Osteoporosis: the role of micronutrients

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ABSTRACT
Osteoporosis and low bone mass are currently estimated to be a major public health threat. Adequate nutrition plays a major role in the prevention and treatment of osteoporosis; the micronutrients of greatest importance are calcium and vitamin D. Calcium has been shown to have beneficial effects on bone mass at all ages, although the results are not always consistent. Higher doses than the current US recommendation (600 IU) of vitamin D in the elderly (age ≥ 65 y) may actually be required for optimal bone health (800–1000 IU/d). The elderly can clearly benefit from increased vitamin D intakes; however, the potential importance of vitamin D in peak bone mass is just being investigated. Vitamin D has been related to falls, with supplementation reducing the number of falls. There are clear fracture benefits demonstrated in randomized clinical trials of calcium and vitamin D supplementation. The other micronutrient needs for optimizing bone health can be easily met by a healthy diet that is rich in fruits and vegetables should optimize the intake of micronutrients required for bone health. Am J Clin Nutr 2005;81(suppl):1232S–9S.

KEY WORDS Calcium, vitamin D, falls, fractures, osteoporosis, micronutrients

INTRODUCTION
The most recent definition of osteoporosis is a disease characterized by loss of bone mass, accompanied by microarchitectural deterioration of bone tissue, which leads to an unacceptable increase in the risk of skeletal failure (fracture). Osteoporosis and low bone mass are currently estimated to be a major public health threat for almost 44 million US men and women aged 50 and older, or 55% of the population in that age range (1). In fact, 1 in 2 women and 1 in 4 men over the age of 50 will fracture at some point in their lifetime. The costs to the healthcare system associated with osteoporotic fracture are ≈17 billion dollars annually (2), with each hip fracture having total medical costs of $40 000.

Adequate nutrition plays a major role in the prevention and treatment of osteoporosis; the nutrients of greatest importance are calcium and vitamin D. Numerous studies have shown that higher calcium intake at various ages are associated with higher bone mineral density compared with the bone mass of those with lower calcium intakes (3). In older postmenopausal women, the benefits of vitamin D and calcium supplementation in preventing bone loss, decreasing bone turnover, and decreasing nonvertebral fractures are clear (4).

An inadequate intake of either calcium, vitamin D, or both will influence calcium-regulating hormones. A deficiency of either calcium or vitamin D will result in reduced calcium absorption and a lower concentration of circulating ionized calcium. When this occurs, parathyroid hormone (PTH) secretion is stimulated and there is a resulting increase in PTH levels. The cumulative effect of higher PTH levels, secondary to poor calcium and vitamin D nutrition (secondary hyperparathyroidism), is an increase in bone remodeling leading to significant loss of bone and an increased fracture risk. Vitamin D supplementation, often in combination with calcium, appears to reduce the degree of secondary hyperparathyroidism associated with poor nutrition.

The recommended calcium intake changes with age and the current recommended intakes are listed in Table 1 (5). One of the highest daily intakes is required after age 50. Important dietary sources of calcium are dairy products (milk, yogurt, cheese), dark green vegetables; canned fish with bones (but not fish fillets); nuts; and more recently, fortified foods (including juices, waffles, cereals, crackers, and snack foods). The average US diet contains only 600 mg calcium a day and thus falls far below the recommended intakes (6). If an adequate calcium intake is not possible in the diet, a calcium supplement may be required and should optimally be taken in doses <500 mg at a time to maximize absorption, because absorption decreases with greater calcium loads. The preferred time to take most supplements is with meals, because calcium is better absorbed with food. Calcium carbonate has more calcium per tablet (40%) than some of the other forms of calcium such as calcium citrate (23%). In most healthy individuals calcium intakes up to 2500 mg/d are safe (5).

In younger individuals, vitamin D synthesis in the skin is the primary determinant of serum 25(OH)D levels; however, the cutaneous synthesis is reduced in the elderly. Elevations in serum PTH and greater bone loss are often associated with lower levels of 25(OH)D. Vitamin D insufficiency is believed to play a strong...
appear to start when serum 25(OH)D fell most 1000 postmenopausal women (10). The rise in serum PTH is a significant (negative) determinant of serum PTH in a study of adults (21–22), in elderly and late postmenopausal women, and in women with low baseline calcium intakes. In large enough doses calcium can reduce the higher PTH levels and lower the rate of bone remodeling (23). Calcium supplementation appears to improve the efficacy of antiresorptive therapy, such as with hormone replacement therapy (HRT), on bone mass (24).

