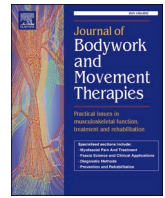




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Effects of low-load blood flow restriction training in healthy adult tendons: A systematic review and meta-analysis[☆]

Ilan Bechan Vergara^{a,*}, Albert Puig-Diví^b, Beñat Amestoy Alonso^c, Raimon Milà-Villarrol^b

^a Blanquerna School of Health Sciences – Ramon Llull University, c/ Padilla, 326, 08025, Barcelona, Spain

^b Blanquerna School of Health Sciences - Ramon Llull University, c/ Padilla, 326, 08025, Barcelona, Spain

^c Neuroscience Lab (part of IDIBAPS, Barcelona), Calle Marina 312 3-4, 08025, Barcelona, Spain

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ABSTRACT

Objective: To systematically review the effects of low-load blood flow restriction training (LL-BFR) on healthy adult tendons.

Design: A systematic review with meta-analysis.

Literature search: Six electronic databases were searched by two researchers.

Study selection criteria: Clinical trials comparing the effects of LL-BFR to high-load resistance training (HL-RT) or low-load resistance training (LL-RT) in healthy adult tendons.

Data synthesis: Two reviewers selected the eligible clinical trials, and one reviewer exported the data. Two reviewers evaluated the study quality and risk of bias using the PEDro scale and the ROB2 scale. We performed meta-analysis where appropriate using a random-effects model. We rated the quality of evidence using GRADE. **Results:** Six studies were eligible. We analyzed tendon cross-sectional area (CSA) and tendon stiffness as the outcomes. Across all comparisons, there was low-to moderate-quality evidence of a difference between LL-BFR and LL-RT immediately after exercise. There was high-quality evidence of no difference between LL-BFR and HL-RT in the long term.

Conclusion: The effects of LL-BFR on the tendons depends on the time and dose of the intervention. LL-BFR could be useful to increase the CSA of the tendons in a similar or superior way to HL-RT after 8 weeks of intervention.

1. Introduction

The benefits of low-load training with blood flow restriction (LL-BFR) have been shown in various areas of training, such as muscle hypertrophy and strength gain (Lixandrão et al., 2018). On the other hand, there are studies that use this tool to rehabilitate older adults with sarcopenia (Rodrigo-Mallorca et al., 2021) or with musculoskeletal pathologies (Hughes et al., 2017). BFR is achieved by applying tourniquets or inflatable cuffs to the proximal portion of the limb (Patterson et al., 2019). LL-BFR at 20%–30% of one repetition maximum (1RM) promotes muscle hypertrophy and increases strength similarly to high-load (HL-RT) resistance training without BFR at 70%–85% of 1RM (Wortman et al., 2021; Grønfelt et al., 2020). The advantage of training with

low loads is that it reduces mechanical stress on the tissues, representing an interesting option for populations that cannot train with submaximal loads (Rodrigo-Mallorca et al., 2021) or for subjects who have contraindications for HL training due to injury or postoperatively (Lu et al., 2020). In addition, LL-BFR is an easy to apply and transfer tool that demands little intervention time to obtain strength gains (Patterson et al., 2019). This could be useful for physiotherapists and strength and conditioning coaches in competition periods where there is not much time to perform resistance training with athletes, reducing the decrease in their strength levels during the season and decreasing the risk of injury. (Bittencourt et al., 2022; Gual et al., 2016; Mersmann et al., 2021; Michener and Kulig 2015) demonstrated that resistance training decreases the incidence of patellar tendinopathy in athletes. Resistance

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* Corresponding author. c/ Padilla, 326 / 08025 Barcelona, Spain.

E-mail addresses: ilanbechan@gmail.com (I. Bechan Vergara), albertpd@blanquerna.url.edu (A. Puig-Diví), amestoybenat@gmail.com (B. Amestoy Alonso), raimonmv@blanquerna.url.edu (R. Milà-Villarrol).

[@puig_divi](https://twitter.com/puig_divi) (A. Puig-Diví), [@RaimonMila](https://twitter.com/RaimonMila) (R. Milà-Villarrol)

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training is considered the gold standard first-line treatment intervention for tendinopathies, particularly in Achilles tendinopathy and patellar tendinopathy, such as eccentric and heavy slow resistance training. (Burton and McCormack 2022).

Mechanical stress and tension induced by strength training can improve the morphological and mechanical properties of tendons, increasing the cross-sectional area (CSA) and stiffness (Arampatzis et al., 2007). Likewise, relative rest or inactivity for longer than 2–3 weeks leads to a reduction in the mechanical capacity of the tendon (Docking and Cook 2019; Kubo et al., 2000). Resistance training causes an increase in the tendon CSA, suggesting that this may be a protective factor for overuse injuries, as it will reduce the force-to-area stress on the tendon (Kongsgaard et al., 2010). Although in pathological tendons there is a loss in the structural organization of the tendon in the stages of deterioration and degeneration, and probably irreversible alteration, it is widely accepted that the pathological tendon responds by increasing the amount of healthy tissue in parallel to the region of disorganized tissue, instead of repairing the pathological area. Because the CSA of the fibrillar structure is generally greater in pathological tendons, this difference allows maintaining the ability of the tendon to meet functional demands (Docking and Cook 2019).

(Ferguson et al., 2018) proposed that the anaerobic conditions of BFR induce an angiogenic stimulus through an increase in vascular endothelial growth factor. Additionally, the hypoxic stimulus caused by BFR mobilizes and recruits endothelial progenitor stem cells (Burr et al., 2019; Ferguson et al., 2018). On the other hand, Picón-Martínez et al., (2021) indicated that LI-BFR exercise provides an adequate stimulus to improve bone metabolic markers due to fluid movement and increased intramedullary pressure, and these effects could extend to the tendons (Loenneke et al., 2012; Picón-Martínez et al., 2021). No previous systematic reviews have analyzed the effects of LI-BFR in the tendons of healthy subjects, and there is great controversy in the literature about the effects caused by this type of training. Consequently, training with BFR could be a new tool to prevent and rehabilitate tendinopathies, although it is necessary to know exactly what its effects before making a recommendation.

