### Osteoporosis: the role of micronutrients<sup>1-4</sup>

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#### ABSTRACT

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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  $\geq$ 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 high in fruits and vegetables to ensure adequate intakes for magnesium, potassium, vitamin C, vitamin K, and other potentially important nutrients. Healthcare professionals need to be aware of the importance of adequate calcium and vitamin D intakes (easily monitored by serum 25(OH)D) for optimal bone health, as well as the prevention of falls and fractures. In addition, a healthy diet that includes 5 servings a day of 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  $\approx 17$  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

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Food and Nutrition Board Dietary Reference Intakes (Recommended Average Intakes for Calcium and Vitamin D)<sup>*I*</sup>

Age (y)	Calcium (mg)	Vitamin D (IU)
3-8	800	200
9–17	1300	200
18-50	1000	400
51-70	1200	400
>70	1200	600

<sup>1</sup> Institute of Medicine: "Dietary Reference Intakes for calcium, magnesium, phosphorus, vitamin D and Fluoride." Food and Nutrition Board, Institute of Medicine. Washington, DC: National Academy Press, 1997.

role in osteoporosis. The current US recommendation for vitamin D intake in people age 51 to 70 y is 10  $\mu$ g/d (400 IU/d) and over age 70 y is 15ug/d (600 IU/d; see Table 1 (5)). However, higher doses of vitamin D (800–1000 IU/d) in the elderly (age  $\geq$ 65 y) may actually be required for optimal bone health, because these vitamin D doses have been shown to reduce fracture risk in this population (3, 4). Rich sources of vitamin D include fatty fish, fish-liver oils (cod liver oil), and liver. Several foods are also fortified with vitamin D including milk, margarine, orange juice, and cereals. There is general agreement that the serum levels of 25(OH)D are the best indication of adequate and inadequate vitamin D levels (7, 8).

In the United States, in the cohort 65 y and older in national health and nutrition examination survey (NHANES) III, 32% of whites, 64% of blacks and 53% of Hispanics had levels of 25(OH)D < 54 nmol/L, the median for the entire NHANES cohort (9). In a recent consensus conference, it was suggested that adequate 25(OH)D levels may be 80 nmol/L or 32 ng/mL, and that intakes of vitamin D of over 1000 IU per day are needed to achieve these serum levels (7). Vitamin D adequacy is often defined in older adults as the level of 25(OH)D needed to maximally suppress PTH levels. Serum 25(OH)D was the most significant (negative) determinant of serum PTH in a study of almost 1000 postmenopausal women (10). The rise in serum PTH appeared to start when serum 25(OH)D fell < 80 nmol/L. These data further suggest that the optimal level of serum 25(OH)D in postmenopausal women may be at least 80 nmol/L.

Suboptimal serum Vitamin D levels are widespread and should be evaluated, particularly in the elderly. However, the following populations are at particularly high risk of vitamin D deficiency: patients with malabsorption syndromes; patients with liver or kidney diseases; patients taking certain medications that interfere with vitamin D metabolism including steroids, dilantin, and phenobarbitol.

#### CALCIUM AND BONE MASS

Considerable epidemiologic data have been accumulated seeking to evaluate the relation between calcium intake and bone density. Peak bone mass, that is attained during adolescence/ young adulthood, can be maximized by raising calcium intake to the adequate intake levels recommended by the 1997 Food and Nutrition Board (see Table 1). Higher calcium intakes have been related to higher bone mass in children, young adults, and post-menopausal women in 64 out of 86 observational epidemiologic studies (11).