VITAMIN D AND BONE MASS

There have been several studies of vitamin D supplementation, typically in combination with calcium (500 to 1200 mg/d). The % difference between treatment with vitamin D and placebo resulted in average differences of 1.0%, 1.2%, and 0.2% respectively for the spine, femoral neck, and forearm (25–28). The prevalence of serum 25(OH)D deficiency and peak bone mass has been recently investigated. In this Finnish study, the median levels of serum 25(OH)D were 44, 24, and 41 nmol/L in July, winter, and again in July. These data indicate a fair number of young men aged 18–20 have low serum 25(OH)D. The authors found a positive correlation between serum 25(OH)D and bone mineral content at all sites (29). This study points to the potential need for intervention studies on the effects of vitamin D supplementation on the attainment of peak bone mass.

### TABLE 1

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Calcium (mg)</th>
<th>Vitamin D (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3–8</td>
<td>800</td>
<td>200</td>
</tr>
<tr>
<td>9–17</td>
<td>1300</td>
<td>200</td>
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<tr>
<td>18–50</td>
<td>1000</td>
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<tr>
<td>51–70</td>
<td>1200</td>
<td>400</td>
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<td>&gt;70</td>
<td>1200</td>
<td>600</td>
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IMPACT OF CALCIUM AND VITAMIN D ON FALLS IN THE ELDERLY

Falls are often the cause of hip fracture, which may result in death, morbidity, and admission to a nursing home. Clearly muscle strength, in particular lower extremity, should be one of the factors assessed and treated in older persons at risk for falls (32). In a recent analysis of NHANES data, in both active and inactive ambulatory elderly subjects, there was a strong improvement in lower extremity function based on walking speed and sit-to-stand speed, in serum 25(OH)D levels between 5 and 40 nmol/L, with continued but less significant improvement up to 90 nmol/L (9). Clearly vitamin D supplementation should be an important part of fall prevention, which in turn may reduce osteoporotic fractures. Adults with vitamin D deficiency have muscle weakness and are more likely to fall (33). In a meta-analysis (34), vitamin D supplementation appeared to reduce falls by 20%, and furthermore if 15 patients were treated with vitamin D, 1 fall could be prevented.

PREVENTION OF FRACTURE WITH CALCIUM AND VITAMIN D

A review of 16 observational studies assessing hip fracture and calcium intake found that an increase in usual calcium intake of 1 g a day was associated with a 24% reduction in the risk of hip fracture (35). A recent prospective cohort study did not show an association between dietary calcium and vitamin D intake and fracture in a cohort of Swedish women aged 50–85 y (36). In a follow-up of the cohort from the Nurses Health Study (37), an adequate vitamin D intake was associated with a lower risk of hip fracture, although neither milk intake nor a high calcium diet were associated with hip fracture reduction. A meta-analysis of observational studies relating calcium intake to fracture risk (38) also failed to show any association between calcium and hip fracture, although there was a suggestion that individuals with extremely low calcium intake may be at increased fracture risk.

However, data from randomized trials are much less prone to bias than the previously discussed observational studies. Two randomized clinical trials, which evaluated calcium supplementation found vertebral fractures to be reduced by 28% and symptomatic fractures to be reduced by 70% in the calcium supplemented group (39–40). Significant reductions in fracture (26 to 54% reduction in hip and non-spine fracture rates) have also been seen in those randomized clinical trials where calcium was given in conjunction with vitamin D (25–27, 41–42). In the studies where fractures were not reduced, the participants had higher baseline serum 25(OH)D levels, were not given additional calcium, or were given a lower dose of vitamin D (400 IU; 28; 43). One important study, published this year, was a randomized double blind controlled trial of 100 000 IU oral vitamin D3 (cholecalciferol) supplementation or matching placebo every 4 mo over 5 y in 2037 men and 649 women aged 65–85 y. The supplements were provided by mail every 4 mo. After 5 y, 268 men and women had incident fractures, of which 147 had fractures in common osteoporotic sites (hip, wrist, or forearm, or vertebrae). Relative risks in the vitamin D group compared with the placebo group were 0.78 (95% CI 0.61 to 0.99, P = 0.04) for any first fracture and 0.67 (0.48 to 0.93, P = 0.02) for first hip, wrist or forearm, or vertebral fracture. This study demonstrated that a widespread public health effort could be successful at preventing fractures without adverse effects in men and women living in the general community (44). Another important public health study of 9605 community dwelling Danish residents reported that 400 IU vitamin D and 1000 mg of calcium supplements significantly reduced fracture by 16% in this Northern European region that is known to be deficient in vitamin D (45).

