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Review

High and low-load resistance training produce similar effects on bone mineral density of middle-aged and older people: A systematic review with meta-analysis of randomized clinical trials

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ABSTRACT

Purpose: To compare the effects of high-load (≥ 70 of 1RM) and low-load (< 70 of 1RM) resistance training (RT) on femoral neck and lumbar spine bone mineral density (BMD) in middle-aged and older people.
Design: Systematic review with meta-analysis.
Data source: English language searches of the electronic databases PubMed/Medline, Scopus and Web of Science. Inclusion criteria: (i) older or middle-aged (≥ 45 years old) participants of both sexes with or without comorbidities, (ii) studies that compared high-load (≥70% 1 RM) versus low-load (< 70% 1RM) RT, (iii) studies that examined femoral neck or lumbar spine BMD.
Results: From 1052 studies found, six were included in qualitative and quantitative analysis. The meta-analysis revealed no difference between groups for femoral neck (weighted mean difference [MD] and 95% confidence interval (CI) = 0.00 g/cm^2 [95% CI, −0.01 to 0.01]; P = 0.63) and lumbar spine (MD = 0.01 g/cm^2 [95% CI, −0.00 to 0.02]; P = 0.12) BDM. There was a substantial heterogeneity for femoral neck (I^2 = 47%; P = 0.07) and lumbar spine (I^2 = 59%; P = 0.02). Subgroup analysis revealed a significant effect of high-load RT on femoral neck BMD when participants presented normal BMD values (MD = 0.01 g/cm^2 [95% CI, −0.00 to 0.02]; P = 0.04) and on interventions lasting up to 6 months (MD = 0.01 g/cm^2 [95% CI, −0.00 to 0.02]; P = 0.03).
Conclusion: Both high- and low-load RT have similar effects on femoral neck and lumbar spine BMD in aging people.

1. Introduction

Bone mass declines as much as 0.5% per year or more after the fourth decade of life regardless sex or ethnicity (Kohrt et al., 2004). There is evidence that reduced bone mineral density (BMD) is associated with an increased risk for fracture (Holroyd et al., 2008), which leads to functional decline, loss of independency, chronic pain, depression and increased mortality (Cauley et al., 2000; Lewiecki, 2004). Hip and spine are the most predominant sites affected by fractures in aging, with femoral neck corresponding to almost half of all hip fractures (Boonen et al., 2008; Holroyd et al., 2008).

During physical activity mechanical forces can be exerted on bones through ground reaction forces, resulting in maintenance or gain of bone mass (Moreira et al., 2014). Based on this, high-impact physical exercises, such as brisk walking, running and jumping, are most commonly recommended to prevent or treat osteoporosis (Moreira et al., 2014). However, the contractile activity of muscles during low impact exercises, such as resistance training (RT) has also been shown to promote positive effects on bone health (Moreira et al., 2014). In agreement with this, previous studies have highlighted resistance training (RT) as one of the most effective non-pharmacological strategies to increase BMD (Kelley et al., 2001; Layne and Nelson, 1999; Martyn-St James and Carroll, 2006). In order to achieve optimal bone adaptations it is generally recommended that aging individuals should perform RT using higher loads (≥70% 1RM) (American College of Sports Medicine, 2009; Fragala et al., 2019; Senderovich and Kosmopoulos, 2018). Indeed, early studies have demonstrated greater increases on BMD in elderly through the performance of high-load RT in

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comparison with non-exercise or usual care controls, suggesting that improvements on BMD is mainly influenced by the magnitude of mechanical stress placed upon bone (Mosti et al., 2013; Nelson et al., 1994; Watson et al., 2015). However, since these studies compared training with non-exercise or usual care controls, it is difficult to determine if high-load RT presents greater effectiveness than low-load.

There is evidence that significant increases in BMD may be achieved using low loads (< 70% 1 RM) and high repetitions (Nicholson et al., 2015; Petersen et al., 2017); however, is not clear if low-load RT is as effective as high-load. Studies making direct comparisons between high- and low-loads seems inconclusive, with some studies reporting benefits for higher loads (Kerr et al., 1996; Maddalozzo and Snow, 2000; Vincent and Braith, 2002), while others did not find differences between different load conditions (Bemben et al., 2000; Bemben and Bemben, 2011; Pruitt et al., 1995). Therefore, it is not clear if RT with higher loads is necessary to provide optimal increases in BMD. This could be recognized as a relevant topic because some older adults' population, such as frail individuals and those in rehabilitation settings, may not be able to perform high-load RT.

Whilst mechanical loading are generally believed to exert a major effect on bone (Skerry, 2008; Skerry and Suva, 2003), there is evidence showing an association between muscle and bone. For example, Gentil et al. (2007) showed that higher levels of muscle mass are associated with reduced prevalence of low bone mineral density. Moreover, previous studies showed that muscle tissue seems to influence bone health (Brotto and Bonewald, 2015; Cianferotti and Brandi, 2014) and factors produced by muscle contractions, such as myokines, might also contribute to bone formation (Bettis et al., 2018; Cianferotti and Brandi, 2014). Considering that these factors might be influenced by different loading conditions, these evidences suggest that triggers for bone synthesis involve more than only mechanical factors; therefore, the load threshold for inducing osteogenic response may be smaller than previously thought. In agreement with this, Karabulut et al. (2011) showed similar increases in osteogenic factors between high-load (80% of 1 RM) and low-load (20% of 1 RM) with blood restriction RT in elderly men.

