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The Role of Nutrients in Bone Health, from A to Z

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Osteoporosis is a major public health problem, affecting millions of individuals. Dietary intake is an important modifiable factor for bone health. Inadequate intake of nutrients important to bone increases the risk for bone loss and subsequent osteoporosis. The process of bone formation requires an adequate and constant supply of nutrients, such as calcium, protein, magnesium, phosphorus, vitamin D, potassium, and fluoride. However, there are several other vitamins and minerals needed for metabolic processes related to bone, including manganese, copper, boron, iron, zinc, vitamin A, vitamin K, vitamin C, and the B vitamins. Although the recommended levels of nutrients traditionally related to bone were aimed to promote bone mass and strength, the recommended levels of the other nutrients that also influence bone were set on different parameters, and may not be optimal for bone health, in view of recent epidemiological studies and clinical trials.

Keywords   bone, minerals, vitamins, dietary reference intakes, osteoporosis

INTRODUCTION

Osteoporosis is a major public health problem worldwide. About 10 million Americans over age 50 have osteoporosis of the hip, and an additional 34 million over age 50 have low bone mass or "osteopenia" of the hip.[1] It is estimated that by 2010, there will be 12 million cases of osteoporosis and 40 million cases of osteopenia in Americans over the age of 50.[1] One of the risk factors for bone loss, and thus the development of osteoporosis, is an inadequate dietary intake of nutrients important to bones. Because bones undergo continuous remodeling, an adequate supply of nutrient substrate is needed to support the formation phase of bone remodeling. In addition to their passive roles as substrate for bone formation, dietary calcium and protein play active roles in bone metabolism, as well as phosphorus and vitamin D. Other vitamins and minerals are also needed for metabolic processes related to bone, directly or indirectly.

The Food and Nutrition Board (FNB) of the National Academy of Sciences, has released in the past few years the new Dietary Reference Intakes (DRI) based on the latest understanding about nutrient requirements for optimizing health.[2] For the bone related nutrients, calcium, magnesium, phosphorus, fluoride, and vitamin D, these recommendations were aimed to promote bone strength and to maintain normal nutritional status for individuals at different stages of life. The DRI of other important nutrients to bone health were based on parameters such as usual intake in healthy individuals and biochemical markers, and were recently revised.

The present review discusses the role of the nutrients that have an influence on bone health and compares the level of nutrient intake required for bone health as a component of the dietary recommendation from the FNB for general health.

PROTEIN

Protein is part of the organic matrix of bone for collagen structure and is essential to maintain the production of hormones and growth factors that modulate bone synthesis. High protein intake has been traditionally referred as a risk factor for osteoporosis,[3,4] since balance studies have found increased urinary calcium excretion with high protein diets.[5] However, a recent study using radiotracers measured the effects of a controlled high and low meat diets on body calcium retention in healthy postmenopausal women for 8 weeks and found no difference in calcium retention or biomarkers of bone metabolism.[6] In fact, protein intake has shown to increase insulin-like growth factor I (IGF-I), which is known to be osteotrophic.[7] High protein and calcium diets have been found to induce favorable changes in bone in children,[8] postmenopausal women,[9] and elderly[10] probably through increase IGF-I. Protein supplementation also improves outcomes after hip fracture in elderly along with calcium supplementation.[11]

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The Recommended Dietary Allowance (RDA) for protein was established at 0.8 grams of protein per kilogram of body weight.[12] This level was set to provide a standard of sufficient protein to prevent deficiency and disease, using nitrogen balance and the factorial method to estimate nitrogen obligatory losses. In young women, varying protein intake from 0.7 kg/body weight, 1 kg/body weight, to 2.1 kg/body weight showed that the high level of protein intake increased bone resorption and urinary calcium excretion with no concomitant increase in bone formation, while the low protein intake decreased calcium absorption and increased PTH.[13] In contrast, the medium protein intake did not change any of these factors. This medium level is higher than current recommendations.

CALCIUM

Calcium is one of the main bone-forming minerals and 99% of the body's calcium resides in the skeleton. There is now substantial evidence that adequate dietary calcium maximizes peak bone mass early in life[14,15] and prevents bone loss later.[16,17] A recent review of the benefit of calcium on bone throughout the lifespan showed that 52 out of 54 randomized, controlled intervention trials increasing calcium intake led to increased calcium balance, increased bone gain during growth, reduced bone loss in later years, or reduced fracture incidence.[18] This review also showed that 64 out of 86 observational studies also showed a positive link between calcium intake and bone mass in children, young adults, and postmenopausal women. Two meta-analysis of randomized, controlled trials have shown that calcium supplementation reduces the relative risk of hip fracture by 25–70%,[19] vertebral fractures by 23% and nonvertebral fractures by 14%.[20] However, the benefits of calcium supplementation in bone is more apparent in those with habitual low calcium intake and these benefits disappear once calcium supplementation is removed, suggesting a need for adequate calcium intake throughout life.