The objective of this review is to systematically review the effects of LL-BFR on the tendons of healthy subjects. We hypothesize that training with BFR increases the thickness (CSA) and stiffness of the tendon similarly to HL strength training.

2. Method

2.1. Protocol and guidelines

This systematic review was conducted in accordance with the standards of the PRISMA statement. The protocol for this review was registered in an international registry on April 27, 2022 (PROSPERO ID: CRD42022332358).

2.2. Search strategy

We conducted a systematic search of PubMed, PEDro, Cochrane Central Register of Controlled Trials, BMC, SPORTDiscus, and CINAHL on February 16, 2022, to identify eligible studies. We did not apply time limits to the search. In the CINAHL and SPORTDiscus databases, we applied the “Academic Publications” filter. The search strategy is presented in Table 1.

In the first step, two evaluators independently screened studies on the basis of the title and abstract according to the inclusion and exclusion criteria. In the event that one or more researchers had doubts as to whether an article met the inclusion criteria based on the title or abstract, the article was included for a review of the abstract and the full text. Two evaluators independently reviewed the full text of the potentially relevant articles. Any disagreement between the evaluators was resolved and agreed upon by a third evaluator. One investigator

Table 1
Search strategy. (1,5 column).

Database	Search strategy	Filters applied	Search date	Final results
PubMed	(Blood flow restriction OR occlusion training OR kaatsu) AND (Tendon OR Tendons)	None	February 16, 2022	70
PEDro	Blood flow restriction “tendon”	None	February 16, 2022	2
CINAHL	Blood flow restriction or occlusion training or partial occlusion or katsu AND tendon	Academic publications	February 16, 2022	8
SPORTDiscus	Blood flow restriction AND Tendon	Academic publication	February 16, 2022	11
Cochrane Library-Central	“Blood flow restriction” AND “Tendon”	None	February 16, 2022	52
BMC	(Blood flow restriction OR occlusion training OR kaatsu) AND (Tendon OR Tendons)	None	February 16, 2022	112

extracted data by following a custom protocol.

2.3. Study selection

After selecting articles for full text review, two evaluators assessed the studies for eligibility based on the inclusion criteria. For this systematic review, studies had to meet the following criteria.

- Subjects had to be ≥ 18 years of age;
- The subjects had to be healthy (no musculoskeletal pathology involving the anatomical region that was subjected to the intervention and evaluation and no metabolic pathologies);
- The studies had to have performed at least one blood flow restriction training intervention and assessed tendon CSA and/or stiffness before and after it;
- The studies had to have compared the intervention with a control group undergoing LL or HL strength training;
- The studies had to be a clinical trial;
- The tendon CSA or thickness had to be measured with ultrasound (US) or magnetic resonance imaging (MRI).

The exclusion criteria were.

- Duplicate studies;
- Studies that did not meet the aforementioned inclusion criteria;
- Animal studies;
- Studies conducted in adults over 65 years of age.

The reasons for excluding an article are indicated in Fig. 1. The reviewers discussed any discrepancies in opinions and if a disagreement could not be resolved, a third reviewer was consulted.

2.4. Outcomes of interest

The outcomes were tendon CSA and stiffness.

2.5. Data extraction

One researcher extracted the data from the selected articles through a structured protocol that guaranteed obtaining the most relevant information from each study (Siddaway et al., 2019).

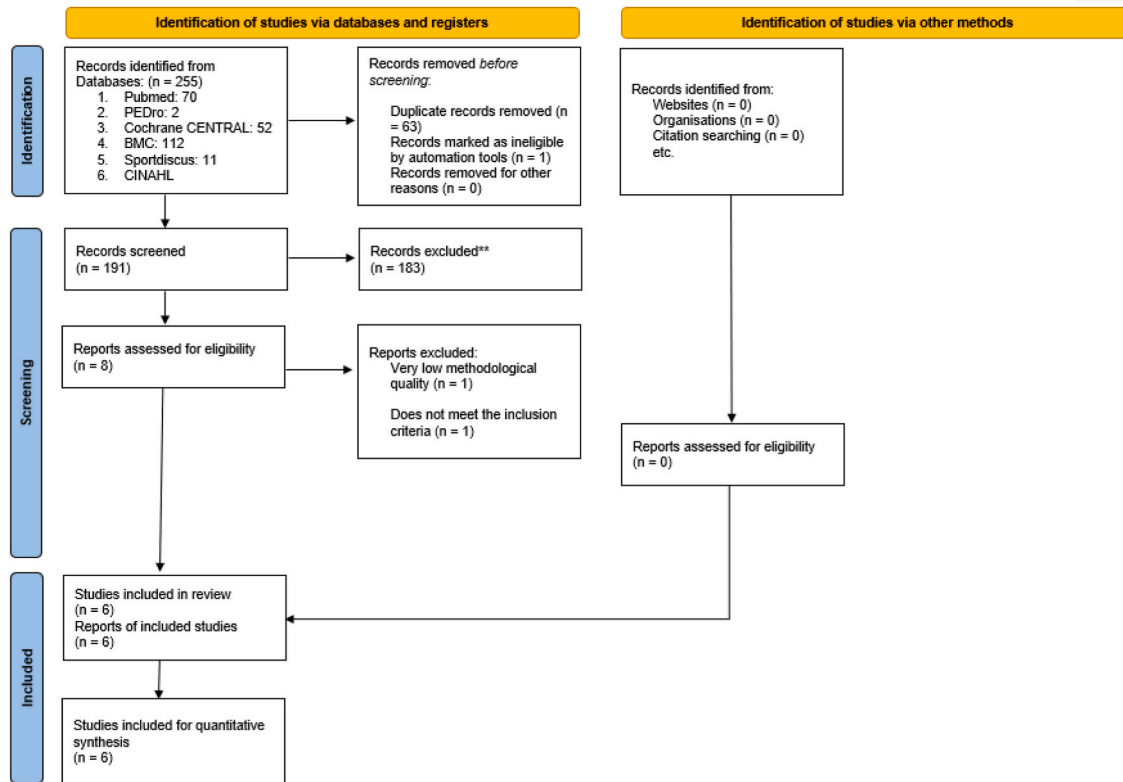


Fig. 1. Flowchart of the selection process. (2 column).