Considering that fracture due to reduced BMD represents a huge burden to public health system (Burge et al., 2010), it is important to determine the RT-load strategy that provides optimal benefits for bone health. A systematic review of the literature will allow stronger conclusions to be reached compared with those achieved by isolated studies and will facilitate readers who may have difficulties to capture and review the evidence provide by primary studies. Therefore, in order to produce more clarity about this topic, our purpose was to summarize the evidence through systematic review and meta-analysis regarding the randomized clinical trials that have compared the effects of high- vs. low-load RT on femoral neck and spine BMD in middle-aged and older people.

2. Methods

2.1. Preliminary settings

The set of items of this systematic review are presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Moher et al., 2009). The systematic review protocol was registered with the International Prospective Register of Systematic Review (PROSPERO; available at: https://www.crd.york.ac.uk/PROSPERO/) on 23 November 2018 (registration number CRD42018104542) (Booth et al., 2012). The study question and other systematic review procedures were addressed with reference to the following PICOS: population: older adults and/or middle age individuals; intervention: high-load RT; comparisons: low-load RT; outcome: bone mineral density.

2.2. Eligibility criteria

The systematic search comprised randomized controlled trials, randomized clinical trial, controlled clinical trials. Studies were considered to be eligible for inclusion according to the following criteria: (i) involving older adults and/or middle age participants (≥ 45 years old) of both sexes with or without comorbidities, (ii) interventions involving exclusively RT that compared high-load (≥70% 1 RM) versus low-load (< 70% 1RM), (iii) studies that examined femoral neck or lumbar spine BMD. Studies were excluded from analysis based on the following criteria: (i) clinical trial registers or non-concluded studies, dissertation and thesis, letter to editor, reviews and observational studies, (ii) interventions with concurrent training or exercises involving impact loading (i.e., plyometric exercises such as squats jumps, drop box).

2.3. Search strategy

English language searches of the electronic databases PubMed/Medline, Scopus and Web of Science were performed from inception to June 2018 with an update in October 2019. Articles were retrieved from electronic databases using the following search strategy: (((((((“resistance exercise”) OR “resistance training”) OR “strength exercise”) OR “strength training”) OR “weight exercise”) OR “weight training”)) AND (((((bone) OR “bone mass content”) OR “bone metabolism”) OR “bone mineral content”) OR “bone density”). Identified articles on systematic search were initially checked for relevance by two independents researchers (DS and MB). Articles were selected after a sequenced reading of title and abstract, always in this order, the agreement rate between reviewers for the title/abstract screening was (kappa = 0.728, $P < 0.001$). Subsequently, the researchers reviewed the full texts of potentially eligible papers. A third researcher (PG) resolved any disagreement for study inclusion between the reviewers. The reference list of the articles was consulted to find possible additional studies. Duplicated items after the search were removed. Fig. 1 presents the flow chart of papers through the study selection process.

2.4. Data extraction

The data extraction was performed by two independent researchers (DS and MB), supported by a third researcher (PG) when necessary. The data extracted from RT interventions included the participant's age, sex, the RT intervention characteristic (e.g., duration, load, frequency, supervision status), as well as the mean and standard deviation pre- and post-intervention data for the study outcomes. The corresponding authors were contacted via email and asked to provide additional data when insufficient statistical information was reported to calculate mean change in bone markers.

2.5. Study quality

Study quality was assessed by two researchers (DS and MB) using the Tool for the Assessment of Study Quality and Reporting in Exercise (TESTEX) scale (Smart et al., 2015), which is considerate an adequate tool for assessing the methodological quality of the studies involving physical exercise and was used to assess each individual study for quality and reporting. The TESTEX include 12 items (5 for study quality and 7 for study reporting), which uses a 15-point scale for assess the study quality. The scale provides a comprehensive review of RT trials. None study was excluded from analysis due low quality.

