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Systematic Review

Does Blood Flow Restriction Therapy in Patients Older Than Age 50 Result in Muscle Hypertrophy, Increased Strength, or Greater Physical Function? A Systematic Review

Breanne S. Baker PhD, Michael S. Stannard MS, Dana L. Duren PhD, James L. Cook DVM, PhD, James P. Stannard MD

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Abstract

Background Blood flow restriction (BFR) is a process of using inflatable cuffs to create vascular occlusion within a limb during exercise. The technique can stimulate muscle hypertrophy and improve physical function; however, most of these studies have enrolled healthy, young men with a focus on athletic performance. Furthermore, much of the information on BFR comes from studies with small samples sizes, limited follow-up time, and varied research designs resulting in greater design, selection, and sampling bias. Despite these limitations, BFR's popularity is increasing as a clinical rehabilitation tool for aging patients. It is important for practitioners to have a clear understanding of the reported effects of BFR specifically in older adults while simultaneously critically evaluating the available literature before deciding to employ the technique.

Questions/purposes (1) Does BFR induce skeletal muscle hypertrophy in adults older than 50 years of age? (2) Does BFR improve muscle strength and/or physical function in adults older than 50 years?

Methods Using PubMed, Google Scholar, Web of Science, and Science Direct, we conducted a systematic review of articles using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

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Each author certifies that his or her institution approved the reporting of this investigation and that all investigations were conducted in conformity with ethical principles of research.
This work was performed at the Missouri Orthopedic Institute, Columbia, MO, USA.

B. S. Baker, M. S. Stannard, D. L. Duren, J. L. Cook, J. P. Stannard, Department of Orthopaedic Surgery, University of Missouri, Columbia, MO, USA

B. S. Baker, D. L. Duren, J. L. Cook, J. P. Stannard, Missouri Orthopedic Institute, Columbia, MO, USA

M. S. Stannard, Department of Biomedical Sciences and Pathobiology, University of Missouri, Columbia, MO, USA

D. L. Duren, Department of Pathology and Anatomical Sciences, University of Missouri, Columbia, MO, USA

J. P. Stannard (✉), Missouri Orthopedic Institute, 4028B, 4th Floor, 1100 Virginia Ave., Columbia, MO 65212 USA, E-mail: stannardj@health.missouri.edu

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guidelines to assess the reported effects of BFR on skeletal muscle in older adults. Included articles enrolled participants 50 years of age or older and used BFR in conjunction with exercise to study the effects of BFR on musculoskeletal outcomes and functionality. The following search terms were used: "blood flow restriction" OR "KAATSU" OR "ischemic training" AND "clinical" AND "elderly." After duplicates were removed, 1574 articles were reviewed for eligibility, and 30 articles were retained with interventions duration ranging from cross-sectional to 16 weeks. Sample sizes ranged from 6 to 56 participants, and exercise tasks included passive mobilization or electrical stimulation; walking; resistance training using machines, free weights, body weight, or elastic bands; and water-based activities. Furthermore, healthy participants and those with cardiovascular disease, osteoarthritis, osteoporosis, sporadic inclusion body myositis, spinal cord injuries, and current coma patients were studied. Lastly, retained articles were assigned a risk of bias score using aspects of the Risk of Bias in Nonrandomized Studies of Interventions and the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials.

Results BFR, in combination with a variety of exercises, was found to result in muscle hypertrophy as measured by muscle cross-sectional area, thickness, volume, mass, or circumference. Effect sizes for BFR's ability to induce muscle hypertrophy were calculated for 16 of the 30 papers and averaged 0.75. BFR was also shown to improve muscle strength and functional performance. Effect sizes were calculated for 21 of the 30 papers averaging 1.15.

Conclusions Available evidence suggests BFR may demonstrate utility in aiding rehabilitation efforts in adults older than 50 years of age, especially for inducing muscle hypertrophy, combating muscle atrophy, increasing muscle strength, and improving muscle function. However, most studies in this systematic review were at moderate or high risk of bias; that being so, the findings in this systematic review should be confirmed, ideally using greater sample sizes, randomization of participants, and extended follow-up durations.

Level of Evidence Level II, systematic review.

Introduction

Aging patients commonly have muscle atrophy and associated physical decline, which are accelerated after musculoskeletal injury or surgery. In the 1990s, Yoskiaki Sato developed KAATSU training, also known as blood flow restriction (BFR) therapy, to combat muscle atrophy [54]. This technique involves using inflatable cuffs around limbs to create vascular occlusion, thereby altering local interstitial pressures and trapping exercise-induced metabolites. BFR therapy has reported efficacy for improving performance in athletes [2, 48, 63, 64], with growing evidence of benefits in hospitalized patients [38, 65, 74], including older adults [4, 25, 29, 62]. Improvements from BFR have been found when it is used in conjunction with a variety of training modalities, such as walking [3, 4, 48], cycling [1], low-load resistance training [29, 61, 62], and body-weight exercises [26].