2.6. Quality assessment

We assessed the methodological quality of the articles included in the systematic review with the PEDro scale (de Morton, 2009), which includes 11 items. A score of 0 points represents the worst possible quality and 10 represent the best. A score of ≥ 7 classifies studies as “high quality,” a score between 5 and 6 points indicates “moderate quality,” and a score of ≤ 4 points specifies “low quality.” To assess risk of bias, we used the Cochrane ROB2 scale (Sterne et al., 2019), following the indications of the Cochrane Manual version 5.1.0. Two raters independently reviewed the quality of the selected studies using the same methodology. Disagreements between reviewers were resolved by discussion with a third reviewer.

2.7. Data analysis

We have reported descriptive data of the participant characteristics as mean (standard deviation [SD]). We conducted all meta-analysis calculations with the R software with the meta and metafor packages for metaanalysis (Version 3.5.1.) We performed descriptive analyses and prepared risk of bias figures using Microsoft Excel for Mac, version 16.29.1. We calculated the mean and standardised mean differences (SMDs; Hedges' g) and the 95% confidence interval (CI) for each group. We analyzed pooled data using a random-effects model (DerSimonian and Laird 1986) to estimate the change for each group at the same measurement time. For the secondary meta-analysis, we determined the mean difference to estimate the change from baseline to each time measurement for each group (control and experimental groups). We weighted SMDs by the inverse of the variance to calculate the effect sizes and 95% CI. We used Cohen's criteria to interpret the magnitude of the effect sizes: $< |0.50|$ is small, $|0.50|$ to $|0.80|$ is moderate, and $> |0.80|$

is large (Cohen 1988). We assessed heterogeneity using Cochran's Q statistic and its corresponding P -value as well as the I^2 statistic, which describes the percentage of variability in effect estimates attributable to heterogeneity rather than chance when I^2 is $>30\%$ (30%–60% represents moderate heterogeneity) (Higgins and Green 2008). We assessed publication bias with funnel plots and Begg's test. We set the significance at $p < 0.05$.

3. Results

3.1. Study selection and collection process

The initial search identified 255 studies from the databases (Table 1). We exported all citations to the Mendeley Desktop program (Version, 1803) reference manager. Once we had collected all the publications in Mendeley Desktop, we eliminated duplicate articles and those that were ineligible through the automation tool. Based on this process, 63 references were duplicates and one reference was rated ineligible by the reference manager.

We reviewed 191 references and included eight candidate references in the systematic review. It is important to note that we did not include any other studies using other methods. After exhaustively reading the eight references and applying the inclusion and exclusion criteria based on the PICOS acronym, we included six articles in the final systematic review (Fig. 1). We later used these same studies for the qualitative synthesis or meta-analysis. The reasons why we excluded the studies were: One study did not use the endpoints specified in the PICOS acronym (Canfer et al., 2021). For the second study (Kubo et al., 2006) the methodological quality was very low, so by consensus we decided to exclude it from the systematic review. We did not include the study by (Brumitt et al., 2020) in the meta-analysis due to the anatomical location

of the intervention, but based on consensus we considered it for the qualitative analysis.

During the search process, we made adjustments based on the different databases. Table 1 shows the searches agreed upon by the two researchers. We did not use MeSH terms because the MeSH term “BFRT” is recent and when performing the search no articles with this term appeared. Boolean commands are not accepted in the PEDro database, so we used the terms “Blood flow restriction” AND “tendon,” previously specified by the two researchers. Regarding the autonomic parameters, studies that included clinical parameters that could be extrapolated for future clinical research in the field of physiotherapy research were accepted.

3.2. Characteristics of the participants and studies

In total, there are 251 subjects represented in this systematic review; the mean number of subjects per study is 42 (SD = 11.3), with a range of 29–56 participants. The mean \pm SD age of the study participants is 25.4 \pm 2.3 years. Of the included subjects, 165 (65.48%) are men and 87 (34.52%) are women.

According to the PICOS criteria specified above, 100% of the subjects were healthy. The regions or structures studied were as follows: four studies (66%) assessed changes in the Achilles tendon, one study (16.5%) assessed the supraspinatus muscle tendon, one study (16.5%) assessed the patellar tendon, and finally one study (16.5%) assessed the rectus femoris tendon.

The articles were published between 2018 and 2021. Regarding the geographical distribution of the studies, two studies (33%) were from Spain, two studies (33%) were from Germany, one study (16.5%) was from the United States, and one study (16.5%) was from Korea. Regarding the methodology of the included studies, five (83%) are randomized clinical trials, while in one study (16.5%) we had doubts about the random generation of the sequence.

Five of the studies (83.3%) used US. Only one study (16.7%) evaluated the tendon CSA with MRI. Regarding the outcome measures, the six studies (100%) assessed the tendon CSA and only two studies (33%) assessed the tendon stiffness.

In terms of study interventions, all studies included an LL-BFR group, four studies (66%) included an LL-RT group, and three studies (50%) included an HL-RT group. Only two studies (33%) included a defined control group. The duration of interventions in the included studies was 24 h in two studies (33.3%), 8 weeks in two studies (33.3%), and 14 weeks in two studies (33.3%).