To rate the quality of the evidence the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool was used. The GRADE offers four levels of evidence: high, moderate, low and very low. Randomized trials begin as higher quality evidence and the quality may be downgraded as a result of limitation in the study design or implementation, imprecision of estimates,

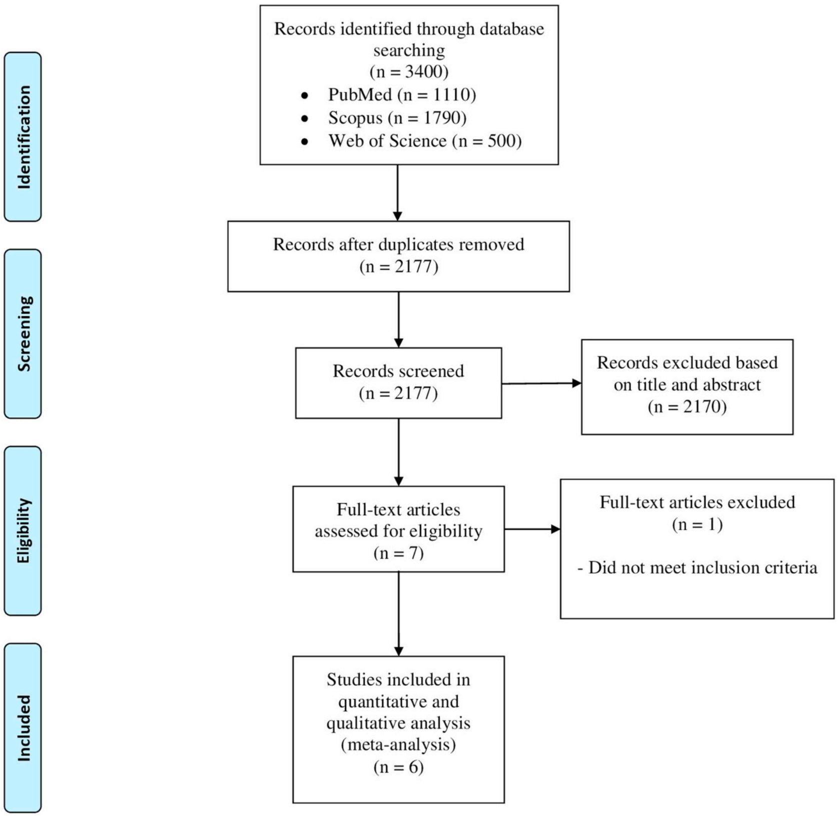

Fig. 1. Flow diagram of the selection of studies.

variability in results, indirectness of evidence and publication bias (Guyatt et al., 2008).

2.6. Statistical analyses

Absolute difference in mean from pre- to post-intervention (changes from baseline) in bone markers (femoral neck and lumbar spine BDM) expressed as g/cm^2 were used to pairwise comparison between conditions (high-load RT versus low-load RT). In absence of absolute change from baseline BMD values in the original article, the mean difference was calculated by subtracting the post-mean from the pre-mean value. When a study lacked the necessary data to estimate the SD change, the following equation was used: $\sqrt{([SDpre]^2 + [SDpost]^2 - (2 \times corr \times SDpre \times SDpost)}$ (Higgins and Green, 2011). Standard deviations were then imputed for these studies using the correlation coefficient (*corr*) value (r) obtained in previous systematic review with meta-analysis about the topic ($corr = 0.99$) (Martyn-St James and Carroll, 2006). The effects for meta-analyses were presented as weighted mean difference (MD) and 95% confidence interval (CI). Statistical heterogeneity of the treatment effect among studies was tested using the Chi^2 test and the inconsistency I^2 test, in which values above 50% and $P < 0.10$ were considered indicative of substantial heterogeneity (Higgins et al., 2003). The random-effects model was preferred due the wide methodological variation between studies. A sensitivity analysis was performed to determine the contribution of each study to the overall improvements by successively omitting the results of each study and using the data from the remaining studies. An additional sensitive analysis was conducted in order to detect the influence of sex (female or mixed), age (≤ or ≥60 years), status of BMD at baseline (normal or low), length of intervention (≤ or > 6 months). All analyses were conducted using the Review Manager software (RevMan 5.3, Nordic Cochrane, Denmark). The accepted level of significance was ($P < 0.05$).

3. Results

3.1. Included studies

Initially, 2657 records were identified through database searching. After removing duplicates, 1052 studies were screened for titles and/or abstracts analyses and 1045 studies were removed for not meeting inclusion criteria. After analyses for eligibility of full-text of remained studies, one study was removed as it did not examine femoral neck or lumbar spine BMD (Taaffe et al., 1996), resulting in a total of 6 articles included in final analyses (Fig. 1). When the study included more than one comparison between high- vs. low-load RT (e.g. different frequency of interventions or sex), the data obtained from each comparison were treated as an independent trial in meta-analyses.

3.2. Quality assessment

The TESTEX results are presented in Table 1. The studies achieved an average score of 10.2 from a total of 15 points. Trials were very similar regarding the quality assessment. The Bemben and Bemben (2011) study achieved 11 from a total of 15 point, while the others studies (Bemben et al., 2000; Kerr et al., 1996; Maddalozzo and Snow, 2000; Pruitt et al., 1995; Vincent and Braith, 2002) presented 10 points. The most prevalent issues related to reduced quality were an adherence < 85%, absence of adverse effect report and intention-to-treat analysis.

3.3. Study summary

Studies' characteristics are described in Table 2. A total of 286 participants were included in qualitative and quantitative analyses, 139 for high-load and 147 for low-load group. The number of participants by group varied from 7 (Pruitt et al., 1995) to 35 (Bemben and Bemben, 2011). The mean age of participants ranged from 55.5 (Bemben et al.,

Table 1
Study quality and reporting of included studies.