Because musculoskeletal injuries often require prolonged healing times, negative downstream disuse effects on bone and muscle may result in chronic detrimental losses in physical function, which is of particular concern to older adults with respect to immobility and resultant physical and mental health decline. As such, cardiovascular, muscular, and skeletal responses to exercise interventions with BFR are of special interest in this large and growing clinical cohort. Of the evidence available, systematic reviews of BFR safety indicate it is not associated with additional cardiovascular stresses or morbidity [10, 23, 36, 50]. Rather, the acute and local elevated blood pressure responses to BFR result in a variety of positive cardiovascular adaptations such as improved vascular endothelial function, peripheral blood circulation [58], and arterial and venous compliance [25, 46]. Plausible mechanisms underlying BFR's ability to induce muscle hypertrophy and/or protect from muscle atrophy include biochemical responses influencing accelerated muscle hypertrophy [16, 17, 21, 30, 32, 53, 62, 63] and enhanced muscle performance because of oxygen-dependent shifts in fiber type recruitment [63, 65, 66].

Patients at risk of muscle atrophy because of extended periods of immobilization, such as those with prolonged bed rest, unilateral limb unloading, or casting, may be excellent candidates for BFR [12], especially because BFR administered on the contralateral limb may result in positive adaptations in the injured limb [39]. Despite the limited research supporting BFR's application in adults older than 50 years, BFR usage is increasing as a clinical rehabilitation tool. It is important for clinicians and practitioners to gain a comprehensive understanding of the reported effects of BFR in older adults and the limitations of that research body before using the technique in their clinics.

To address these knowledge gaps, the objective of this systematic review was to answer two clinically relevant questions: (1) Does BFR induce skeletal muscle hypertrophy in adults older than 50 years of age? (2) Does BFR improve muscle strength and/or physical function in adults older than 50 years?

Materials and Methods

Search Strategy and Criteria

We searched for potential research publications describing the clinical utility of BFR in the following databases: PubMed, Web of Science, Google Scholar, and Science Direct, using a Boolean equation with the search terms "blood flow restriction" OR "KAATSU" OR "ischemic training" AND "clinical" AND "elderly." Once the title and abstract of each study were reviewed—and when they did not provide sufficient information regarding eligibility—the full-text article was reviewed. Two authors (BSB, MSS) independently conducted the search and cataloged all articles. Information collected from each article was sample size, age, and health status of the participants; exercise intervention used; and BFR application methods. Additionally, methods including the measurement of muscle mass, cross-sectional area, volume, circumference, and thickness were used to address our first research question regarding BFR's effects on muscle hypertrophy. Changes in isometric and dynamic strength and torque and functional capacity, balance, gait speed, and dynamic movement task measurements were used to address our second research question regarding BFR's effects on functionality and strength.

Articles were included if they were published in English between January 1, 1990 and January 1, 2019. Research designs included prospective randomized control trials, prospective cohort studies, or cross-sectional designs using BFR therapy with exercise interventions in adults 50 years and older. All articles included a control condition such as a pre-assessment, contralateral limb without BFR therapy, exercising control, or a sedentary control group to compare against BFR conditions. Studies were not excluded for different BFR methodologies such as occlusion pressures, duration, or frequency of application. Articles were excluded if they did not include a description of experimentation, were not full-text articles published in scientific peer-reviewed journals, were a case series, did not use BFR during rehabilitation/exercise, or did not include musculoskeletal outcome measures specific to our two research questions. The results of the search are reported in a Preferred Reporting Items for Systematic Reviews and Meta-analysis study flowchart [42] (Fig. 1). The search yielded 2189 articles and after duplicates were removed, 1574 articles were assessed for initial eligibility and 30 were retained (Table 1).

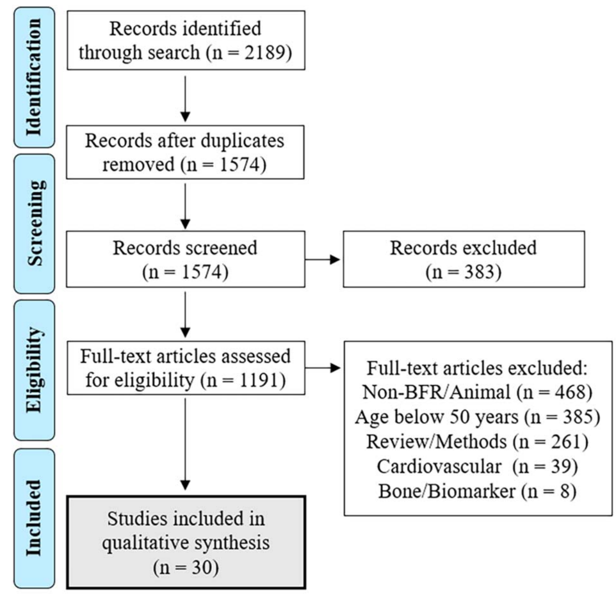

Fig. 1 This PRISMA flowchart shows study selection.