Clinical trials with calcium supplements in children and adolescents have been short term (1 to 3 y) and have shown an overall positive effect of calcium on bone mass accrual between 1 and 6% per year in the total body and between 1% and 10% at each skeletal region compared with placebo (3, 12). In children, results are often dependent on pubertal stage. For example, in one recent study, postmenarcheal adolescent girls (<15.5 y of age) with baseline low calcium intakes (<800 mg/d). Those who were given calcium supplementation (1000 mg per day) had enhanced bone mineral acquisition compared with girls given placebo, especially in girls > 2 y past the onset of menarche (13). A meta-analysis of calcium intake in slightly older premenopausal women concluded that calcium supplementation led to an average increase in bone density at the spine and forearm of 1.1% per year compared with women receiving placebo (14). However, in most studies, the benefit of added calcium on bone mass disappears when supplementation is halted (15, 16), although one trial showed a persistent benefit persisting after 3-4 y (17). These data suggest that adequate calcium intake needs to be maintained throughout childhood, adolescence, and young adulthood to have a lasting impact on peak bone mass.

Considerable epidemiologic data have been accumulated seeking to evaluate the relation between calcium intake and bone density. In postmenopausal women, reviews of over 20 studies have concluded that calcium supplementation can decrease bone loss by  $\approx 1\%$  per year (18). In a meta-analysis of 13 trials, calcium induced significant mean gains (or slowed loss) of 0.6% at the forearm, 3% at the spine and 2.6% at the femoral neck (19). A more recent meta-analysis found that in 15 trials, calcium changes were 1.66% at the lumbar spine and 1.64% at the hip (20). Therefore, calcium supplementation has been shown to be effective in retarding bone loss in postmenopausal women. The beneficial effect of calcium intake on bone mass in postmenopausal women may be modified by factors including age, number of years since menopause, baseline calcium intake before supplementation, and possibly physical activity level. In addition, the effect of calcium may be greater at the sites with more cortical bone (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. A French study reported that supplementation with 500 mg calcium and 400 IU of vitamin D given to women with serum 25(OH)D < 12 ng/mL, compared with placebo significantly decreased PTH and markers of bone turnover and improved bone mineral density (BMD). In this study, short-term changes in bone resorption markers can predict long term variations in bone density in elderly women with vitamin D insufficiency receiving vitamin D and calcium (30).

In another study of younger women (1 to 10 y postmenopausal), who had normal 25(OH)D levels (mean 82 nmol/L), the addition of 10 000 IU vitamin D per week to calcium supplementation at 1000 mg per day did not confer any benefits on BMD beyond that which was achieved with calcium supplementation alone (31). Although the elderly clearly require supplementation, in younger populations, there may be less benefit of vitamin D supplementation if serum 25(OH)D levels are normal.

# 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

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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  $\mu$ g for men and 90  $\mu$ g 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 phylloquinone (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  $\mu$ g/d retinol equivalent (RE) for females and 1000  $\mu$ g/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  $\beta$ -carotene (and other carotenoids). Excess vitamin A may be detrimental to bone health with intakes of higher than 1500  $\mu$ g 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  $\beta$ -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

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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, vegetable, 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

- 1. America's bone health: the state of osteoporosis and low bone mass in our nation. A report of the National Osteoporosis Foundation, 2002.
- Ray NF, Chan JK, Thamer M, Melton LJ 3rd. Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995:

report from the National Osteoporosis Foundation. J Bone Miner Res 1997;12:24–35.