Reference	Study quality					Score (0–5)	Study reporting										Score (0 – 10)	Total score (0–15)
	1	2	3	4	5		6a	6b	6c	7	8a	8b	9	10	11	12		
Bemben and Bemben, 2011	+	+	+	+	−	4	+	−	+	−	+	+	+	NA	+	+	7	**11**
Vincent and Braith, 2002	+	+	+	+	−	4	−	+	+	−	+	+	−	−	+	+	6	**10**
Bemben et al., 2000	+	+	+	+	+	5	−	−	+	−	+	+	−	NA	+	+	5	**10**
Maddalozzo and Snow, 2000	+	+	+	+	−	4	−	+	+	−	+	+	−	NA	+	+	6	**10**
Kerr et al., 1996	+	+	+	+	−	4	−	+	+	−	+	+	−	NA	+	+	5	**10**
Pruitt et al., 1995	+	+	+	+	−	4	−	−	+	−	+	+	−	+	+	+	6	**10**

+ meet the criteria; − do not meet the criteria; NA not applicable.

2000) to 67.6 years (Vincent and Braith, 2002). From the six studies, three involved exclusively postmenopausal women (Bemben et al., 2000; Kerr et al., 1996; Pruitt et al., 1995), while three involved participants of both sexes (Bemben and Bemben, 2011; Maddalozzo and Snow, 2000; Vincent and Braith, 2002). Regarding studies involving both sexes, one study included 45 men and 79 women in analysis (Bemben and Bemben, 2011), one study did not report proportion between men and women (Vincent and Braith, 2002), while one study presented separated analysis for each sex (Maddalozzo and Snow, 2000), which was treated in meta-analyses as independent interventions. Two studies involving menopausal women included participants under hormone replacement (Bemben and Bemben, 2011; Pruitt et al., 1995). With exception for Kerr et al. (1996), the diet and calcium intake were controlled through validated food questionnaires. Five studies evaluated BMD for both femoral neck and lumbar spine (Bemben et al., 2000; Bemben and Bemben, 2011; Maddalozzo and Snow, 2000; Pruitt et al., 1995; Vincent and Braith, 2002), while one study evaluated only femoral neck (Kerr et al., 1996). All BMD measures were determined by dual-energy X-ray absorptiometry (DXA).

3.4. Interventions characteristics

The characteristics of interventions are described in Table 3. In all studies, training sessions were supervised to monitor proper lifting techniques and load progression. Only two studies reported the supervision ration, Maddalozzo and Snow (2000) adopted supervision ratio of 1 trainer by 2 participants (1,2) and Vincent and Braith (2002)) adopted supervision ratio of 1 trainer by 1 participant (1,1). The length of intervention varied from 6 months (Bemben et al., 2000; Maddalozzo and Snow, 2000; Vincent and Braith, 2002) to 1-year (Kerr et al., 1996; Pruitt et al., 1995). Training sessions lasted approximately 60–75 min, with exception for Vincent and Braith (2002), that lasted 30 min. Regarding exercise selection, RT protocols involved both multi- and single-joint exercises with emphasis on hip and lumbar spine. Four studies performed RT exclusively in weight machine (Bemben et al., 2000; Bemben and Bemben, 2011; Pruitt et al., 1995; Vincent and Braith, 2002), whereas the other two used both machines and free-weight exercises. In the Kerr et al. (1996) study, participants performed unilateral exercises and the contralateral limb served as non-exercise control. All studies included provided direct comparison between high and low-load condition. Most studies adopted method to control load was percentage of 1RM, varying from 40 to 60% for the low-load and 70 to 90% for the high-load groups. Only one study (Kerr et al., 1996) adopted a different approach (i.e., the maximum amount of load that can be lifted for a given number of repetitions; e.g. 8 RM). Two studies reported no adverse effects or serious injuries related to RT programs (Kerr et al., 1996; Maddalozzo and Snow, 2000). While 6 participants (low-load = 2, high-load = 4) experienced joint discomfort and reduced training for 2 weeks in study by Vincent and Braith (2002).

3.5. Meta-analysis

The comparisons between groups on the effects of high- and low-load on femoral neck and lumbar spine BDM (g/cm^2) are presented in Fig. 2.

There is moderate evidence (Fig. 3) that the meta-analyses revealed no statistical difference between groups on femoral neck (high-load, n = 139 versus low-load, n = 147; MD = 0.00 g/cm^2 [95%CI, −0.01 to 0.01]; P = 0.63) and lumbar spine (high-load, n = 115 versus low-load, n = 128; MD = 0.01 g/cm^2 [95%CI, −0.00 to 0.02]; P = 0.12). There was substantial heterogeneity in the analysis for femoral neck (I^2 = 47%; P = 0.07) and lumbar spine (I^2 = 59%; P = 0.02). The sensitive analysis, that includes checking outliers studies by graphic inspection and subgroup analysis procedures, found no changes in differences between groups on femoral neck (P-value ranged from 0.26 to 0.91) and lumbar spine (P-value ranged from 0.06 to 0.28) after removal of each one of the included intervention.