Methodological Quality Assessment

Two authors (BSB, MSS) used the Risk of Bias in Nonrandomized Studies of Interventions [60] and the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials [24] to jointly create an overall risk of bias score (low risk, moderate, or high risk). Two areas of special concern were patient selection and the presence and type of a reference standard or group. Studies that included more groups, enrolled a larger sample size, and had a longer duration were at less risk of bias (Table 2). Nearly two thirds of the studies were considered to be at moderate or high risk of bias because of research design, lack of randomization of participants, and the sparse use of multiple groups including non-BFR exercise controls and sedentary reference populations.

Study Outcomes

Our first aim was to understand if, and to what extent, does BFR induce muscle hypertrophy in adults older than 50 years. Muscle hypertrophy describes the increase in muscle size and is often measured as cross-sectional area, volume, thickness, circumferences, or mass. Twenty studies in this review quantified muscle size and were used to examine the first question. Study duration ranged from cross-sectional to 16 weeks, sample size ranged from 9 to 48 with a total of 413 participants (males n = 101; females n = 278; sex not reported n = 34) and average age was 63 years. In all, 80% of articles enrolled healthy participants, but patients in a coma [7], those with a spinal cord injury (incomplete tetraplegia) [22], and osteoarthritis (OA) [15, 56] were included.

Our second aim was to understand if muscle strength and physical function responded to BFR in adults older than 50 years. Muscle strength, or the ability to exert force, was measured as the maximal voluntary contraction

Table 1. Articles analyzing either skeletal muscle and/or functional performance are ordered by length of intervention and summarized below.

Author	Number, sex, mean age and weight	Design and duration	Intervention	Occlusion pressure	Results and conclusions	Study quality
Fukuda et al. [19]	Six men, 69 years, kg NR	Cross-sectional; within-subject	Patients with CVD—elastic band bicep curl with and without BFR	Ranged between 110 mmHg and 160 mmHg	BFR resulted in 40% greater muscle activation than CON[a]; BFR condition also had greater RPE than CON[a] in patients with CVD	Moderate risk
Natsume et al. [43]	18 (eight women), 68 years, 61 kg	Cross-sectional	Walking with BFR for 20 minutes with assessments before and after	Variable pressure based on thigh circumference	Muscle thickness increased from pre- to post-exercise[a], but knee extensor isometric strength decreased[b]	High risk
Barbalho et al. [7]	20 (three women), 66 years, 80 kg	Prospective; 11 days, within-subject	Patients with coma—passive mobilization with and without BFR	Pressure was 80% of patients' tibial artery systolic BP	Patients' muscle thickness decreased by 19% instead of 25%[b]; thigh circumference was protected by BFR[b]	Moderate risk
Kim et al. [31]	Old: nine patients, 63 years, 82 kg Young eight patients, 22 years, 73 kg, sex NR	Prospective; 4 weeks, three groups	3 x per week, handgrip at HI and LI + BFR, younger patients used LI + BFR	130% of systolic BP, mean young = 150 mmHg, mean old = 160 mmHg	All conditions increased muscle strength[a]. BFR increased forearm girth in younger and older adults more than HI[a]	Moderate risk
Patterson and Ferguson [49]	10 (two women), 67 years, 78 kg	Prospective; 4 weeks, within-subject	3 x per week, plantar flexion with and without BFR (CON)	110 mmHg for all patients	Leg BFR increased plantar flexion 1RM, MVC, and isokinetic torque[a]	Moderate risk
Segal et al. [55]	41 men, 56 years, kg NR	RCT; 4 weeks, two groups	Patients with OA: 3 x per week, leg press with or without BFR (CON)	Ramp protocol increased from 100 mmHg to 200 mmHg	Leg strength improved in both groups[b] and BFR condition did not improve strength or pain scores more than without BFR.	Moderate risk
Segal et al. [56]	40 women, 55 years, 82 kg	RCT; 4 weeks, two groups	Patients with OA—3 x per week, leg press with or without BFR (CON)	Ramp protocol increased from 100 mmHg to 200 mmHg	Leg press 1RM and quadriceps strength increased in BFR more than in CON[a], but no difference in knee pain scores or mCSA	Moderate risk