3.3. Results of included studies

A summary of the results is presented in Table 2. The following paragraphs provide the main findings.

Chulvi-Medrano et al., (2021) compared an LL-BFR group with an LL-RT control group on the Achilles tendon CSA, taking a measurement at the end of the intervention and then 24 h later. The Achilles tendon CSA decreased significantly in the immediate post-exercise measurement in both groups, but it increased significantly in the LL-RT group after 24 h.

Picón-Martínez et al., (2021) performed a training session to assess changes in the Achilles tendon CSA, comparing LL-BFR, LL-RT, and HL-RT. The LL-RT and HL-RT groups did not generate acute morphological changes in the tendon, while the LL-BFR group generated a significant decrease in tendon CSA immediately after the intervention and 24 h later.

Brumitt et al., (2020) performed an 8-week protocol to compare changes in Achilles tendon morphology, comparing an LL-BFR intervention group with an LL-RT control group. Although there were significant changes between the groups, the intervention was not significantly superior to the control group in increasing the Achilles tendon CSA.

Centner et al., (2019) evaluated 14 weeks of training to compare morphological and stiffness changes in the Achilles tendon between two groups: HL-RT as a control group compared with an LL-BFR intervention. Although CSA and stiffness increased significantly in both groups, there were no significant differences between the groups.

Centner et al., (2022) investigated the effects of LL-BFR on the patellar tendon compared with an LL-RT intervention. After 14 weeks, the patellar tendon CSA and stiffness had increased significantly in both groups. However, there were no significant changes between the groups.

(Park and Kim 2018) conducted an 8-week study comparing the effects of LL-BFR with a control intervention of LL-RT on Achilles tendon and rectus femoris tendon CSA. The thickness of both tendons increased significantly, and there were significant time \times group interactions at the end of the study.

3.4. Risk of bias and methodological quality of the studies

The summary of the risk of bias analysis obtained from the Risk of Bias scale is shown in Fig. 2, and the percentages of risk of bias are found in Fig. 3.

Regarding the PEDro scale (Table 3), three studies obtained a score of 8 out of 10, one study obtained a score of 7 out of 10, one study obtained a score of 5 out of 10, and one study obtained a score of 4 out of 10. Therefore, four studies in this review are of high quality (66.6%), one study is of moderate quality (16.6%), and one study is of low quality (16.6%). The average score of all the studies on the PEDro scale was 6.7 points. Within the qualitative analysis of methodological quality according to GRADE, three studies were rated as high quality, one study as moderate quality, and two studies as low quality (Table 4).

3.5. Meta-analysis results

We included six articles in the meta-analysis comparing the effects of LL-BFR with two RT modalities. We performed three quantitative analyses representing the post-exercise effect, the effect after 24 h, and the effect after \geq 8 weeks (we pooled the results after 8, 12, and 14 weeks). We compared the effects of LL-BFR with the effects of LL-RT and HL-RT. The results refer to Achilles tendon and knee tendon, which we grouped together. We decided not to include the article studying the effects on the supraspinatus (Brumitt et al., 2020), as the anatomical area was very different and would not likely benefit from the local hypoxic effects of LL-BFR on the pressure sleeve.

Fig. 4 shows the results for the HL-RT versus LL-BFR comparison. There were no significant differences between the two groups (random-effects model: SMD 0.365; 95% CI [-0.1137; 0.845]; $P = 0.135$; $I^2 = 45.9\%$). The effect of the intervention in all cases was positive, with an increase in tendon thickness. However, when considering a fixed-effects model, the result suggests a significant improvement for LL-BFR compared with HL-RT (fixed-effects model: SMD 0.367; 95% CI [0.0164; 0.717]; $P = 0.042$; $I^2 = 45.9\%$, $P = 0.12$).

Only two studies compared the effect of LL-BFR versus LL-RT right after exercise (Picón-Martínez et al., 2021; Chulvi-Medrano et al., 2021). LL-RT significantly increased tendon thickness compared with LL-BFR (random-effects model: SMD -0.491; 95% CI [-0.071]; $P = 0.0217$; $I^2 = 0\%$; $P = 0.90$; Fig. 5).

Chulvi-Medrano et al., (2021) and Picón-Martínez et al., (2021) evaluated the effect of LL-RT versus LL-BFR on tendon thickness 24 h the intervention. Unlike what the authors observed immediately after exercise, after 24 h there were no significant differences between the two groups (random-effects model: SMD -0.342; 95% CI [-0.759; -0.074]; $P = 0.1072$; $I^2 = 0\%$; $P = 0.62$; Fig. 6).

Table 2
A summary of the most important features of the included studies. (2 column).

