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The effect of dietary interventions and nutritional supplementation on bone mineral density in otherwise healthy adults with osteopenia: A systematic review

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Abstract

There are many health and economic consequences for patients with osteopenia, the precursor to osteoporosis. A range of treatments may provide positive outcomes for otherwise healthy adults, including dietary and exercise approaches, either alone or in combination. The primary aim of this systematic review was to evaluate the effect of dietary approaches (including diet alone, diet with dietary supplements, both with or without physical activity intervention) on bone mineral density (BMD) to treat adults aged ≥18 years who were classified as having osteopenia. Six databases (Ovid MEDLINE including Ovid Medline in process, Cochrane Library, EMBASE, CINAHL Plus, Web of Science and Scopus) were searched systematically to identify randomised controlled trials of dietary approaches to treat osteopenic adults published from 1994 to November 2014. Study eligibility was determined, and included studies were assessed for risk of bias. Outcome data, particularly the primary outcomes of BMD T- and Z-scores or other measures of bone density, were combined narratively. The searches yielded 3511 papers, with three studies fulfilling the inclusion criteria. These studies included 254 participants, all free-living post-menopausal females with confirmed osteopenia. Vitamin D interventions were tested in all included studies, with none showing significant differences between intervention and placebo groups on BMD. This review has identified a lack of evidence to guide clinical practice in this area. Opportunities exist for future research to determine the effect of non-pharmacological approaches to osteopenia treatment in healthy populations, especially research that considers younger-aged and male populations, physical activity, habitual dietary intake and key bone health nutrients.

Keywords: adults, bone mineral density, dietary interventions, osteopenia, systematic review

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Introduction

The economic and health implications associated with osteoporosis for older adults are cited within the scientific and wider community. In Europe, osteoporotic fractures have been reported to account for more disability-adjusted life years (DALYs) lost than common cancers, with the exception of lung cancer (Johnell & Kanis 2006). Comprehensive programmes directed towards both prevention and treatment are required in order to reduce the direct medical costs for osteoporotic fractures. The combined cost of social and hospital care for people with osteoporotic fractures has been reported as more than £1.8 billion per year in the UK. Whilst fractures in those aged over 60 years involve more than two million bed-days in England alone, frailty-related falls account for another two million bed-days in patients over the age of 75 years (Hippisley-Cox *et al.* 2007). Similarly, in Australia the costs of osteoporosis are predicted to increase to $A33.6 billion over the next 10 years (Ebeling *et al.* 2013).

Osteoporosis is often considered a 'silent disease' as it is not typically diagnosed until a fracture occurs. The hip and/or lumbar spine are the diagnostic site(s) used, and the bone mineral density (BMD) T-score, measured by dual-energy X-ray absorptiometry (DXA), is the qualifying statistic. A T-score between 1 and 2.5 standard deviations below the reference population value identifies osteopenia, whilst a T-score of more than 2.5 standard deviations below is indicative of osteoporosis (WHO 2007). The clinical significance both of osteopenia and osteoporosis differ with age due to increases in fracture risk (Kanis *et al.* 2001). Fragility fractures frequently occur in men and women with T-scores above the osteoporotic range (*i.e.* within the osteopenic range) (Kanis *et al.* 2001; Siris *et al.* 2001). Clinical trials provide evidence of high rates of osteopenia in younger adults in both typical and clinically atypical population groups. In younger adults, the prevalence of abnormal BMD has been reported to range from 10.6–43.6% (Díaz Curiel *et al.* 2001; Liu *et al.* 2008; Begum *et al.* 2014; Lee *et al.* 2015). Modelling suggests that the development of osteoporosis can be delayed by 13 years if a 10% higher peak bone mass is achieved in the third decade of life (Hernandez *et al.* 2003). Yet, whilst there is a general consensus on treating individuals with osteoporosis and prevalent low-energy fractures, treatment approaches for osteopenia without fracture have been debated (Eriksen 2012). Treatment of osteopenia and prevention of further fractures may occur through a range of approaches, with pharmacological treatment, dietary factors including vitamin D (Bischoff-Ferrari *et al.* 2005) and other modifiable lifestyle factors, such as weight-bearing physical activity (WHO 2007; Rizzoli *et al.* 2010; Ebeling *et al.* 2013), making contributions.

