Osteoporosis Prevention and Nutrition

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Although calcium and vitamin D have been the primary focus of nutritional prevention of osteoporosis, recent research has clarified the importance of several additional nutrients and food constituents. Further, results of calcium and vitamin D supplementation trials have been inconsistent, suggesting that reliance on this intervention may be inadequate. In addition to dairy, fruit and vegetable intake has emerged as an important modifiable protective factor for bone health. Several nutrients, including magnesium, potassium, vitamin C, vitamin K, several B vitamins, and carotenoids, have been shown to be more important than previously realized. Rather than having a negative effect on bone, protein intake appears to benefit bone status, particularly in older adults. Regular intake of cola beverages shows negative effects and moderate alcohol intake shows positive effects on bone, particularly in older women. Current research on diet and bone status supports encouragement of balanced diets with plenty of fruit and vegetables, adequate dairy and other protein foods, and limitation of foods with low nutrient density.

Introduction

Until recently, the primary focus for nutrition and osteoporosis prevention has been almost exclusively on calcium and vitamin D. In recent years, attention has shifted to the role of several other nutrients in determining bone mineral density (BMD) and preventing fracture. These include the controversial role of protein, several minerals (including magnesium and potassium), vitamins (including vitamin K, B vitamins, and antioxidant vitamin C), and carotenoids. In addition, foods and food components (including fruit and vegetables, carbonated beverages, and alcohol) have recently been examined. Although many of these micronutrients affect bone through their effects on calcium absorption, others act as cofactors and stimulate bone resorption or formation factors. A well-balanced, high-quality diet is a key factor in preventing bone loss and fracture, in addition to adequate intake of calcium and vitamin D.

Calcium

Calcium intake recommendations in the United States currently range from 400 mg/d for infants through 6 months of age, to 1500 mg/d for those over 65 years of age and for all postmenopausal women not on estrogen, with 1000 to 1200 mg/d for most adults. Particularly high recommendations were set for older adults because of accelerating bone turnover and loss. Because few older adults consume this amount of calcium from foods, most physicians recommend that their older patients use calcium supplements. However, the actual effectiveness of calcium supplements in fracture prevention remains unclear.

One review noted that all but two of 52 controlled calcium intervention studies showed reduced bone loss or reduced fracture risk, and 75% of 86 observational studies showed protective effects of high calcium intake [1]. However, a more recent meta-analysis of prospective cohort studies and randomized controlled trials also found no effect of calcium on hip fracture risk in men and women [2••]. Further, analysis of data from another five clinical trials also showed no effect of calcium supplementation (800–1600 mg/d) on nonvertebral fracture risk and actually reported a 64% increased risk of hip fracture with calcium supplementation relative to placebo [2••]. Importantly, a follow-up after completion of a large, 3-year, placebo-controlled trial of calcium and vitamin D supplementation in older men and women showed that almost all of the BMD benefits accrued during the trial were lost 2 years after the supplementation ended [3].

As the major source of calcium in the US diet, the importance of milk intake in childhood is generally accepted. Several studies have shown that recalled milk consumption during childhood and adolescence was significantly associated with later bone status. For example, an analysis of adult women in NHANES III (Third National Health and Nutrition Examination Survey) found that low recalled milk intake during childhood and adolescence was associated with significantly lower hip BMD and, further, that low milk intake during childhood was associated with a doubling of fracture risk among women 50 years of age and older [4]. Intervention studies with calcium-rich foods rather than supplements have shown beneficial effects on markers of bone turnover. In

one, three servings per day of yogurt added to the diet of older women led to significant reduction in urinary excretion of N-telopeptide, suggesting reduced bone turnover, relative to control subjects after 1 week [5].

Taken together, the evidence suggests that calcium intake is protective, but leaves the long-term effectiveness of supplemental calcium in question. Although it is possible that some supplement use is a result of a diagnosis of osteoporosis, it is also possible that the calcium in foods such as milk is more effectively used because it comes packaged with other important nutrients, including vitamin D, protein, potassium, and magnesium. This natural complex may have a greater effect on enduring skeletal integrity than short-term calcium supplementation.

