Effects of blood flow restriction exercises on bone metabolism: A systematic review

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REVIEW ARTICLE

Effects of blood flow restriction exercises on bone metabolism: a systematic review

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Summary

This study analysed the effect of low-intensity (LI) exercises with blood flow restriction (BFR) on bone metabolism compared with high-intensity (HI) exercises without BFR. The following databases were searched using the keywords therapeutic occlusion training OR BFR training OR vascular occlusion training OR KAATSU training OR ischaemia training AND osteogenesis OR bone biomarkers OR bone metabolic marker OR bone mass OR bone turnover OR osteoporosis OR osteopenia: PubMed, Web of Science, SPORTDiscus, CINAHL, Science Direct, Cochrane and Google Scholar. Two researchers, independently and blindly, selected the studies based on established inclusion and exclusion criteria. Electronic and manual searches located 170 articles published in English; after screening, only four studies showed that BFR training increases the expression of bone formation markers (e.g. bone-specific alkaline phosphatase) and decreases bone resorption markers (e.g. the amino-terminal telopeptides of type I collagen) after both aerobic and anaerobic exercise across several populations. The results of this study show that few studies have confirmed the positive effect of exercise with BFR on bone metabolism, formation and resorption. Furthermore, no methodological standardization of the samples, exercise type, intervention frequency or duration was observed.

Introduction

High-intensity strength training (ST) with more than 70% of one-repetition maximum (1RM) is associated with numerous positive effects in general populations; however, elderly people and patients undergoing rehabilitation are often limited to low-intensity exercise (ACSM, 2009).

The blood flow restriction (BFR) technique has been shown to attenuate limb muscle atrophy and, when combined with low-intensity (LI) exercises, increases muscle volume and strength across different age groups. BFR or KAATSU training is a technique created 50 years ago in Japan, in which the blood flow for the individual's lower or upper limbs is restricted using cuffs. It is applied to decrease arterial and occlude the venous blood flow of the muscle. When the necessary precautions are taken, the possible risks to health are the same as the high-intensity (HI) exercises, however, with reduced mechanical effort of the joints (Loenneke *et al.*, 2011).

One study found that the use of the BFR without exercise during the postoperative period attenuated muscle atrophy compared with a control group (Takarada *et al.*, 2000). In addition, previous clinical studies using BFR (Inoue *et al.*, 2002; Odagiri, 2004) showed improved skeletal bone mass patterns in people with certain diseases (e.g. avascular necrosis of the femoral head and osteopenia or osteoporosis), and other papers (Loenneke *et al.*, 2012a; Loenneke *et al.*, 2012b) showed that LI exercise combined with BFR may provide not only an increase in muscle adaptation, but also in bone and consequently modification in its biomarkers.

Studies analysed two biomarkers (bone alkaline phosphatase and amino-terminal telopeptides, respectively) and found that BFR training also accelerates bone metabolism (Beekley *et al.*, 2005; Bemben *et al.*, 2007). The possible mechanisms responsible for this effect are as follows: increased intramedullary pressure and interstitial fluid within the bone caused by venous occlusion (Maher *et al.*, 2003). In addition to these mechanisms, it was reported that BFR activates hypoxiainduced transcription factor (HIF), thereby increasing the expression of vascular endothelial growth factor (VEGF) and the formation of microblood vessels in bone tissue (Araldi & Schipani, 2010).

The bone mass is the end product of two metabolic processes (formation and resorption) that support the mechanical load of the body and its maturation, can be influenced by the deposition of calcium and minerals. Blood and urinary molecules (bone-specific alkaline phosphatase, osteocalcin, amino-terminal telopeptides of type I collagen, among others) had been identified as bone formation or resorption markers. The main advantage of these markers is that they can instantaneously reveal the dynamics of bone metabolism in response to exercise, depending on the exercise intensity (Seibel, 2005).

For improving bone health, the American College of Sports Medicine (ACSM, 2009) recommends moderate-to-high-intensity resistance exercises or high-impact exercises (e.g. jumps) to stimulate bone metabolism or to maintain it in the case of the elderly. Therefore, it is essential to investigate the effects of LI exercises with BFR on bone metabolism because the elderly, especially the ones in some special situations (e.g. chronic diseases, obesity, sedentary people and others) may not be able to perform HI exercises.

Thus, this study aimed to analyse the effect of LI exercises with BFR compared with HI exercises without BFR on bone metabolism.