Clinical and epidemiological evidence exists to indicate that adequate calcium status during periods of growth (childhood and adolescence) may impact on BMD and inadvertently play a role in later osteoporosis risk (Matkovic 1992). The pioneering work in this area was a Yugoslavian study reporting that habitual calcium intake affected not only peak bone mass but also later fracture risk (Matkovic *et al.* 1979). Fracture risk prediction can be enhanced through the addition of clinical risk factors that contribute to fracture risk independently of BMD (Kanis 2002). FRAX®, the WHO fracture risk calculator, calculates the 10-year probability of a major osteoporotic fracture (WHO 2007; Kanis *et al.* 2013). However, the National Institute for Health and Care Excellence guidelines (2012) for the assessment of fragility fracture risk recommend not to 'routinely assess fracture risk in people aged under 50 years unless they have major risk factors'. The National Osteoporosis Foundation (2014) has published evidence-based recommendations for physician practices with regard to the prevention, detection and treatment of osteoporosis in women. Yet, in a US survey, only a small minority of high-risk women (12–34%) reported having had their BMD tested (Gallagher *et al.* 2002). Provision of DXA results and advice to increase calcium intakes in women with osteoporosis or osteopenia resulted in an increase in calcium intake; advice to increase physical activity, however, was not acted upon (Estok *et al.* 2007).

Most guidelines for osteopenic patients primarily emphasise lifestyle changes including smoking cessation, nutritional improvements, calcium and vitamin D supplementation, and exercise regimens as primary interventions (National Osteoporosis Foundation 2014). There are limited reports of the effects of pharmacological agents such as bisphosphonates in the *FIT II* and *FOSIT* studies (Cummings *et al.* 1998). Although alendronate did not result in a significant reduction in the incidence of clinical fractures in women who presented with baseline T-scores in the osteopenic range (*FIT II* study), a significant reduction (44%) of morphometric vertebral fractures was observed after treatment (Cummings *et al.* 1998). Alendronate also significantly reduced the incidence of non-vertebral fractures (47% reduction) in postmenopausal women who participated in the *FOSIT* study (Pols *et al.* 1999). Concern has been raised about the long-term safety of bisphosphonates, but the

best data available so far (Black *et al.* 2006) suggest that 10 years with 90% suppression of bone turnover is safe. The dietary messages for patients identified with osteopenia are less clear.

In the UK, NICE (2012) recommendations for primary fracture prevention are fundamentally diet- and lifestyle-based. Despite this advice, and the previously reported value of physical activity and diet in influencing peak bone mass, the extent of the contribution of dietary approaches as treatment strategies for osteopenia has not been systematically defined (Ebeling *et al.* 2013). Given the extensive costs, reduction in quality of life and associated trauma concomitant with osteoporosis, recommendations for at risk populations prior to a fracture or development of overt osteoporosis should be established.

The primary aim of the review was to evaluate the effect of dietary approaches (including diet alone, and with dietary supplements, both with or without physical activity intervention) on BMD in healthy adults with osteopenia. A secondary objective was to develop recommendations to inform research and clinical practice in osteopenia, to enable practitioners and researchers to facilitate the delivery of evidence-based treatment for this patient group.

Methods

This review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Moher *et al.* 2009). The review protocol was registered with PROSPERO (www.crd.york.ac.uk/PROSPERO), registration number CRD4201501895.

Eligibility criteria

Original research using randomised, controlled trial design was only considered for the review in order to evaluate the highest quality evidence. Table 1 summarises the criteria used to determine whether studies were eligible for inclusion using the Participant-Intervention-Comparator-Outcomes-Study design (PICOS) format of Liberati *et al.* (2009). Inclusions were restricted to research published in the previous 20 years, from January 1994 until November 2014. Osteopenic healthy adults were the focus of the review, enabling a consensus to be developed for presentations of this group in the clinical setting. Multiple additional disease states were excluded from the review due to the effect of these illnesses and their treatments on bone status. In order to obtain the level of methodological detail required, conference abstracts and other short reports were ineligible for inclusion.

Interventions considered for inclusion in the review were as follows: dietary treatment alone (including food and beverages); dietary supplementation in addition to usual dietary intake; dietary treatment (including food and beverages) or supplementation with an additional physical activity component. Excluded interventions were dietary treatments combined with pharmacological interventions, and stand-alone physical activity or pharmacological interventions.

Table 1 Inclusion and exclusion criteria for the osteopenia systematic review

PICOS	Inclusion	Exclusion
Population	Adults >18 years with osteopenia T-score of −1.0 to −2.5 SD	Children Adults with normal BMD or osteoporosis Adults with any disease known to impact on bone health where osteopenia is likely to be a secondary outcome (*e.g.* cancer, eating disorders, IBD including Crohn's disease and ulcerative colitis, any declared long-term steroid use) Animals
Intervention	Dietary treatment ± exercise Dietary supplementation ± exercise	Physical activity alone Pharmacological interventions alone or in combination with any other intervention
Comparator	Osteopenic control group	No control group or control group not osteopenic
Outcome	Measures of BMD: Z-score; T-score; or raw data	Any other measures
Study design	RCT (including crossover RCT) in English language only	All other study designs and other languages

PICOS, Participant-Intervention-Comparator-Outcomes-Study design format (Liberati *et al.* 2009); BMD, bone mineral density; IBD, irritable bowel disease; RCT, randomised control trial.