A meta-analysis found that vitamin D decreased vertebral fractures and may decrease nonvertebral fractures (46).

To sustain the benefits of increased calcium and vitamin D the higher intake of these nutrients must be maintained. In a 2-year follow-up of participants in the Dawson-Hughes trial, the bone density gains were lost and bone turnover markers increased (47).

PHOSPHORUS

Phosphorus intake does not seem to influence skeletal homeostasis within normal ranges of intake (RDA 700 mg/d), although excessive intakes particularly when combined with low calcium intake may be deleterious (48). Alternatively, adequate phosphorus intake is essential for bone building during growth and low serum phosphate will limit bone formation and mineralization (49). Foods that are high in phosphorus are milk, milk products, poultry, fish, meat, eggs, grains and legumes, and sodas, with only milk (and milk products) also having high amounts of calcium. High phosphorus intakes in the face of low calcium intake may lead to secondary hyperparathyroidism and bone loss. A diet adequate in calcium, with moderate protein and sufficient phosphorus was related to higher bone density (50). Phosphorus deficiency may be a marker of general nutritional inadequacy, similar to protein deficiency seen in the elderly, and in that regard could lead to an increased risk of fracture. These low phosphorus intakes or negative phosphorus balance due to food phosphorus being bound to supplemental calcium may create a relative phosphorus deficiency, which could limit osteoblast function and enhance osteoclastic bone resorption (51). At any age, the ratio of phosphorus to calcium is probably more important than the intake of phosphorus alone (51–52).

SALT

Sodium causes an increase in renal calcium excretion. The mean urinary calcium loss is 1 mmol per 100 mmol sodium (53). If absorbed calcium is less than the amount needed to offset these
obligatory calcium losses that are related to sodium intake, then bone mass will be negatively impacted. In observational studies, higher salt intake leads to higher levels of PTH and greater rates of bone resorption in postmenopausal women and men (54, 55). Furthermore, those with low calcium and high salt diets have lower BMD (55–58). The optimal intake of sodium for calcium conservation and to meet the American Heart Association (AHA) guideline is 2400 mg per day. An adequate intake of calcium allows a more liberal use of sodium in the diet. Recently, the Dietary Approaches to Stop Hypertension (DASH) diet was shown to reduce bone turnover (59). Increased sodium intake leads to increased renal calcium excretion. However, if AHA guidelines are followed (2400 mg sodium/d) there will be no negative impact on bone health. Markers of bone resorption do relate to sodium intake but generally BMD does not relate to sodium intake. The anion is important with sodium chloride increasing urinary calcium more than other salts such as sodium bicarbonate or sodium acetate (60). Sodium intake will not be a problem in the face of adequate calcium intake (61) or potassium (55).

POTASSIUM

The main importance of potassium is based on the influence of potassium on calcium homeostasis, particularly the urinary conservation and excretion of calcium. Low potassium diets increase urinary calcium losses and high potassium diets reduce it. Potassium is found in several vegetables, fruits, legumes, and milk and tends to have alkaline ash characteristics. There have been some studies relating the Net Endogenous Acid Production (NEAP) to potassium intake and bone density (62–63). Furthermore, increased intake of potassium citrate was able to ameliorate the higher bone resorption seen with high salt diets (55). Higher potassium intake, primarily from fruits and vegetables, was associated with higher baseline BMD and less bone loss (64). The need to ensure adequate potassium intake from fruits and vegetables is a strong rationale for the “5 to 10 servings per day recommendation” (65).

VITAMIN K

Vitamin K is a fat-soluble vitamin that functions as a cofactor in enzymes involved in the synthesis of blood coagulation factors and may be required for bone metabolism, to facilitate carboxylation of proteins such as osteocalcin (involved in bone formation) and to reduce urinary calcium excretion (66–67). Vitamin K is present in dark green leafy vegetables, fruits, and vegetable oils with small amounts in dairy products and grains. Vitamin K<sub>2</sub> is found in fermented dairy and soy products, fish, meat, liver, and egg. The current adequate intake (AI) for vitamin K is set at 120 µg for men and 90 µg for women.