Study details	Participant details	Type of intervention	Duration of intervention	Assessments	Outcome measures	Results	Conclusion
Chulvi-Medrano et al. (2021) RCT Spain	56 healthy adult subjects with resistance training experience Average age: 24.86 (SD 4.08) EG: 14 F, 14 M CG: 14 F, 14 M	LL-BFR: The dominant leg performed plantar flexion in a leg press with LL-BFR (30% 1RM, 30% AOP) and the non-dominant leg was considered the control. 1 × 30 reps 3 × 15 reps 30 s between series 12-cm-wide cuff LL-RT: Plantar flexed leg press LL-RT without BFR (30% 1RM) 1 × 30 reps 3 × 15 reps 30 s rest between sets	24 h	Assessment of Achilles tendon CSA 7 cm on the base of the calcaneus in a neutral position in the prone position with dorsiflexion of 90° and knee extension. The measurement was performed by an expert using 10 MHz Doppler US Thickness was assessed before the intervention, immediately after the intervention, and 24 h after the intervention	Achilles tendon CSA	In the LL-BFR group, tendon thickness decreased significantly in both conditions, immediately post-exercise ($P < 0.5$) and 24 h post-exercise ($P < 0.05$) In the LL-BFR group, tendon thickness decreased significantly in both conditions, immediately post-exercise ($P < 0.5$) and 24 h post-exercise ($P < 0.05$) In the LL-RT group, tendon thickness decreased significantly immediately post-intervention ($P < 0.05$), but did not decrease significantly after 24 h ($P = 0.80$) Achilles tendon thickness in the EG was significantly greater than in the LL-RT after 24 h ($P < 0.05$)	LL-BFR does not affect tendon thickness, unlike LL-RT The behavior of the tendon was similar immediately post training, but 24 h after the intervention, it only increased in LL-RT The results suggest carrying out LL-BFR vs HL-RT evaluation
Centner et al. (2019) RCT Germany	38 untrained healthy adult subjects (38 M) Average age: 26.1 (SD 4.2) HL-RT: n = 14 LL-BFR: n = 11 CG: n = 13	HL-RT: Performed seated and standing calf raise training on body-solid seated calf raise machines (Genius Eco Multi Press) The load was at 70%–85% of 1RM and they progressed every 4 weeks. 6–12 reps 1 min rest between sets 3 min rest between exercises Frequency: 3 times a week LL-BFR: Performed the same exercises as the HL-RT group for 14 weeks, but with 50% AOP blood flow restriction, and 20–35% 1RM load. The load was increased by 5% every 4 weeks 1 × 30 reps 3 × 15 reps 60 s rest between sets without deflating the pressure cuff 3 min rest between exercises with the pressure cuff deflated	14 weeks	Assessment of the CSA using 8 MHz US in 25% of the length of the Achilles tendon The length was measured from the tuberosity of the calcaneus to the most distal part of the gastrocnemius muscle For the assessment of Achilles tendon stiffness, tendon elongation in an isometric ramp contraction for 3–5 s was measured with 100 Hz B-Mode US at the medial gastrocnemius myotendinous junction Plantar flexion torque and two-dimensional kinematic data were measured Tendon thickness and stiffness were assessed before the intervention and after 14 weeks of intervention	Achilles tendon CSA and stiffness	Achilles tendon CSA increased significantly in both groups and similarly compared with the control group after 14 weeks HL: +4.6% LL-BFR: +7.8% Time × group interaction: $P < 0.05$ The control group had no significant changes Tendon stiffness increased significantly in both groups after 14 weeks of intervention LH: +40.7%, $P < 0.05$ LL-BFR: +36.1%, $P < 0.05$ Time × group interaction: $P < 0.01$ The control group had no significant changes	LL-BFR produces adaptations in the Achilles tendon CSA and mechanical properties similarly to HL-RT
Brumitt et al. (2020)	46 healthy adult subjects	LL-BFR: Performed lateral decubitus	8 weeks	Assessment of the CSA of the dominant	Supraspinatus tendon	Both groups had a significant increase	Performing lateral decubitus shoulder

(continued on next page)

Table 2 (continued)

Study details	Participant details	Type of intervention	Duration of intervention	Assessments	Outcome measures	Results	Conclusion
RCT United States	(26 F, 20 M) Mean age: 25.0 (SD 2.2) LL-BFR (n = 24) LL-RT (n = 22)	external rotation 1 × 30 reps 2–4 × 15 reps 30 s rest between sets Frequency 2/week 50% AOP 8 min under occlusion Custom cuff width LL-RT: performed the same as the LL-BFR group but without blood flow restriction		supraspinatus tendon in three positions on the short axis lateral to the tendon of the long head of the biceps by means of 5–10 MHz US		in tendon CSA; however, there was no difference between LL-BFR and LL-RT LL-BFR: P < 0.041	external rotations with BFR does not produce a greater increase in supraspinatus tendon CSA when compared to low-load exercise without BFR Multiple sets of high repetitions with low load generate an increase in the CSA of the dominant supraspinatus tendon
Picón-Martínez et al. (2021) CT Spain	52 healthy active adult subjects (19 F, 34 M) Mean age: 27.3 (SD: 7) HL-RT: (n = 15) LL-RT: (n = 13)	LL-BFR: Performed plantar flexion on a leg press machine at 30% 1RM 1 × 30 reps 3 × 15 reps 60 s rest between sets with cuff deflated 30% AOP 9 cm wide cuff LL-RT: performed the same as the LL-BFR group, but without blood flow restriction HL-RT: performed plantar flexion on a leg press machine. 1 × 30 reps at 30% 1RM 3 × 10 reps at 75% 1RM 90 s rest between sets	24 h	Assessment of the Achille tendon CSA 3 cm proximal to the insertion of the calcaneus, by means of 10 MHz US in a neutral prone position with dorsiflexion of 90° and knee extension Measurements were made pre-test, after 60 min, and after 24 h		Achilles tendon CSA decreased significantly in the LL-BFR group immediately post-intervention (P < 0.001), 1 h after (P < 0.001), and 24 h after (P < 0.002) Achilles tendon thickness was significantly smaller in LL-BFR when compared to HL-RT immediately post-intervention (P = 0.003) and after 1 h (P = 0.0012)	A resistance training session with BFR induces a reduction in Achilles tendon thickness in asymptomatic adult subjects HL-RT and the LL-RT did not generate acute morphological changes in the Achilles tendon thickness after one session
Park and Kim (2018) Korea	30 healthy adults subjects (10 F, 20 M) Mean age: 21.26 (SD 1.16) LL-BFR: (n = 15) LL-RT: (n = 15)	LL-BFR: Performed knee extension with BFR and biofeedback in a sitting position 5 × 15 reps 1 min rest between sets Frequency: 3/week 30 min long First 4 weeks: 150 mmHg of pressure Last 4 weeks: 200 mmHg of pressure	8 weeks	Assessment of the thickness of the rectus femoris tendon and the Achilles tendon using 6.5–8.5 MHz US The rectus femoris tendon was measured in standing position with knee flexion at 80° Achilles tendon thickness was measured in the prone position with an ankle cushion Measurements were made pre-intervention, after 4 weeks, and after 8 weeks		The thickness of both tendons increased significantly (P < 0.05) Significant time × group interactions (P < 0.05)	Exercise methods that use blood flow restriction are likely to be useful as a method to strengthen tendons The thickness of both tendons increased significantly after the intervention The effects are probably due to the hypoxic environment created by the occlusion, which triggers the release of growth hormone and IGF-1
Centner et al. (2022) RCT Germany	29 untrained healthy adults subjects (29 M) Mean age: 27.6 (SD 4.3) HL-RT: (n = 15) LL-BFR: (n = 14)	HL-RT: Performed seated and standing calf raise training on body-solid seated calf raise machines (Genius Eco Multi Press) The load was at 70%–85% of 1RM and they progressed every 4 weeks 6–12 reps 1 min rest between sets 3 min rest between exercises. Frequency: 3 times a week LL-BFR: Performed the same exercises as the HL-RT group for	14 weeks	Patellar tendon CSA assessment with an axial MRI scan in a direction perpendicular to the tendon, from the apex of the patella to the tibial tuberosity Assessment of tendon stiffness using 10 MHz B-mode US (frequency of 100 Hz), with an isometric contraction in maximum ramp performed on an isokinetic dynamometer for 3–5 s, in a knee flexion position of 90° and hip flexion 60° Measurements were made before and after		Patellar tendon CSA increased significantly based on the time effect in all zones, (P < 0.01), except at 90% and 100% of its length (P = 0.105 and 0.395, respectively) Interaction effects were only significant at 70% tendon length with larger changes in LL-BFR (time × group interaction: P = 0.018) Stiffness of the patellar tendon increased significantly over time for both groups.	Patellar tendon CSA and stiffness increased significantly in both groups after 14 weeks At 70% tendon length, CSA increased to a greater extent in the LL-BFR group Tendon stiffness increased by 22.5% in HL-RT, and by 25.2% in LL-BFR The effects of BFR on the tendon are probably due to a release of anabolic growth factors, caused by the hypoxia that the tissues are subjected to due to blood occlusion 14 weeks of intervention could be superior to 12

