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NON-PHARMACOLOGICAL INTERVENTIONS IN OSTEOSARCOPENIA: A SYSTEMATIC REVIEW

R. ATLIHAN[1,2], B. KIRK[1,2], G. DUQUE[1,2]

1. Department of Medicine-Western Health, Melbourne Medical School, University of Melbourne, St Albans, Melbourne, VIC, Australia; 2. Australian Institute for Musculoskeletal Science (AIMSS), University of Melbourne and Western Health, St Albans, Melbourne, VIC, Australia. Corresponding author: Prof. Gustavo Duque, MD, Ph.D., FRACP, FGSA, Australian Institute for Musculoskeletal Science (AIMSS), University of Melbourne and Western Health, 176 Furlong Road, St. Albans, VIC, Australia 3121, Tel: +61 3 8395 8121, E-mail: gustavo.duque@unimelb.edu.au

Abstract: *Background:* Osteosarcopenia is a geriatric syndrome defined by the concomitant presence of osteopenia/osteoporosis (loss of bone mineral density (BMD)) and sarcopenia (loss of muscle mass and/or function), which increases the risk of falls, fractures, and premature mortality. *Objective:* To examine the efficacy of non-pharmacological (exercise and/or nutritional) interventions on musculoskeletal measures and outcomes in osteosarcopenic adults by reviewing findings from randomized controlled trials (RCTs). *Methods:* This review was registered at PROSPERO (registration number: CRD42020179292) and conducted in accordance with the PRISMA guidelines. Electronic databases were searched for RCTs assessing the effect of at least one non-pharmacological intervention (any form of exercise and/or supplementation with protein, vitamin D, calcium or creatine) on any musculoskeletal measure/outcome of interest (BMD, bone strength/turnover, muscle mass and strength, physical performance, falls/fractures) in adults with osteosarcopenia as defined by any proposed criteria. *Results:* Two RCTs (of n=106 older osteosarcopenic adults (≥65 years)) assessing the effects of progressive resistance training (RT) (via resistance bands or machines; 2-3 times/week; ~60 minutes in duration) were eligible for inclusion. The two RCTs demonstrated moderate quality evidence that RT increases muscle mass, strength, and quality, with changes in strength and quality occurring before muscle mass (12 vs 28 weeks). There was low quality evidence that RT increases lumbar spine BMD and maintains total hip BMD when performed for 12 and 18 months, respectively, and moderate quality evidence that RT has no effect on markers of bone turnover or physical performance. No major adverse effects were recorded in either of the RCTs. There were no eligible RCTs examining the impact of nutritional interventions. *Conclusion:* Chronic RT is safe and effective at potentiating gains in muscle mass, strength, and quality, and increasing or maintaining BMD in older osteosarcopenic adults. No RCT has examined the effects of protein, vitamin D, calcium, or creatine against a control/placebo in this high-risk population.

Key words: Bone, muscle, nutrition, osteosarcopenia, resistance training.

Introduction

Osteosarcopenia, defined as the age-related concomitant loss of BMD and muscle mass and/or function, is a strong predictor of functional impairments, falls, fractures and earlier death in older adults (1). As the older section of society continues to grow, so too will the prevalence of osteosarcopenia and the socioeconomic burdening associated with this geriatric syndrome.

Two major risk factors for osteosarcopenia are reductions in physical activity and poor nutritional status, particularly low intake of protein, vitamin D and calcium (2-4). Declines in physical activity result in a loss of BMD and muscle mass (5) due to reduced stimulation of muscle fibres and a decrease in the mechanical forces that promote osteogenesis (6). Multimodal exercise, incorporating resistance, weight-bearing impact and/or balance training has been suggested as a dual therapy (4, 7, 8) to improve aspects of osteosarcopenia such as BMD and muscle mass, strength or physical performance (9, 10).

In addition to physical activity, a number of nutrients play a fundamental role in the structure and function of muscle and bone(11). Vitamin D and calcium supplementation has been shown to improve BMD and muscle strength and reduce falls and fractures in community-dwelling adults deficient in these nutrients (12, 13). Observational studies have demonstrated a relationship between a higher intake of protein (above the recommended dietary guidelines) and greater retention of lean (muscle) mass and BMD in older adults (14-16). Lastly, in healthy older adults, creatine supplementation has consistently shown to augment the benefits of RT (17), although the effect in clinical populations with compromised muscle and bone health is yet to be determined.