The subgroup analysis revealed a significant effect of BMD status at baseline (normal vs low) and length of intervention (≤ vs > 6 months) on femoral neck BMD (Table 4); however, no significant effect was found on lumbar spine BDM. No effect of sex or age was found on femoral neck or lumbar spine BDM.

4. Discussion

The purpose of the present study was to summarize the evidence through systematic review and meta-analysis of the randomized clinical trials that have compared the effects of high- and low-load RT on femoral neck and lumbar spine BMD in middle-aged and older people. The meta-analysis combined the results of six studies involving 286 participants of both sexes over 45 years old. As main results, we did not find significant difference between high- and low-load RT protocols on femoral neck and lumbar spine BMD. Therefore, the present meta-analysis did not confirm the assumptions of a superiority of high-load against low-load RT on femoral neck and lumbar spine BMD. The level of confidence of our results was classified as moderate according to GRADE (Guyatt et al., 2008). These findings are particularly important, since aging people occasionally present physical limitations that prevent them to perform resistance exercise with higher loads, like joint pains, arthritis and arthrosis. Therefore, low-load RT might be a feasible strategy to promote benefits in terms of BMD.

Considering the heterogeneity of the methods and results, we critically reviewed each study protocol as an attempt to better understand the factors that might explain their results, as previously suggested (Gentil et al., 2017). The study by Pruitt et al. (1995) compared the effects of high- and low-load RT on BMD in postmenopausal women and showed similar effects between loading conditions. Regarding training protocol, the high-load group performed 1 set of 14 repetitions at 40% of 1RM as warm-up, followed by 2 sets of 7 repetitions at 80% of 1RM, while the participants of low-load group performed 3 sets of 14 repetitions. It is important to highlight, that neither group achieved

Table 2
Summary of included interventions.

Reference	Participants characteristics	N sample	Male/female (%)	Age range (year)	Study design	BMD (g/cm^2) assessed
Bemben and Bemben, 2011	Elderly subjects	124	36/64	65 to 74	Randomized clinical trials	DXA at the femoral neck and lumbar spine (L2-4)
Vincent and Braith, 2002	Elderly subjects	46	N/R	62 to 83	Randomized controlled trials	DXA at the femoral neck and lumbar spine (L1-4)
Bemben et al., 2000	Postmenopausal women	17	0/100	41 to 60	Randomized controlled trials	DXA at the femoral neck and lumbar spine (L2-4)
Maddalozzo and Snow, 2000	Middle-aged and elderly subjects	42	57/43	50 to 60	Randomized clinical trials	DXA at the femoral neck and lumbar spine (L2-4)
Kerr et al., 1996	Postmenopausal women	42	0/100	58.4 ± 3.7	Randomized clinical trials	DXA at the femoral neck
Pruitt et al., 1995	Postmenopausal women	15	0/100	67.0 ± 0.5	Randomized controlled trials	DXA at the femoral neck and lumbar spine (L2-4)

BMD, Bone mineral density; DXA, dual-energy X-ray absorptiometry.

statistically significant improvement for any BMD site, which suggests that the intensity threshold might not have been reached for any group. The lack of results might be explained by the use of hormone replacement and the higher lumbar BMD of the participants, according with to normative values for age.

Bemben et al. (2000) also did not find difference between load conditions for femoral neck and lumbar spine BMD in postmenopausal women. Similar to the previous study, the RT protocols were initially matched by volume-load. The participants performed 8 repetitions at 80% of 1RM or 16 repetitions at 40% of 1RM for high- and low-load groups, respectively. Both groups experienced a load progression based on prescribed number of repetitions throughout to the intervention; however, there was a 30% greater volume-load progression for low-load in comparison with high-load group, which suggested a high volume load for the low-load group at the end of the study. Similar to Pruitt et al. (1995), there was no significant improvement in BMD, suggesting that the osteogenic threshold was not reached. Moreover, is important to note that participants of both studies had BMD values close the reference values of young adults, which may have influenced in the results as it would limit the margin for increase.

The lack of superior benefits for higher loads were confirmed later by the same research group in a study involving elderly of both sexes divided into 4 groups (low-load 2 times a week, low-load 3 times a week, high-load 2 times a week and high-load 3 times a week) (Bemben and Bemben, 2011). According to the results, both high- and low-load groups obtained similar improvements on lumbar spine BMD regardless of training frequency, while no difference was observed for BMD femoral neck for neither group. High and low-load RT protocols were matched by volume-workload similar to previous study (Bemben et al., 2000) and participants were older, with 25 to 35% of each group diagnosed with osteopenia in the lumbar spine. Considering that training protocols were similar between studies (Bemben et al., 2000; Bemben and Bemben, 2011), is reasonable suggest that the initial BMD values might explain the divergent results, since only the latter study achieved significant increase on lumbar spine BMD.