Search strategy

A three-step search strategy was undertaken of published English-language studies in six electronic databases.

An initial limited search of Ovid MEDLINE and CINAHL was conducted followed by an analysis of text words contained in the title, abstract and index terms, supported by a medical librarian. A second expanded search using all identified keywords and index terms was completed across the following electronic databases: Ovid MEDLINE, Cochrane Library, EMBASE, CINAHL Plus, Web of Science (all databases), Scopus and Ovid Medline in process (see Table 2). Finally the reference lists of all identified studies were searched to identify any additional studies that may have been missed by the original search. Unpublished works (*e.g.* research theses) were not considered.

Study selection

The database search was imported into Endnote and duplicates manually removed. Reviewers worked in pairs following papers through to inclusion in the library of final papers. All studies identified via the database search were assessed against the PICOS, based on information contained in the title, abstract and description by two independent reviewers. Discussion between reviewers enabled consensus to be reached. Full articles were obtained of all studies that met the inclusion criteria. Where eligibility was unclear, the study was also retrieved to seek further clarification. Full papers were assessed against the PICOS independently by two reviewers, with consensus again reached by discussion.

Data were independently extracted in duplicate from each included study into standardised tables for reporting. The primary outcome investigated was change in bone density following the intervention. Data of other key results, study design and study population were extracted. Methodological quality of the final library of included studies was assessed independently by two authors using the Cochrane risk of bias tool (Higgins & Green 2011), addressing seven specific domains (sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and 'other issues'). Any difference of opinion between authors was resolved by discussion and consensus. A risk of bias graph and risk of bias summary table were completed. Data were not considered appropriate for further synthesis into a meta-analysis due to the absence of homogeneous interventions and outcomes.

Table 2 Search strategy

Keyword search terms	Details of search strategy
Osteopeni* AND (Food and beverage OR Diet or Supplement*)	Osteopeni*AND Diet – mapped to subject heading, Explode or as a keyword; OR Food and beverage – mapped to subject heading, Explode or as a keyword; OR Supplement* – mapped to dietary supplement or as a keyword

Results

After the removal of duplicates, the search identified 3511 citations, including many with a focus on animal studies or interventional studies in adults with osteoporosis. Forty-three papers were considered to have potential relevance based on their title and abstract. The full text of these papers was reviewed for eligibility. Studies at the final pass were excluded for reasons consistent with the inclusion/exclusion criteria including ineligible population ($n = 15$) and wrong/no comparator ($n = 10$) (Fig. 1).

Three studies met the inclusion criteria and incorporated six different interventions with a total of 254 participants (Son & Chun 2001; Albertazzi *et al.* 2004; DeLuca *et al.* 2011). All participants within these studies were free-living post-menopausal females with confirmed osteopenia. Table 3 summarises the intervention and population characteristics of the three included studies. Importantly, the studies of DeLuca *et al.* (2011) and Son and Chun (2001) tested supplementation with the active metabolite of vitamin D (hydroxylated metabolites), a different form of vitamin D to that found traditionally in vitamin D supplements.

There was no significant effect between intervention and placebo on BMD in any of the three studies (Table 4). Son and Chun (2001) compared BMD within treatment groups only and demonstrated a significant increase in lumbar spine BMD following alfacalcidol for 10 months. However, risk of bias assessment identified significant bias in this study (Fig. 2).

Bias was identified across all included studies, summarised in Figures 2 and 3. However, the study by Albertazzi *et al.* (2004) rated positively across most domains, indicating a lower risk of bias overall compared to the other two studies. Conversely, the study