Several systematic reviews and meta-analyses have been carried out to evaluate the effects of exercise and nutritional interventions in osteopenic/osteoporotic and sarcopenic populations (18-22), however, at present, there is a lack of studies evaluating the efficacy of these non-pharmacological interventions separately in osteosarcopenic individuals using proposed criteria.

Therefore, this systematic review aims to examine the effects of exercise and/or nutritional interventions with protein, calcium, vitamin D and creatine on measures and outcomes relating to musculoskeletal health in older adults with osteosarcopenia.

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Methods

Search strategy

This review was registered in PROSPERO (University of York; registration number: CRD42020179292) and conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (23). A systematic search was conducted in April 2020 in six electronic databases including MEDLINE, PUBMED, Cochrane Register of Controlled Trials, EMBASE, EMCARE and CINAHL to identify all studies of non-pharmacological interventions in osteosarcopenic participants published since the inception of each database. The following terms and their variants were included in the literature search: Osteosarcopenia, Sarco-osteopenia, Osteo-sarcopenia, Osteoporosis, Osteopenia, Sarcopenia, Exercise, Protein Supplements, Vitamin D, Calcium and Creatine. A detailed example of the search strategy used for MEDLINE can be found in Table 1. The reference lists of the included studies or key texts were also screened to identify additional relevant studies. We attempted to contact authors if full texts were not available and studies were excluded if this attempt was unsuccessful.

Table 1
Example of search strategy for OVID MEDLINE

OVID MEDLINE search strategy from 15/4/20	
1.	(osteosarcopeni* or osteo-sarcopeni* or sarco-osteopeni* or sarco-osteoporo*)
2.	(osteoporo* or osteopeni*)
3.	Sarcopeni*
4.	(exercise* or (physical adj2 (activit* or exertion)) or training)
5.	((Supplement* or intake or dietary) adj protein*)
6.	creatine
7.	calcium
8.	vitamin D
9.	2 and 3
10.	1 or 9
11.	4 or 5 or 6 or 7 or 8
12.	(randomi*ed controlled or RCT or Controlled trial or clinical trial)
13.	10 and 11 and 12

Study selection

All search results were exported into Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia), where duplicates were removed and then two reviewers (RA and BK) independently screened all titles and abstracts. Any conflicts were resolved independently by a third reviewer (GD). The full texts of remaining studies were assessed for inclusion by a single reviewer (RA).

Studies were included if they met the following criteria: 1) Participants were diagnosed with both osteopenia/osteoporosis and sarcopenia according to any proposed criteria or cutpoints for musculoskeletal measures; 2) at least one non-pharmacological intervention of interest (any form of exercise and/or intake of protein, vitamin D, calcium or creatine) was being compared against a control or placebo intervention; 3) at least one musculoskeletal measure or outcome was reported, including falls, fractures, BMD, muscle mass, muscle strength, physical performance or bone turnover markers and 4); the study was an RCT. Reasons for exclusion of studies included if they: 1) were reviews; 2) were not randomized; 3) did not use a control or placebo group; 4) were animal studies; 5) did not include participants diagnosed with both osteopenia/osteoporosis and sarcopenia according to any proposed criteria or cutpoints for musculoskeletal measures; 6) were duplicate studies; 7) full texts in English were unattainable and 8), did not report musculoskeletal outcomes or measures.

Data extraction and Quality assessment

The methodological quality of included studies was assessed by one reviewer (RA) and then confirmed with a second reviewer (BK) according to the Cochrane Collaborations tool for assessing risk of bias as described in the Cochrane Handbook for Systematic Reviews of Interventions (24). Studies were classified as either 'low risk', 'high risk' or 'unclear risk'.

Data was extracted by one reviewer (RA) and organized into an evidence table presenting the following: author, year, study design, country, eligibility criteria, sample characteristics (average age, sex), sample size, intervention, control, duration, compliance, results and statistical analysis data for outcomes/measures in falls, fractures, BMD, muscle mass, muscle strength, physical performance and bone turnover markers.