Kerr et al. (1996) showed greater effects on trochanter and intertrochanter BMD for high-load RT, but there was no difference for femoral neck and lumbar spine BMD, which is in agreement with the previous studies. The participants performed 3 sets of 8 RM for high-load and 3 sets of 20 RM for low-load. The study reported that the participants were encouraged to perform maximal repetitions. This might have difficulted the progression of training load, especially for low-load group, due the higher perceived discomfort during higher repetitions (Steele et al., 2017). Furthermore, is important to note, that the study by Kerr et al. (1996) did not perform direct comparison between high- and low-load condition, but the difference between exercising limb and non-exercising control side.

According to Maddalozzo and Snow (2000), high-load RT provided greater improvement on lumbar spine BMD in comparison with low-load in elderly men, but no difference was observed for elderly women at any bone site. High-load group performed progressive load RT from 70 to 90% of participants' 1 RM, while low-load group performed 10 to 13 repetitions at 40 to 60% of 1 RM. However, in contrast with the other studies, the authors also adopted different exercise selection. Low-load group performed exclusively seated weight machines exercises, while high-load group performed both seated weight machines and free-weight in stand position. Therefore, it is not possible to determine whether the superior increases achieved by the high-load group in men was due load scheme or due the exercise choice.

Vincent and Braith (2002) reported greater improvements on femoral neck BMD for the high-load in comparison with low-load RT group in older men and women. High-load group performed 8 repetitions with the load corresponding to 80% of participants' 1 RM, whereas that low-load group performed 13 repetitions with 50% of 1 RM. The progression of load for both conditions was based on the rating of perceived effort (RPE). In this context, whilst the volume was

Table 3
Interventions characteristics of included studies.

Reference	Resistance training protocol	Length of intervention	Weekly frequency	BMD outcomes
Bemben and Bemben, 2011	High load RT (80% 1RM) using weight machine	40 weeks	2	↑LS ↔FN
–	Low load RT (40% 1RM) using weight machine	–	2	–
–	High load RT (80% 1RM) using weight machine	–	3	–
–	Low load RT (40% 1RM) using weight machine	–	3	–
Vincent and Braith, 2002	Low-load (80% 1RM) using weight machine	6 months	3	↔LS ↔FN
–	High-load (50% 1RM) using weight machine			↔LS ↑FN
Bemben et al., 2000	High-load (80% 1RM) using weight machines	24 weeks	3	↔LS ↔FN
–	Low-load (40% 1RM) using weight machines	–	–	↔LS ↔FN
Maddalozzo and Snow, 2000	Low-load (40 to 60% 1RM) using weight machine (males)	24 weeks	3	↔LS ↔FN
–	High-load (70 to 90% 1RM) using weight machine and free-weight (males)			↔LS ↑FN
–	Low-load (40 to 60% 1RM) using weight machine (females)			↔LS ↔FN
–	High-load (70 to 90% 1RM) using weight machine and free-weight (female)			↔LS ↔FN
Kerr et al., 1996	High-load (8 RM) using weight machines and free weight	52 weeks	3	↔LS ↔FN
–	Low-load (20 RM) using weight machines and free weight	–	–	↔LS ↔FN
Pruitt et al., 1995	High-load (80% 1RM) using weight machine and free-weight	12 months	3	↔LS ↔FN
–	Low-load (40% 1RM) using weight machine and free-weight	–	–	↔LS ↔FN

BMD, Bone mineral density; LS, Lumbar spine; FN, Femoral neck; ↑ denotes significant increases; ↔ denotes lack of changes.