- Nieves JW. Nutrition and osteoporosis. In: Cummings S, Cosman F, Jamal S, eds. Osteoporosis: an evidence based approach to the prevention and management. Philadelphia: American College of Physicians, 2002.
- Nieves JW. Calcium, vitamin D, and nutrition in elderly adults. Clin Geriatr Med 2003;19:321–35.
- Institute of Medicine. Dietary Reference Intakes for calcium, magnesium, phosphorus, vitamin D and fluoride. Food and Nutrition Board, Institute of Medicine. Washington DC: National Academy Press, 1997.
- Wright JD, Wang CY, Kennedy-Stephenson J, Ervin RB. Dietary intake of ten key nutrients for public health, United States:1999-2000. Adv Data 2003 Apr 17;(334):1-4.
- Dawson-Hughes B, Heaney RP, Holick M, Lips P, Meunier PJ, Vieth R. Vitamin D roundtable. In: Burckhardt P, Dawson-Hughes B, Heany RP, eds. Nutritional aspects of osteoporosis. San Diego: Academic Press, 2004;263–8.
- Malabanan AO, Holick MF. Vitamin D and bone health in postmenopausal women. J Womens Health 2003;12:151–6.
- Bischoff HA, Dietrich T, Orav EJ, et al. Higher 25-hydroxyvitamin D levels are associated with inactive and active ambulatory elderly in the US. ASBMR 2003 Meeting (abstr).
- Need AG, O'Loughlin PD, Morris HA, Horowitz M, Nordin BEC. The effects of age and other variables on serum parathyroid hormone in postmenopausal women attending an osteoporosis center. J Clin Endocrinol Metab 2004;89:1646–9.
- Heaney RP. Calcium, dairy products and osteoporosis J Am Coll Nutr. 2000;(suppl):83S–99S.
- Matkovic V, Badenhop-Stevens N, Ha E-J, Crncevic-Orlic Z, Clairmont A. Nutrition and bone health in children and adolescents In: Nutrition and bone health. Holick, MF and Dawson-Hughes, B eds. Totowa, NJ: Humana Press Inc., 2004.
- Rozen GS, Rennert G, Dodiuk-Gad RP, et al. Calcium supplementation provides an extended window of opportunity for bone mass accretion after menarche. Am J Clin Nutr 2003;78:993–8.
- Welten DC, Kemper HCG, Post GB, Van Staveren WA. A metaanalysis of the effect of calcium intake on bone mass in young and middle aged females and males. J Nutr 1995;125:2802–13.
- Lee WT, Leung SS, Leung DM, Cheng JC. A follow-up study on the effects of calcium-supplement withdrawal and puberty on bone acquisition of children. Am J Clin Nutr 1996;64:71–7.
- Johnston CC Jr, Miller JZ, Slemenda CW, et al. Calcium supplementation and increases in bone mineral density in children. N Engl J Med 1992;327:82–7.
- Bonjour JP, Carrie AL, Ferrari S, et al. Calcium-enriched foods and bone mass growth in prepubertal girls: a randomized, double-blind, placebo-controlled trial. J Clin Invest 1997;99:1287–97.
- 18. Nordin BEC. Calcium and osteoporosis. Nutrition 1997;13:664-86.
- Mackerras D, Lumley T. First- and second-year effects in trials of calcium supplementation on the loss of bone density in postmenopausal women. Bone 1997;21:527–33.
- Shea B, Wells G, Cranney A, et al; Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group. Meta-analyses of therapies for postmenopausal osteoporosis. VII. Meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis. Endocr Rev 2002;23:552–9.
- Ho SC, Chen YM, Woo JL, Lam SS. High habitual calcium intake attenuates bone loss in early postmenopausal Chinese women: an 18month follow-up study. J Clin Endocrinol Metab 2004;89:2166–70.
- 22. Suzuki Y, Davison KS, Chilibeck PD. Total calcium intake is associated with cortical bone mineral density in a cohort of postmenopausal women not taking estrogen. J Nutr Health Aging 2003;7:296–9.
- McKane WR, Khosla S, Egan KS, Robins SP, Burritt MF, Riggs BL. Role of calcium intake in modulating age-related increases in parathyroid function and bone resorption. J Clin Endocrinol Metab 1996;81: 1699–703.
- Nieves JW, Komar L, Cosman F, Lindsay R. Calcium potentiates the effect of estrogen and calcitonin on bone mass: review and analysis. Am J Clin Nutr 1998;67:18–24.
- Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med 1997;337:670–76.
- 26. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D and calcium to

prevent hip fractures in elderly women. N Engl J Med 1992;327: 1637-42.

