Curr Osteoporos Rep (2015) 13:245–255
DOI 10.1007/s11914-015-0272-1

NUTRITION, EXERCISE, AND LIFESTYLE IN OSTEOPOROSIS (CM WEAVER AND R DALY, SECTION EDITORS)

Dietary Approaches for Bone Health: Lessons from the Framingham Osteoporosis Study

Shivani Sahni[1] · **Kelsey M. Mangano**[1] · **Robert R. McLean**[1] · **Marian T. Hannan**[1] · **Douglas P. Kiel**[1]

Published online: 5 June 2015

Abstract Osteoporosis is characterized by systemic impairment of bone mass, strength, and microarchitecture, resulting in increased risk for fragility fracture, disability, loss of independence, and even death. Adequate nutrition is important in achieving and maintaining optimal bone mass, as well as preventing this debilitating disease. It is widely accepted that adequate calcium and vitamin D intake are necessary for good bone health; however, nutritional benefits to bone go beyond these two nutrients. This review article will provide updated information on all nutrients and foods now understood to alter bone health. Specifically, this paper will focus on related research from the Framingham Osteoporosis Study, an ancillary study of the Framingham Heart Study, with data on more than 5000 adult men and women.

Keywords Nutrition · Diet · Bone mineral density · Fracture

This article is part of the Topical Collection on *Nutrition, Exercise, and Lifestyle in Osteoporosis*

✉ Shivani Sahni
ShivaniSahni@hsl.harvard.edu

Kelsey M. Mangano
KelseyMangano@hsl.harvard.edu

Robert R. McLean
RMcLean@hsl.harvard.edu

Marian T. Hannan
Hannan@hsl.harvard.edu

Douglas P. Kiel
Kiel@hsl.harvard.edu

[1] Institute for Aging Research, Hebrew SeniorLife, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, 1200 Centre St., Boston, MA 02131, USA

Introduction

Osteoporosis is a major public health problem for adults worldwide. Osteoporosis is responsible for two million broken bones and $19 billion in related costs every year [1]. Historically, calcium and vitamin D are the primary nutrients considered for osteoporosis prevention in older adults. Other recommended prevention approaches include engaging in regular exercise, avoiding smoking and limiting alcohol intake. In the last two decades, several advancements have been made, which warrant reconsideration of existing dietary strategies for osteoporosis prevention. To date, numerous studies have related additional nutrients with bone health, such as vitamins A, B, C, E, K; minerals (potassium, magnesium, silicon); and macronutrients (protein and fats). Studies have also gone beyond single nutrient associations and linked foods, food groups, and dietary patterns with bone health. It is important to synthesize this body of work to determine which dietary approaches can be maximized for optimal bone health and osteoporosis prevention. In this paper, we review research studies on the relation between bone health with nutrients, foods, and dietary patterns originating from the Framingham Osteoporosis Study.

The Framingham Osteoporosis Study is an ancillary study of the Framingham Heart Study, a population-based cohort that began in 1948 to examine risk factors for heart disease. This review will focus on studies from the Framingham Original Cohort, which includes older men and women (5209 men and women enrolled, mean age 77 years, range 68–96), and the Framingham Offspring Cohort, which includes adult children of the Framingham Original Cohort and their spouses (5124 men and women, mean age 55 years, range 26–86). In both cohorts, diet was measured using the Willett food frequency questionnaire [2, 3] at baseline, and bone health was assessed across several bone mineral density

(BMD) measurements and hip fractures were confirmed across follow-up.

Fruit and Vegetable Intake

Fruits and vegetables provide a multitude of micronutrients such as vitamin K, folate, magnesium, potassium as well as antioxidants such as vitamin C and carotenoids. Higher fruit and vegetable intakes have been associated with higher BMD [4] and less BMD loss over time [5]. A systematic review of eight studies concluded that in post-menopausal women, cross-sectional studies support the positive relation between fruit and vegetable intake with bone health. However, the evidence of a beneficial effect of fruits and vegetables in osteoporosis prevention in prospective cohorts and randomized controlled trials is less clear [6]. A recent study in middle-aged and older men and women linked fruit and vegetable intake less than the recommended five servings/day with higher risk of hip fracture [7•]. In the Framingham Original cohort, fruit and vegetable intake was positively associated with BMD in both men and women (in a cross-sectional analysis) and with less BMD loss at the hip in men alone [8]. Furthermore, dietary patterns rich in fruits and vegetables were linked with higher BMD in men [9]. This review summarizes reports on selected nutrients within fruits and vegetables and the evidence for their role in bone health.

Vitamin C

Several studies have implicated oxidative stress in the pathogenesis of osteoporosis [10–12]. Antioxidants such as vitamin C suppress osteoclast activity through their antioxidant action. Additionally, vitamin C acts as a cofactor in promoting osteoblast differentiation [13] and acts as a cofactor for collagen formation and synthesis of hydroxyproline and hydroxylysine required for the formation of stable triple helixes [14]. In line with this thought, several epidemiologic studies have examined the association of vitamin C in relation to BMD [15–19] and fractures [20, 21]. Results from these studies indicate a complex association involving interaction of vitamin C with nutritional factors [vitamin E and calcium intake [16] and non-nutritional factors [smoking [21], estrogen use/hormonal therapy after menopause].

In the Framingham Original cohort, among men, higher dietary vitamin C intake was associated with less femoral neck BMD loss [0.021 g/cm^2 less bone loss in the highest tertile of dietary vitamin C (median intake of 209 mg/day) vs. lowest tertile of dietary vitamin C (median intake of 86 mg/day)]. No significant associations were observed among women. In subgroup analyses, negative cross-sectional associations were observed between total and supplemental vitamin C intake and trochanter BMD among current male smokers [22]. In contrast, among male non-smokers, total vitamin C intake was positively associated with femoral neck BMD. In the same cohort, participants in the highest tertile of total vitamin C intake (diet+supplements; median=313 mg/day) had 44 % lower hip fracture risk over 15 years compared to those in the lowest tertile (median=94 mg/day) [23]. Participants in the highest category of supplemental vitamin C intake (median=260 mg/day) had 69 % lower hip fractures risk compared to non-supplement users. The level of vitamin C intake for protection against hip fracture in this study and for BMD in a previous study [16] was much higher than that of the USA recommended dietary allowance of 90 mg/day for men and 75 mg/day for women. Interestingly, in a recent double-blind, controlled clinical trial of 90 older adults over a 12-month period, administration of 1000 mg of ascorbic acid together with 400 IU of alpha-tocopherol was shown to be useful in decreasing hip BMD loss significantly, compared to no treatment (12 month within group difference in hip BMD was 0.0087 g/cm^2 (in treatment group) vs. −0.0056 g/cm^2 (placebo group), *P* treatment vs. Placebo=0.047) [24]. Further research is needed to ascertain optimal intakes of vitamin C for osteoporosis and fracture prevention with particular attention to its interaction with smoking and alpha-tocopherol intakes.