Vitamin D

Although vitamin D's importance to calcium absorption and bone health is well known, the epidemiologic evidence has not been consistent. In the Framingham Osteoporosis Study, 4-year bone loss in elderly men and women was not associated with serum 25-hydroxyvitamin D [6]. Conversely, several studies have shown protection effects of high vitamin D concentrations against fracture risk. Notably, serum 25-hydroxyvitamin D concentrations of more than 60 nM were associated with a 36% reduction in risk of hip fracture in men and women ≥ 65 years of age in NHANES III [7••].

Some clinical trials combining vitamin D with calcium have shown significantly lower fracture incidence relative to placebo. However, a meta-analysis of randomized controlled trials showed significant fracture reduction only with at least 700 to 800 IU/d of cholecalciferol [8]. A recent meta-analysis confirmed that low-dose vitamin D (< 400 IU/d) was ineffective in fracture prevention, with decreased risk only in institutionalized individuals receiving 700 IU or more per day [9]. The effect of vitamin D supplements on bone status and fracture prevention is complicated and may depend on dose, in relation with other factors.

Magnesium and Potassium

Two electrolyte minerals that contribute to an alkaline environment and, thereby, protect bone are magnesium and potassium. In addition, magnesium is incorporated into the bone matrix and is thought to contribute to bone strength. In rodents, magnesium deficiency has been shown to decrease osteoprotegerin and to increase receptor activator of nuclear factor-κB ligand (RANKL), contributing to increased osteoclastogenesis [10].

Several population-based studies have shown protective effects of magnesium and/or potassium on bone. A study in the United Kingdom showed that magnesium intake accounted for 12.3% of the variation in pyridinoline excretion, and 12% in deoxypyridinoline excretion in perimenopausal women [11]. In the Framingham Osteoporosis Study [12], magnesium and potassium were positively associated with BMD in men and women. However, protective effects against 4-year bone loss (of 3% to 4%) were seen only in men.

Potassium intake promotes renal calcium retention and protects against bone loss by maintaining an acid-base balance. A prospective study of elderly women showed that those with the highest (vs lowest) baseline quartile of urinary potassium excretion had 4% to 11% greater BMD at 5 years [13]. A recent review noted that the modern human diet tends to be deficient in potassium (2500 vs 7000 mg/d) and excess in sodium (600 vs ~ 4000 mg/d), and this combination is damaging to bone [14].

Fruit and Vegetables

Few studies had considered fruit and vegetables as important foods for fracture prevention. However, they are major food contributors of magnesium and potassium, which may help in maintaining an acid-base balance, as well as vitamin C, carotenoids, and other food constituents that may contribute to antioxidant protection. In the Framingham Osteoporosis cohort, each additional serving of fruit or vegetable was significantly associated with an approximately 1% greater BMD in men and women at baseline. Longitudinally, fruit and vegetable intakes were associated with up to 0.8% less bone loss per additional serving over 4 years of follow-up in men but not women [12]. Protective associations of fruit and vegetables with BMD have been reported in several other populations, including premenopausal women in the United Kingdom [11].

In addition to acid-base considerations, there is growing evidence that several bioactive constituents in fruit and vegetables offer protection. Studies in rats have shown that vegetable concentrates protected bone, including compounds from onions, herbs, and essential oils [15]. The authors noted inhibition of bone resorption that remained after buffering with potassium citrate. Although the mechanisms remain unclear, the phenolic and flavonoid compounds in these and other fruits and vegetables require further investigation in this context.

Carotenoids

One group of important phytochemicals in fruit and vegetables is carotenoids, which could protect BMD by reducing the effects of oxidative stress. Oxidative stress can increase bone resorption through activation of nuclear factor-κB, a mediator of tumor necrosis factor-α and osteoclastogenetic activity. In the Framingham Osteoporosis Study, a cross-sectional analysis showed significant positive associations for α-carotene and BMD in women and for β-carotene and BMD in men. In longitudinal analyses, total carotenoids, β-carotene, lycopene, and lutein plus zeaxanthin were each inversely associated with 4-year loss in trochanter BMD in men; men in the lowest intake tertiles of these carotenoids lost 4% to 5% BMD over the 4 years, relative to very little

loss among men in the highest tertiles. In contrast, only lycopene intake was significantly protective against 4-year loss in lumbar spine BMD in women [16]. In an Australian study, protective associations for total body and lumbar spine BMD were seen for lycopene intake in men, and for lycopene and lutein/zeaxanthin intake in premenopausal women. Additionally, dietary β-carotene appeared protective at the lumbar spine in postmenopausal women [17]. Conversely, the Women's Health Initiative Study found no significant protective associations at any BMD site with serum carotenoids [18].