(continued on next page)

Table 2 (continued)

Study details	Participant details	Type of intervention	Duration of intervention	Assessments	Outcome measures	Results	Conclusion
		14 weeks, but with 50% AOP blood flow restriction and 20%–35% 1RM load. The load was increased by 5% every 4 weeks up to 35% 1RM 1 × 30 reps 3 × 15 reps 60 s of rest between sets without deflating the pressure cuff 3 min rest between exercises with the pressure cuff deflated 12 cm cuff thickness	14 weeks of intervention.			($P < 0.001$), but time × group interaction not significant HL-RT: +22.5%, ($P = 0.024$) LL-BFR: +25.2%, ($P = 0.003$)	weeks in terms of the effects of BFR on the tendon Future studies should carry out the intervention in subjects with tendinopathy in the field of rehabilitation

Abbreviations: 1RM: one repetition maximum; AOP: arterial occlusion pressure; BFR: blood flow restriction; CG: control group; CSA: cross-sectional area; EG: experimental group; F: females; HL-RT: high-load resistance training; IGF-1: insulin-like growth factor 1; LL-BFR: low-load blood flow restriction; LL-RT: low-load resistance training; M: males; P: P value; RCT: randomized controlled trial; SD: standard deviation; US: ultrasound.

4. Discussion

4.1. Main findings

Regarding the effects of this training method on tendon CSA, we found that there is a dose–time relationship. [Chulvi-Medrano et al., \(2021\)](#) and [Picón-Martínez et al., \(2021\)](#) concluded that immediately after the intervention and after 24 h, LL-BFR significantly decreases Achilles tendon CSA, and this decrease is greater when compared with LL-RT or HL-RT. However, our meta-analysis indicates that the CSA of the tendon is lower only immediately after the LL-BFR intervention. The quality of the studies is moderate and low, respectively. On the other hand, the study by [Brumitt et al., \(2020\)](#) which is of high quality, concluded that supraspinatus tendon CSA increases similarly when comparing 8 weeks of LL-BFR with LL-RT. This indicates that LL-BFR would not be recommended for the supraspinatus tendon. We suggest that there have been no physiological effects similar to the studies that have been carried out on the lower limb. This was the only study that evaluated the supraspinatus tendon; therefore, additional studies in this area are needed to draw conclusions. We hypothesize that the supraspinatus tendon and tendons of the muscles proximal to the pressure cuff do not benefit from the effect of local hypoxia and metabolic stress.

In their high-quality studies, [Centner et al. 2019, 2022](#) concluded that after a 14-week LL-BFR intervention, the Achilles and patellar tendon CSA and stiffness increase significantly, and there are similar effects to what is obtained with HL-RT. [Park and Kim 2018](#) also found an increase in CSA after 8 weeks; they concluded that the rectus femoris tendon CSA increases after 8 weeks of intervention with LL-BFR and that it is superior to LL-RT. However, the above-mentioned study is of low quality. These conclusions are opposite to those of [Kubo et al., 2006](#): Those authors stated that LL-BFR fails to improve the patellar tendon CSA and stiffness after 12 weeks of training. A possible reason for this discrepancy is the very low methodological quality of their study.