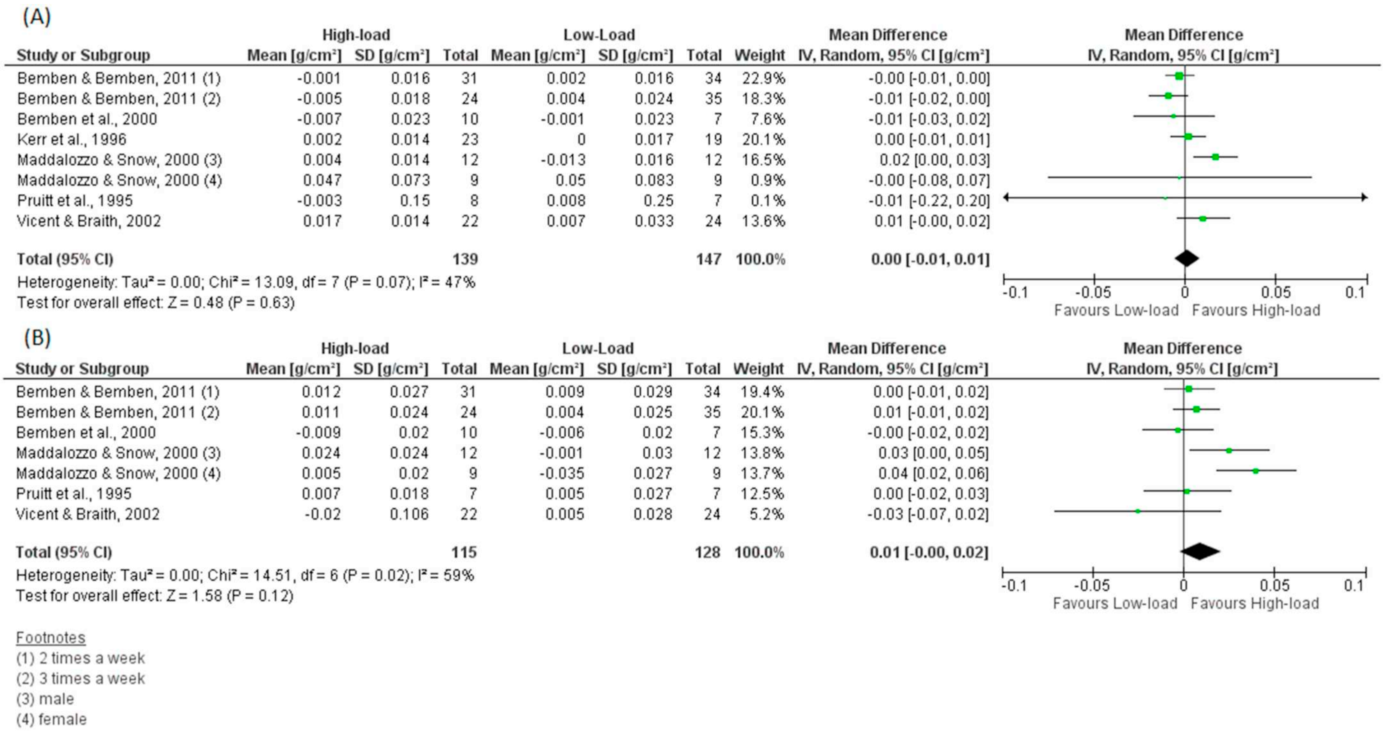

Fig. 2. Forest plot of the between-group comparison of the effects of high-load (70 to 90% of 1 RM) versus low-load (40 to 60% of 1 RM) protocols on bone mineral density (BMD) at femoral neck (A) and lumbar spine (B). SD standard deviation, CI confidence interval, IV random effects.

initially equated, it might be possible that the higher discomfort perceived during the performance of higher repetitions in low-load RT (Fisher and Steele, 2017; Steele et al., 2017; Stuart et al., 2018) might have limited load progression in comparison with high-load.

Therefore, the analysis of the studies showed that load progression, intensity of effort and exercise selection might have influenced comparisons. However, in general, our analysis does not confirm the suggestion that the intensity of load is the main variable to provide significant increases on femoral neck and lumbar spine BMD (American College of Sports Medicine, 2009; Senderovich and Kosmopoulos,

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High-load RT	Low-load RT	Relative (95% CI)	Absolute (95% CI)		
BMD Femoral neck (g/cm²)												
6	randomised trials	not serious	not serious	not serious	serious [a]	none	142	147	-	MD **0 g/cm²** (0.01 lower to 0.08 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
BMD Lumbar spine (g/cm²)												
5	randomised trials	not serious	not serious	not serious	serious [b]	none	118	128	-	MD **0 g/cm²** (0 to 0.02 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Downgrade one level due to OIS (Optimal Information Size)
b. Downgrade one level due to OIS (Optimal Information Size)

Fig. 3. Grading of Recommendations, Assessment, Development and Evaluation (GRADE) of evidences for femoral neck lumbar spine BMD. The GRADE offers four levels of evidence: high, moderate, low and very low.

2018). It seems that both high- and low-load RT protocols provide similar effects in BMD, which suggests that the intensity threshold to provide adaptations might be as low as 40% of 1RM, as long as effort is adequate.

The possible explanation for this might be in the association between muscle and bone (Gentil et al., 2007; Whiteford et al., 2010; Woo et al., 2007). In this regard, previous studies suggested that muscle tissue seems to influence bone health, which could be mediated by the action of muscle-derived factors (i.e. myokines) (Bettis et al., 2018; Kaji, 2016; Karsenty and Mera, 2018; Lombardi et al., 2016). In this regard myostatin, which is inhibited by RT, is involved in osteoclast formation and bone destruction. Numerous other myokines that are regulated by exercise, including transforming growth factor-β, follistatin, insulin-like growth factor-I, fibroblast growth factor-2, osteoglycin, FAM5C, irisin, interleukin-6, leukemia inhibitory factor, IL-7, IL-15, monocyte chemoattractant protein-1, ciliary neurotrophic factor, osteonectin and matrix metalloproteinase 2 have been suggested to influence bone metabolism (Kaji, 2016; Lombardi et al., 2016). Therefore, RT might improve bone health through factors that are not necessarily dependent on the use of high loads, like muscle hypertrophy (Laurent et al., 2016; Yakabe et al., 2019) and contraction (Huh, 2018; Lombardi et al., 2016).