Observational studies indicate that vitamin K intake and serum levels are positively related to bone density (68–71) and patients who sustain fractures have been reported to have lower serum vitamin K levels. Epidemiologic studies have also found that higher vitamin K intake is related to lower fracture incidence (72–75). Furthermore, a high percentage of undercarboxylated serum osteocalcin as seen with low serum vitamin K may be a predictor of fracture risk (66, 76–78), although many of these studies are confounded by overall poor nutrition. However, in healthy girls with a typical US diet, better vitamin K status was associated with decreased bone turnover (79).

Deficiency or antagonism of vitamin K (coumarin derivatives) can result in the undercarboxylation of specific proteins involved in bone metabolism including osteocalcin. In cohort studies, warfarin use for more than 1 year was an independent predictor of spine and hip fracture (80) but this was not confirmed in a separate study (81), perhaps because of the small number of women on warfarin.

Several small controlled vitamin K supplementation studies have found reductions in calcium excretion, bone resorption, and the undercarboxylated fraction of osteocalcin. A compound derived from vitamin K (MK4) had a positive effect on BMD in large doses when given to women with osteoporosis (82) and strokes (83). High, pharmacologic doses of vitamin K2 (45 mg) were also related to lower rates of bone loss and a lower incidence of fractures (84–85).

Based on the current evidence of observational studies, studies on intermediate endpoints, and small studies with bone density and limited fracture data, there are insufficient data to recommend the required level of vitamin K supplementation for optimal bone health. One trial with a 3-y supplementation of phyloquinone (1 mg/d) with calcium and vitamin D reduced hip bone loss (86). A healthy diet, high in fruits and vegetables, ensures that vitamin K intake is adequate for most of the population.

VITAMIN C

Vitamin C is an essential cofactor for collagen formation and synthesis of hydroxyproline and hydroxylysine. Rich dietary sources of vitamin C include citrus fruit and juices, peppers, broccoli, and tomato products and green leafy vegetables. The dietary reference intakes (DRIs) for vitamin C are 75 mg/d for adult women and 90 mg/d for adult men. Epidemiologic studies show a positive association between vitamin C and bone mass; low intakes of vitamin C are associated with a faster rate of BMD loss, and one study found that higher vitamin C was associated with fewer fractures; however, there are no randomized clinical trials (87–94). Recommended intakes of 5 or more servings of fruits and vegetables should supply enough vitamin C for bone health.

VITAMIN A

Recommended dietary allowance of vitamin A is 800 µg/d retinol equivalent (RE) for females and 1000 µg/d RE for males. Vitamin A is a fat-soluble vitamin required for vision, growth, fighting infection, and for bone remodeling. There are different types of vitamin A in the diet and in supplements: retinol and β-carotene (and other carotenoids). Excess vitamin A may be detrimental to bone health with intakes of higher than 1500 µg of RE related to a 2-fold increased risk of hip fracture in the United States and Sweden but not in Iceland or in another US study (95–98). These population studies show excess vitamin A intake from retinol appeared to increase the risk of hip fracture.

There is no evidence of any association between β-carotene intake and osteoporosis or related fracture. Vitamin A from fruits and vegetables (carotenoids) does not negatively affect bone health.
MAGNESIUM

Magnesium, complexed with adenosine triphosphate (ATP) takes part in many enzyme reactions including synthesis of proteins and nucleic acid. The intake recommended for healthy adult males is 420 mg/d and for women is 320 mg/d. Because magnesium is present in most foods—particularly legumes, vegetables, nuts, seeds, fruits, grains, fish and dairy—severe magnesium deficiency is rarely seen in healthy people. However, many intakes in the United States fall below this recommended level. Furthermore, a magnesium supplement may be required in frail elderly with poor diets (99) or persons with intestinal disease (100), alcoholics, or persons on treatment with diuretics or chemotherapy that depletes magnesium. In addition, as calcium supplements sometimes result in constipation, a supplement with magnesium might be useful to keep bowel habits regular.

Magnesium deficiency is easily detected with biochemical symptoms (eg, low serum magnesium, low serum calcium, resistance to vitamin D) or clinical symptoms (eg, muscle twitching, muscle cramps, high blood pressure, irregular heartbeat). Lastly, magnesium deficiency is easily treated.