Materials and methods

Identification and selection of studies

The research was carried out on the following databases: PubMed, Web of Science, SPORTDiscus, CINAHL, Science Direct, Cochrane and Google Scholar; in addition, manual searches of the studies' references were performed. The keywords therapeutic occlusion training OR blood flow restriction training OR vascular occlusion training OR KAATSU training OR ischaemia training AND osteogenesis OR bone biomarkers OR bone metabolic marker OR bone mass OR bone turnover OR osteoporosis OR osteopenia were used according to the Medical Subjects Headings (MeSH) using Boolean operators (OR and AND), and the keywords that were not located in the abstracts were located after reading the manuscripts that referred to the same subject.

The following inclusion criteria were considered for the bibliographic research: (i) published between 1990 and 2016; (ii) undefined target populations; (iii) the use of exercises associated with BFR as an intervention; (iv) outcomes of interest related to bone metabolism; (v) well-established methodological criteria; (vi) published in English; and (vii) original articles only.

Articles were excluded if they (i) had scores lower than three on the Physiotherapy Evidence Database (PEDro) scale; (ii) had the same main text under a different title; and (iii) were repeated across other databases.

To select the studies, two blinded and independent researchers (Bittar & Pfeiffer) who strictly complied with the established inclusion and exclusion criteria evaluated the titles and abstracts identified in the initial search. When the title and the abstract did not match (e.g. the title talks about adults while on the abstract the subjects are elderly), the researchers took into account the guiding question of the review to select or not the manuscript. Disagreements between the two researchers were resolved via the opinion of a third evaluator.

Methodological quality: PEDro Scale

Currently, the most used scale in the area of rehabilitation is the PEDro scale (http://www.pedro.fhs.usyd.edu.au), which was developed by the Physiotherapy Evidence Database for use with regard to experimental studies. This scale has a maximum total score of 10 points and includes criteria concerning the evaluation of internal validity and the presentation of the statistical analysis used. For each criterion defined in the scale, one point (1·0) is attributed to the presence of indicators regarding the quality of the evidence presented, and zero points (0·0) are attributed to its absence.

The PEDro scale is composed of the following elements: (i) the specification of inclusion criteria (item not scored); (ii) random allocation; (iii) concealment of allocation; (iv) similarity of the groups at baseline or the initial phase; (v) blinding of all participants; (vi) blinding of all therapists; (vii) blinding of all assessors; (viii) measures of at least one primary outcome obtained from more than 85% of participants allocated; (ix) 'intention to treat' analysis; (x) between-group comparisons of at least one primary outcome; and (xi) reports of measures of variability and estimations of parameters concerning at least one primary variable (Maher *et al.*, 2003). The researchers used the PEDro scale independently. After its use, they analysed their agreement using the Kappa (K) index.

This study was conducted according to standardization of PRISMA scale (Liberati *et al.*, 2009). Data analysis was carried out based on a critical review of content, using the following criteria: title, abstract, rationale, objectives, protocol, risk of bias across studies, study characteristics, results of individual studies, limitations and conclusions.

Results

The search in the seven databases (PubMed, Web of Science, SPORTDiscus, CINAHL, Science Direct, Cochrane and Google Scholar), in addition to the manual search (i.e. the analysis of references), revealed 170 articles. After discarding duplicate articles and analysing whether the titles were consistent with the object of study, nine articles remained for screening (eight from the databases and one from the manual search). In the second step, the eligibility criteria for the manuscripts to be included in the systematic review were analysed, and five articles were excluded as follows: one case study; one annals abstract; one of which did not match the abstract (although the title was in accordance with the topic of this review); one duplicate; and one narrative review (Fig. 1).

With respect to the four studies selected and included for analysis, all were relatively recent (2005–2013) with heterogeneous samples (young and older adults including trained and untrained, active and sedentary, and male and female participants). The interventions were based on strength and aerobic training and varied in duration from a minimum of 2 weeks (Bemben *et al.*, 2007) to a maximum of 6 weeks (Karabulut *et al.*, 2011) with frequency of at least one time (Bemben *et al.*, 2007) and at most three times per week (Beekley *et al.*, 2005; Karabulut *et al.*, 2011; Kim *et al.*, 2012). All of the articles specified the muscles worked during the training, the BFR method used, and the duration and type of exercises performed (anaerobic or aerobic). Furthermore, it is important to highlight that all of the manuscripts selected for the systematic review had as the major dependent variable the bone biomarkers (see Table 1).