Carotenoids

Data from several in vitro [25–27] and in vivo [28–30] studies suggest that further investigation into the relationship between carotenoids and bone health is warranted due to their antioxidant properties. In particular, an inverse relation of carotenoid and lycopene with biochemical markers of bone turnover has recently been shown in post-menopausal women [28]. However, few longitudinal studies have examined the association between carotenoids other than β-carotene [31] with bone loss or fracture risk. In the Framingham Original cohort, associations between intake of total carotenoids and individual carotenoids were evaluated with bone loss at the hip, spine, and radial shaft over 4 years of follow-up. In women, lycopene intake was protective against lumbar spine BMD loss over 4 years. In men, intakes of total carotenoids, β-carotene, lycopene, and lutein+zeaxanthin were protective against trochanter bone loss [32]. Further, participants in the highest tertile of total carotenoid intake had 46 % lower hip fracture risk and participants with higher lycopene intake had 34 % lower risk of hip fracture and 34 % lower risk of non-vertebral fracture [33]. No significant associations were observed with other carotenoids. Data from other cohorts support the link between individual carotenoids and reduction of hip fracture risk [34]. Specific to lycopene, restriction studies of lycopene have shown significant increases in oxidative stress parameters and the bone resorption marker N-telopeptide of type I collagen in post-menopausal women, which were reversed with lycopene supplementation [35, 36]. Taken together, these

results suggest a protective role of several carotenoids for BMD and fracture risk in older adults with most consistent results for lycopene intake.

Folate and B12

In the USA, refined grain products, including enriched breads, cereals, and flour, along with fruits and vegetables, have become a primary source of folate since the 1998 FDA mandate on folic acid fortification. There is little evidence that folate has any direct involvement with bone biology; however, it may indirectly influence bone quality and fracture risk through its role in homocysteine metabolism. Data from the Framingham Original cohort were among the first to identify elevated plasma homocysteine concentration as a strong risk factor for hip fracture [37]. Although the biologic mechanism linking homocysteine to bone health remains unclear, McLean's initial findings published in 2004 stimulated a surge in research investigating the relations of folate and vitamin B12 with bone health because low status of these vitamins is a primary determinant of elevated homocysteine in older adults. Unlike folate, vitamin B12 is not present in plant foods but is found primarily in animal products and fortified breakfast cereals. Because modification of dietary intakes of folate and vitamin B12 can effectively lower blood homocysteine concentrations, these nutrients were hypothesized as potential dietary interventions for improving bone health.

Our work in the Framingham Study suggests that vitamin B12, though perhaps not folate, may be an important determinant of bone health. In the Framingham Offspring cohort, participants with plasma vitamin B12 concentrations <148 pM (250 pg/ml; a commonly used cut-off for vitamin B12 deficiency) had significantly lower BMD than those with B12 above the cut-off [38]. In the Framingham Original cohort, neither plasma folate nor plasma vitamin B12 concentrations were associated with BMD loss over time [39]. Further, plasma folate was not associated with risk of hip fracture, though participants with plasma vitamin B12 concentrations in the deficient range (<148 pM) had increased risk for hip fracture compared to those with "normal" plasma vitamin B12 (≥258 pM). This association was attenuated after adjustment for baseline BMD, suggesting that the effect of vitamin B12 on fracture risk may be through its influence on BMD.

A meta-analysis of 27 observational studies investigating the relation of folate and vitamin B12 with bone health suggested a 4 % reduction in fracture risk per 50 pM increase in vitamin B12 concentration (RR=0.96, 95 % CI=0.92, 1.00) [40]. For folate and fracture risk, there were not enough studies to allow a robust conclusion. Thus, the evidence from Framingham and other studies suggests that folate may not be important for bone health, while low vitamin B12 status may be a modest risk factor for fracture. Supplementation with vitamin B12 and folic acid has shown mixed results [41–44]. Thus, little evidence supports folate or vitamin B12 supplementation as a means to prevent fracture.

Vitamin K

In Western diets, the major form of dietary vitamin K is phylloquinone (vitamin K1). Vitamin K is a necessary factor for the carboxylation of osteocalcin, a bone-specific protein produced by osteoblasts that is among the most abundant bone matrix proteins and also plays a role in bone mineralization [45]. Insufficient vitamin K may lead to undercarboxylation of osteocalcin and consequently contribute to age-related bone loss and fractures.

In the Framingham Original cohort, those with dietary phylloquinone intake in the highest quartile (median 254 μg/day) had 65 % lower hip fracture risk than those in the lowest quartile (median 56 μg/day), yet intake was not associated with either BMD at baseline or BMD loss at any of the sites examined (hip, spine, wrist) [46]. In the younger Offspring cohort, phylloquinone intake was similarly not associated with BMD in men, but women in the lowest intake quartile (mean 70.2 μg/day) had significantly lower mean hip (but not spine BMD) than women in the highest quartile (mean 309 μg/day) [47]. In contrast to dietary intakes, lower plasma phylloquinone and higher percent serum undercarboxylated osteocalcin (%ucOC) were significantly associated with lower BMD at the hip, but not the spine. Among women, lower plasma phylloquinone was associated with lower spine BMD only in post-menopausal women using estrogen [48]. In the same cohort, plasma phylloquinone, but not %ucOC was positively associated with heel ultrasound measures in men only, while there was no association with dietary phylloquinone intake [49]. Our Framingham results reflect the totality of the evidence from observational studies, which has been previously reviewed [50, 51] and provides moderate to weak evidence supporting low vitamin K status as a risk factor for poor bone health.

Several randomized trials have assessed the effect of vitamin K supplementation (particularly menaquinone, vitamin K2) on BMD and fractures, the results of which have been summarized in recent systematic reviews and meta-analyses [52–55]. The evidence suggests that vitamin K supplementation reduces the rate of bone loss, though the effect is very modest. Menaquinone supplementation may reduce fracture risk, though there is not enough evidence to draw definitive conclusions regarding the effect of phylloquinones.

Potassium, Magnesium, and Alkaline Diets

Research suggests that an alkaline diet may prevent bone loss and fracture. Potassium and magnesium are two dietary constituents found in fruits and vegetables that contribute to a higher alkaline state within the body. In the Framingham

Original cohort, cross-sectional analysis showing higher potassium and magnesium intakes were associated with greater BMD at the hip and radius [8]. Greater intakes of potassium and magnesium were associated with less BMD loss at the hip in men. Dietary intakes of potassium and magnesium were similar across the sexes, suggesting that sex differences could be due to differing hormonal changes with age.

Dietary acid load can be estimated by the net endogenous acid production (NEAP), which includes dietary intakes of protein, potassium, phosphorus, magnesium, and calcium to calculate an estimate of dietary contribution to the overall acid–base balance. It is theorized that chronic disruption of the body's acid–base balance would be detrimental to bone health [56]. One RCT showed pharmacologic doses of potassium citrate (alkaline substance) to be beneficial to bone health [57••]; however, two other RCTs showed no effect on BMD [58, 59]. Among men in the Framingham Original Cohort, dietary acid load estimated by NEAP was inversely related with femoral neck BMD, but no association was observed at the spine; no significant associations were observed in women [60]. No associations between NEAP and BMD were observed among men or women from the younger, Framingham Offspring cohort. These results suggest that with the possible exception of older men, dietary acid load as estimated by dietary intake is not associated with BMD.

Overall, results from the Framingham studies show that potassium and magnesium are positively related to bone health, and these associations are likely independent of their contribution to an alkaline state. Potassium may alter bone metabolism by promoting calcium retention at the kidney [61]. Further, magnesium is essential for appropriate calcium metabolism [62]. Future research should examine interactions between potassium, magnesium, and calcium intakes and also examine long-term effects of an alkaline diet on fracture outcomes.