- Komulainen MH, Kroger H, Tuppurainen MT, et al. HRT and Vitamin D in prevention of non-vertebral fractures in postmenopausal women. A 5 year randomized trial. Maturitas 1998;31:45–54.
- Lips P, Graafmans WC, Ooms ME, Bezemer PD, Bouter LM. Vitamin D supplementation and fracture incidence in elderly persons: a randomized, placebo-controlled clinical trial. Ann Intern Med 1996;124: 400–6.
- Valimaki VV, Alfthan H, Lehmuskallio E, et al. Vitamin D status as a determinant of peak bone mass in young Finnish men. J Clin Endocrinol Metab 2004;89:76–80.
- 30. Grados F, Brazier M, Kamel S, et al. Prediction of bone mass density variation by bone remodeling markers in postmenopausal women with vitamin D insufficiency treated with calcium and vitamin D supplementation. J Clin Endocrinol Metab 2003;88:5175–9.
- Cooper L, Clifton-Bligh PB, Nery ML, et al. Vitamin D supplementation and bone mineral density in early postmenopausal women. Am J Clin Nutr 2003;77:1324–9.
- Moreland JD, Richardson JA, Goldsmith CH, Clase CM. Muscle weakness and falls in older adults: a systematic review and meta-analysis. J Am Geriatr Soc 2004;52:1121–9.
- Bischoff HA, Stahelin HB, Dick W, et al. Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial. J Bone Miner Res 2003;18:343–51.
- Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et al. Effect of Vitamin D on falls: a meta-analysis. JAMA 2004;291:1999–2006.
- Cummings RG, Nevitt MC. Calcium for prevention of osteoporotic fractures in postmenopausal women. J Bone Miner Res 1997;12: 1321–29.
- Michaelsson K, Melhus H, Bellocco R, Wolk A. Dietary calcium and vitamin D intake in relation to osteoporotic fracture risk. Bone 2003; 32:694–703.
- Feskanish D, Willett WC, Colditz GA. Calcium, vitamin D, milk consumption, and hip fractures: a prospective study among postmenopausal women. Am J Clin Nutr 2003;77:504–11.
- Xu L, McElduff P, D'Este C, Attia J. Does dietary calcium have a protective effect on bone fractures in women? A meta-analysis of observational studies. Br J Nutr 2004;91:625–34.
- Recker RR, Hinders S, Davies KM, et al. Correcting calcium nutritional deficiency prevents spine fractures in elderly women. J Bone Miner Res 1996;11:1961–6.
- Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ. Long-term effects of calcium supplementation on bone loss and fractures in postmenopausal women: a randomized controlled trial. Am J Med 1995; 98:331–5.
- Chevalley T, Rizzoli R, Nydegger V, et al. Effects of calcium supplements on femoral bone mineral density and vertebral fracture rate in vitamin D replete elderly patients. Osteoporos Int 1994;4:245–52.
- 42. Chapuy MC, Pamphile R, Paris E, et al. Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalyos II study. Osteoporos Int 2002;13:257–64.
- 43. Meyer HE, Smedshaug GB, Kvaavik E, Falch JA, Tverdal A, Pedersen JI. Can vitamin D supplementation reduce the risk of fracture in the elderly? A randomized controlled trial. J Bone Miner Res 2002;17: 709–15.
- 44. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ 2003;1:326:469–74.
- 45. Larsen ER, Mosekilde I, Foldspang A. Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents: A pragmatic population-based 3 year intervention study. J Bone Miner Res 2004;19:370–8.
- 46. Papadimitropoulos E, Wells G, Shea B, et al; Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group. Metaanalyses of therapies for postmenopausal osteoporosis. VIII: Metaanalysis of the efficacy of vitamin D treatment in preventing osteoporosis in postmenopausal women. Endocr Rev 2002;23:560–9.
- Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of withdrawal of calcium and vitamin D supplements on bone mass in elderly men and women. Am J Clin Nutr 2000;72:745–50.