Total carotenoids and lycopene reduced 15-year hip fracture incidence by 46% and 34%, respectively (highest vs lowest intake tertile) in women and men in the Framingham Osteoporosis Study [19••]. Limited information is available on individual carotenoids with respect to bone health, as other studies have focused mainly on β-carotene. Laboratory studies suggest that lycopene may inhibit formation of osteoclasts and the associated bone resorption, while stimulating osteoblasts [20]. Carotenoids may play a protective role in bone health, thereby explaining part of the observed protective effect of fruit and vegetable intake.

Vitamin C

Another important antioxidant in fruit and vegetables is Vitamin C. As with carotenoids, vitamin C may reduce oxidative stress and inhibit bone resorption. In addition, vitamin C is a well-known essential cofactor for collagen formation, and deficiency has been associated with defective connective tissue.

Observational studies of vitamin C and bone have reported mixed results. The Framingham Osteoporosis Study recently showed protective cross-sectional associations between total vitamin C intake and BMD in nonsmoking men. Protective effects of dietary vitamin C were also evident against 4-year BMD loss in men, but were again conditional, with significant effects of total vitamin C only among men with low calcium intakes. No significant associations were seen in women [21]. Recently, the Women's Health Initiative observed that BMD was significantly (0.7%) higher among current users of hormonal therapy in the highest quartile, relative to lower vitamin C intakes [18].

No associations were seen with supplemental vitamin C or dietary vitamin C on 15-year risk of hip fracture in the combined sample of Framingham men and women, although a protective association was observed for supplemental vitamin C among women [22]. The NHANES III (1988–1994) showed that vitamin C intake was associated nonlinearly with self-reported hip fracture in men (with lowest prevalence at ~ 200 mg/d). For postmenopausal women, a significant 49% lower prevalence of hip fracture was seen per standard deviation increase in serum ascorbic acid, but only for women with a history of smoking and a history of estrogen therapy [23]. These studies provide some evidence for vitamin C's protective effect on bone status and fracture risk, although they point to complex interaction with several other factors (eg, sex, smoking status, calcium intake, and current estrogen use) that needs further investigation.

Vitamin K

Vitamin K is another vitamin present in green leafy vegetables. Vitamin K's role in bone health is through its role in the carboxylation, and thus activation, of important bone proteins. If γ-carboxylation is impaired, undercarboxylated osteocalcin accumulates, and the latter has been associated with increased risk of hip fracture [24].

Vitamin K intake was associated with a 65% reduced risk of hip fracture (comparing the highest to lowest quartile of intake) in the Framingham original cohort of women and men [25,26]. In a recent prospective study, Japanese women with low plasma phylloquinone concentrations were more than three times as likely to have incident vertebral fracture compared to those with high concentrations [27].

In addition to green leafy vegetables, vegetable oils are an important dietary source of vitamin K. The hydrogenation of vegetable oils changes the natural form of phylloquinone (vitamin K_1) to dihydrophylloquinone. Men and women with dihydrophylloquinone intakes in the highest tertile had an approximately 2% lower mean BMD at the femoral neck, trochanter, and spine relative to the lowest intake tertile in the Framingham Offspring Study [28]. Thus, these differing types of vitamin K, and the level of hydrogenation of oils consumed, must be considered carefully when assessing vitamin K status. Fortunately, other negative effects of trans fats on health have been recognized, and they are being reduced in the food supply.

A 2-year randomized controlled trial in healthy women showed that supplementation with 200 μg of vitamin K, 10 μg of vitamin D, and 1000 mg of calcium increased BMD of the ultradistal radius significantly more than with vitamin D plus calcium only [29]. However, a recent 3-year, double-blind controlled trial found no differences in BMD change between the group that received 500 μg/d of phylloquinone with 600 mg of elemental calcium and 400 IU of vitamin D relative to those who received the supplements without phylloquinone [30]. Current evidence shows that vitamin K is important to bone, but more research is needed to better understand the optimal forms and amounts. The lack of effect of supplementation trials suggests that inclusion of vegetables and nonhydrogenated oils with vitamin K is an important component of dietary planning for bone health.