Seafood

The Framingham Osteoporosis Study has shown both men and women with fish intakes ≥3 servings per week gain hip BMD over 4 years compared to individuals with low to moderate weekly fish intakes who lose BMD [63]. Cross-sectional studies in large cohorts of post-menopausal Chinese women also support that habitual intake of fish is associated with greater BMD [64, 65]. The positive relation of fish intake with BMD is likely due to many nutritional factors. In addition to protein (reviewed below), certain seafood are high in polyunsaturated fatty acids (PUFA) and, specifically, the n-3 fatty acid (FA) family, which have been positively linked with bone health due to their anti-inflammatory properties [66••].

Omega-3 Fatty Acids

Although total PUFA intakes have been positively linked with bone health [67, 68], the complex interactions between individual FA and bone are gaining attention based on studies published from the Framingham cohorts. In summary, no significant associations were observed with intakes of individual PUFA and BMD in either sex [63]; however, women whose eicosapentaenoic acid (EPA)+docosahexaenoic acid (DHA) intakes (both n-3 FA)≥median (0.14 g daily) had higher femoral neck BMD with higher intake of the n-6 FA arachidonic acid (AA). This interaction was also observed in men where individuals in the highest quartile of AA intakes lost more hip BMD than those with lowest intakes, but only among individuals with low EPA+DHA consumption. Therefore, the protective effects of a diet high in AA may be dependent upon adequate EPA+DHA intakes. Also, plasma phosphatidylcholine (PC) concentrations of individual PUFA (n-3 FA DHA and n-6 FA's AA and linoleic acid) were related with femoral neck BMD [69]. The associations between individual PUFA and BMD differed by sex. In women, no significant associations were observed; however, in men, a trend toward higher BMD was seen with higher plasma PC AA.

The association between PUFA and risk of hip fracture remains uncertain. In the Framingham Original cohort, dietary alpha linolenic acid (ALA; n-3 FA) was protective against hip fracture over 11 years of follow-up (54 % lower risk in the highest vs. lowest quartile of intake) [70]. In men, those in the highest quartiles of AA intakes (n-6 FA) had an 80 % lower risk of hip fracture than those in the lowest quartile of intake. Men and women with the highest plasma AA concentrations demonstrated 51 % lower hip fracture risk than those with the lowest AA concentrations, supportive of the dietary association observed only in men. These findings indicate that the protective association of PUFA with bone health is complex. Further insight is needed into the sex differences observed, and well designed clinical trials are needed to elucidate whether bone health can be improved by greater fish intake and test whether certain individual PUFA are driving these effects.

Dairy Foods

Dairy foods are a complex source of essential nutrients and contribute to calcium, magnesium, vitamin D, vitamin B12, zinc, riboflavin, and protein intake in the typical US diet [71]. Given that dairy foods are an essential resource of bone-building nutrients, numerous studies have examined whether dairy food intake (mainly milk) confers protection against osteoporosis. Research on other dairy products such as yogurt, cheese, and cream is limited. While several cross-sectional studies have reported a positive link between childhood milk consumption and bone density later in life [72–76], evidence

for a beneficial role of milk intake on osteoporotic fracture is less convincing [72, 77, 78, 79••].

In the Framingham Offspring Study, the association of milk, yogurt, cheese, cream, total dairy without cream, and fluid dairy (milk+yogurt) was examined with hip and spine BMD [80]. Higher intake of total dairy without cream was associated with higher hip and spine BMD. Intake of fluid dairy and milk was related to hip, but not spine BMD, while yogurt intake was associated with trochanter BMD alone. Cheese and cream intakes were not associated with BMD. In final models, adjusting for other dairy products, yogurt intake remained positively associated with trochanter BMD, while cream tended to be negatively associated with femoral neck BMD. In the same cohort, with 43 incident hip fractures over 12-year follow-up, no significant associations were observed between dairy foods and hip fracture risk.

In subsequent analyses of dairy products and hip fracture over 11 years of follow-up in the Framingham Original Cohort, participants with medium (>1 and <7 servings/week) or higher (≥7 servings/week) milk intake had 39 and 42 % lower hip fracture risk, respectively, than those with low milk (≤1 serving/week) intake [81••]. A threshold effect for milk was reported, with 40 % lower hip fracture risk among those with medium/high milk intake compared to those with low intake. These associations were attenuated after adjustment for femoral neck BMD, suggesting that greater intakes of milk and milk+yogurt may lower risk for hip fracture in older adults through mechanisms that are partially, but not entirely, attributable to effects on BMD. Not all dairy products may be equally beneficial for the skeleton. Therefore, examination of dairy foods other than milk and careful consideration of study designs and confounding factors is necessary to reconcile the divergent results, particularly from cohort studies of hip fracture. Current knowledge on nutrients within dairy foods, such as protein, potassium, and magnesium, is reviewed below for likely links with bone.

Protein

Protein intake has been implicated in previous studies as being both detrimental and beneficial to bone health [82]. While dietary protein has long been known to increase renal calcium excretion and create negative calcium balance [83–85], many population-based studies [86–92], but not all [93–97] have shown that protein intake is beneficial for bone. Our work from the Framingham Original cohort showed an association between low protein intake and greater bone loss [86] and hip fractures [98] in older adults. Similar positive associations were also reported in the younger Framingham Offspring women but not in men [99]. Recent studies suggest that the influence of protein on bone health may differ according to calcium intake. In the Framingham Offspring Cohort, significant interactions were observed between percent energy from protein intake and total calcium intake in women at all bone sites [99], where protein was positively associated with BMD only among women with low calcium intakes (<800 mg/day). In longitudinal analyses, men with higher protein intakes had more trochanter bone loss while no associations were seen in women, regardless of calcium intake. Similar interactions were also observed between animal protein intake and risk of hip fracture, where men and women with calcium intakes <800 mg/day had 2.8 times the risk of hip fracture in the highest tertile of animal protein intake vs. the lowest tertile [100]. In the ≥800 mg calcium per day group, the highest tertile of animal protein had an 85 % reduced hip fracture vs. the lowest tertile of intake. Total protein intake was not associated with hip fracture risk. These results suggest that greater protein intake benefits BMD and protects against fracture risk among adults with adequate calcium intake. Thus, calcium intake modifies the association of dietary protein with bone measures, which may explain the lack of concordance seen in previous studies.

Alcohol Containing Beverages

Beer and Silicon

After oxygen, silicon is the most abundant element in the earth's crust. In the early 1970s, Carlisle and colleagues reported that dietary silicon may contribute to bone mineralization [101]. In fact, studies in chickens demonstrated that bone formation was impaired in diets deficient in silicon [102]. Silicon, as orthosilicic acid [Si(OH)4], is available from fluids (such as drinking water and beer), and it was later determined that silicon was also available from foods, in which it exists as polymeric or phytolithic silica [103]. The role of dietary silicon on bone health was further investigated in a cross-sectional study of men and pre- and post-menopausal women aged 30–87 years from the Framingham Offspring cohort [104]. We found silicon intake to be associated with BMD in men and younger women; however, additional analyses suggested that the association of beer intake and BMD was in part accounted for by the silicon content of beer, which is relatively high [105]. Subsequently, a randomized trial of choline-stabilized orthosilicic acid (silicon) supplementation, as an adjunct to calcium/vitamin D3, showed that the orthosilicic acid stimulated markers of bone formation in osteopenic females [106].

