS, Bailey L, Wilk KE, et al. Blood flow restriction training. *J Athl Train*. 2021;56(9):937-944.
31. Mahmoudian A, Lohmander LS, Mobasheri A, Englund M, Luyten FP. Early-stage symptomatic osteoarthritis of the knee—time for action. *Nat Rev Rheumatol*. 2021;17(10):621-632.
32. Malorgio A, Malorgio M, Benedetti M, et al. High intensity resistance training as intervention method to knee osteoarthritis. *Sports Med Health Sci*. 2021;3(1):46-48.
33. Minniti MC, Statkevich AP, Kelly RL, et al. The safety of blood flow restriction training as a therapeutic intervention for patients with musculoskeletal disorders: a systematic review. *Am J Sports Med*. 2020;48(7):1773-1785.
34. Mittal A, Bhatnagar S, Kumar A, et al. The TWEAK-Fn14 system is a critical regulator of denervation-induced skeletal muscle atrophy in mice. *J Cell Biol*. 2010;188(6):833-849.
35. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.
36. Munukka M, Waller B, Häkkinen A, et al. Effects of progressive aquatic resistance training on symptoms and quality of life in women with knee osteoarthritis: a secondary analysis. *Scand J Med Sci Sports*. 2020;30(6):1064-1072.
37. O'Neill TW, Felson DT. Mechanisms of osteoarthritis (OA) pain. *Curr Osteoporos Rep*, 2018;16:611-616.
38. Pazit L, Jeremy D, Nancy B, Michael B, George E, Hill KD. Safety and feasibility of high speed resistance training with and without balance exercises for knee osteoarthritis: a pilot randomised controlled trial. *Phys Ther Sport*. 2018;34:154-163.
39. Pollock ML, Carroll JF, Graves JE, et al. Injuries and adherence to walk/jog and resistance training programs in the elderly. *Med Sci Sports Exerc*. 1991;23(10):1194-1200.
40. Schoenfeld BJ. The mechanisms of muscle hypertrophy and their application to resistance training. *J Strength Cond Res*. 2010;24(10):2857-2872.
41. Scott BR, Slattery KM, Sculley DV, et al. Hypoxia and resistance exercise: a comparison of localized and systemic methods. *Sports Med*. 2014;44:1037-1054.
42. Segal N, Davis MD, Mikesky AE. Efficacy of blood flow-restricted low-load resistance training for quadriceps strengthening in men at risk of symptomatic knee osteoarthritis. *Geriatr Orthop Surg Rehabil*. 2015;6(3):160-167.
43. Segal NA, Williams GN, Davis MC, Wallace RB, Mikesky AE. Efficacy of blood flow-restricted, low-load resistance training in women with risk factors for symptomatic knee osteoarthritis. *PM R*. 2015;7(4):376-384.
44. Shakeel R, Khan AA, Ayyub A, Masood Z. Impact of strengthening exercises with and without blood flow restriction on quadriceps of knee osteoarthritis patients. *J Pak Med Assoc*. 2021;71(9):2173-2176.

45. Sharma L. Osteoarthritis of the knee. *N Engl J Med*. 2021;384(1):51-59.
46. Sheikh AM, Vissing J. Exercise therapy for muscle and lower motor neuron diseases. *Acta Myol*. 2019;38(4):215-232.
47. Shinohara M, Kouzaki M, Yoshihisa T, Fukunaga T. Efficacy of tourniquet ischemia for strength training with low resistance. *Eur J Appl Physiol Occup Physiol*. 1998;77(1-2):189-191.
48. Smith BE, Hendrick P, Smith TO, et al. Should exercises be painful in the management of chronic musculoskeletal pain? A systematic review and meta-analysis. *Br J Sports Med*. 2017;51(23):1679-1687.
49. Sumide T, Sakuraba K, Sawaki K, Ohmura H, Tamura Y. Effect of resistance exercise training combined with relatively low vascular occlusion. *J Sci Med Sport*. 2009;12(1):107-112.
50. Takano H, Morita T, Iida H, et al. Hemodynamic and hormonal responses to a short-term low-intensity resistance exercise with the reduction of muscle blood flow. *Eur J Appl Physiol*. 2005; 95:65-73.
51. Takarada Y, Tsuruta T, Ishii N. Cooperative effects of exercise and occlusive stimuli on muscular function in low-intensity resistance exercise with moderate vascular occlusion. *The Japan J Physiol*. 2004;54(6):585-592.
52. Teixeira EL, Barroso R, Silva-Batista C, et al. Blood flow restriction increases metabolic stress but decreases muscle activation during high-load resistance exercise. *Muscle Nerve*. 2018;57(1):107-111.
53. Teixeira EL, Ugrinowitsch C, de Salles Painelli V, et al. Blood flow restriction does not promote additional effects on muscle adaptations when combined with high-load resistance training regardless of blood flow restriction protocol. *J Strength Cond Res*. 2021; 35(5):1194-1200.
54. Wang HN, Chen Y, Cheng L, Cai YH, Li W, Ni GX. Efficacy and safety of blood flow restriction training in patients with knee osteoarthritis: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)*. 2022;74(1):89-98.
55. World Alliance For Patient Safety Drafting Group, Sherman H, Castro G, et al. Towards an International Classification for Patient Safety: the conceptual framework. *Int J Qual Health Care*. 2009;21(1):2-8.
56. Young BE, Ong SWX, Kalimuddin S, et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. *JAMA*. 2020;323(15):1488-1494.
57. Zeng CY, Zhang ZR, Tang ZM, Hua FZ. Benefits and mechanisms of exercise training for knee osteoarthritis. *Front Physiol*. 2021;12: 794062.
58. Zhang Z, Huang C, Jiang Q, et al. Guidelines for the diagnosis and treatment of osteoarthritis in China (2019 edition). *Ann Transl Med*. 2020;8(19):1213.