Protein

Consistent with the acid-base hypothesis, metabolic studies have shown that high protein intake is a determinant

of urinary calcium loss. Therefore, it has been assumed that the sulfur amino acid content of meat contributes to bone loss through an increase in the acid load. However, recent studies have challenged that assumption.

Although excess protein intake can contribute to negative calcium balance, low protein intake has also been associated with increased risk of fracture in the elderly. In the Iowa women's cohort, incident hip fractures were unexpectedly associated with lower rather than higher total protein intake. Furthermore, despite the expectation that animal protein may have a negative effect because of its sulfur amino acid content, animal rather than vegetable sources of protein appeared to particularly confer benefit with respect to hip fracture risk [31]. In the Framingham Osteoporosis Study, with baseline average protein intakes at about 16% of total energy intake, those in the lowest protein intake quartile had significantly greater 4-year bone loss at the femur and spine than those in the highest quartile of protein intakes, with protective effects similar to an additional 10 lb of weight [32]. The current recommended dietary allowance (RDA) for protein intake is 0.8 g/kg, and approximately 32% of the Framingham cohort had a protein intake below this RDA. However, beyond the effect of inadequate protein, those with protein intake several times greater than the RDA had the least bone loss, after controlling for known confounders [32].

Several trials in patients with hip fracture have shown beneficial effects of protein supplementation on bone. For example, one study noted significant attenuation in bone loss with supplementation of 20 g of protein per day [31]. This contradicts the metabolic studies showing calcium loss. It is possible that as long as calcium intakes are adequate, the calciuric effect of protein may be offset by increased intestinal calcium absorption. Using data from a longitudinal calcium supplementation trial, Dawson-Hughes and Harris [33] found that those in the highest tertile of protein intake had significantly less BMD loss over a 3-year follow-up period than those in the lowest protein intake group only if they were taking calcium and vitamin D supplements. They suggested that greater calcium in the supplemented group may have offset potential negative effects of protein on calcium balance.

The beneficial effects of protein on bone and hip fracture risk have been noted most consistently in elderly participants. One likely mechanism is through its stimulation of serum insulin-like growth factor 1, an osteotrophic hormone [34]. The relationship between protein intake and calcium balance is complex. The most recent evidence suggests that within the range of general population intake, protein intake does not result in bone loss. Further work is needed to better understand the conditions under which it has optimal effect. However, the convergence of information suggests that rather than avoiding protein-rich foods for the purpose of improving bone status, many older persons may benefit from higher protein intakes.

B Vitamins

Although well-known for their metabolic cofactors important to cardiovascular and other diseases, vitamin B's role to bone status has only recently been noted. Vitamin B_{12} is a required cofactor in metabolic reactions associated with methionine synthase, is necessary for synthesis of DNA, and may stimulate osteoblast activity and bone formation. Osteoporosis and greater fracture risk have been recognized in patients with pernicious anemia. Several observational studies have examined the relationship between vitamin B_{12}, BMD, and fracture risk. A cross-sectional analysis of participants in the Framingham Offspring Study showed significantly lower BMD in men and women with deficient plasma vitamin B_{12} concentrations (< 148 pmol/L) [35]. In the NHANES III, the prevalence of osteoporosis was approximately two times greater in those with serum vitamin B_{12} concentrations in the lowest quartile relative to the highest quartile [36]. In a 4-year follow-up of the Framingham Osteoporosis Study, vitamin B_{12} less than 148 pmol/L was also significantly associated with hip fracture risk, but the association was attenuated after controlling for baseline BMD and homocysteine, suggesting that the association may operate through these intermediate effects [37]. High homocysteine, which results from inadequate B vitamin status, has been linked with impaired collagen cross-linking and may therefore affect fracture risk through effects on parameters of bone strength other than BMD. Given the high prevalence of low vitamin B_{12} status in the older population [38], the association between this vitamin and bone status deserves more attention.