Based on the present results, if the purpose is to promote positive changes in BMD, both low- and high-load RT seems to be effective. However, whilst the results of the meta-analysis showed similar results to low- and high-load RT, it is important to note that half of the included studies found superior results for high-load RT in at least one measure, while no study found superior results for low load RT. Furthermore, the use of high-loads seems to promote superior effects regarding femoral neck BMD in comparison with low-loads in individuals with normal initial BMD values. In this sense, individuals with low initial BMD seem more responsive to RT regardless the load used. Other important aspect to consider is the duration of intervention, since interventions lasting up to 6 months can favours the effects of high-load RT on femoral neck BMD, which might be of practical importance when seeking for more rapid results. Although there is not a clear reason for that, it is possible to suggest that the discomfort caused by low loads RT performed to, or close to, muscle failure (Fisher et al., 2017; Fisher and Steele, 2017) might prevent to reach high efforts, which can impair RT progression and BMD adaptations, especially in a short-term intervention.

From a practical standpoint, the protocol choice might be more related to logistical and individual aspects. For example, the use of high load might require specific equipment and a closer supervision. On the other hand, the performance of RT with lower loads and higher repetitions are associated with higher discomfort (Fisher et al., 2017; Fisher and Steele, 2017; Stuart et al., 2018) and higher cardiovascular stress (Lovell et al., 2011; Vale et al., 2018).

Table 4
Summary of High vs Low-Load resistance training on femoral neck and lumbar spine BMD.

Outcome (subgroup)	Interventions (n)	MD (95% CI)	*P*-value	I^2 (%)	*P*-value
Femoral neck BMD (g/cm²)					
Sex: female	3	0.00 [−0.01 to 0.01]	0.88	0	0.93
Sex: mixed	4	−0.00 [−0.01 to 0.01]	0.69	54	0.12
Age: ≥ 60	2	0.01 [−0.00, 0.02]	0.18	0	0.85
Age: ≤ 60	3	0.01 [−0.01, 0.03]	0.39	4	0.19
BMD values: normal	**6**	**0.01 [−0.00 to 0.02]**	**0.04**	**5**	**0.38**
BMD values: low	2	−0.01 [−0.01 to 0.00]	0.11	0	0.38
Length of intervention: ≤ 6 months	**4**	**0.01 [−0.00, 0.02]**	**0.03**	**11**	**0.34**
Length of intervention: > 6 months	4	−0.00 [−0.01 to 0.00]	0.27	0	0.52
Lumbar spine BMD (g/cm²)					
Sex: female	2	−0.00 [−0.02 to 0.01]	0.89	0	0.75
Sex: mixed	4	0.01 [−0.01 to 0.03]	0.26	72	0.01
Age: ≥ 60	4	−0.00 [−0.03, 0.02]	0.71	5	0.31
Age: ≤ 60	3	0.02 [−0.01 to 0.05]	0.12	77	0.01
BMD: normal	5	0.01 [−0.01 to 0.03]	0.27	69	0.01
BMD: low	2	0.01 [−0.00 to 0.01]	0.28	0	0.67
Length of intervention: ≤ 6 months	4	0.01 [−0.01 to 0.04]	0.3	75	0.007
Length of intervention: > 6 months	3	0.00 [−0.00 to 0.01]	0.28	0	0.89

BMD, bone mineral density.
Significant p values are indicated in bold.

It should be point out that although the quality of evidence was classified as moderate (important) according with GRADE, the few studies available and the moderate to substantial heterogeneity observed between studies may reduce the external validity of findings and suggest that one should be careful in generalizing the results. However, the subgroup analysis might help to understand what main variables might have influenced the results. Also, it is important to highlight that the present meta-analysis limited to compare the effects of low- and high-load RT on femoral neck and lumbar spine BMD and did not allow to conclude about the effects of each intervention separately or to extrapolate these results to others BMD sites. Notwithstanding, a huge quantity of evidence have demonstrated the positive effects of high-load RT on bone health in aging people, increasing or preserving bone mass (Fragala et al., 2019; Kohrt et al., 2004; Martyn-St James and Carroll, 2009; Nelson et al., 1994).

5. Conclusion

According to our findings low-load RT may be an effective alternative strategy to high-load RT to counteract the age-related bone mass loss on femoral neck and lumbar spine in aging people, especially when individuals present reduced bone mineral density. However, high load RT seems to provide higher results when over shorter periods and for people with higher BMD. Thus, health professionals that work with this population may choose the RT load strategy based on convenience and characteristics of the patients.

Contributors

DS and MB carried out the screenings and reviews. DS and WM carried out the analysis of the articles. DS and PG drafted and revised the manuscript. WM, RC, MB, and PG revised the manuscript. All authors read and approved the final manuscript.

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Declaration of competing interest

Daniel Souza, Matheus Barbalho, Rodrigo Ramirez-Campillo, Wagner Martins and Paulo Gentil declare that they have no conflict of interest.

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