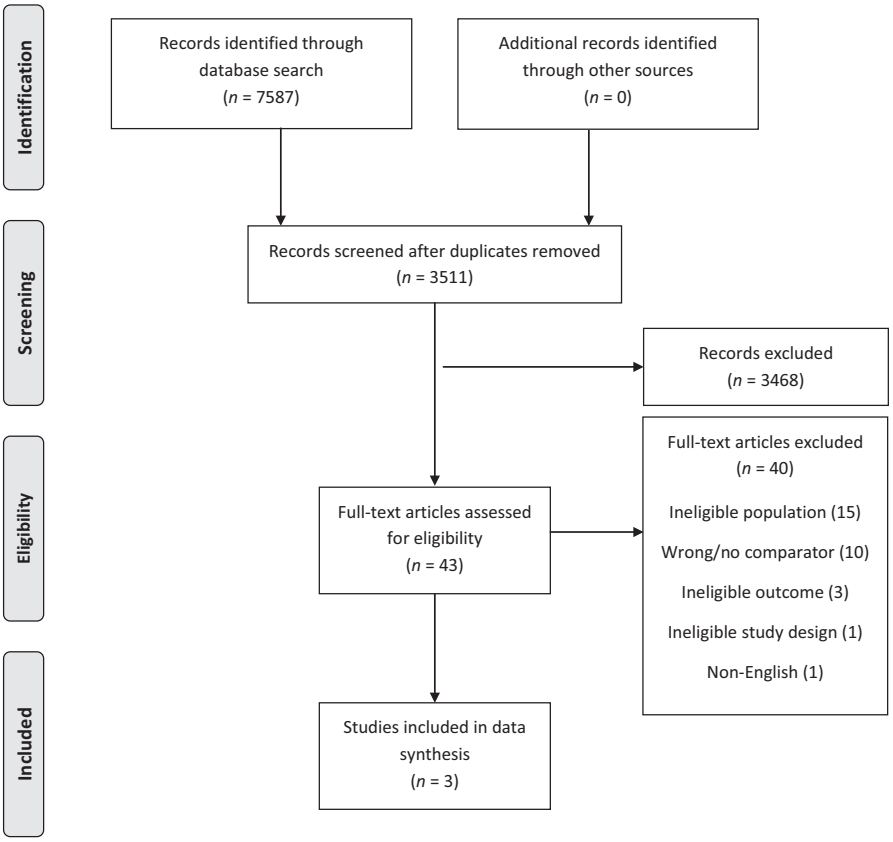

Figure 1 Study flow diagram (Liberati *et al.* 2009).

by Son and Chun (2001) did not rate positively in any aspects of study design considered suggesting a high risk of bias overall. The reporting of the study methodology was often unclear or not addressed, and this contributed to this rating. With the limited number of included papers, trends of study bias were difficult to identify.

Discussion

Internationally, the scale of bone decline is vast, with many countries reporting up to 50% of certain subpopulations as having osteopenia. For example, in Russia 20 million residents are estimated to have osteopenia (International Osteoporosis Foundation 2011); vertebral osteopenia prevalence in Latin American women aged ≥50 years is estimated at 45.5–49.7% (Morales-Torres & Gutierrez-Urena 2004); in Egypt, estimates indicate 53.9% of postmenopausal women have osteopenia (International Osteoporosis Foundation 2011); in India, a study of women aged 30–60 years from low-income groups identified BMD, at all skeletal sites, as being much lower than values reported from developed countries, with a high prevalence of osteopenia (52%) and osteoporosis (29%) thought to be due to inadequate nutrition (Shatrugna *et al.* 2005); and it is estimated that 6.3 million Australians have osteopenia (Sanders *et al.* 1999). The clinical progression to osteoporosis is a global problem.

Within the strict inclusion criteria defined for this review, we identified limited evidence to support the role of nutrition in the management of osteopenia. Only three randomised controlled trials studies met the inclusion criteria for review, with all studies focused on calcium or vitamin D supplementation for varied durations in post-menopausal women. This is both surprising and concerning, considering the review assessed all relevant investigations within the past 20 years on healthy individuals of both genders, and accepted a concomitant physical activity component. The findings of the studies included in the current review indicate that nutritional supplementation does not appear to increase BMD (or decrease BMD at the same rate) compared with placebo in otherwise healthy post-menopausal woman with osteopenia. Strong evidence, therefore, to determine the efficacy of dietary or nutritional supplement intervention, with

Table 3 Intervention and population characteristics of studies investigating the effect of dietary intervention on bone mineral density in osteopenic adults

Author (year)	Study design (LOE)	Location and setting	Inclusion	Exclusion	Maximum length of follow-up	Group	*n*	Dietary intervention	Population characteristics
Albertazzi *et al.* (2004)	Double-blind RCT (II)	Hull and East Yorkshire UK; free-living participants	PM, osteopenic women, aged ≥60 years, T-score at LS/FN −1 to −2.5 on DXA, Ca intake <1000 mg/day	Secondary causes of bone loss; prior treatment with sodium fluoride, bisphosphonates, corticosteroids, HRT in past 6 months; hormonal implants in the last year	6 months[a]	I	52	OHC: 500 mg of Ca with organic component with IGF-I, IGF-II, TGF-β, osteocalcin	67.7 (5.6) years; BMI 25.6 (4.2); Ca intake 563.1 (230.6) mg; HRT 21.1%; years of amenorrhoea 20.9 (7.3); LS BMD 1.056 (0.118) g/cm^2; FN BMD 0.828 (0.075) g/cm^2
						I	51	TCP: 500 mg Ca with organic matrix destroyed by ashing	68.6 (5.0) years; BMI 25.3 (3.5); Ca intake 650.8 (225.3) mg; HRT 21.6%; years of amenorrhoea 21.8 (7.7); LS BMD 1.089 (0.143) g/cm^2; FN BMD 0.828 (0.071) g/cm^2
						C	50	Placebo: capsule containing fructose	68.1 (5.1) years; BMI 24.6 (3.5); Ca intake 678.8 (194.4); HRT 20.0%; years of amenorrhoea 20.5 (7.4); LS BMD 1.051 (0.117) g/cm^2; FN BMD 0.825 (0.097) g/cm^2