Wine and Resveratrol

Findings from the Framingham Osteoporosis Study previously identified red wine as particularly beneficial to bone in women [107]. This finding led to speculation that resveratrol may be a potential contributor to the association. Resveratrol

is a naturally occurring polyphenolic compound that is relatively abundant in red wine, grapes, and even nuts. It has enjoyed a great deal of notoriety based on observations that it increased longevity in animals [108]. Salutary skeletal effects of resveratrol have been suggested based on observations that it enhances osteoblast differentiation [109], inhibits osteoclast formation [110], and prevents bone loss in ovariectomized animals [111]. Resveratrol has been tested in a small clinical trial of 74 middle-aged men, mean age 49 years with metabolic syndrome who were randomized to 500 mg/day, 150 mg per day or placebo transresveratrol for 16 weeks. There were significant increases in volumetric spine BMD measured by QCT in the high dose group compared to placebo, but no differences for any other skeletal measures. At all time-points during the 16 weeks of treatment, the higher dose group had significantly greater increase in bone-specific alkaline phosphatase from baseline compared with the placebo group [112••].

A review of studies investigating alcohol intake and bone health suggested a "J"-shaped curve, where moderate ingestion of alcohol may offer maximum protection; however, intakes beyond this level show negative effects on the skeleton [113]. The above observations emerging from studies of alcohol containing beverages suggest that specific components found in these beverages in addition to the alcohol may also have effects on skeletal health.

Dietary Patterns

Traditionally, nutrition research has focused on single nutrients in relation to health. Yet, this approach is limited in that: (1) it does not account for dietary quality or nutrient synergy [114], (2) it cannot isolate individual effects due to high correlation of nutrients within foods, and (3) the effect of a single nutrient may be too small to detect [115]. Most importantly, isolating nutrients makes it difficult to translate results into dietary recommendations. To overcome these limitations, some investigators have proposed a "*dietary patterns*" approach. Results from the Framingham Study Cohorts have shown dietary patterns to be predictive of BMD among adults. In the Framingham Original Cohort, six dietary patterns were identified with the greatest proportions of energy intake from the following groups: (1) meat, dairy, and bread; (2) meat and sweet baked products; (3) sweet baked products; (4) alcohol; (5) candy; (6) fruit, vegetables, and cereal [9]. For men, the fruit, vegetables, and cereal group had the greatest BMD at all bone sites examined. The advantage of the fruit, vegetables, and cereal group was not as clear in the women, but their BMD tended to be higher than in other groups. In both men and women, the candy group had the lowest BMD at most sites.

As dietary protein is important for bone health, we have recently examined patterns of dietary protein intake with bone health. Protein-specific dietary patterns were created by cluster analysis in the Offspring cohort. This type of cluster analysis is similar to methods of whole diet pattern analysis but differs by clustering individuals based on their protein intakes (% contribution of each food to total protein intake). Overall, this study identified five protein food clusters, with the greatest proportion of protein intake from: (1) chicken, (2) fish, (3) processed foods (e.g., processed meats, pizza, and french fries), (4) red meat, and (5) low-fat milk [116]. Three of these food clusters showed associations with BMD. In both men and women, the red meat protein food cluster presented with significantly lower femoral neck BMD compared to the low-fat milk cluster. Further, the processed foods protein cluster presented with significantly lower femoral neck BMD compared to the low-fat milk cluster. A similar, yet non-significant trend was observed for other BMD sites.

Data from other cohorts support the findings that diets rich in fat and processed foods are detrimental to bone health in Iranian [117] and Scottish populations [118], whereas diets rich in fruits, vegetables, and fish are positively associated with BMD [119]. Although these studies show similar results in how BMD varies across dietary patterns, statistical methodologies used to determine these dietary patterns were different across the studies. Future research should focus on the reproducibility of these dietary patterns while assessing dietary patterns with fracture outcomes and longitudinal changes in bone across time. Research in dietary patterns and bone health requires a more in-depth look at sex differences and how changes in dietary pattern intakes across the lifespan may alter bone health over time.

Nutrition Bone Genetics

With advances in genomic technology and personalized medicine, the fields of nutrigenomics and nutrigenetics have recently emerged. Nutrigenomics is the study of how common dietary ingredients influence the genome, whereas nutrigenetics is the study of how an individual's genetic makeup influences one's response to dietary intakes and how this relates to various diseases. In the Framingham Osteoporosis Study, several nutrigenetic studies have been conducted to examine specific nutrient effects on the skeleton according to genetic makeup. One of the earliest studies investigated the interaction of polymorphisms in the vitamin D receptor gene on the association between calcium intake and BMD. In that early study, it was shown that calcium intakes above 800 mg per day were associated with higher BMD only in individuals who had the bb genotype for the *Bsm*I restriction fragment length polymorphism [120].

Based on observations that B-vitamins may have effects on skeletal health, and that genetic studies in Framingham had identified suggestive linkage to bone measures on chromosome 1pter-1p36.3 [121], a region containing a potential candidate genes for bone status, (*MTHFR* gene), the Framingham Study investigated the association between the C677T polymorphism in the methylenetetrahydrofolate reductase (*MTHFR*) gene and bone phenotypes. BMD measures did not differ between C677T groups. Although all participants with plasma folate concentrations ≥4 ng/ml had ~2 % higher BMD than those with folate <4 ng/ml, the association disappeared after controlling for tHcy. Suggestive interactions between folate status and the C677T group (CC+CT vs. TT) were found for hip BMD ($p \leq 0.05$) and BUA ($p = 0.11$). Compared with CC+CT participants, TT individuals had lower mean BUA ($p = 0.06$) and Ward's area BMD ($p = 0.08$) within the folate <4 ng/ml group and significantly higher hip BMD ($p \leq 0.05$) within the folate ≥4 ng/ml group. Thus, this study demonstrated that the influence of a genetic polymorphism on BMD was dependent on folate status.

Subsequently, the Framingham Osteoporosis study showed that dietary fat intake had differential effects on BMD according to variants in the peroxisome proliferator-activated receptor gamma (*PPARG*) gene, as fat is known to be an endogenous ligand of PPARG. These findings using epidemiologic methods in the Framingham Study were corroborated in an inbred mouse strain fed a high-fat diet [122].

As the goal of personalized medicine becomes more of a reality, findings such as these from the Framingham Osteoporosis Study suggest the possibility that nutrition will also become personalized depending on one's genetic makeup.

Conclusion

Dietary approaches can be an important strategy for the prevention of osteoporosis. Emerging evidence indicates that diet at the level of vitamins, minerals, food groups, and dietary patterns play an important role in skeletal health. This review presented our current understanding of the vitamins, minerals, and macronutrients present within food groups and dietary pattern as they relate to bone health in adults and older adults, with a focus on the findings from the Framingham Osteoporosis Study cross-sectional and prospective studies. Several studies provide evidence for inclusion of fruits and vegetables, seafood, specific dairy products, and alcohol containing beverages, in moderation, for beneficial effects on bone health.

Further research comparing nutrients to dietary sources to supplement use would advance our understanding of the underlying mechanisms and aid in creating recommendations for osteoporosis prevention. Prospective studies, in particular for fracture outcome and controlled trials, are needed to determine whether treatment with specific dietary supplements can improve BMD or reduce fracture risk. Observational studies have both supported and shown disagreement with controlled trials. Longer-term prospective intervention studies are needed to further examine the dietary effects on bone loss and fracture.

Acknowledgments DP Kiel received grant (R01 AR 41398) from National Institute for Arthritis Musculoskeletal and Skin Diseases, during the conduct of the study.