Table 1. continued

Author	Number, sex, mean age and weight	Design and duration	Intervention	Occlusion pressure	Results and conclusions	Study quality
Bryk et al. [9]	34 women, 61 years	RCT; 6 weeks, two groups	Patients with OA—3 x per week, knee extension with and without BFR	200 mmHg for all patients	Both groups had increased strength and functional assessments scores[a]; BFR patients reportedless knee pain[a]	Moderate risk
Clarkson et al. [11]	19 (eight women), 80 years, 77 kg	RCT; 6 weeks, two groups	4 x per week, walking with LI BFR or without (CON)	60% of total limb occlusion pressure	BFR improved walking performance by 2.5–4.5-fold[a], RPE was greater in LI BFR walk throughout[a] in older adults	Moderate risk
Gorgey et al. [22]	Nine men, 18-65 years, kg NR	Prospective; 6 weeks, within-subject	Patients with SCI—2 x per week stimulated forearm training with and without BFR	30% above systolic BP	Electrical stimulated forearm training with BFR increased extensor mCSA and one hand task[a], no change in wrist size and other four hand task performances	Moderate risk
Abe et al. [4]	19 (15 women), 60-78 years	RCT; 6 weeks, two groups	5 x per week, walking with or without BFR (CON)	Ramp protocol increased from 160 mmHg to 200 mmHg	BFR increased knee extension/flexion strength, mCSA, mass, TUG, and chair stand performance[a]	Moderate risk
Fahs et al. [14]	17 (six women), 55 years, 83 kg	Prospective; 6 weeks, within-subject	3 x per week knee extension to fatigue with and without BFR (CON)	Ramp protocol increased from 150 mmHg to 240 mmHg	BFR to fatigue elicited similar muscle and performance adaptations to volitional fatigue training[a]	Moderate risk
Karabulut et al. [28]	37 men, 57 years, 85 kg	Prospective; 6 weeks, three groups	3 x per week, upper and lower body RT either HI, LI + BFR, or CON	Ramp protocol based on percieved exertion, mean = 205 mmHg	HI and LI + BFR conditions improved upper body and leg press strength more than CON[b], and HI and LI + BFR induced similar absolute strength gains in older men[a]	Moderate risk

Table 1. continued

Author	Number, sex, mean age and weight	Design and duration	Intervention	Occlusion pressure	Results and conclusions	Study quality
Thiebaud et al. [67]	14 women, 61 years, 76 kg	RCT; 8 weeks, two groups	3 x per week, band exercises at moderate-high intensity or LI + BFR	Ramp protocol increased from 80 mmHg to 120 mmHg	Muscle strength increased for most exercises; lean mass did not change for BFR and elastic band groups[a]	Moderate risk
Yokokawa et al. [75]	51 (34 women), 72 years, kg NR	RCT; 8 weeks, two groups	2 x per week, core/lower body exercises with BFR or 1 x per week, balance training	Ramp protocol increased from 70 mmHg to 150 mmHg	Balance improved over time for both conditions[a]; BFR improved knee extension and TUG[a]; BFR can be a surrogate to balance training	Moderate risk
Araújo et al. [5]	28 women, 54 years, 61 kg	RCT; 8 weeks, three groups	3 x per week, lower body exercises in water with or without BFR (CON)	80% of total limb occlusion pressure, mean = 101 mmHg	Increased lower body strength was found only with BFR + water-based exercises[a]	Low risk
Ozaki et al. [46]	23 (18 women), 67 years, 56 kg	Prospective; 10 weeks, two groups	4 x per week, walking with and without BFR	Ramp protocol increased from 14 0mmHg to 200 mmHg	BFR increased knee extension/flexion torques and thigh mCSA[b] in older adults	Moderate risk
Ozaki et al. [47]	18 women, 66 years, 53 kg	Prospective; 10 weeks, two groups	4 x per week, 20 minutes of walking with and without BFR	Ramp protocol increased from 140 mmHg to 200 mmHg	BFR increased knee extension/flexion torques, thigh mCSA, TUG, and chair stand performance in older women[a]	Moderate risk
Yasuda et al. [72]	30 women, 70 years, 50 kg	RCT; 12 weeks, three groups	2 x per week, EB with BFR, moderate intensity without BFR, or CON	Ramp protocol increased from 120 mmHg to 270 mmHg	BFR with EB training increased quadriceps mCSA and knee extension MVC more than without BFR in older women[a]	Low risk
Yasuda et al. [70]	19 (14 women), 70 years, 54 kg	RCT; 12 weeks, two groups	2 x per week knee extension and leg press with and without BFR	Ramp protocol increased from 120 mmHg to 270 mmHg	BFR increased quadriceps mCSA, leg strength, and chair stand performance while CON did not improve	Moderate risk
Libardi et al. [34]	25, 65 years, sex NR, 69 kgs	RCT; 12 weeks, 3 groups	4x/week, training with and without BFR, CON	50% of total limb occlusion pressure, mean=67 mmHg	Quadriceps mCSA and 1RM[b] increased similarly in both BFR and exercise conditions	High risk