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- Calvo MS, Kumar R, Heath H. Persistently elevated parathyroid hormone secretion and action in young women after four weeks of ingesting high phosphorus, low calcium diets. J Clin Endocrinol Metab 1990; 70:1334–40.
- Heaney RP. Phosphorus nutrition and the treatment of osteoporosis. Mayo Clin Proc 2004;79:91–7.
- Whiting SJ, Boyle JL, Thompson A, Mirwald RL, Faulkner RA. Dietary protein, phosphorus and potassium are beneficial to bone mineral density in adult men consuming adequate dietary calcium. J Am Coll Nutr 2002;21:402–9.
- Heaney RP, Nordin BE. Calcium effects on phosphorus absorption: implications for the prevention and co-therapy of osteoporosis. J Am Coll Nutr 2002;21:239–44.
- 52. Shapiro R, Heaney RP. Co-dependence of calcium and phosphorus for growth and bone development under conditions of varying deficiency. Bone 2003;32:532–40.
- Teucher B, Fairweather-Tait S. Dietary sodium as a risk factor for osteoporosis: where is the evidence? Proc Nutr Soc 2003;62:859–66.
- 54. Jones G, Beard T, Parameswaran V, Greenaway T, von Witt R. A population-based study of the relationship between salt intake, bone resorption and bone mass. Eur J Clin Nutr 1997;51:561–5.
- Harrington M, Cashman KD. High salt intake appears to increase bone resorption in postmenopausal women but high potassium intake ameliorates this adverse effect. Nutr Rev 2003;61:179–83.
- Devine A, Criddle RA, Dick IM, Kerr DA, Prince RL. A longitudinal study of the effect of sodium and calcium intakes on regional bone density in postmenopausal women. Amer J Clin Nutr 1995;62:740–5.
- Mizushima S, Tsuchida K, Yamori Y. Preventive nutritional factors in epidemiology: interaction between sodium and calcium. Clin Exp Pharmacol Physiol 1999;26:573–5.
- Massey LK, Whiting SJ. Dietary salt, urinary calcium, and bone loss. J Bone Miner Res 1996;11:731–6.
- Lin PH, Ginty F, Appel LJ, Aickin M, Bohannon A, Garnero P, Barclay D, Svetkey LP. The DASH diet and sodium reduction improve markers of bone turnover and calcium metabolism in adults. J Nutr 2003;133: 3130-6.
- 60. Frassetto L, Morris RC Jr., Sellmeyer DE, Todd K, Sebastian A. Diet, evolution and aging-the pathophysiologic effects of the postagricultural inversion of the potassium-to-sodium and base-to-chloride ratios in the human diet. Eur J Nutr 2001;40:200–13.
- Carbone LD, Bush AJ, Barrow KD, Kang AH. The relationship of sodium intake to calcium and sodium excretion and bone mineral density of the hip in postmenopausal African-American and Caucasian women. J Bone Miner Metab 2003;21:415–20.
- Buchlin T, Cosma M, Appenzeller M, et al. Diet Acids and alkalis influence calcium retention in bone. Osteoporos Int 2001;12:493–9.
- 63. New SA, Robins SP, Campbell MK, et al. Dietary influences on bone mass and bone metabolism: further evidence of a positive link between fruit and vegetable consumption and bone health? Am J Clin Nutr 2000;71:142–51.
- Tucker KL, Hannan MT, Kiel DP. The acid-base hypothesis: diet and bone in the Framingham Osteoporosis Study. Eur J Nutr 2001;40: 231–7.
- Demigne C, Sabboh H, Remesy C, Meneton P. Protective effects of high dietary potassium: nutritional and metabolic aspects. J Nutr 2004; 134:2903–6.
- Booth SL. Skeletal functions of vitamin K-dependent proteins: not just for clotting anymore. Nutr Rev 1997;55:282–4.
- Vermeer C, Knapen MHJ, Jie K-S G, Grobbee DE. Physiological importance of extra-hepatic vitamin K-dependent carboxylation reactions. Ann N Y Acad Sci 1992;669:21–33.
- Tamatani M, Morimoto S, Nakajima M, et al. Decreased circulating levels of vitamin K and 25OHD in osteoporotic elderly men. Metabolism 1998;47:195–9.
- Szulc P, Chapuy MC, Meuniere PJ, Delmas PD. Serum undercarboxylated osteocalcin is a marker of the risk of hip fracture in elderly women. J Clin Invest 1993;91:1769–74.
- Hart JP, Shearer MJ, Klenerman L, et al. Electrochemical detection of depressed circulating levels of vitamin K1 in osteoporosis. J Clin Endocrinol Metab 1985;60:1268–9.
- Booth SL, Broe KE, Gagnon DR, et al. Vitamin K intake and bone mineral density in women and men. Am J Clin Nutr 2003;77:512–6.
- 72. Hodges SJ, Akesson K, Vergnaud P, Obrant K, Delmas PD. Circulating