The studies selected by the authors were evaluated using the PEDro scale (http://www.pedro.fhs.usyd.edu.au), and the four articles selected received a score of 8 from the two evaluators (Beekley *et al.*, 2005; Bemben *et al.*, 2007; Karabulut *et al.*, 2011; Kim *et al.*, 2012). Table 2 demonstrates in detail the individual scores of each item between each article.

None of the selected manuscripts were evaluated with the maximum score on the PEDro Scale because they all failed on meeting the following criteria: blinding of all participants, blinding of all therapists and blinding of all assessors. After the evaluation of methodological quality, the Kappa index was used to analyse the agreement between the scores given by the evaluators, and perfect agreement was obtained (ICC = 1·00, $P < 0{\cdot}025$).

Discussion

This is the first systematic review to address the effect of BFR on bone metabolism in adults and the elderly. Regarding the

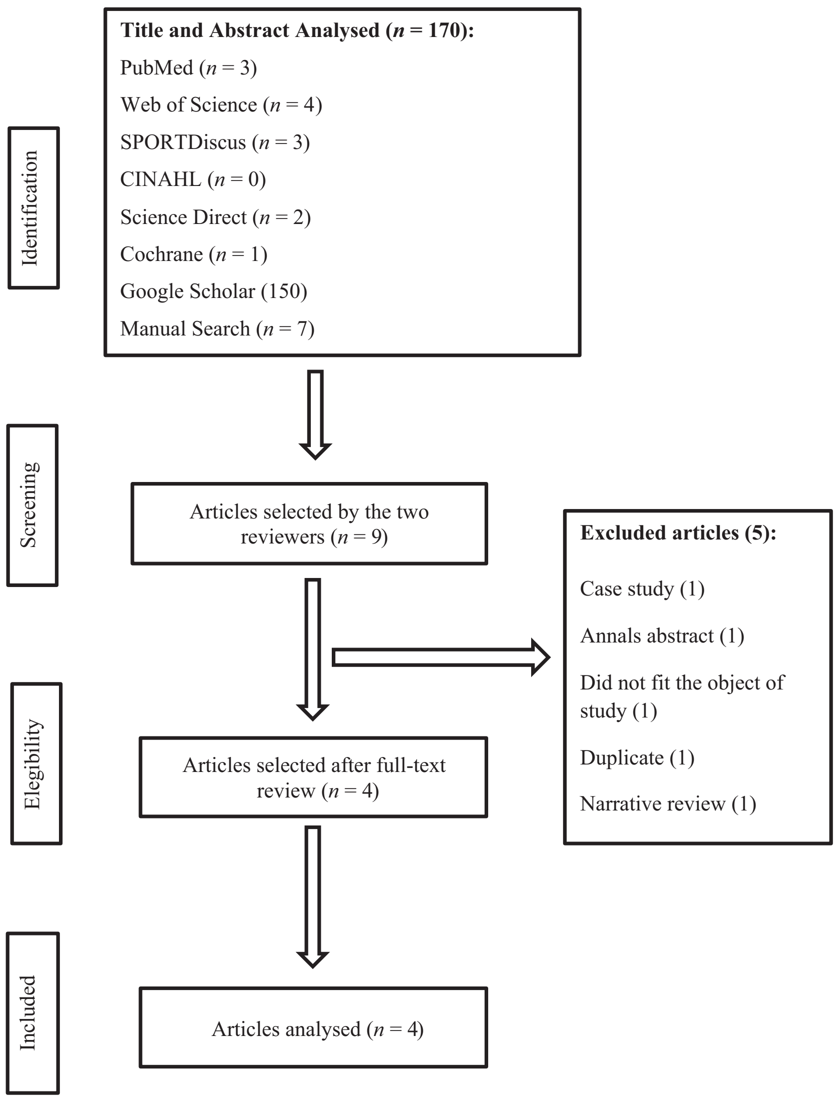

Figure 1 Flow chart of the study selection process.

Table 1 Studies that analysed BFR and bone biomarkers.