The quality of results was assessed by one reviewer (RA) and then confirmed with a second reviewer (BK) as either 'very low', 'low', 'moderate' or 'high' according to the Grading of recommendations assessment development and evaluation (GRADE) criteria (25) which involved evaluating eight domains including risk of bias, directness of evidence, consistency and precision of results, publication bias, magnitude of effect, dose-response and influence of confounding factors.

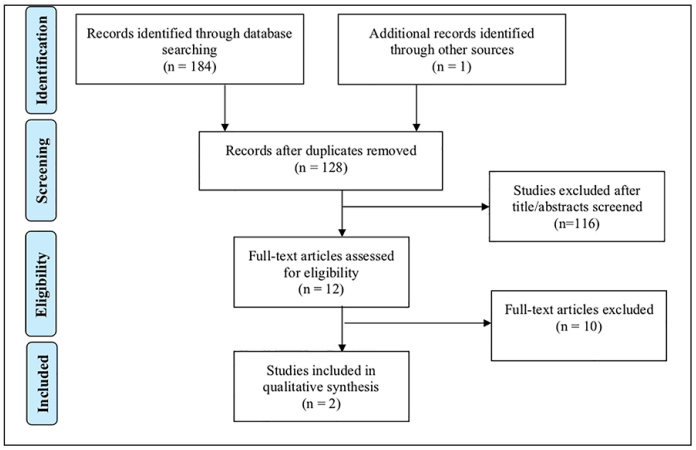
Results

Study Characteristics

Figure 1 illustrates the PRISMA flow diagram through the different phases of the study screening process. A total of 184 articles were identified in the literature search. After duplicates were removed (n=56), 128 articles were remaining of which 116 were excluded based on title and abstract. After full-text review of the remaining 12 articles, a further nine were

excluded due to being published only as conference abstracts or being incomplete trials. Bibliographic search revealed one more eligible article while another additional article was published during the course of the study. A total of five articles remained which fitted eligibility criteria. Four of these articles reported findings from different time points in the same study, leaving a total of 2 studies to be included in our qualitative analysis. The intervention used in both studies was a form of RT (resistance bands or machines). There were no RCTs identified which assessed the effects of protein, vitamin D, calcium, or creatine against a control/placebo in osteosarcopenic individuals.

Figure 1
PRISMA flow diagram for the screening of database records



The included studies were conducted in Germany and Iran and comprised of a total of 106 participants. The mean age (± standard deviation) of the participants in the studies ranged from 64.05 ± 3.35 to 79.2 ± 4.7 years and the total percentage of females across the studies were 59.4%. The follow-up duration ranged from 12 to 78 weeks. All participants were classified as osteosarcopenic by low BMD and low muscle mass by DXA. Both studies defined osteopenia as having a BMD T-score less than -1SD at either the lumbar spine or proximal femur. The Frost study(26-29) defined sarcopenia as having a skeletal muscle index of less than 7.26kg/m^2 while Banitalebi et al. (30) classified sarcopenia based on a gait speed less than 1m/s and a skeletal muscle mass index (SMI) less than 28% body mass or less than 7.76kg/m^2.

The Frost study consisting of four articles which published findings after 28 (26), 36 (27), 54 (28) and 78 weeks (29), included 43 osteosarcopenic men aged over 72 years and allocated them to either a High-Intensity RT (HI-RT) program or a non-exercise control group. Any participant with a baseline serum 25-hydroxy vitamin D (25-OHD) less than 30ng/mL was given 10,000 IU/week of vitamin D while those with serum 25-OHD between 30-40ng/mL were administered 5,000 IU/week. Calcium supplements were provided to all participants with low dietary intake of calcium to achieve a level of ~1000mg/day. The HI-RT and control were supplemented with protein to reach a daily intake of 1.5g/kg/day and 1.2g/kg/day, respectively. In order to achieve this daily protein intake, 95% of the HI-RT group required supplementation as opposed to only 30% in the control group. HI-RT consisted of a structured progressive RT program using resistance machines for 60-minute sessions biweekly for the duration of the study. Gym attendance was recorded electronically and in training logs. Adherence to diet was monitored for all participants with distribution logs, biweekly phone calls and personal interviews. Assessments were performed at baseline and 28, 36, 54 and 78 weeks.