Compliance with Ethics Guidelines

Conflict of Interest S Sahni has received research grants from General Mills Bell Institute of Health and Nutrition. KM Mangano declares no conflicts of interest. RR McLean has received research grants from General Mills Bell Institute of Health and Nutrition. MT Hannan has received research grants from General Mills Bell Institute of Health and Nutrition. DP Kiel declares no conflicts of interest.

Human and Animal Rights and Informed Consent All studies by S Sahni, KM Mangano, RR McLean, MT Hannan, and DP Kiel involving animal and/or human subjects were performed after approval by the appropriate institutional review boards. When required, written informed consent was obtained from all participants.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. What is Osteoporosis? National Osteoporosis Foundation http://nof.org/articles/7.
2. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol. 1992;135(10):1114–26. **discussion 1127–1136**.
3. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol. 1985;122(1):51–65.
4. Prynne CJ, Mishra GD, O'Connell MA, Muniz G, Laskey MA, Yan L, et al. Fruit and vegetable intakes and bone mineral status: a cross sectional study in 5 age and sex cohorts. Am J Clin Nutr. 2006;83(6):1420–8.
5. Macdonald HM, New SA, Golden MH, Campbell MK, Reid DM. Nutritional associations with bone loss during the menopausal transition: evidence of a beneficial effect of calcium, alcohol, and fruit and vegetable nutrients and of a detrimental effect of fatty acids. Am J Clin Nutr. 2004;79(1):155–65.
6. Hamidi M, Boucher BA, Cheung AM, Beyene J, Shah PS. Fruit and vegetable intake and bone health in women aged 45 years and over: a systematic review. Osteoporos Int. 2011;22(6):1681–93.
7.• Byberg L, Bellavia A, Orsini N, Wolk A, Michaelsson K. Fruit and vegetable intake and risk of hip fracture: A cohort study of Swedish men and women. J Bone Miner Res 2014. **This paper**

is of importance as many men and women were examined for their risk of fracture and a protective dose–response pattern was seen between fruit & vegetable intake with hip fracture.

8. Tucker KL, Hannan MT, Chen H, Cupples LA, Wilson PW, Kiel DP. Potassium, magnesium, and fruit and vegetable intakes are associated with greater bone mineral density in elderly men and women. Am J Clin Nutr. 1999;69(4):727–36.
9. Tucker KL, Chen H, Hannan MT, Cupples LA, Wilson PW, Felson D, et al. Bone mineral density and dietary patterns in older adults: the Framingham Osteoporosis Study. Am J Clin Nutr. 2002;76(1):245–52.
10. Garrett IR, Boyce BF, Oreffo RO, Bonewald L, Poser J, Mundy GR. Oxygen-derived free radicals stimulate osteoclastic bone resorption in rodent bone in vitro and in vivo. J Clin Invest. 1990;85(3):632–9.
11. Basu S, Michaelsson K, Olofsson H, Johansson S, Melhus H. Association between oxidative stress and bone mineral density. Biochem Biophys Res Commun. 2001;288(1):275–9.
12. Key Jr LL, Ries WL, Taylor RG, Hays BD, Pitzer BL. Oxygen derived free radicals in osteoclasts: the specificity and location of the nitroblue tetrazolium reaction. Bone. 1990;11(2):115–9.
13. Gabbay KH, Bohren KM, Morello R, Bertin T, Liu J, Vogel P. Ascorbate synthesis pathway: dual role of ascorbate in bone homeostasis. J Biol Chem. 2010;285(25):19510–20.
14. Peterkofsky B. Ascorbate requirement for hydroxylation and secretion of procollagen: relationship to inhibition of collagen synthesis in scurvy. Am J Clin Nutr. 1991;54(6 Suppl):1135S–40.
15. Simon JA, Hudes ES. Relation of ascorbic acid to bone mineral density and self-reported fractures among US adults. Am J Epidemiol. 2001;154(5):427–33.
16. Hall SL, Greendale GA. The relation of dietary vitamin C intake to bone mineral density: results from the PEPI study. Calcif Tissue Int. 1998;63(3):183–9.
17. Morton DJ, Barrett-Connor EL, Schneider DL. Vitamin C supplement use and bone mineral density in postmenopausal women. J Bone Miner Res. 2001;16(1):135–40.
18. Leveille SG, LaCroix AZ, Koepsell TD, Beresford SA, Van Belle G, Buchner DM. Dietary vitamin C and bone mineral density in postmenopausal women in Washington State. USA J Epidemiol Community Health. 1997;51(5):479–85.
19. Maggio D, Barabani M, Pierandrei M, Polidori MC, Catani M, Mecocci P, et al. Marked decrease in plasma antioxidants in aged osteoporotic women: results of a cross-sectional study. J Clin Endocrinol Metab. 2003;88(4):1523–7.
20. Melhus H, Michaelsson K, Holmberg L, Wolk A, Ljunghall S. Smoking, antioxidant vitamins, and the risk of hip fracture. J Bone Miner Res. 1999;14(1):129–35.
21. Zhang J, Munger RG, West NA, Cutler DR, Wengreen HJ, Corcoran CD. Antioxidant intake and risk of osteoporotic hip fracture in Utah: an effect modified by smoking status. Am J Epidemiol. 2006;163(1):9–17.
22. Sahni S, Hannan MT, Gagnon D, Blumberg J, Cupples LA, Kiel DP, et al. High vitamin C intake is associated with lower 4-year bone loss in elderly men. J Nutr. 2008;138(10):1931–8.
23. Sahni S, Hannan MT, Gagnon D, Blumberg J, Cupples LA, Kiel DP, et al. Protective effect of total and supplemental vitamin C intake on the risk of hip fracture—a 17-year follow-up from the Framingham Osteoporosis Study. Osteoporos Int. 2009;20(11):1853–61.
24. Ruiz-Ramos M, Vargas LA, Van der Goes TI F, Cervantes-Sandoval A, Mendoza-Nunez VM. Supplementation of ascorbic acid and alpha-tocopherol is useful to preventing bone loss linked to oxidative stress in elderly. J Nutr Health Aging. 2010;14(6):467–72.
25. Yamaguchi M, Uchiyama S. beta-Cryptoxanthin stimulates bone formation and inhibits bone resorption in tissue culture in vitro. Mol Cell Biochem. 2004;258(1–2):137–44.
26. Rao LG, Krishnadev N, Banasikowska K, Rao AV. Lycopene I—effect on osteoclasts: lycopene inhibits basal and parathyroid hormone-stimulated osteoclast formation and mineral resorption mediated by reactive oxygen species in rat bone marrow cultures. J Med Food. 2003;6(2):69–78.
27. Yamaguchi M, Uchiyama S. Effect of carotenoid on calcium content and alkaline phosphatase activity in rat femoral tissues in vitro: the unique anabolic effect of b-cryptoxanthin. Biol Pharm Bull. 2003;26(8):1188–91.
28. Rao LG, Mackinnon ES, Josse RG, Murray TM, Strauss A, Rao AV. Lycopene consumption decreases oxidative stress and bone resorption markers in postmenopausal women. Osteoporos Int. 2007;18(1):109–15.
29. Uchiyama S, Sumida T, Yamaguchi M. Oral administration of beta-cryptoxanthin induces anabolic effects on bone components in the femoral tissues of rats in vivo. Biol Pharm Bull. 2004;27(2):232–5.
30. Yamaguchi M, Igarashi A, Uchiyama S, Morita S, Sugawara K, Sumida T. Prolonged intake of juice (Citrus Unshiu) reinforced with β-cryptoxanthin has an effect on circulating bone biochemical markers in normal individuals. J Home Sci. 2004;50(6):619–24.
31. Barker ME, McCloskey E, Saha S, Gossiel F, Charlesworth D, Powers HJ, et al. Serum retinoids and beta-carotene as predictors of hip and other fractures in elderly women. J Bone Miner Res. 2005;20(6):913–20.
32. Sahni S, Hannan MT, Blumberg J, Cupples LA, Kiel DP, Tucker KL. Inverse association of carotenoid intakes with 4-year change in bone mineral density in elderly men and women: the Framingham Osteoporosis Study. Am J Clin Nutr. 2009;89(1):416–24.
33. Sahni S, Hannan MT, Blumberg J, Cupples LA, Kiel DP, Tucker KL. Protective effect of total carotenoid and lycopene intake on the risk of hip fracture: a 17-year follow-up from the Framingham Osteoporosis Study. J Bone Miner Res. 2009;24(6):1086–94.
34. Dai Z, Wang R, Ang LW, Low YL, Yuan JM, Koh WP. Protective effects of dietary carotenoids on risk of hip fracture in men: the Singapore Chinese Health Study. J Bone Miner Res. 2014;29(2):408–17.
35. Mackinnon ES, Rao AV, Josse RG, Rao LG. Supplementation with the antioxidant lycopene significantly decreases oxidative stress parameters and the bone resorption marker N-telopeptide of type I collagen in postmenopausal women. Osteoporos Int. 2011;22(4):1091–101.
36. Mackinnon ES, Rao AV, Rao LG. Dietary restriction of lycopene for a period of 1 month resulted in significantly increased biomarkers of oxidative stress and bone resorption in postmenopausal women. J Nutr Health Aging. 2011;15(2):133–8.
37. McLean RR, Jacques PF, Selhub J, Tucker KL, Samelson EJ, Broe KE, et al. Homocysteine as a predictive factor for hip fracture in older persons. N Engl J Med. 2004;350(20):2042–9.
38. Tucker KL, Hannan MT, Qiao N, Jacques PF, Selhub J, Cupples LA, et al. Low Plasma Vitamin B(12) is associated with lower BMD: the Framingham Osteoporosis Study. J Bone Miner Res. 2005;20(1):152–8.
39. McLean RR, Jacques PF, Selhub J, Fredman L, Tucker KL, Samelson EJ, et al. Plasma B vitamins, homocysteine, and their relation with bone loss and hip fracture in elderly men and women. J Clin Endocrinol Metab. 2008;93(6):2206–12.
40. van Wijngaarden JP, Doets EL, Szczecinska A, Souverein OW, Duffy ME, Dullemeijer C, et al. Vitamin B12, folate, homocysteine, and bone health in adults and elderly people: a systematic review with meta-analyses. J Nutr Metab. 2013;2013:486186.