levels of vitamin K1 and K2 decreased in elderly women with hip fracture. J Bone Miner Res 1993;8:1241–5.

- Booth SLF, Tucker KL, Chen H, 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;71:1201–8.
- 74. Stone K, Duong T, Sellmeyer D, Cauley J, Wolfe R, Cummings S. Broccoli may be good for bones: dietary vitamin K-1, rates of bone loss and risk of hip fracture in a prospective study of elderly women. J Bone Miner Res 1999;14(suppl):S263 (abstr).
- Feskanich D, Weber P, Willett WC, Rockett H, Booth SL, Colditz GA. Vitamin K intake and hip fractures in women: a prospective study. Am J Clin Nutr 1999;69:74–9.
- Luukinen H, Kakonen SM, Pettersson K, et al. Strong prediction of fractures among older adults by the ratio of carboxylated to total serum osteocalcin. J Bone Miner Res 2000;15:2473–8.
- Vergnaud P, Garnero P, Meunier PJ, Breart G, Kamihagi K, Delmas PD. Undercarboxylated osteocalcin measured with a specific immunoassay predicts hip fracture in elderly women: the EPIDOS Study. J Clin Endocrinol Metab 1997;82:719–24.
- Kohlmeier M, Saupe J, Shearer MJ, Schaefer K, Asmus G. Bone health of adult hemodialysis patients is related to vitamin K status. Kidney Int 1997;51:1218–21.
- Kalkwarf HJ, Khoury JC, Bean J, Elliot JG. Vitamin K, bone turnover, and bone mass in girls. Am J Clin Nutr 2004;80:1075–80.
- Caraballo PJ, Heit JA, Atkinson EJ, et al. Long term use of oral anticoagulants and the risk of fracture. Arch Intern Med 1999;159:1750–6.
- Jamal SA, Browner WS, Bauer DC, Cummings SR. Warfarin use and risk for osteoporosis in elderly women. Study of osteoporotic fractures research group. Ann Intern Med 1998;128:829–32.
- Orimo H, Shiraki M, Tomita A, Morii A, Fujita F, Ohata M. Effects of menatetrenone on the bone and calcium metabolism in osteoporosis. A double-blinded placebo-controlled study. J Bone Miner Metab 1998; 16:106–12.
- Sato Y, Honda Y, Kuno H, Oizumi K. Menatetrenone ameliorates osteopenia in disuse-affected limbs of vitamin D- and K-deficient stroke patients. Bone 1998;23:291–6.
- 84. Miki T, Nakatsuka K, Naka H, et al. Vitamin K(2) (menaquinone 4) reduces serum undercarboxylated osteocalcin level as early as 2 weeks in elderly women with established osteoporosis. J Bone Miner Metab 2003;21:161–5.
- Shiraki M, Shiraki Y, Aoki C, Miura M. Vitamin K<sub>2</sub> (menatetrenone) effectively prevents fractures and sustains lumbar bone mineral density in osteoporosis. J Bone Miner Res 2000;15(3):515–521.
- Braam LA, Knapen MH, Geusens P, Brouns F, Vermeer C. Vitamin K1 supplementation retards bone loss in postmenopausal women between 50 and 60 years of age. Calcif Tissue Int 2003;73:21–6.
- Hall SL, Greendale GA. The relationship of dietary vitamin C intake to bone mineral density: results from the PEPI study. Calcif Tissue Int 1998;63:183–9.
- Odaland LM, Mason RL, Alexeff AI. Bone density and dietary findings of 409 Tennessee subject. I. Bone density considerations Am J Clin Nutr 1972;25:905–907.
- Sowers MR, Wallace RB, Lemke JH. Correlates of mid-radius bone density among postmenopausal women: a community study. Am J Clin Nutr 1985;41;1045–1053.
- Freudenheim LJ, 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; 863–876.
- Hernandez-Avila M, Stampfer MJ, Ravnikar VA, et al. Caffeine and other predictors of bone density among pre- and perimenopausal women. Epidemiology 1993;4:128–34.
- Leveille SG, LaCroix AZ, Koepsell TD, et al. Dietary vitamin C and bone mineral density in postmenopausal women in Washington State, USA. J Epidemiol Community Health 1997;51:479–85.
- Weber P. The role of vitamins in the prevention of osteoporosis—a brief status report. Int J Vitam Nutr Res 1999;69:194–7.
- 94. Kaptoge S, Welch A, McTaggart A, et al. Effects of dietary nutrients and food groups on bone loss from the proximal femur in men and women in the 7th and 8th decades of age. Osteoporos Int 2003;14: 418–28.
- Melhus H, Michaelsson K, Kindmark A, et al. Excessive dietary intake of vitamin A is associated with reduced bone mineral density and increased risk for hip fracture. Ann Intern Med 1998;15:129:770–8.