The physiological reasons for the effects of LL-BFR on increased tendon thickness and stiffness are unclear. The effects of LL-BFR on a tendon are probably due to a release of anabolic growth factors, caused by the hypoxia that the tissues are subjected to thanks to blood occlusion [\(Centner et al., 2022; Park and Kim 2018\)](#) These growth factors can be released by mobilized and recruited endothelial progenitor stem cells [\(Burr et al., 2019; Ferguson et al., 2018\)](#). On the other hand, [\(Picón-Martínez et al., 2021\)](#) demonstrated that LI-BFR exercise provides an adequate stimulus to improve bone metabolic markers due to fluid movement and increased intramedullary pressure, and these effects could extend to the tendons [\(Loenneke et al., 2012; Picón-Martínez et al., 2021\)](#). However, more studies are needed to better understand

what happens physiologically in the tendons with this technique.

4.2. Clinical implications

Regarding clinical implications for the professionals that can use these therapeutic approach, mainly physiotherapists and strength and conditioning coaches, The most promising aspect of the effects of LL-BFR on tendons is that it could be a tool for subjects with tendinopathies, and it could be beneficial in all stages of this pathology. In the case of acute and reactive tendinopathies in which there is an increase in CSA [\(Cook et al., 2001\)](#) it could have positive effects because we have shown that LL-BFR decreases the Achilles tendon CSA immediately after the exercise. On the other hand, in the case of chronic tendinopathies of the Achilles tendon and knee tendons that are in a dysrepair or degenerative phase, tendon thickness and stiffness could increase after an 8–14-week intervention in a similar or superior way to HL-RT. This ability would allow the tendon to suffer less stress because it would have a larger area [\(Kongsgaard et al., 2010\)](#) and would align the healthy fibers that allow it to adapt functionally [\(Docking and Cook 2019\)](#). We postulate that LL-BFR could contribute to the prevention of tendon injuries in athletes who are subjected to high loads, because it could increase CSA and stiffness in the long term in a similar or superior way to HL-RT and could allow training at a greater intensity, with a shorter duration, and with a low load at times when the frequency of competition and training are high and there is not much time to perform resistance training. According to the most current evidence, resistance training is considered the gold standard first-line treatment intervention for tendinopathies and is widely used for their prevention. Perhaps the belief that resistance training in tendinopathies should include high training loads has been a limiting factor in the application of LL-BFR and may explain why it is an underutilized tool in the rehabilitation and prevention of these injuries [\(Burton and McCormack 2022\)](#). However, if LL-BFR generates similar or greater long-term effects on CSA and stiffness, it could be a tool of highest clinical interest for tendinopathy prevention and rehabilitation due to its ease of implementation and transportability.

We consider it a major challenge for clinicians to establish an intervention protocol, as the included studies differ in occlusion pressures. In addition, it would be advisable for future researchers to carry out randomized controlled trials that study the effects of LL-BFR in the short, medium, and long term in subjects with tendinopathies in the reactive phase, and in subjects with tendinopathies in the non-reparative and degenerative phase. Another interesting intervention would be to perform a randomized controlled trial that measures the effects of plyometric training with LL-BFR on the mechanical and morphological properties of the tendons of injured subjects, because [\(Sancho et al.,](#)

	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
Brumitt J et al. 2020	+	?	-	+	+	+	?
Centner C et al. 2019	+	+	-	+	+	+	+
Centner C et al. 2021	+	+	-	+	+	+	+
Chulvi-Medrano I et al. 2021	?	?	-	-	+	+	?
Jae Cheol Park et al. 2018	+	?	?	?	-	+	?
Picon-Martinez et al. 2021	+	-	-	-	+	+	?

Fig. 2. Risk of bias summary: judgements about each risk of bias item for each included study. (Single column).

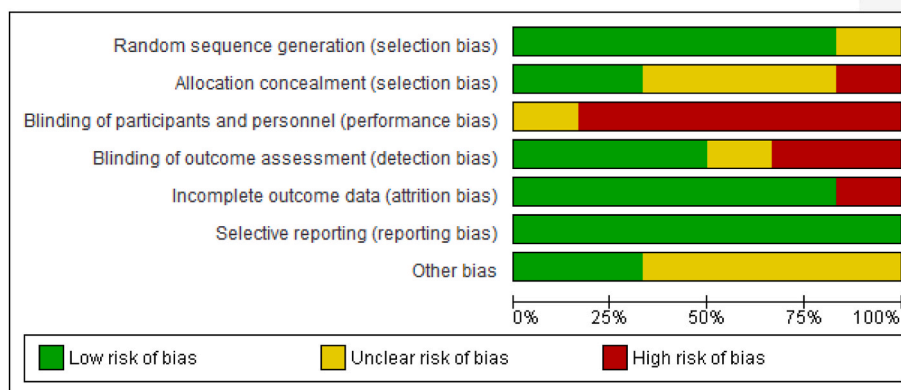


Fig. 3. Risk of bias graph: judgements about each risk of bias item presented as percentages across all included studies. (1.5 column).

Table 3
PEDro Scale scoring of methodological quality (2 column).

Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Total
Centner et al. (2019)	α	α	α	α	×	×	α	×	α	α	α	8/10
Chulvi-Medrano et al. (2021)	α	α	α	α	×	×	×	α	×	α	α	7/10
Brumitt et al. (2020)	α	α	α	α	×	×	α	α	×	α	α	8/10
Picón-Martínez et al. (2021)	α	α	×	×	×	×	×	α	×	α	α	4/10
Park and Kim (2018)	α	α	×	α	×	×	×	×	×	α	α	5/10
Centner et al. (2022)	α	α	α	α	×	×	α	α	×	α	α	8/10

Table 4
GRADE rating. (Single column).

Study	Qualification
Centner et al. (2019)	High (++++)
Chulvi-Medrano et al. (2021)	Low (++)
Brumitt et al. (2020)	High (++++)
Picón-Martínez et al. (2021)	Moderate (+++)
Park and Kim (2018)	Low (++)
Centner et al. (2022)	High (++++)

2019) mentioned that it could have good results in runners with tendinopathies in the middle portion of the Achilles tendon.