41. Sato Y, Honda Y, Iwamoto J, Kanoko T, Satoh K. Effect of folate and mecobalamin on hip fractures in patients with stroke: a randomized controlled trial. JAMA. 2005;293(9):1082–8.
42. Sawka AM, Ray JG, Yi Q, Josse RG, Lonn E. Randomized clinical trial of homocysteine level lowering therapy and fractures. Arch Intern Med. 2007;167(19):2136–9.
43. Gommans J, Yi Q, Eikelboom JW, Hankey GJ, Chen C, Rodgers H, et al. The effect of homocysteine-lowering with B-vitamins on osteoporotic fractures in patients with cerebrovascular disease: substudy of VITATOPS, a randomised placebo-controlled trial. BMC Geriatr. 2013;13:88.
44. van Wijngaarden JP, Swart KM, Enneman AW, Dhonukshe-Rutten RA, van Dijk SC, Ham AC, et al. Effect of daily vitamin B-12 and folic acid supplementation on fracture incidence in elderly individuals with an elevated plasma homocysteine concentration: B-PROOF, a randomized controlled trial. Am J Clin Nutr. 2014;100(6):1578–86.
45. Binkley NC, Suttie JW. Vitamin K nutrition and osteoporosis. J Nutr. 1995;125(7):1812–21.
46. Booth SL, Tucker KL, Chen H, Hannan MT, Gagnon DR, Cupples LA, et al. Dietary vitamin K intakes are associated with hip fracture but not with bone mineral density in elderly men and women. Am J Clin Nutr. 2000;71(5):1201–8.
47. Booth SL, Broe KE, Gagnon DR, Tucker KL, Hannan MT, McLean RR, et al. Vitamin K intake and bone mineral density in women and men. Am J Clin Nutr. 2003;77(2):512–6.
48. Booth SL, Broe KE, Peterson JW, Cheng DM, Dawson-Hughes B, Gundberg CM, et al. Associations between vitamin K biochemical measures and bone mineral density in men and women. J Clin Endocrinol Metab. 2004;89(10):4904–9.
49. McLean RR, Booth SL, Kiel DP, Broe KE, Gagnon DR, Tucker KL, et al. Association of dietary and biochemical measures of vitamin K with quantitative ultrasound of the heel in men and women. Osteoporos Int. 2006;17(4):600–7.
50. Hamidi MS, Gajic-Veljanoski O, Cheung AM. Vitamin K and bone health. J Clin Densitom. 2013;16(4):409–13.
51. Shah K, Gleason L, Villareal DT. Vitamin K and bone health in older adults. J Nutr Gerontol Geriatr. 2014;33(1):10–22.
52. Cockayne S, Adamson J, Lanham-New S, Shearer MJ, Gilbody S, Torgerson DJ. Vitamin K and the prevention of fractures: systematic review and meta-analysis of randomized controlled trials. Arch Intern Med. 2006;166(12):1256–61.
53. Iwamoto J, Matsumoto H, Takeda T. Efficacy of menatetrenone (vitamin K2) against non-vertebral and hip fractures in patients with neurological diseases: meta-analysis of three randomized, controlled trials. Clin Drug Invest. 2009;29(7):471–9.
54. Fang Y, Hu C, Tao X, Wan Y, Tao F. Effect of vitamin K on bone mineral density: a meta-analysis of randomized controlled trials. J Bone Miner Metab. 2012;30(1):60–8.
55. Huang ZB, Wan SL, Lu YJ, Ning L, Liu C, Fan SW. Does vitamin K2 play a role in the prevention and treatment of osteoporosis for postmenopausal women: a meta-analysis of randomized controlled trials. Osteoporos Int. 2015;26(3):1175–86.
56. Bushinsky DA. Acid–base imbalance and the skeleton. Eur J Nutr. 2001;40(5):238–44.
57.•• Jehle S, Hulter HN, Krapf R. Effect of potassium citrate on bone density, microarchitecture, and fracture risk in healthy older adults without osteoporosis: a randomized controlled trial. J Clin Endocrinol Metab. 2013;98(1):207–17. **This paper is of major importance as the RCT reports effects on BMD, bone microarchitecture as well as fracture outcomes**.
58. Frassetto LA, Hardcastle AC, Sebastian A, Aucott L, Fraser WD, Reid DM, et al. No evidence that the skeletal non-response to potassium alkali supplements in healthy postmenopausal women depends on blood pressure or sodium chloride intake. Eur J Clin Nutr. 2012;66(12):1315–22.
59. Macdonald HM, Black AJ, Aucott L, Duthie G, Duthie S, Sandison R, et al. Effect of potassium citrate supplementation or increased fruit and vegetable intake on bone metabolism in healthy postmenopausal women: a randomized controlled trial. Am J Clin Nutr. 2008;88(2):465–74.
60. McLean RR, Qiao N, Broe KE, Tucker KL, Casey V, Cupples LA, et al. Dietary acid load is not associated with lower bone mineral density except in older men. J Nutr. 2011;141(4):588–94.
61. Lemann Jr J, Pleuss JA, Gray RW. Potassium causes calcium retention in healthy adults. J Nutr. 1993;123(9):1623–6.
62. Kenney MA, McCoy H, Williams L. Effects of magnesium deficiency on strength, mass, and composition of rat femur. Calcif Tissue Int. 1994;54(1):44–9.
63. Farina EK, Kiel DP, Roubenoff R, Schaefer EJ, Cupples LA, Tucker KL. Protective effects of fish intake and interactive effects of long-chain polyunsaturated fatty acid intakes on hip bone mineral density in older adults: the Framingham Osteoporosis Study. Am J Clin Nutr. 2011;93(5):1142–51.
64. Chen YM, Ho SC, Lam SS. Higher sea fish intake is associated with greater bone mass and lower osteoporosis risk in postmenopausal Chinese women. Osteoporos Int. 2010;21(6):939–46.
65. Zalloua PA, Hsu YH, Terwedow H, Zang T, Wu D, Tang G, et al. Impact of seafood and fruit consumption on bone mineral density. Maturitas. 2007;56(1):1–11.
66.•• Mangano KM, Sahni S, Kerstetter JE, Kenny AM, Hannan MT. Polyunsaturated fatty acids and their relation with bone and muscle health in adults. Curr Osteoporos Rep 2013. **This paper is of major importance as it is an extensive review of the current knowledge and the gaps in knowledge for PUFA with bone and muscle**.
67. Jarvinen R, Tuppurainen M, Erkkila AT, Penttinen P, Karkkainen M, Salovaara K, Jurvelin JS, Kroger H. Associations of dietary polyunsaturated fatty acids with bone mineral density in elderly women. Eur J Clin Nutr 2011.
68. Rousseau JH, Kleppinger A, Kenny AM. Self-reported dietary intake of omega-3 fatty acids and association with bone and lower extremity function. J Am Geriatr Soc. 2009;57(10):1781–8.
69. Farina EK, Kiel DP, Roubenoff R, Schaefer EJ, Cupples LA, Tucker KL. Plasma phosphatidylcholine concentrations of polyunsaturated fatty acids are differentially associated with hip bone mineral density and hip fracture in older adults: the Framingham Osteoporosis Study. J Bone Miner Res. 2012;27(5):1222–30.
70. Farina EK, Kiel DP, Roubenoff R, Schaefer EJ, Cupples LA, Tucker KL. Dietary intakes of arachidonic acid and alpha-linolenic acid are associated with reduced risk of hip fracture in older adults. J Nutr. 2011;141(6):1146–53.
71. Dietary guidelines for Americans (2005). Dietary Guidelines Advisory Committee Report, 6th edn. U.S. Department of Health and Human Services and U.S. Department of Agriculture. In. Washington DC U.S. Government; 2005.
72. Kalkwarf HJ, Khoury JC, Lanphear BP. Milk intake during childhood and adolescence, adult bone density, and osteoporotic fractures in US women. Am J Clin Nutr. 2003;77(1):257–65.
73. Kull M, Kallikorm R, Lember M. Impact of molecularly defined hypolactasia, self-perceived milk intolerance and milk consumption on bone mineral density in a population sample in Northern Europe. Scand J Gastroenterol. 2009;44(4):415–21.
74. McCabe LD, Martin BR, McCabe GP, Johnston CC, Weaver CM, Peacock M. Dairy intakes affect bone density in the elderly. Am J Clin Nutr. 2004;80(4):1066–74.
75. Murphy S, Khaw KT, May H, Compston JE. Milk consumption and bone mineral density in middle aged and elderly women. BMJ. 1994;308(6934):939–41.
76. Teegarden D, Lyle RM, Proulx WR, Johnston CC, Weaver CM. Previous milk consumption is associated with greater bone density in young women. Am J Clin Nutr. 1999;69(5):1014–7.

77. Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, Kanis JA, Orav EJ, Staehelin HB, et al. Milk intake and risk of hip fracture in men and women: a meta-analysis of prospective cohort studies. J Bone Miner Res. 2011;26(4):833–9.
78. Feskanich D, Willett WC, Colditz GA. Calcium, vitamin D, milk consumption, and hip fractures: a prospective study among postmenopausal women. Am J Clin Nutr. 2003;77(2):504–11.
79.•• Feskanich D, Bischoff-Ferrari HA, Frazier AL, Willett WC. Milk consumption during teenage years and risk of hip fractures in older adults. JAMA Pediatr. 2014;168(1):54–60. **This paper is of major importance as it is a pivotal examination of milk consumption during bone accumulation and the possible fracture sequela in older adults**.
80. Sahni S, Tucker KL, Kiel DP, Quach L, Casey VA, Hannan MT. Milk and yogurt consumption are linked with higher bone mineral density but not with hip fracture: the Framingham Offspring Study. Arch Osteoporos. 2013;8(1–2):119.
81.•• Sahni S, Mangano KM, Tucker KL, Kiel DP, Casey VA, Hannan MT. Protective association of milk intake on the risk of hip fracture: results from the Framingham Original Cohort. J Bone Miner Res. 2014;29(8):1756–62. **This paper is of major importance as it examines a population-based cohort and finds milk as consumed as an older adult to be protective against subsequent fracture**.
82. Heaney RP, Layman DK. Amount and type of protein influences bone health. Am J Clin Nutr. 2008;87(5):1567S–70.
83. Itoh R, Nishiyama N, Suyama Y. Dietary protein intake and urinary excretion of calcium: a cross-sectional study in a healthy Japanese population. Am J Clin Nutr. 1998;67(3):438–44.
84. Johnson NE, Alcantara EN, Linkswiler H. Effect of level of protein intake on urinary and fecal calcium and calcium retention of young adult males. J Nutr. 1970;100(12):1425–30.
85. Kerstetter JE, Allen LH. Dietary protein increases urinary calcium. J Nutr. 1990;120(1):134–6.
86. Hannan MT, Tucker KL, Dawson-Hughes B, Cupples LA, Felson DT, Kiel DP. Effect of dietary protein on bone loss in elderly men and women: the Framingham Osteoporosis Study. J Bone Miner Res. 2000;15(12):2504–12.
87. Munger RG, Cerhan JR, Chiu BC. Prospective study of dietary protein intake and risk of hip fracture in postmenopausal women. Am J Clin Nutr. 1999;69(1):147–52.
88. Promislow JH, Goodman-Gruen D, Slymen DJ, Barrett-Connor E. Protein consumption and bone mineral density in the elderly: the Rancho Bernardo Study. Am J Epidemiol. 2002;155(7):636–44.
89. Cooper C, Atkinson EJ, Hensrud DD, Wahner HW, O'Fallon WM, Riggs BL, et al. Dietary protein intake and bone mass in women. Calcif Tissue Int. 1996;58(5):320–5.
90. Kerstetter JE, Looker AC, Insogna KL. Low dietary protein and low bone density. Calcif Tissue Int. 2000;66(4):313.
91. Freudenheim JL, Johnson NE, Smith EL. Relationships between usual nutrient intake and bone-mineral content of women 35–65 years of age: longitudinal and cross-sectional analysis. Am J Clin Nutr. 1986;44(6):863–76.
92. Geinoz G, Rapin CH, Rizzoli R, Kraemer R, Buchs B, Slosman D, et al. Relationship between bone mineral density and dietary intakes in the elderly. Osteoporos Int. 1993;3(5):242–8.
93. Mazess RB, Barden HS. Bone density in premenopausal women: effects of age, dietary intake, physical activity, smoking, and birth-control pills [see comments]. Am J Clin Nutr. 1991;53(1):132–42.
94. Metz JA, Anderson JJ, Gallagher Jr PN. Intakes of calcium, phosphorus, and protein, and physical-activity level are related to radial bone mass in young adult women [see comments]. Am J Clin Nutr. 1993;58(4):537–42.
95. Nieves JW. Osteoporosis: the role of micronutrients. Am J Clin Nutr. 2005;81(5):1232S–9.
96. Henderson NK, Price RI, Cole JH, Gutteridge DH, Bhagat CI. Bone density in young women is associated with body weight and muscle strength but not dietary intakes. J Bone Miner Res. 1995;10(3):384–93.
97. Wang MC, Luz Villa M, Marcus R, Kelsey JL. Associations of vitamin C, calcium and protein with bone mass in postmenopausal Mexican American women. Osteoporos Int. 1997;7(6):533–8.
98. Misra D, Berry SD, Broe KE, McLean RR, Cupples LA, Tucker KL, et al. Does dietary protein reduce hip fracture risk in elders? The Framingham Osteoporosis Study. Osteoporos Int. 2011;22(1):345–9.
99. Sahni S, Broe KE, Tucker KL, McLean RR, Kiel DP, Cupples LA, et al. Association of total protein intake with bone mineral density and bone loss in men and women from the Framingham Offspring Study. Public Health Nutr. 2014;17(11):2570–6.
100. Sahni S, Cupples LA, McLean RR, Tucker KL, Broe KE, Kiel DP, et al. Protective effect of high protein and calcium intake on the risk of hip fracture in the Framingham offspring cohort. J Bone Miner Res. 2010;25(12):2770–6.
101. Carlisle EM. Silicon an essential element for the chick. Science. 1972;178:619–21.
102. Carlisle EM. Silicon: a requirement in bone formation independent of vitamin D1. Calcif Tissue Int. 1981;33(1):27–34.
103. Carlisle EM. Silicon. In: O'Dell BL, Sunde RA, editors. Handbook of nutritionally essential mineral elements. New York: Marcel Dekker, Inc; 1997. p. 603–18.
104. Jugdaohsingh R, Reffitt DM, Oldham C, Day JP, Fifield LK, Thompson RPH, et al. Oligomeric but not monomeric silica prevents aluminum absorption in humans. Am J Clin Nutr. 2000;71:944–9.
105. Sripanyakorn S, Jugdaohsingh R, Elliott H, Walker C, Mehta P, Shoukru S, et al. The silicon content of beer and its bioavailability in healthy volunteers. Br J Nutr. 2004;91(3):403–9.
106. Spector TD, Calomme MR, Anderson SH, Clement G, Bevan L, Demeester N, et al. Choline-stabilized orthosilicic acid supplementation as an adjunct to calcium/vitamin D3 stimulates markers of bone formation in osteopenic females: a randomized, placebo-controlled trial. BMC Musculoskelet Disord. 2008;9:85.
107. Tucker KL, Jugdaohsingh R, Powell JJ, Qiao N, Hannan MT, Sripanyakorn S, et al. Effects of beer, wine, and liquor intakes on bone mineral density in older men and women. Am J Clin Nutr. 2009;89(4):1188–96.
108. Baur JA, Pearson KJ, Price NL, Jamieson HA, Lerin C, Kalra A, et al. Resveratrol improves health and survival of mice on a high-calorie diet. Nature. 2006;444(7117):337–42.
109. Zhou H, Shang L, Li X, Zhang X, Gao G, Guo C, et al. Resveratrol augments the canonical Wnt signaling pathway in promoting osteoblastic differentiation of multipotent mesenchymal cells. Exp Cell Res. 2009;315(17):2953–62.
110. Shakibaei M, Buhrmann C, Mobasheri A. Resveratrol-mediated SIRT-1 interactions with p300 modulate receptor activator of NF-kappaB ligand (RANKL) activation of NF-kappaB signaling and inhibit osteoclastogenesis in bone-derived cells. J Biol Chem. 2011;286(13):11492–505.
111. Zhao H, Li X, Li N, Liu T, Liu J, Li Z, et al. Long-term resveratrol treatment prevents ovariectomy-induced osteopenia in rats without hyperplastic effects on the uterus. Br J Nutr. 2014;111(5):836–46.
112.•• Ornstrup MJ, Harslof T, Kjaer TN, Langdahl BL, Pedersen SB. Resveratrol increases bone mineral density and bone alkaline phosphatase in obese men: a randomized placebo-controlled trial. J Clin Endocrinol Metab. 2014;99(12):4720–9. **This paper is of major importance as one of the first studies to examine resveratrol with BMD and bone marker in a RCT**.
113. Sahni S, Kiel DP. Smoking, alcohol, and bone health. In: Holick MF, Nieves JW, editors. Nutrition and Bone Health. 2nd edn. New York © Springer New York; 2015, XXXIX, 30: 489–504.