Banitalebi et al.'s study (30) included 63 women with osteosarcopenic obesity aged 60-80 years who were allocated to either an elastic band resistance training program (EBRT) or a control group. The training sessions were run for 60 minutes, three times/week while the control group received telephone calls or had face-to-face interviews on a weekly basis to maintain their typical diet and activity habits. Assessments were performed at baseline and after 12 weeks.

Main outcomes

Table 2 shows findings from included RCTs. The Frost study (26-29) had a compliance rate of 95±5% for the HI-RT program and demonstrated a significant between-group difference in SMI and handgrip strength (both $p<0.001$ vs control) but not gait speed ($p=0.064$) at week 28. After 36 weeks, the HI-RT group showed improvements in total and thigh lean body mass and leg extensor strength (all $p<0.001$ vs control). At week 54, there was a significant increase in lumbar spine BMD ($p=0.006$) and SMI and leg extensor strength (both $p<0.001$) but not total hip BMD ($p=0.064$) when compared to control. At the final time point (week 78), HI-RT significantly increased lumbar spine BMD ($p=0.024$), SMI ($p<0.001$) and handgrip strength ($p=0.008$), and maintained total hip BMD ($p=0.025$ vs control who lost total hip BMD). Gait speed did not change ($p=0.209$). Apart from delayed-onset muscle soreness in the HI-RT group and one man who experienced worsening of existing knee and shoulder pain, there were no serious adverse effects of the training regimen.

The EBRT program in Banitalebi et al.'s study (30) had a compliance of 85% in training sessions and demonstrated a significant gains in muscle strength (handgrip strength ($p=0.013$); chair stand test ($p=0.036$)) and muscle quality ($p=0.043$) in the EBRT group compared to control. However, no improvement in physical performance as measured by 6-minute walk test (6MWT) ($p=0.284$), timed up and go (TUG) ($p=0.225$) and gait speed ($p=0.220$) were observed. Neither BMD ($p=0.564$) nor bone turnover as measured by C-terminal telopeptide (CTX) ($p=0.067$) showed improvements compared to control. There were no significant adverse effects reported in either the intervention or control group however, 25% of participants in the EBRT group experienced temporary muscle soreness, knee pain and shoulder pain in the first three training sessions.

Table 2
Study characteristics and results

Study	Author, Year, Location	Study design	Eligibility criteria	Sample size	Age (years) [mean +-SD] and Sex	Intervention	Control	Supplements	Relevant Results
1.	Lichtenberg et al.(26), 2019 Kemmler et al.(27), 2020 Kemmler et al.(28), 2020 Kemmler et al.(29), 2020 Germany	RCT	a) Community-dwelling status b) BMD T score <-1 c) SMI < 7.26kg/m^2	43	CG: 79.2±4.7 HI-RT: 77.8±3.6 100% male	18 months of HI-RT. Two 60-minute sessions/week. 1.5-1.6g/kg/day protein.	1.2g/kg/day protein	Vitamin D: 10,000 IE/week if serum 25-OHD at baseline was less than 30ng/mL. 5,000 IE/week if serum 25-OHD at baseline was 30-40ng/mL Calcium: Supplementation to increase intake to at least 1000mg/day.	Difference in MV (95%CI), p value 28 Weeks Skeletal Muscle Mass Index (DSM-BIA): 0.33 (0.19 to 0.46), p<0.001 Gait Speed: 0.020 (–0.01 to 0.06), p=0.091 Handgrip Strength: 2.19 (0.78 to 3.06), p<0.001 36 Weeks Lean Body Mass (DXA): 1.45 (0.65 to 2.26), <0.001 Thigh Lean Body Mass (DXA): 259 (114 to 405), <0.001 Leg Extensor Strength (Leg Press): 446 (328 to 564), <0.001 54 Weeks Lumber Spine BMD (QCT): 7.0 (2.2 to 11.8), p=.006 Skeletal Muscle Mass Index (DXA): 0.32 (0.22 to 0.43), p<.001 Total Hip BMD (DXA): 0.010 (.001 to .020), p=0.064 Leg Extensor Strength (Leg Press): 506 (359 to 656), p<.001 78 Weeks Lumber Spine BMD (DXA): 0.012 (0.001 to 0.020), 0.024 Total Hip BMD (DXA): 0.013 (0.002 to 0.022), 0.025 Skeletal Muscle Mass Index (DXA): 0.34 (0.23 to 0.45), <0.001 Handgrip Strength: 2.65 (0.75 to 4.56), 0.008 Gait Speed: 0.02 (–0.06 to 0.01), 0.209
2.	Banitalebi et al.(30), 2020 Iran	RCT	a) Aged 60–80 years b) Body fat percentage (BFP) > 32% c) Body mass index (BMI) > 30 kg/m^2 d) −2.5 ≤ T-score ≤ −1.0 of L1-L4 and/or total femur or femoral neck e) gait speed ≤ 1 m/s^2 f) SMI ≤ 28% or ≤7.76 kg/m^2	63	CG: 64.05±3.35 EBRT: 64.11 ± 3.81 100% female	12 weeks of EBRT Three x 60-minute sessions/week	Weekly telephone calls and face-face interviews to maintain typical diet and activity habits	None	Effect Size (ES), p value 12 Weeks 6-Minute Walk Test: ES=0.017, p = 0.284 Timed Up and Go: ES = 0.022, p = 0.225 Gait Speed: ES = 0.016, p = 0.220 Chair stand test: ES =0.063, p = 0.036 Handgrip Strength: ES = 0.065, p = 0.013 Muscle Quality: ES = 0.044, p = 0.043 BMD (DXA): ES = 0.004, p = 0.564 CTX: ES = 0.036, p = 0.067