Table 1. continued

Author	Number, sex, mean age and weight	Design and duration	Intervention	Occlusion pressure	Results and conclusions	Study quality
Yasuda et al. [73]	17 (14 women), 70 years, 53 kgs	Prospective; 12 weeks, 2 groups	2x/week, elbow extension /flexion with EBs with and without BFR	Ramp protocol ↑ from 120-270 mmHg, mean = 196 mmHg	Elbow flexors and extensors mCSA and MVC increased in BFR group only[a]	Moderate risk
Yasuda et al. [71]	14 women, 70 years, 47 kgs	RCT; 12 weeks + 12 weeks detraining, 2 groups	Previous study methods + detraining period	Ramp protocol ↑ from 120-270 mmHg	mCSA and MVC gains post BFR intervention were well maintained in older women[a]	Moderate risk
Cook et al. [13]	36 (21 women), 76 years, 74 kgs	RCT; 12 weeks, 3 groups	2x/week, knee extension/ flexion at HI, LI with BFR, or upper body	1.5 times brachial systolic BP, mean 184 mmHg	HI and BFR improved strength and thigh mCSA more than CON[a], all conditions improved walking speed[b] and was deemed safe	High risk
Jørgensen et al. [27]	22 (4 women), 69 years, 78 kgs	RCT; 12 weeks, 2 groups	SIBM patients −2x/ week, lower body training with and without BFR	110 mmHg for all patients	BFR improved survey scores[a] and maintained leg strength[a] in patients with sporadic inclusion body myositis	Moderate risk
Vechin et al. [69]	23 (9 women), 64 years, 73 kgs	RCT; 12 weeks, 3 groups	2x/week, leg press at HI, LI with or without BFR (CON)	50% of total tibial artery occlusion pressure	BFR and HI improved thigh mCSA[b] and HI increased leg press 1RM[a]. BFR was an effective surrogate to HI.	Low risk
Ferraz et al. [15]	48 women, 60 years, 74 kgs	RCT; 12 weeks, 3 groups	OA patients - 2x/week, RT at LI with and without BFR, or at HI	80% of total tibial artery occlusion pressure, mean = 97 mmHg	Leg strength, mCSA, and standing performance increased more in BFR and HI[b] conditions and functional and pain scores improved[a]	Low risk
Pereira Neto et al. [52]	20 women, 62 years, 62 kgs	RCT; 12 weeks, 4 groups	Osteoporotic women - 2x/week, walking + BFR, LI + BFR or HI knee extension, CON	80% of total tibial artery occlusion pressure	All exercise groups increased dynamic strength[a] and both BFR conditions improved strength in women with osteoporosis	Low risk

Table 1. continued

Author	Number, sex, mean age and weight	Design and duration	Intervention	Occlusion pressure	Results and conclusions	Study quality
Silva et al. [59]	18 women, 62 years, 65 kgs	RCT; 16 weeks, 2 groups	2x/week, bar squatting with LI and BFR, or at HI without BFR	50% of total tibial artery occlusion pressure	LI + BFR was not more effective than HI training at inducing body composition changes	Low risk
Letieri et al. [33]	56 women, 69 years, 67 kgs	RCT; 16 weeks training + 6 weeks detraining 5 groups	3x/week, lower body RT at LI or HI, with low (LBFR) and high (HBFR)	Low BFR = 80% of total tibial artery occlusion pressure, high BFR pressure was calculated (41)	Lower body strength increased in all conditions except LI and CON[a], after 6 weeks detraining, strength gains were best preserved in the HI, LBFR, and HBFR conditions[a]	Low risk

[a]$p < 0.05$.
[b]$p < 0.01$; Q = Study quality/risk of bias: low risk, moderate risk, high risk; NR = not reported; CVD = cardiovascular disease; BFR = blood flow restriction; CON = control; BP = blood pressure; HI = high-intensity/load; LI = low or light-intensity/load; 1RM = 1 repetition maximum; MVC = maximal voluntary contraction; RCT = randomized control trial; OA = osteoarthritis; mCSA = muscle cross-sectional area; RPE = rating of perceived exertion; SCI = spinal cord injury; TUG = timed up and go task; RT = resistance training; EB = elastic bands; SIBM = sporadic inclusion body myositis.

force, maximal voluntary isometric contraction force, torque, muscle activation, or one repetition maximum; while functional performance included the 30 second sit-to-stand (30STS) and the 8 feet timed up and go (TUG). Twenty-five of 30 studies reported muscular strength outcome measures and eight studies included measures of the 30STS and/or TUG. Study duration ranged from cross-sectional to 16 weeks, sample size ranged from 6 to 56 with a total of 694 participants (males n = 205; females n = 455; sex not reported n = 34) and average age was 66 years. Overall, 74% of articles enrolled healthy participants, but patients with OA [9, 15, 55, 56], osteoporosis [52], cardiovascular disease [19], and sporadic inclusion body myositis [27] were included.

Percent changes and effect sizes were calculated for outcome variables when raw means and SDs for pre- and post-data were available. Percent changes were calculated using the equation: % change = [(post-mean – pre-mean)/pre-mean] *100. Positive values indicate an increase while negative values indicate a decrease over time. Effect sizes were calculated using the equation: ES = (post mean – pre mean)/pre-SD. Effect sizes indicate the magnitude of difference between BFR and non-BFR group means, with larger numbers (that is, greater than 0.8) indicating a greater difference between values.

Results

Does BFR Induce Skeletal Muscle Hypertrophy in Adults Older than 50 Years?

Using muscle cross-sectional area, volume, mass, thickness, or limb circumference, 20 of 30 studies addressed the question of muscle hypertrophy and 15 of those studies reported increased skeletal muscle size after the BFR intervention with percent changes and effect sizes ranging from -5.5% to 17.5% and 0.11 to 3.6, respectively (Fig. 2) [4, 13-15, 22, 31, 34, 43, 46, 47, 69-73]. Additionally, studying 20 patients in a coma, Barbalho et al. [7] reported that passive mobilization using BFR better protected lower body muscles from atrophy. The contralateral limb, which did not receive BFR lost more than 25% of muscle thickness in an average of 11 days compared with the BFR treated limb which only lost 19% (effect size = 1.25). Three of 18 studies found no difference in muscle measurements compared with controls [56, 59, 67].