Table 3 *Continued*

Author (year)	Study design (LOE)	Location and setting	Inclusion	Exclusion	Maximum length of follow-up	Group	*n*	Dietary intervention	Population characteristics
DeLuca *et al.* (2011)	Double-blind RCT (II)	US (9 clinical sites); free-living participants	PM, osteopenic women, amenorrhoeic ≥5 years, age 55–80 years, BMI 18–35, healthy	Acute/unstable chronic liver, kidney, endocrine, lung, gastro, cardio, psychiatric or neurologic diseases; medications that affect VD metabolism, Ca balance, bone turnover; any prior IV bisphosphonates, oral bisphosphonates >3 months in last 12 months; QTc >450 ms, creatinine clearance ≤50 ml/min, urinary Ca >300 mg/24 h, serum 25(OH)D level <10 ng/mL, dietary Ca intake >1000 mg/day, VD intake >2000 IU/day, illicit drug use or history of alcohol abuse	52 weeks	I	54	220 ng: 2-methylene-19-nor-(20S)-1a,25-dihydroxyvitamin D_3 (2MD) + vitamin D_3 600 IU/day	61.6 (5.5) years; height 161.1 (6.6) cm; weight 66.2 (11.0) kg; LS BMD 0.894 (0.078) g/cm^2; FN BMD 0.726 (0.105) g/cm^2; 25(OH)D 30 (10) ng/ml; Ca intake 709 (299) mg; VD intake 132 (139) IU; years PM 12.5 (6.1)
						I	53	440 ng: 2-methylene-19-nor-(20S)-1a,25-dihydroxyvitamin D_3 (2MD) + vitamin D_3 600 IU/day	61.9 (5.3) years; height 160.4 (7.1) cm; weight 69.8 (12.8) kg; LS BMD 0.899 (0.089) g/cm^2; FN BMD 0.738 (0.094) g/cm^2; 25(OH)D 32 (12) ng/ml; Ca intake 633 (294) mg; VD intake 104 (101) IU; years PM 13.3(6.4)
						C	49	Placebo: capsule + vitamin D_3 600 IU/day	61.1 (6.5) years; height 159.6 (6.7) cm; weight 69.0 (11.0) kg; LS BMD 0.88 (0.073) g/cm^2; FN BMD 0.718 (0.097) g/cm^2; 25(OH)D 29 (10) ng/ml; Ca intake 642 (240) mg; VD intake 114 (105) IU; years PM 13.2 (7.9)

Table 3 *Continued*

Author (year)	Study design (LOE)	Location and setting	Inclusion	Exclusion	Maximum length of follow-up	Group	*n*	Dietary intervention	Population characteristics
Son and Chun (2001)	RCT (II)	Korea; free-living participants	Age >65 years, T-score (−2.5<T<−1) for LS or FN BMD	History of or current osteoporosis or other disease affecting Ca/VD status	10 months	I	22	Ca carbonate 1000 mg	72.5 (5.0) years, height 147.9 (5.1) cm; weight 50.9 (6.5) kg; LS BMD 0.869 (0.159) g/cm^2; FN BMD 0.612 (0.109) g/cm^2; dietary intake: 1031.6 (359.0) kcal, 34.1 (13.3) g protein, 16.6 (6.7) g fat; 405.3 (122.3) mg Ca; 1.10 (0.70) μg VD
						I	20	Alfacalcidol 0.5 μg	71.8 (4.2) years, height 146.8 (5.2) cm; weight 50.8 (8.3) kg; LS BMD 0.760 (0.062) g/cm^2; FN BMD 0.589 (0.123) g/cm^2; dietary intake: 1115.0 (375.8) kcal, 37.7 (12.0) g protein, 15.9 (6.7) g fat; 435.9 (114.7) mg Ca; 1.30 (0.70) μg VD
						C	21	Placebo containing lactose	72.2 (4.2) years, height 148.2 (4.9) cm; weight 51.6 (9.9) kg; LS BMD 0.828 (0.150) g/cm^2; FN BMD 0.621 (0.099) g/cm^2; dietary intake: 1190.2 (368.8) kcal, 40.2 (13.2) g protein, 18.3 (8.2) g fat; 458.2 (106.2) mg Ca; 1.41 (0.80) μg VD