CG, control group; HI-RT, High Intensity Resistance Training; EBRT, Elastic Band Resistance Training; DSM-BIA, Direct Segmental Multi-Frequency Bioelectrical Impedance Analysis; DXA, Dual-energy X-ray absorptiometry; QCT, Quantitative Computed Tomography; CTX, C-terminal telopeptide

Table 3
Risk of bias assessment

Study	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other sources of bias	Comments
Frost study(26-29)	Low	Low	Low	Low	High[1]	Unclear[2]	1. Trial registration reported LS-BMD at 12 months was to be measured by DXA however QCT results were reported. Kemmler et al(29) mention that they found no significant effect of HI-RT on LS-BMD at 12 months when measured by DXA however, in their 12 month results, Kemmler et al.(28) reported lumbar spine BMD as measured by QCT which did show a significant change. 2. Unclear risk of bias due to significant difference between baseline protein intake of study groups.
Banitalebi et al.(30)	Low	Low	Low	Low	High3	Low	3. Skeletal muscle mass findings were not reported.

LS, Lumbar spine; DXA, Dual-energy X-ray absorptiometry; QCT, Quantitative Computed Tomography

Table 4
Quality of evidence assessment for each individual outcome

Outcome	No. of studies	Risk of Bias	Inconsistency	Indirectedness	Imprecision	Publication Bias[3]	Upgradable criteria[4]	Quality
Skeletal muscle index	1/2	No serious ROB	No inconsistency	No indirectedness	Imprecision present	Not detected	None[5]	Moderate
Bone mineral density	2/2	Possible ROB[1]	Inconsistency not an issue[2]	No indirectedness	Imprecision present	Not detected	None	Low
Handgrip strength	2/2	No serious ROB	No inconsistency	No indirectedness	Imprecision present	Not detected	None5	Moderate
Leg strength	1/2	No serious ROB	No inconsistency	No indirectedness	Imprecision present	Not detected	None5	Moderate
Chair stand test	1/2	No serious ROB	No inconsistency	No indirectedness	Imprecision present	Not detected	None	Moderate
Gait speed	2/2	No serious ROB	No inconsistency	No indirectedness	Imprecision present	Not detected	None	Moderate
TUG	1/2	No serious ROB	No inconsistency	No indirectedness	Imprecision present	Not detected	None	Moderate
6MWT	1/2	No serious ROB	No inconsistency	No indirectedness	Imprecision present	Not detected	None	Moderate
CTX	1/2	No serious ROB	No inconsistency	No indirectedness	Imprecision present	Not detected	None	Moderate
Muscle Quality	1/2	No serious ROB	No inconsistency	No indirectedness	Imprecision present	Not detected	None	Moderate