Does BFR Improve Muscle Strength and/or Physical Function in Adults Older Than 50 Years?

Of the 30 studies included, 25 addressed muscle strength and eight addressed physical function. Eighteen reported

Table 2. Risk of bias assessment for each included article

Article	Patient selection bias	Reference standard (con) bias	Overall risk
Fukuda et al. [19]	Within-subject, some concerns	Crossover design, some concerns	Moderate risk
Natsume et al. [43]	BFR only, high risk	Crossover design, some concerns	High risk
Barbalho et al. [7]	Within-subject, some concerns	Contralateral CON, some concerns	Moderate risk
Kim et al. [31]	Non-randomized, some concerns	Exercise CON, some concerns	Moderate risk
Patterson & Ferguson [49]	Within-subject, some concerns	Contralateral CON, some concerns	Moderate risk
Segal et al. [55]	Randomized control, low risk	Exercise CON, some concerns	Moderate risk
Segal et al. [56]	Randomized control, low risk	Exercise CON, some concerns	Moderate risk
Bryk et al. [9]	Randomized control, low risk	Exercise CON, some concerns	Moderate risk
Clarkson et al. [11]	Randomized control, low risk	Exercise CON, some concerns	Moderate risk
Gorgey et al. [22]	Within-subject, some concern	Contralateral CON, some concerns	Moderate risk
Abe et al. [4]	Randomized control, low risk	No exercise CON, some concerns	Moderate risk
Fahs et al. [14]	Within-subject, some concerns	Contralateral CON, some concerns	Moderate risk
Karabulut et al. [28]	Non-randomized, some concerns	Exercise and no exercise CON, low risk	Moderate risk
Thiebaud et al. [67]	Randomized control, low risk	Exercise CON, some concerns	Moderate risk
Yokokawa et al. [75]	Randomized control, low risk	Exercise CON, some concerns	Moderate risk
Araújo et al. [5]	Randomized control, low risk	Exercise and no exercise CON, low risk	Low risk
Ozaki et al. [46]	Non-randomized, some concerns	Exercise CON, some concerns	Moderate risk
Ozaki et al. [47]	Non-randomized, some concerns	Exercise CON, some concerns	Moderate risk
Yasuda et al. [72]	Randomized control, low risk	Exercise and no exercise CON, low risk	Low risk
Yasuda et al. [70]	Randomized control, low risk	No exercise CON, some concerns	Moderate risk
Libardi et al. [34]	Randomized control, low risk	Exercise and no exercise CON, low risk	Low risk
Yasuda et al. [73]	Non-randomized, some concerns	Exercise CON, some concerns	Moderate risk
Yasuda et al. [71]	Randomized control, low risk	Exercise CON, some concerns	Moderate risk
Cook et al. [13]	Randomized control, low risk	Two different exercise CON, low risk	Low risk
Jørgensen et al. [27]	Randomized control, low risk	No exercise CON, some concerns	Moderate risk
Vechin et al. [69]	Randomized control, low risk	Exercise and no exercise CON, low risk	Low risk
Ferraz et al. [15]	Randomized control, low risk	Exercise and no exercise CON, low risk	Low risk
Pereira Neto et al. [52]	Randomized control, low risk	Exercise and no exercise CON, low risk	Low risk
Silva et al. [59]	Randomized control, low risk	Exercise and no exercise CON, low risk	Low risk
Letieri et al. [33]	Randomized control, low risk	Exercise and no exercise CON, low risk	Low risk

BFR = blood flow restriction; CON = control.

increases in muscle strength, with percent changes and effect sizes ranging from -5.2% to 42.0% and 0.55 to 4.34, respectively (Fig. 3) [4-6, 14, 15, 28, 33, 34, 46, 47, 49, 52, 56, 70-73, 75]. Six reported that BFR does not induce a greater increase in muscle strength than other non-BFR conditions [9, 13, 14, 55, 67, 69]. The only adverse effect was reported by Natsume et al. [43], who found a 5.2% reduction in maximal voluntary isometric contractions immediately after walking with BFR for 20 minutes. Performance of the TUG and 30STS improved with the addition of BFR [4, 5, 11, 15, 70, 75]. The effects of BFR were not different according to Bryk et al. [9], who reported a 1.2 second reduction in TUG time in patients with knee OA and Jørgensen et al. [27] reported no difference in TUG or 30STS performance in those with sporadic inclusion body myositis.