Data reported as mean (standard deviation; SD) or as percentage (%); DXA, dual-energy X-ray absorptiometry; LOE, Level of Evidence assigned from NHMRC (2009); RCT, randomised controlled trial; PM, post-menopausal; I, intervention; C, control; BMI, body mass index; HRT, hormone replacement therapy; BMD, bone mineral density; LS, lumbar spine; FN, femoral neck; 25(OH)D, 25-hydroxyvitamin D; VD, vitamin D; Ca, calcium; OHC, ossein-hydroxyapatite compound; TCP, tricalcium phosphate.

[a]DXA conducted at 12 months for those allocated to ossein-hydroxyapatite compound (OHC) if they opted to continue taking.

Table 4 Effects of dietary interventions for osteopenia on primary outcomes

Author (year)	Outcome(s) measured	Comparison of study groups (i.e. at baseline)	Compliance to intervention/study	Follow-up – proportion of participants/group followed up	Findings/results [Mean (SD)]
Albertazzi *et al.* (2004)	BMD by DXA at femoral neck and lumbar spine conducted at baseline, 6 months, 12 months (OHC group only) Biochemical markers of bone turnover and bone formation Adverse events	No difference except for Ca intake at baseline was significantly lower in the OHC group	Compliance measured by returned supplements but outcome not reported	16 participants (10.5%) dropped out prematurely => 89.5% participants followed up No difference in drop out across three groups	No significant differences between treatment groups in % mean change in the following BMD measures **Lumbar spine BMD:** OHC: +0.5% (4.3) at 6 months, +0.86% (4.6) at 12 months (NS compared to baseline); TCP: −0.7% (4.2) at 6 months; Placebo: −0.8% (4.2) at 6 months **Femoral neck BMD:** OHC: −0.4% at 6 months, +0.2% at 12 months (NS compared to baseline); TCP: −0.2% at 6 months; Placebo: −0.5% at 6 months **Other:** No change in markers of bone resorption; OHC and TCP associated with reduction in markers of bone formation compared to placebo **Adverse events:** No difference between OHC, TCP and placebo
DeLuca *et al.* (2011)	BMD by DXA at femoral neck and lumbar spine conducted at screening, baseline, week 26, and week 52 Biochemical markers of bone turnover and bone formation Adverse events	No analysis reported for comparison of study groups at baseline. Groups appear similar	Based on capsule counts. Overall compliance not reported; however, those with compliance >80% only were included in the secondary analysis	220 ng: 43 of 54 completed (80%) 440 ng: 21 of 53 completed (40%) – dose reduced to 330 ng because of high prevalence of biochemical abnormalities (urinary calcium elevations) Placebo: 43 of 49 completed (88%)	**BMD:** No significant differences between treatment groups in mean % change. Actual % not provided (presented graphically) **Other:** Markers of bone resorption and formation increased in both treatment groups **Adverse events:** Serum and urinary Ca elevations occurred more frequently within the 440 ng group compared to the 220 ng group (significance not assessed)

Table 4 *Continued*

Author (year)	Outcome(s) measured	Comparison of study groups (i.e. at baseline)	Compliance to intervention/study	Follow-up – proportion of participants/group followed up	Findings/results [Mean (SD)]
Son and Chun (2001)	BMD by DXA at femoral neck and lumbar spine conducted at baseline and 10 months Dietary intakes from 24 hour recall at baseline and 10 months Biochemical markers of bone turnover and bone formation at baseline and 10 months	No difference between groups for age, height and weight. No comparison provided for dietary intake or BMD	Reported as 91.3%	63 of 69 (91.3%) compliance. Analysis completed in 63	Significant increase in lumbar spine BMD *within* alfacalcidol treatment group only. Significant changes in BMD in Ward's triangle *within* all study groups (Ca, alfacalcidol and placebo) following treatment **Lumbar spine BMD:** Ca: 0.869 (0.159) to 0.885 (0.168) Alfacalcidol: 0.760 (0.062) to 0.782 (0.064)* Placebo: 0.828 (0.150) to 0.808 (0.156) **Femoral neck BMD:** Ca: 0.612 (0.109) to 0.619 (0.102) Alfacalcidol: 0.589 (0.123) to 0.595 (0.120) Placebo: 0.621 (0.099) to 0.595 (0.083) **Ward's triangle BMD:** Ca: 0.439 (0.135) to 0.470 (0.113)* Alfacalcidol: 0.431 (0.065) to 0.451 (0.068)* Placebo: 0.474 (0.089) to 0.449 (0.079)* **Other:** All groups had similar nutrient intakes after 10 months with the exception of the Ca group where there was a significant increase in Ca intake

Data reported as mean (standard deviation; SD) or as percentage (%); DXA, dual-energy X-ray absorptiometry; BMD, bone mineral density; Ca, calcium, OHC, ossein-hydroxyapatite; TCP, tricalcium phosphate; NS, not significant.