1. Some risk of selective reporting; 2. Inconsistent results explained by large heterogeneity of studies (duration, intensity, dietary supplements, and sex of participants); 3. Insufficient data to produce funnel plots; 4. Includes large magnitude of effect, dose-response relationship, and influence of confounding factors; 5. Although these outcomes demonstrated a large magnitude of effect in one study(26-29), this needs to be consistent across at least two studies; TUG, Timed up and go; 6MWT, 6-minute walk test; CTX, C-terminal telopeptide

Quality and bias assessment

Table 3 presents findings of the quality assessment of included studies. There was a low risk of bias due to sequence generation, allocation concealment and incomplete outcome data for both of the studies. There was a high risk of reporting bias in both studies and an unclear risk for baseline confounding bias in the Frost study (26-29).

Ten individual outcomes were assessed for quality of evidence of which nine were moderate and one was low in certainty of evidence (Table 4). Outcomes measuring similar musculoskeletal attributes were reported together in Table 5 for simplicity.

Discussion

We examined the effects of non-pharmacological interventions (exercise and/or nutritional) on osteosarcopenia and found low-quality evidence that RT increases lumbar spine BMD and maintains total hip BMD over 12 and 18 months, respectively. We also found moderate-quality evidence that RT increases muscle strength and quality (≥12 weeks) and muscle mass over a longer duration (≥6 months) in older osteosarcopenic adults. Furthermore, we found there was moderate-quality evidence that RT has no effect on bone turnover or physical performance. However, we were not able to evaluate the efficacy of nutritional supplementation with protein, vitamin D, calcium, or creatine against a control/placebo in this population due to no available RCTs.

Although there are a plethora of systematic reviews/meta-analyses supporting the role of exercise in osteopenic (19, 21, 22, 31) or sarcopenic (18, 20, 32) adults, we are the first to systematically examine the evidence on non-pharmacological interventions in osteosarcopenic individuals. This is important as it evaluates the efficacy, safety, and adherence in this target population. While longer-term adherence (>18 months) still requires further investigation, our findings indicate

Table 5
Summary of findings from included RCTs

Outcome	Method of measurement	No. of studies	Main Findings	Certainty of evidence
Muscle mass	Skeletal Muscle Index using DXA and BIA	1/2	RT for ≥ 6 months increased muscle mass in OS individuals	Moderate
Bone mineral density	DXA and QCT	2/2	RT (12-18 months) improved LS-BMD and TH-BMD	Low
Muscle strength	Handgrip strength, Leg extensor strength, Chair stand test	2/2	RT improved muscle strength in OS individuals	Moderate
Physical performance	Gait speed, TUG, 6MWT	2/2	RT did not have a significant effect on physical performance	Moderate
Bone turnover	CTX	1/2	12 weeks of RT did not reduce bone turnover markers	Moderate
Muscle Quality	Leg length × 0.4 x body mass × gravity × 10/time sit-stand	1/2	12 weeks of RT improved muscle quality in OS individuals	Moderate

DXA, Dual-energy X-ray absorptiometry; QCT, Quantitative Computed Tomography; LS, Lumbar spine; TH, Total hip; TUG, Timed up and go; 6MWT, 6-minute walk test; CTX, C-terminal telopeptide; OS, Osteosarcopenic.

that a supervised RT program is safe and effective for older osteosarcopenic adults, with no serious adverse effects reported in the included studies. Thus, relevant treatment pathways with supervised, moderate-high intensity RT should be encouraged in clinical settings for those with osteosarcopenia. For upstream prevention of osteosarcopenia, government guidelines should focus on large scale, RT programs aiming to increase participation of older adults. These recommendations may ultimately reduce the socioeconomic burdening of this geriatric syndrome.