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- Whiting SJ, Lemke B. Excess retinol intake may explain the high incidence of osteoporosis in northern Europe. Nutr Rev 1999;57:192–5.
- 97. Sigurdsson G. Dietary vitamin A intake and risk for hip fracture. Ann Intern Med 1999;7:131:392.
- Lim LS, Harnack LJ, Lazovich D, Folsom AR. Vitamin A intake and the risk of hip fracture in postmenopausal women: the Iowa Women's Health Study. Osteoporos Int 2004;15:552–9.
- Durlach J, Bac P, Durlach V, Rayssiguier Y, Bara M, Guiet-Bara A. Magnesium status and ageing: an update. Magnes Res 1998;11:25–42.
- Rude RK, Olerich M. Magnesium deficiency: possible role in osteoporosis associated with gluten-sensitive enteropathy. Osteoporos Int 1996;6:453–61.
- 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;69:727–36.
- Nielsen, FH. Studies on the relationship between boron and magnesium which possibly affects the formation and maintenance of bones. Mag Tr Elem 1990;9:61–9.
- Stendig-Lindberg G, Tepper R, Leichter I. Trabecular bone density in a two year controlled trial of peroral magnesium in osteoporosis. Magnes Res 1993;6:155–63.
- 104. Jackson RD, Bassford T, Cauley J, et al. The impact of magnesium intake on fractures: results from the women's health initiative observational study (WHI-OS). ASBMR 2003 (abstr).
- Cauley JA, Murphy PA, Riley TJ, Buhari AM. Effects of fluoridated drinking water on bone mass and fractures: the study of osteoporotic fractures. J Bone Miner Res 1995;10:1076–86.
- Suarez-Almazor ME, Flowerdew G, Saunders LD, Soskolne CL, Russell AS. The fluoridation of drinking water and hip fracture hospitalization rates in two Canadian communities. Am J Public Health 1993; 83:689–93.
- Kurltio P, Gustavsson N, Vartiomen T, Pekkanen J. Exposure to natural fluoride in well water and hip fracture: a cohort analysis. Am J Epidemiol 1999;150:817–24.
- Riggs BL. Treatment of osteoporosis with sodium fluoride or parathyroid hormone. Am J Med 1993;95:625–65.
- Strause L, Saltman P, Smith KT, et al. Spinal bone loss in postmenopausal women supplemented with calcium and trace minerals. J Nutr 1994;124:1060–4.
- Gur A, Colpan L, Nas K, et al. The role of trace minerals in the pathogenesis of postmenopausal osteoporosis and a new effect of calcitonin. J Bone Miner Metab 2002;20:39–43.
- Nielsen FH, Hunter CD, Mullen LM, Hunt JR. Effect of dietary boron on mineral, estrogen, and testosterone metabolism in postmenopausal women, FASEB J 1987;1:394–7.
- 112. Baker A, Harvey L, Majassk-Newman G, et al. Effect of dietary copper