*Within-group comparison $P < 0.05$. No between-group comparisons available.

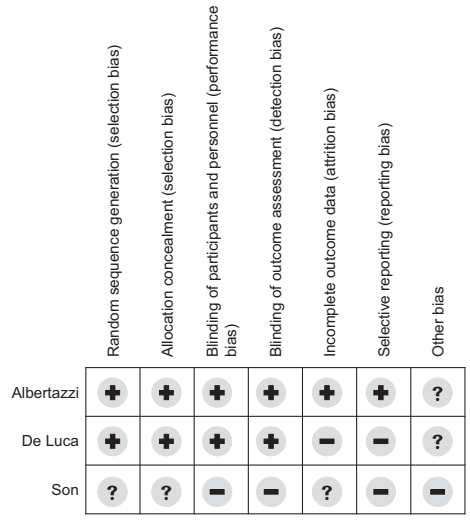

Figure 2 Risk of bias[1] assessed across individual studies. [1]Risk of bias measured using the Cochrane risk of bias tool (Higgins, Green and eds 2011). + indicates low risk of bias; – indicates high risk of bias; ? indicates unclear risk of bias in each respective aspect of study design.

and without physical activity, in the prevention and/or management of osteopenia is lacking.

Much of the research effort to this point has been to determine strategies to maximise peak bone mass in the early decades of life (Hind & Burrows 2007; Behringer *et al.* 2014; Harvey *et al.* 2014) and to manage patient outcomes for those with established osteoporosis (Kanis *et al.* 2013). Focusing on the prevention and treatment of osteopenia is warranted as it will inevitably influence the progression and management strategies for osteoporosis. On current published evidence, it is unclear if dietary intervention can slow the progression between osteopenia and osteoporosis.

The current systematic review highlights the absence of research investigating the role of food-based dietary intake (*i.e.* dairy and/or vitamin D-rich foods) on changes to BMD in the presence of osteopenia throughout the life span. This is surprising considering that younger populations are now being diagnosed with osteopenia (Singer 2006; Begum *et al.* 2014; Lee *et al.* 2015). Energy and protein malnutrition have previously been reported to accelerate degradation to the hydroxyapatite matrix, possibly directly by lowered intake of amino acids (*e.g.* proline and lysine) needed for collagen synthesis and indirectly through suppressed intake of other bone health nutrients (*i.e.* calcium, ascorbic acid and pyridoxine) induced by low and/or restricted food intake (Masse *et al.* 2010). At present, it is still unclear whether meeting or increasing the availability of essential bone health nutrients will affect BMD in osteopenic patients.

Vitamin D analogues have been used to stimulate bone formation and enhancing BMD in osteoporosis (MacLean *et al.* 2008); importantly, the vitamin D analogue used by DeLuca *et al.* (2011) increased markers of bone formation but did not increase BMD. These outcomes are possibly due to adjunct increases in bone resorption markers (*i.e.* s-CTX, osteocalcin, PINP and iPTH), suggesting a greater bone remodelling turnover. Similarly, Albertazzi *et al.* (2004) demonstrated that, in the absence of changes to BMD, their intervention did not result in changes to bone resorption markers but it did reduce markers of bone formation. The prescription of vitamin D analogues may not be within the scope of practice for dietitians and other health professionals across many countries.

The monitoring of daily physical activity or exercise uptake in participants in the included studies was not clearly reported, reflective of poor study control. Taking into account the role of exercise stress on bone remodelling (biomarkers and BMD), monitoring of this would have complemented the interpretation of the study outcome. Thus, the outcome from Son and

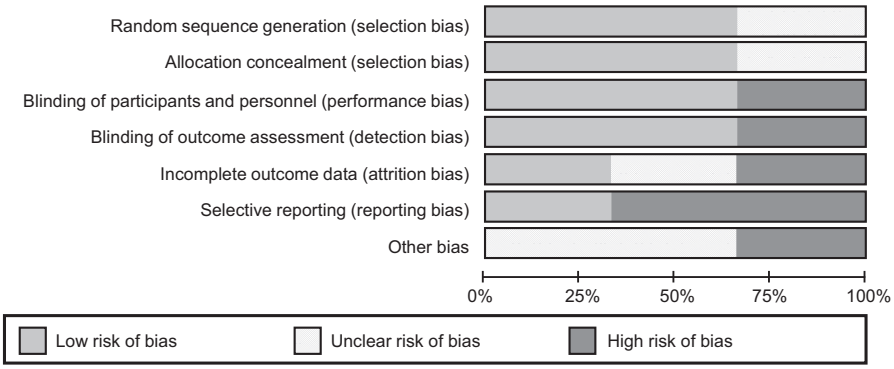

Figure 3 Risk of bias summary[1] of the three included studies. [1]Risk of bias measured using the Cochrane risk of bias tool (Higgins, Green and eds 2011). The bars represent the proportion of studies with low, high or unclear risk of bias in each respective aspect of study design.