The findings of this systematic review are in line with the current literature demonstrating the safety and efficacy of RT for conferring gains in BMD and muscle mass and strength in older adults (33-36). Although some previous studies have shown RT to improve physical performance in older adults (37), neither of the studies included in this systematic review demonstrated a significant change in gait speed, TUG or 6MWT. A Cochrane review showed that RT alone induced a small, clinically meaningful improvement in gait speed but did not observe a significant change in other physical performance parameters like TUG (38). Given gait speed, TUG and 6MWT were secondary outcomes, the included studies may have lacked the statistical power to test the effects of the interventions on these outcomes. Alternatively, Lichtenberg et al. (26) suggests that other factors including motor neuron degeneration, joint range of motion and non-muscular factors like cognitive status and depression may influence gait speed, while muscle mass itself plays a minor role in physical performance. In regards to bone turnover, Banitalebi et al. (30) observed no effect of 12 weeks of RT which is consistent with findings of two RCTs of similar duration (39, 40). It appears a longer RT program is required to induce changes in bone turnover as Hinton et al. (35) demonstrated a significant decrease in CTX after 6 months of RT.

The observed effect of RT on BMD was not consistent across the included RCTs. Compared to control, Kemmler et al. (28) determined that 12 months of HI-RT improved QCT-derived lumbar spine BMD, however did not significantly change DXA-derived hip BMD. Previous research has shown mixed findings in regards to total hip BMD in osteopenic men with some studies demonstrating a significant benefit of RT (35) and others showing no effect (41). Considering Kemmler et al. (29) were able to show a significant maintenance of total hip BMD versus control at month 18 of the study, it is reasonable that the duration or sample size were limiting factors in the 12 month of the intervention reporting of results. In the other study included in our systematic review, Banitalebi et al. (30) found no change in total BMD compared to control after 12 weeks of moderate-intensity EBRT. Considering the bone remodelling cycle takes 4-6 months and there is some delay before BMD changes can be detected radiologically (36, 37, 42), it is likely the 12-week EBRT program was not sufficient in duration to observe significant changes in BMD. In addition to the duration, the intensity of the EBRT program (consisting of elastic band RT) may also explain the lack of significant changes to BMD with a recent RCT demonstrating that lumbar spine and femoral neck BMD show greater increases with high-intensity RT (combined with impact training) compared to low-intensity RT (37).

Some additional drawbacks should be acknowledged in the included studies. Firstly, with respect to the Frost study (26-29), the inconsistent use of imaging machines (QCT vs DXA) to assess BMD introduces a potential source of bias and has consequently led to the downgrading of quality of evidence for this outcome (as shown in Table 4). In addition, since there was a higher intake of protein in the HI-RT compared to the non-exercise control (1.5-1.6 vs 1.2g/kg/day, respectively), it is difficult to specify how much of the observed benefit can be attributed to RT alone. A limitation of the Banitalebi et al. (30) study in the context of this review is that it was designed in consideration of the primary outcomes, muscle quality and serum biomarkers of muscle quality, not to detect changes in BMD. Lastly, neither study included data on clinically meaningfully outcomes on falls and fractures.

There are some strength and drawbacks of our systematic review. We are the first to systematically examine the evidence on non-pharmacological interventions in osteosarcopenic individuals. Unfortunately, only two RCTs fitted the inclusion

criteria, which impacted the precision of our results and therefore the certainty of evidence in all outcomes (Table 4). In addition to this, there was significant heterogeneity in our included RCTs regarding sex (men vs women) and RT duration (12 weeks vs 18 months), which precluded a meta-analysis being conducted. Finally, given there were no RCTs assessing the effect of protein, vitamin D, calcium, or creatine in osteosarcopenic individuals using proposed cutpoints, we were unable to evaluate the efficacy of these nutritional interventions alone or in combination with RT. As poor nutritional status is a modifiable risk factor for osteosarcopenia, this highlights the need for future high-quality research in this population.

Conclusion

In conclusion, progressive RT is safe and effective in improving several aspects of osteosarcopenia including lumbar spine and total hip BMD and muscle mass, strength, and quality, but not physical performance or bone turnover. There is currently no evidence for other non-pharmacological interventions such as protein, vitamin D, calcium, or creatine in osteosarcopenic individuals. Future research should utilize a RCT design, lasting at least 6 months, and examine the impact of these nutrients (with or without RT) in older osteosarcopenic adults and include clinically relevant outcomes on activities of daily living, falls and fractures.

Conflicts of interest: The authors have no conflicts of interest to declare.

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Ethical standards: The authors declare that the review comply with the current laws of the country in which it was performed.

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