intakes on biochemical markers of bone metabolism in healthy adult males. Eur J Clin Nutr 1999;53:408–12.

- Baker A, Turley E, Bonham MP, et al. No effect of copper supplementation on biochemical markers of bone metabolism in healthy adults. Br J Nutr 1999;82:283–90.
- 114. Cashman KD, Baker A, Ginty F, et al. No effect of copper supplementation on biochemical markers of bone metabolism in healthy young adult females, despite apparently improved copper status. Eur J Clin Nutr 2001;55:525–31.
- 115. Jugdaohsingh R, Tucker KL, Qiao N, Cupples LA, Kiel DP, Powell JJ. Dietary silicon intake is positively associated with bone mineral density in men and premenopausal women of the Framingham Offspring cohort. J Bone Miner Res 2004;19:297–307.
- 116. Dhonukshe-Rutten RA, Lips M, de Jong N, et al. Vitamin B-12 status is associated with bone mineral content and bone mineral density in frail elderly women but not in men. J Nutr 2003;133:801–7.
- 117. Tucker KL, Hannan MT, Qiao N, et al. Low plasma vitamin B(12) is associated with lower BMD: the Framingham osteoporosis study. J Bone Miner Res 2005;20:152–8.
- Harris MM, Houtkooper LB, Stanford VA, et al. Dietary iron is associated with bone mineral density in healthy postmenopausal women. J Nutr 2003;133:3598–602.
- Hearney RP, Dowell MS, Hale CA, Bendich A. Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D. J Am Coll Nutr 2003;22:142–6.
- Wu F, Staykova T, Horne A, et al. Efficacy of an oral, 10-day course of high-dose calciferol in correcting vitamin D deficiency. N Z Med J 2003;116(1179):U536 (abstr).
- Lilliu H, Pamphile R, Chapuy MC, Schulten J, Arlot M, Meunier PJ. Calcium-vitamin D3 supplementation is cost-effective in hip fractures prevention. Maturitas 2003;44:299–305.
- 122. Boonen S, Rizzoli R, Meunier PJ, et al. The need for clinical guidance in the use of calcium and vitamin D in the management of osteoporosis: a consensus report. Osteoporos Int 2004;15:511–9.
- 123. Nieves JW, Cosman F. The treatment of osteoporosis and interaction of medications and nutrition. In: New S, Bonjour JP, eds. Nutritional aspects of bone health. Cambridge: The Royal Society for Chemistry, 2003;565–88.
- Prynne CJ, Ginty F, Paul AA, et al. Dietary acid-base balance and intake of bone-related nutrients in Cambridge teenagers. Eur J Clin Nutr 2004;58:155–8.
- 125. 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;79:155–65.
- Burns L, Ashwell M, Berry J, et al. UK Food Standards Agency Optimal Nutrition Status Workshop: environmental factors that affect bone health throughout life. Br J Nutr 2003;89:835–40.

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