4.3. Strengths and limitations

We prospectively registered this review and conducted it according to PRISMA recommendations. The quality of the evidence is moderate, but we must consider that the number of studies is small, that the sample of subjects is relatively small, and that they were healthy subjects. It is important to note that only two of the included studies evaluated stiffness and we did not carry out a meta-analysis of this variable, so more studies are needed to draw further conclusions. In addition, the location of the analyzed tendons was not the same in all the studies. Another

important limitation that we must highlight is the time of intervention and the moment at which the measurements were made in the studies, because two studies measured the acute effects, and four studies measured the effects after >8 weeks. However, we must consider that the arterial occlusion pressure and the intervention protocols were not the same in all the studies.

5. Conclusion

We found low- and moderate-quality evidence that LL-BFR decreases the Achilles tendon CSA immediately after exercise and is superior to LL-RT. Conversely, we found high-quality evidence that LL-BFR produces a similar or greater increase in the Achilles and patellar tendon CSA and stiffness compared with HL-RT after a > 8-week intervention in healthy subjects. However, we do not suggest LL-BFR for the supraspinatus tendon as there was no difference compared with LL-RT. The conclusions of this review must be viewed by considering the limitations mentioned in section 4.3. The effects of LL-BFR on the tendon CSA and stiffness depend on the time of the intervention, and this technique could be a useful tool to improve the morphological and mechanical properties of tendons in subjects who cannot perform HL-RT for various reasons.

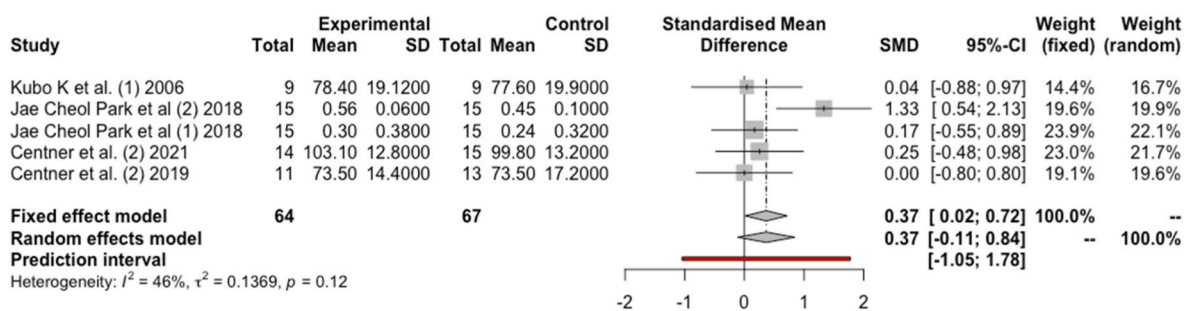


Fig. 4. The effects of low-load blood flow restriction versus high-load resistance training on tendon thickness after 8–14 weeks of intervention (2 column). **Abbreviations:** SMD: Standardised mean difference; SD: Standard deviation; CI: Confidence Interval.

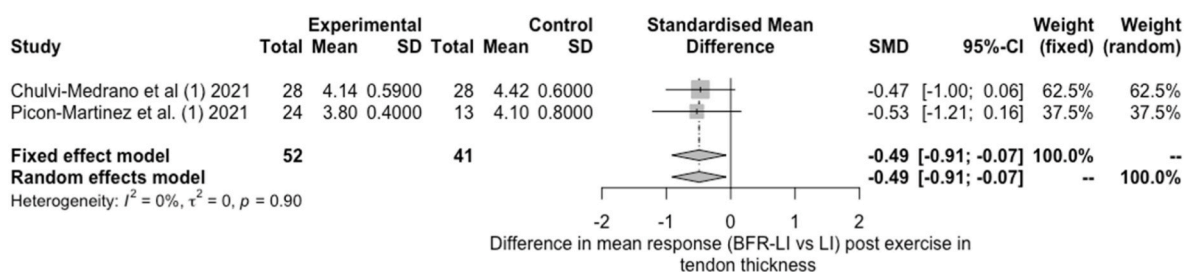


Fig. 5. The effects of low-load blood flow restriction versus low-load resistance training on tendon thickness immediately after the intervention. (2 column). **Abbreviations:** SMD: Standardised mean difference; SD: Standard deviation; CI: Confidence Interval.

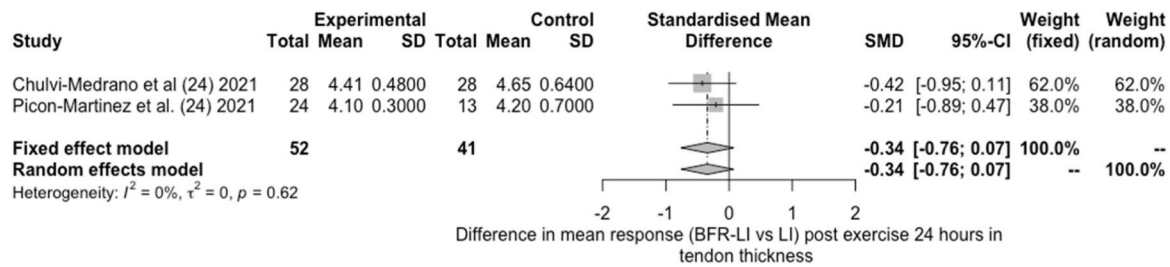


Fig. 6. The effects of low-load blood flow restriction versus low-load resistance training on tendon thickness 24 h after the intervention. (2 column). **Abbreviations:** SMD: Standardised mean difference; SD: Standard deviation; CI: Confidence Interval.

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CRedit authorship contribution statement

Ilan Bechan Vergara: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing, Project administration, Resources. **Albert Puig-Diví:** Funding acquisition, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Beñat Amestoy Alonso:** Methodology, Resources, Software, Writing – original draft, Writing – review & editing. **Raimon Milà-Villarrol:** Data curation, Formal analysis, Resources, Software.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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