Discussion

BFR therapy is receiving increased attention and use as a therapeutic modality in sports medicine and has been the focus of more than 2000 publications since 2015. Available evidence for BFR use in athletes consistently shows that strength gains and muscle hypertrophy can be achieved in shorter periods of time with lower training volumes compared with traditional high-intensity resistance training [1, 40, 50, 64, 66]. Based on these cited benefits, BFR may be an effective intervention for older patients for whom high-intensity resistance exercise is contraindicated because of musculoskeletal disease or injury [70, 72, 73]. However, to date, the evidence supporting BFR's use in older adults stems from studies with limited samples sizes and varied research designs putting these results at greater risk for

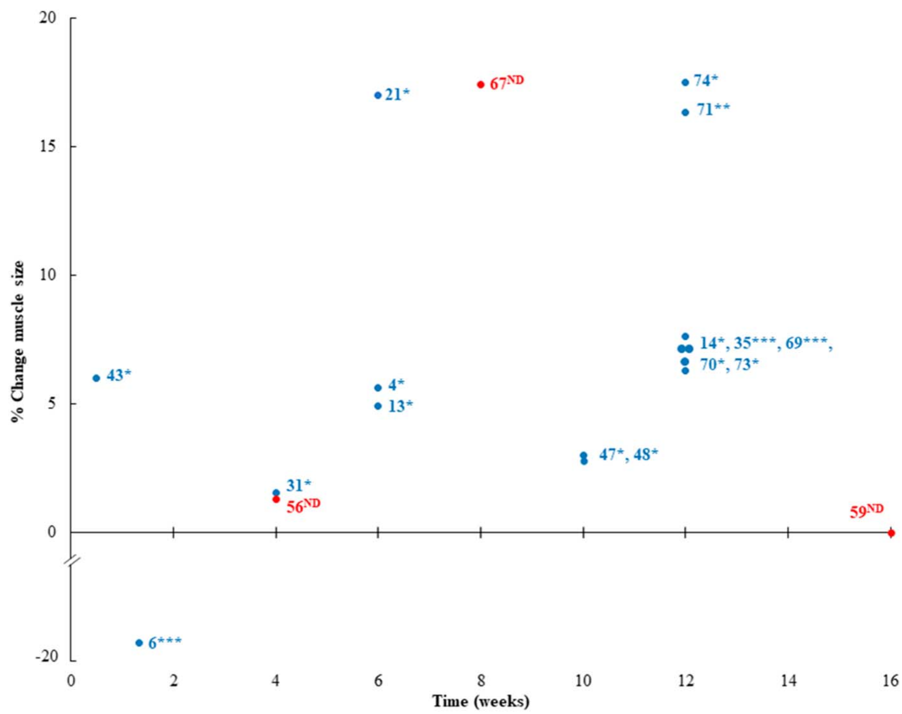

Fig. 2 Twenty studies examining muscle size were separated by the magnitude of the effect of BFR on change in muscle size and the duration of the intervention. Data in blue represent studies with findings that report substantial positive effects of BFR on skeletal muscle size, while data in red represent no-difference (ND) or unsupportive findings of the first aim of our study; $*p < 0.05$; $^{**}p < 0.01$, $^{***}p < 0.001$.

bias. Therefore, this systematic review aimed to determine the documented effects of BFR on skeletal muscle size, strength, and function in older adults. Available evidence suggests BFR can induce positive adaptations to muscle size, strength, and physical performance in older adults.

Two important limitations of this body of evidence that clinicians and practitioners need to carefully consider are the heterogeneity of BFR protocols and the disparate participant ages and health conditions among the included studies. One example of BFR protocol heterogeneity is occlusion pressure, which can vary widely between days, exercise conditions, and participants. Some studies used a patient-dependent pressure ramp protocol while others relied on fixed pressure throughout the intervention, and these varying occlusion pressures make direct comparisons between study results difficult [35]. Much research on the ideal BFR methodology and application has already been published in young adults [8, 35, 37, 50], but to date no consensus exists for adults older than 50 years of age, which is a necessary next step to ensure practical and safe implementation in the clinical setting. Another important limitation to consider is the variability in participant age and health status. Despite the positive effects of BFR reported in most of the studies included in this review, the average age of participants was 64 years. The extent to which adults older than 80 years may respond to BFR is still unknown, which is of concern as this age group comprises a large proportion of orthopaedic patients. Furthermore, particular medical conditions may be more influential than others on BFR's effects. For instance in patients with OA [9, 15, 55, 56] and those who were completely immobilized [7, 22], the percent change and effect sizes ranged from 3.3% to 42.0% and 0.45 to 1.9, respectively. In patients with sporadic inclusion body myositis [27] and osteoporosis [52], the percent change and effect sizes ranged from 9 to 24.25 and 0 to 0.68, respectively. Future studies are needed to specifically target adults older than 80 years who are healthy and battling a variety of diseases to better understand the potential utility of BFR as a clinical rehabilitation tool.