Other B vitamins closely connected with B_{12} in metabolic pathways include folate and vitamin B_6. Folate is critical for DNA methylation and thus could indirectly affect cells specific to bone remodeling. The large Hordaland Homocysteine Study found a 2.4 times greater risk of hip fracture in women with folate concentrations less than 2.9 nmol/L relative to ≥ 6.6 nmol/L. In the Framingham Osteoporosis Study, the association between folate status and BMD was dependent on the methylene tetrahydrofolate reductase genotype; participants with the TT allele and low plasma folate had lower BMD, whereas those with the TT allele and high plasma folate had higher BMD relative to the CC or CT alleles [39].

Little is known about the effects of vitamin B_6 on bone health. Evidence from animal studies suggests that vitamin B_6 deficiency may influence bone turnover by decreasing concentrations of alkaline phosphatase. The Rotterdam Study showed that individuals in the highest quartile of vitamin B_6 intake had a 23% to 45% lower risk of fracture, relative to lower intakes [40]. Another study showed that hip fracture cases had lower enzymatic cross-links and vitamin B_6 concentrations than control subjects [41].

Several randomized trials have been conducted to test B vitamins as an intervention for osteoporosis. Supplementation with 2.5 mg of folic acid, 0.5 mg of vitamin B_{12}, and

25 mg of vitamin B_6 for 1 year had no effect on markers of bone turnover or BMD in adults with osteoporosis [42]. In contrast, a Japanese study of patients 65 years of age and older providing 5 mg of folic acid and 1500 μg of mecobalamin or placebo daily for 2 years showed an 80% reduction in risk of hip fracture [43]. Subjects in this study had a relatively high baseline homocysteine concentration (mean, 20 ± 21 μmol/L), which might explain the ability to detect a reduction in fracture risk. The evidence suggests an important role for B vitamins on bone health, but more research is needed to confirm the mechanisms.

Cola

Carbonated soft drink consumption has increased in recent decades, and among soft drinks, cola is popular. Colas differ from other soft drinks in that they contain phosphoric acid (H_3PO_4). Theoretically, in an environment of high phosphorus and low calcium, calcium binds with phosphorus, reducing serum calcium and stimulating parathyroid hormone. Continual secretion of parathyroid hormone causes resorption of bone to return serum calcium to homeostatic concentrations. There is some evidence of detrimental effects of phosphoric acid on bone from animal studies. One study gave cola to ovariectomized rats for 2 months and noted development of hypocalcemia and significantly lower femoral BMD, relative to a control group [44].

Most epidemiologic studies of carbonated beverages and bone status have been with children and, although most have found an inverse association with BMD, it has generally been seen with all types of soft drinks and attributed to displacement of milk in the diet. Few studies have examined this hypothesis in adults. In the Framingham Osteoporosis Study, a dose-response relationship was observed between the amount of cola consumed and BMD in women. For example, the mean hip BMD of those consuming cola daily was 4% to 5% lower than of those who consumed less than one serving of cola per month [45]. Although no effect was seen in men, the inverse association between cola intake and BMD in women was seen with regular, decaffeinated, and diet cola consumption, but, notably, not with non-cola soft drinks. These results point to phosphoric acid as the unique characteristic shared by these cola beverages.

One case-control study found that postmenopausal women with hypocalcemia were significantly more likely to report daily consumption of phosphoric acid–containing soft drinks relative to control subjects with normal concentrations of serum calcium [46]. Another study did not find associations between carbonated beverage consumption and BMD in postmenopausal women, but cola consumption was quite low in that population [47].

Heaney and Rafferty [48] examined the effect of carbonated beverages on short-term urinary calcium excretion in women and reported that beverages containing phosphoric acid but no caffeine did not produce excess calciuria. Although the amount of phosphoric acid in cola may not be sufficient to affect the overall daily calcium/phosphorus ratio, repeated regular use of beverages with phosphoric acid, no calcium, and no other neutralizing components may have long-term negative effects on BMD. In addition, phosphoric acid in the gut may bind with calcium from the diet, blocking absorption and thereby reducing calciuria, but producing a negative effect on bone by reducing calcium availability. Because cola is a popular beverage, this is of considerable public health importance. Unless further evidence contradicts a negative effect, women concerned about osteoporosis may want to avoid regular use of cola beverages.