Several small epidemiologic studies have found that higher magnesium intakes are associated with higher BMD in elderly men and women (101). There have been only small controlled clinical trials of magnesium supplementation (102–103) that were primarily effective in magnesium-depleted subjects. There is little evidence that magnesium is needed to prevent osteoporosis in the general population. Overall, observational and clinical trial data concerning magnesium and bone density or fractures are inconclusive and, in fact, one recent study from the WHI reported that higher intakes of magnesium were associated with a higher risk of wrist fracture (104).

FLUORIDE

Fluoride is an essential trace element that is required for skeletal and dental development. The adequate daily adult intake is 4 mg for males and 3 mg for females. The concentration of fluoride in the soil, water, and many foods varies by geographic region. Major dietary sources include drinking water, tea, coffee, rice, soybeans, spinach, onions, and lettuce. There is no need to add fluoride supplements to an adult diet for skeletal health. The lower doses of fluoride typically found in drinking water have no effect on bone density or on fractures (105–107); however, in some endemic high fluoride areas, higher hip fracture rates have been seen. Excess fluoride ingestion causes fluorosis, a painful condition associated with extra-osseous calcification and brittle bones. High doses of fluoride can stimulate osteoblasts; however, the quality of bone that is formed may be abnormal and the effect on fracture rates is unclear (108).

OTHER NUTRIENTS

The effects of trace metals on bone remain unknown. Three studies have shown that a combination of several minerals (zinc, manganese and copper) with calcium was able to reduce spinal bone loss in postmenopausal women (109–110).

Boron is not an essential nutrient so there are no recommended intakes. Although studies have found that 3 mg daily of boron may have a positive effect on bone (102, 111), controlled trials are needed. Boron is present in several foods such as fruits, vegetables, nuts, eggs, wine, and dried foods. Copper is an essential element required by many enzymes including lysyl oxidase, which is required for cross linking of collagen. Severe deficiency does have profound effects on bone. There have only been a few intervention trials with variable results on bone turnover and bone density (112–114), or a mixture of trace elements has been studied (109). Profound zinc deficiency leads to reduced bone growth and maturation. However, there is little evidence that zinc has an effect on bone mass or osteoporotic fractures.

Dietary silicon intake was reported to correlate with BMD at the hip in a cohort of men and premenopausal women (115). These results will require further follow-up.

In 2 recent studies, poor vitamin B12 status was associated with low BMD in men and women, and osteoporosis in elderly women but not men (116,117). It is unclear whether associations such as this are really an indication of overall poor nutrition and frailty. Similarly, in another study increased dietary iron intake was associated with greater bone mineral density at all sites (118).

RECOMMENDATIONS

The nutritional needs for optimizing bone health can be easily met by a healthy diet with adequate calcium and vitamin D intakes through dairy or calcium fortified foods. Foods are a preferred source to maintain calcium balance because there are other essential nutrients that are found in high calcium foods. For those individuals where there is inadequate calcium intake from diet, supplemental calcium can be used. Supplemental or dietary calcium should be spread out throughout the day with 500 mg or less being consumed at each meal to optimize absorption.

In all individuals over the age of 70, vitamin D intakes of at least 600 IU per day (ideally 800-1000 IU/d) are recommended, in addition to the calcium requirement of 1200 mg/d. Vitamin D from foods, supplements, and/or multivitamins can be used to meet the vitamin D requirement. Recent evidence suggests that the optimal level of serum 25(OH)D may be close to 80 nmol/L (7, 8). Severe vitamin D deficiency can be easily treated by giving the patient an oral dose of 50 000 IU of vitamin D once a week for 8 wk or by giving 50 000 IU of vitamin D daily for 10 days (119–120). The fortification of food products is becoming frequently used as a method to improve calcium intake and may also be a reasonable method to increase the vitamin D intake of the population and reduce the prevalence of hypovitaminosis D. The use of calcium and vitamin D supplements in an elderly population has been shown to be cost-effective for hip fracture prevention (121–122). Medical professionals need to be aware of the importance of ensuring adequate calcium and vitamin D intakes for patients on osteoporosis therapy (123).

The effects of calcium and vitamin D on bone cannot be considered in isolation from the other components of the diet (124). The other micronutrient needs for optimizing bone health can be easily met by a healthy diet that is high in fruits and vegetables (5 servings per day) for magnesium, potassium, vitamin C, vitamin K and other potentially important nutrients (125–126).

REFERENCES