Author/Year	Study sample	Intervention type and duration	Cuff pressure	Experimental events	Results	Conclusion
Beekley *et al.* (2005)	n = 18 healthy men (21–28 years old).	15-min walk (50 m min^{-1}) on the treadmill, 2 × /day, (4-h interval between sessions) for 3 weeks, 6 days $week^{-1}$	KAATSU (160–230 mmHg)	Walk with KAATSU (n = 9) or without (control n = 9). The vascular restriction was in the most proximal portion of the thighs and was maintained during the protocol of five sets of 2 min with 1-min interval	Increased CSA (5·8%)**, 1RM strength (7·5%)[b], and BAP levels (10·8%)* in the BFRG compared with the CG	Aerobic training combined with BFR, increased the levels of BAP
Bemben *et al.* (2007)	n = 9 active men (18–30 years old).	Two sessions of ST with BFR and control (ST without BFR): 20% 1RM for both groups with a 48-h interval in random order	KAATSU (140–180 mmHg)	ST with BFR: one session of 30 reps + three sessions of 15 reps with a 30-s interval between sets, occlusion maintained for 10 min throughout the protocol. Blood samples were obtained immediately, before and after exercise, and 30 min after the end of the exercise for the bone biomarker analysis	Decreased plasma volume[a] immediately after exercise in the BFRG. Time × training effect for NTx levels (13·3%)*; 30 min after exercise NTx levels decreased* compared with baseline	LI training combined with BFR decreased bone metabolism (NTx) during an acute bout
Karabulut *et al.* (2011)	n = 37 healthy elderly men (58·8 ± 0·6 years old)	ST: 3 × /week for 6 weeks	KAATSU (120–180 mmHg)	HISTG (n = 13): three sets of eight reps at 80% 1RM. LISTG + BFR (n = 13): one set of 30 reps + two sets of 15 reps at 20% 1RM, with inflated cuffs for 6–8 min. CG (n = 11). Blood samples were collected 6 weeks before and after to measure the concentrations of bone biomarkers	Time × CTX decrease in the exercise groups* Increase in BAP of 21% for the LISTG + BFR, 23% for the HISTG and 4·7% for CG	LISTG showed significant changes in bone ALP concentrations and bone ALP.
Kim *et al.* (2012)	n = 30 healthy untrained men (18–35 years old)	ST: 3 × /week for 3 weeks	KAATSU (120 mmHg)	Randomized (LISTG + BFR, n = 10): 20% 1RM, (HISTG, n = 10): 80% 1RM and BFRG (n = 10). Both the LISTG + BFR and the HISTG performed leg press, and isotonic knee extension–flexion exercises (3 × /week, two sets of 10 reps). The BFRG was subjected to the same procedure, without the exercise protocol, for 10 min and 3 × /week	Increase in quadriceps CSA*, but the HISTG had a greater increase (3·48%) compared with LISTG + BFR (1·15%). The HISTG showed an increase in fasting BAP after training (50·91%)**	HISTG was most effective than LISTG for eliciting bone formation and muscle hypertrophy responses.

CSA, cross-sectional area; BAP, bone-specific alkaline phosphatase (bone formation biomarker); BFRG, BFR group; CG, control group; ST with BFR, ST with BFR; NTx, bone resorption biomarker; HISTG, HI ST group; LISTG + BFR, LI ST group with BFR; CTX, bone resorption biomarker; BFRG, group that only performs BFR; UL, upper limbs.

*$p < 0·05$.

**$p < 0·01$.

Table 2 PEDro Scale of quality for eligible randomized controlled trial.

Study	Criteria 1	2	3	4	5	6	7	8	9	10	11	Total
Beekley *et al.* (2005)	1	1	1	1	0	0	0	1	1	1	1	8
Bemben *et al.* (2007)	1	1	1	1	0	0	0	1	1	1	1	8
Karabulut *et al.* (2011)	1	1	1	1	0	0	0	1	1	1	1	8
Kim *et al.* (2012)	1	1	1	1	0	0	0	1	1	1	1	8

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

articles reviewed, three of them (Beekley *et al.*, 2005; Karabulut *et al.*, 2011; Kim *et al.*, 2012) evaluated the bone-specific alkaline phosphatase biomarker; these were measured with serum, whereas two of them (Bemben *et al.*, 2007; Karabulut *et al.*, 2011) analysed serum markers of bone resorption (telopeptides of type I collagen).

One study evaluated 18 healthy men ageing $21{\cdot}3 \pm 2{\cdot}3$ years (9 = control; 9 = BFR) for 3 weeks (6 days week^{-1}, 2 times day^{-1}, 4-h rest between sessions) using treadmill-walking training at a speed of 50 m min^{-1} and observed that BFR generated a 10·8% gain ($P < 0{\cdot}05$) in serum alkaline phosphatase levels, thereby demonstrating the efficiency of BFR when combined with aerobic training in relation to this biomarker (Beekley *et al.*, 2005). According to the authors, these results may be due to the fact that RFS training increases the levels of GH and IGF-1, which are responsible for bone turnover and show that even in healthy young subjects practising low-intensity aerobic exercise, the use of BFR can be feasible and applicable in relation to the bone formation biomarker.