Chun (2001) should be interpreted with caution. BMD was determined by DXA in each of the included studies; however it is not specified how many technicians conducted the scans and thus results may be influenced by variations in inter-rater reliability, which was not reported. Studies also included biomarkers of bone remodelling/resorption and formation, but these were not corrected for potential changes in plasma volume and coefficient variations were also not clear from the analysis.

Considering the influence of physical activity, especially weight-bearing exercise, in osteoblast and osteoclast activity, and subsequent bone remodelling and resorption activity (Prestwood & Raisz 2000; Hind & Burrows 2007; Keen 2007), it is surprising that no studies were identified that investigated nutritional interventions in conjunction with exercise interventions as part of optimising management of osteopenia. Another gap in the literature identified in the current systematic review was the absence of nutritional (dietary or supplementation) interventions in male populations, with the included studies and broader osteoporosis research predominantly targeting post-menopausal women. This is of concern, considering the incidence of osteopenia and osteoporosis are growing in number amongst male populations due to the increased and ageing world population (Gass & Dawson-Hughes 2006). Thus, it appears that a lack of thorough research into non-pharmacological approaches to osteopenia treatment in healthy populations exists, particularly those involving younger-aged and male populations, physical activity, habitual dietary intake, and key bone health nutrients (apart from vitamin D and calcium).

It is important to note that the definition of osteopenia for the review, with diagnostic T- or Z-scores, or publication of raw BMD data, may have contributed to the small number of included studies. Another limitation of this review was the homogeneity of the population groups studied – healthy post-menopausal women with no co-existing health complaints. Given the prevalence of comorbidities in this age group, this limits interpretation and extrapolation of results to the broader population, including males. Patients with common co-existing conditions, such as coeliac disease and other inflammatory disorders, and those with eating disorders who have compromised bone health were excluded from the review specifically to enable the evaluation of a more homogeneous cohort. Also, several studies were excluded due to the combining of data of patients with osteopenia and osteoporosis. Furthermore there may be incomplete retrieval of relevant studies with restrictions to those published only in English and hence a failure to potentially identify multicultural literature. The restriction of dates to the last 20 years of research was to contain the evidence to the most current being applied in clinical practice. It is possible that the date restriction meant that some research was missed that otherwise may have been suitable for inclusion. Finally, we had anticipated that a considerable number of original studies would be included in this review, based on previous work by some members of our review team. We envisaged that data extraction would occur within the two themes of diet and dietary supplements, enabling a discussion of the implications for each approach, consistent with practice in clinical settings, where patients may seek advice regarding diet and/or dietary supplements from healthcare professionals. However, due to the small number of identified studies, we were unable to compare and contrast dietary and nutritional supplement interventions as planned.

This review highlights the paucity of literature investigating dietary interventions in the management and treatment of osteopenia. There is no consensus or definitive guidance to support or guide clinicians' approaches to managing patients with osteopenia. Large gaps exist in regard to habitual dietary intake and supplementation of key nutrients that play a role in bone remodelling, and external influential factors (genotype, physical activity, disease status, and lifestyle and social factors). These factors should all be considered in future research. Additionally, a consistent definition of osteopenia, and the separate reporting of results when both osteopenic and osteoporotic patients are included within the same studies, should be considered in future work.

Conclusion

The lack of recommendations and evidence-based approaches to support clinicians in providing advice for osteopenic patients is highlighted by this review. There are significant gains to be made if patients with osteopenia can be prevented or delayed from progressing to osteoporosis and the subsequent burden of fractures, chronicity and associated health and economic burden that can follow. Future research is required to explore nutrition and lifestyle interventions approaches in the management and treatment of osteopenia.

Conflict of interest

All authors declare no conflict of interest to the present review. No grants were received for this review.

Authorship

All authors contributed to the conceptualisation of the review and the assessment of papers for inclusion. ZD conducted the database searches; ZD and LR extracted results and completed the quality assessments of included studies. All authors except MA prepared the manuscript. JP co-ordinated the review. All authors have read and approved the final manuscript submitted for publication.

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