Most studies in this systematic review reported positive effects of BFR on muscle size in adults older than 50 years of age, with effect sizes ranging from moderate to large. A potential initial mechanism for these findings is mammalian target of rapamycin complex 1 (MTOR1) signaling, which increases muscle protein synthesis and has been shown to increase after BFR in younger [17] and older men [16]. However, other important mechanisms of muscle

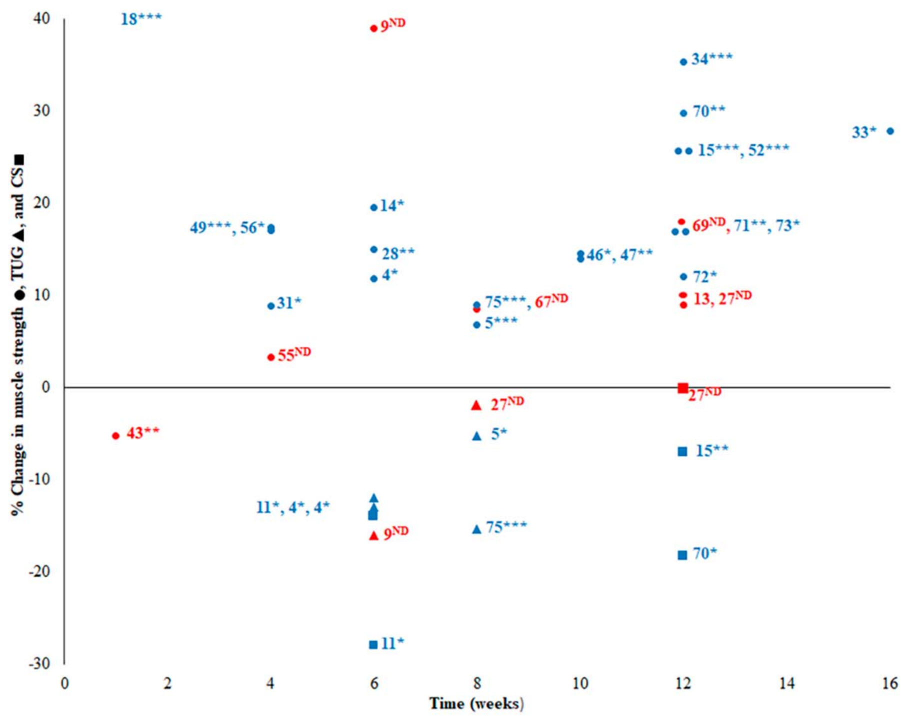

Fig. 3 Twenty-five studies reported changes in muscle strength ●, four reported changes in chair-stand performance ■, and five reported changes in timed-up-and-go performance ▲. Each study is plotted according to the magnitude of change in response to BFR therapy and the duration of the intervention. Data in blue represent studies with findings that report substantial positive effects of BFR on skeletal muscle strength or performance, while data in red represent no-difference (ND) or unsupportive findings of the second aim of our study. For the chair-stand and timed-up-and-go tasks, negative values indicate a reduction in time to completion and an improvement in performance. $^{*}p < 0.05$; $^{**}p < 0.01$, $^{***}p < 0.001$; TUG = timed-up and-go; CS= chair-stand.

hypertrophy include anabolic and sex hormones, which have been shown to increase [40, 45, 51, 57] or not change [29, 51] after BFR in older adults. Older males have a blunted growth hormone response after BFR exercise compared with younger males [40], suggesting age could be an underlying factor influencing the incidence and magnitude of muscle hypertrophy in response to BFR. Furthermore, postmenopausal females have an added challenge to maintaining and building new muscle related to estrogen deficiency. In this systematic review, three studies exclusively enrolled postmenopausal females and found no change in muscle size between the BFR and comparative groups. Although this could indicate a limitation to BFR in this population, the comparative group for each of these studies engaged in a high-intensity exercise intervention, which influences interpretations of results. To fully understand the clinical utility of BFR for inducing muscle hypertrophy, the relationship between hormone status, sex, and age must be further characterized. Additionally, nearly 70% of papers included in this systematic review were at moderate or high risk of bias due to study design features. Future studies must employ larger sample sizes, participant randomization techniques, greater follow-up durations, and active recruitment of more diverse study participants to increase the generalizability of results while reducing the risk of bias.

The long-term goal of most exercise interventions in older adults is to improve muscular strength and functional performance. Most included studies demonstrated BFR's ability to increase muscle strength, which has consistently been associated with reduced mortality rates in healthy and unhealthy adults [20, 41, 44]. Two included studies [9, 69] reported increases in muscle strength but those differences were not different than the comparative group, who engaged in high-intensity (> 70% one repetition of maximal voluntary contraction) resistance training. Furthermore, because lower body strength is closely linked to gait, balance, and coordination [18, 68], the observed BFR-related strength gains may also indirectly mitigate many of the factors associated with the risk of falling. The clinical advantages of BFR were apparent even in patients with OA as Bryk et al. [9] found BFR's effects were not different from those elicited by high-intensity exercise for improving physical performance while substantially reducing patient-reported pain. Additionally, Yokokawa et al. [75] reported BFR training resulted in improvements in gait, reaction time, and balance in older adults that were not different when compared with a dynamic balance training program, while only patients in the BFR group benefited from substantial muscle strength gains.

Available evidence suggests BFR can induce muscle hypertrophy, thus increasing muscle strength and improving physical function in older adults. However, these findings must be considered carefully, as most studies were at moderate or high risk for bias and featured only small sample sizes. Future studies need to determine appropriate indications for prescription in older orthopaedic patients by extending the follow-up periods, enrolling larger and more diverse sample sizes, and using randomization techniques.

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