The effect of ST combined with BFR on bone-specific alkaline phosphatase was analysed in two studies (Karabulut *et al.*, 2011; Kim *et al.*, 2012). In the first study (Karabulut *et al.*, 2011), the authors divided 37 healthy elderly men ($56{\cdot}8 \pm 0{\cdot}6$ years old) into three randomized groups (HI + ST, 80% 1RM; LI + ST, 20% 1RM combined with BFR; and a control group). After training three times a week for 6 weeks, these authors found increases of 23% and 21% for the HI and LI combined with BFR (LI + BFR) groups, respectively. In the second study (Kim *et al.*, 2012), 30 healthy untrained men aged 18–35 years old were also divided into three randomized groups (ST + HI: 80% 1RM; ST + LI: 20% 1 RM combined with BFR; BFR only), but only the ST + HI: 80% 1RM group showed an increase ($50{\cdot}1 \pm 12{\cdot}77\%$, $P < 0{\cdot}01$) in their levels of bone-specific alkaline phosphatase. Although these two studies used ST as the variable of interest, the difference in their results may be caused by the differences in participant characteristics, such as age and level of physical activity, or duration of intervention (3 and 6 weeks, respectively) (Karabulut *et al.*, 2011; Kim *et al.*, 2012).

In addition to analysing the effects of BFR on bone formation markers (e.g. bone-specific alkaline phosphatase), two studies (Bemben *et al.*, 2007; Karabulut *et al.*, 2011) also found significant results with regard to serum markers of bone resorption. The acute effect of ST ST + LI combined (or not) with BFR was analysed in nine physically active men ($24{\cdot}9 \pm 2{\cdot}5$ years old) who performed two training sessions with a 48-h interval between them (Bemben *et al.*, 2007).

These authors observed that NTx levels (amino-terminal telopeptide of type I collagen) decreased ($13{\cdot}3 \pm 3{\cdot}4\%$; $P < 0{\cdot}05$) from baseline 30 min after ST + LI with BFR. Although this marker responds faster to the stimulus of the exercises than bone formation markers, it ensures that the bone metabolism is under constant formation and resorption. Then, while resorption biomarkers decrease with the practice of BFR exercise, there is a trend towards increasing bone formation (Bemben *et al.*, 2007; Karabulut *et al.*, 2011). This decrease in NTx can be explained by the increase in substances circulating in the blood, such as hormones and proteins (Ahmadizad *et al.*, 2006).

In addition, a descriptive decrease was found in carboxy-terminal telopeptide of type I collagen (CTX) concentration in the exercise groups (7·7% for ST + LI 20% 1RM with BFR; 4·1% for ST + HI 80% 1RM), and a 3·3% increase for CON, after training for 6 weeks, 3 times a week; however, this difference between groups was not statistically significant (Karabulut *et al.*, 2011). Therefore, the results observed in different age groups, and intervention durations suggest that exercise is important for the prevention of diseases that weaken bone structure and might delay the osteopenia and osteoporosis caused by ageing.

The results presented by the selected studies showed that both aerobic and anaerobic exercises combined with BFR can provide satisfactory results related to the bone biomarkers. Thus, this technique (BFR) is a feasible and applicable alternative to many population groups (elderly, young, physically active or not), that aim to treat or slow up the effects of bone diseases. Finally, the current studies which approach this theme only show short-term results justifying the use of biomarkers that reflect in a dynamic way the bone metabolism. However, it is believed that this technique combined with low-intensity training, can also bring long-term satisfactory results that must be evaluated in the bone structure, showing that future studies are necessary to clarify these doubts related to the long-term effects of BFR over bone adaptations.

The limitations of the present study include (i) the small number of articles; (ii) the lack of methodological standardization (sample 'n'; study design; intervention duration); and (iii) the divergences in the exercise protocols.

Conclusions

The results of this study may assist future clinical research with the method of RFS and bone metabolism (formation and resorption) and show the positive effect of this technique combined with exercise in the prevention and treatment of bone diseases. Furthermore, no methodological standardization was observed across these samples regarding exercise type, intervention frequency or duration. Therefore, additional studies are needed to justify the quality of evidence regarding BFR studies on bone metabolism.

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Conflict of interest

The authors have no conflict of interests.

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