114. Jacobs Jr DR, Gross MD, Tapsell LC. Food synergy: an operational concept for understanding nutrition. Am J Clin Nutr. 2009;89(5):1543S–8.
115. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr Opin Lipidol. 2002;13(1):3–9.
116. Mangano KM SS, Kiel DP, Tucker KL, Hannan MT. Individual protein food sources are associated with greater bone mineral density among men and women from the Framingham Offspring Study. American Society of Nutrition, Experimental Biology Annual Meeting, San Diego, CA 2014.
117. Karamati M, Jessri M, Shariati-Bafghi SE, Rashidkhani B. Dietary patterns in relation to bone mineral density among menopausal Iranian women. Calcif Tissue Int. 2012;91(1):40–9.
118. Hardcastle AC, Aucott L, Fraser WD, Reid DM, Macdonald HM. Dietary patterns, bone resorption and bone mineral density in early post-menopausal Scottish women. Eur J Clin Nutr. 2011;65(3):378–85.
119. Okubo H, Sasaki S, Horiguchi H, Oguma E, Miyamoto K, Hosoi Y, et al. Dietary patterns associated with bone mineral density in premenopausal Japanese farmwomen. Am J Clin Nutr. 2006;83(5):1185–92.
120. Kiel DP, Myers RH, Cupples LA, Kong XF, Zhu XH, Ordovas J, et al. The BsmI vitamin D receptor restriction fragment length polymorphism (bb) influences the effect of calcium intake on bone mineral density. J Bone Miner Res. 1997;12(7):1049–57.
121. Karasik D, Myers RH, Hannan MT, Gagnon D, McLean RR, Cupples LA, et al. Mapping of quantitative ultrasound of the calcaneus bone to chromosome 1 by genome-wide linkage analysis. Osteoporos Int. 2002;13(10):796–802.
122. Ackert-Bicknell CL, Demissie S, Marin de Evsikova C, Hsu YH, DeMambro VE, Karasik D, et al. PPARG by dietary fat interaction influences bone mass in mice and humans. J Bone Miner Res. 2008;23(9):1398–408.