Alcohol

Although alcoholism is well known to contribute to osteoporosis, recent studies have noted positive associations between moderate alcohol intake and BMD. One study showed that postmenopausal women with moderate alcohol intake had a 5% to 10% greater BMD relative to nondrinkers [49]. Importantly, when examined by amount of alcohol consumed, a U-shaped curve was evident, with the greatest BMD and lowest bone turnover markers with approximately one to two drinks per day. Several large epidemiologic studies have confirmed the protective effect of alcohol in women. The NHANES III study showed 2% greater BMD in men reporting up to or more than one drinking occasion per day, and 4% greater BMD in postmenopausal women with more than one drinking occasion per day relative to nondrinkers [50]. Few studies have examined bone status by type of alcohol. BMD was 6% to 8% greater among postmenopausal women consuming more than two drinks per day of wine relative to nondrinkers, and 6% greater among men drinking one to two beers per day relative to nondrinkers in the Framingham Osteoporosis Study [51]. In contrast, men consuming more than two drinks per day of distilled spirits had the lowest BMD compared to those with lower alcohol intake.

The mechanism for a protective effect is unclear, but alcohol may suppress bone resorption through the stimulation of estrogen production, which could also explain why stronger results have been noted in postmenopausal relative to premenopausal women. The apparently stronger effects of wine or beer, rather than distilled spirits, may be from additional constituents. One mineral present in beer, and less so in wine, is silicon, which has been shown to promote bone formation [52]. A constituent of wine that could have potential bioactive effects is resveratrol, but more research is needed to confirm its effect. The observation of alcohol's protective effect must be placed within the context of well-known harmful effects, including increased risk for falls and greater risk for breast cancer.

Dietary Patterns

Increasing evidence that multiple nutrients and food constituents confer protection on the skeleton suggests that a

balanced diet may offer better protection than supplementation with calcium and/or vitamin D alone. Therefore, a dietary pattern that maximizes these key nutrients should be associated with bone status, but few studies have examined the overall effect of dietary pattern on bone and fracture outcomes.

In the Framingham Osteoporosis Study, food group intakes, expressed as percent contribution to total energy intake, were entered into a cluster analysis algorithm that maximally separates intake patterns [53]. Men consuming a diet high in fruit, vegetables, and breakfast cereal had significantly greater BMD than men consuming other diet patterns, such as those high in meat or baked products, whereas those consuming a diet high in candy and sweets had the lowest BMD [52]. Women who reported a pattern high in candy and sweets (mean, 20% of energy intake) consistently had the lowest BMD relative to all other patterns; whereas women who consumed high amounts of fruit and vegetables and women who consumed the most alcohol had relatively higher BMD. The dairy group, traditionally expected to have the highest BMD, along with the meat group, traditionally expected to have the lowest BMD, both tended to have BMD that was intermediate. Not surprisingly, the fruit and vegetable group had the highest intakes of magnesium, potassium, vitamin C, and vitamin K, whereas the candy group had the lowest intakes of these important nutrients. The alcohol group in this study consumed, on average, about 17% of their energy intake from alcohol and had moderate intakes of several micronutrients. The results from these overall dietary patterns confirm the associations seen by several individual dietary components, including the importance of fruit and vegetables, the protective effect of moderate alcohol intake in women, and the generally negative effect of consuming large amounts of empty calories (eg, sweets), with consequent low intakes of key micronutrients.

Conclusions

These results for dietary patterns confirm the findings of individual nutrients and foods described earlier and strongly suggest that food choices are associated with bone health. A good quality diet with high intake of fruit and vegetables, but including breakfast cereal, milk, other lean protein sources, and limited in less nutrient-dense foods, may contribute to better accumulated BMD in older age, particularly among men. Among women, alcohol, consumed in moderation, also appears to be protective. Although calcium and vitamin D have long been the primary focus for preventing and treating osteoporosis, important roles of other nutrients and food constituents are emerging and, in some cases, the new evidence is challenging older views. Among the latter are the protective effects of fruit and vegetable intake, the benefits of higher, rather than lower protein intake, and the protective effect of moderate alcohol intake. Additional questions remain, particularly as studies begin to note nutrient–nutrient and gene–nutrient interactions. The role of nutrient supplements remains unclear, but current evidence suggests that, for most nutrients, careful food choices may contribute to significantly improved bone health and reduced risk of fracture.

Disclosure

No potential conflict of interest relevant to this article was reported.

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