Calcium recommendations were set at levels associated with the development of maximal peak bone mass during growth and the lessening of bone loss thereafter at 1300 mg/d for adolescents, 1000 mg/d for adults, and 1200 mg/d for 51 y and older.[21] These levels were based on maximum retention of calcium, the intake which provides no additional benefit in retention, within the genetic potential. Data from calcium retention in balance studies at different ages, and from randomized clinical trials, cross-sectional, and epidemiological studies measuring bone mineral density (BMD) changes over time were taken into consideration.[14−17,22−38] Studies in menopausal and post-menopausal women have shown that intakes above 1 g/d, which is approximately the adequate intake (AI), leads to higher BMD, lower bone loss, and positive calcium balance.[18]

PHOSPHORUS

Phosphorus is an essential bone-forming element because it is required for the appropriate mineralization of the skeleton. A depletion of phosphorus leads to impaired mineralization, however, there is little evidence that in healthy individuals, dietary phosphorus affects the incidence of osteoporosis. There is more concern on the effects of high dietary phosphorus on bone, especially if combined with a low calcium diet. A diet high in phosphorus and low in calcium increased parathyroid hormone (PTH) levels in young adults after 4 weeks,[39] but these effects are also shown with a low calcium diet alone.[40] Human studies showed no effect on bone with phosphorus supplementation.[41] Another concern is the rise in phosphorus rich carbonated drinks consumption on bone health, which has been association with an increase in fracture rates and lower bone mass in adults.[42,43] However, Heaney and Rafferty[44] showed negligible effects on calcium excretion with consumption of these drinks and concluded that the skeletal effects of carbonated beverage consumption are likely due primarily to milk displacement. Healthy individuals can adjust to a wide range in phosphorus consumption, whereas their ability to adapt to low calcium intakes appears to be limited, therefore, the ratio of phosphorus to calcium intake seems to be more important in bone health than the absolute intake of phosphorus.[45,46]

Nutritional recommendations were based on maintaining phosphorus balance and normal serum phosphate levels in adults, thus setting this level at 1250 mg/d for adolescents, 700 mg/d for adults, and 580 mg/d for 51 y and older.[21] The serum phosphate levels are directly affected by dietary intakes, and levels above the lower end of the normal range are considered adequate phosphorus intake to meet cellular and bone formation needs of healthy individuals.

MAGNESIUM

Approximately 60% of the magnesium in the body is in bone. Magnesium influences mineral metabolism indirectly through its role in ATP metabolism and as a cofactor for over 300 enzymes, and by direct effects on bone quality by decreasing hydroxyapatite crystal size, thereby preventing larger, more perfect mineral crystals that result in brittle bone. As with calcium, magnesium is at risk for being deficient in the diet. Deficiency of this mineral could affect bone growth, osteoblastic and osteoclastic activity, osteopenia, bone fragility, and alter calcium metabolism.[47] In addition, it was suggested that high calcium diets could intensify magnesium deficiency, but long term balance studies do not support this.[48] The scant clinical data available support a relationship between dietary magnesium and bone at different sites.[49,50] Magnesium supplementation has also been found to increase BMD after 1–2 y in menopausal women,[51] in postmenopausal women,[52,53] and reduce bone turnover in men.[54] However, a study in 89,717 postmenopausal women age 50–79 years enrolled in the Women's Health Initiative found that those in the highest quintile of magnesium intake had the highest rate of wrist/lower arm fractures.[55] Therefore, the data on the relationship between magnesium intake and bone is still inconclusive.

The RDA for magnesium was increased based on the results of recent, tightly controlled balance studies that utilized more accurate methods of measuring magnesium.[21] The RDA, set to meet tissue needs and offset losses, was established at 310 and 400 mg/d in 19–30 y, and 320 and 420 mg/d in >30 y, in females and males, respectively. Studies in menopausal women and in the elderly have shown that intakes close to the RDA are related to greater BMD and lower bone resorption,[49,50] and suppression of bone turnover in young men.[54]

FLUORIDE

Fluoride in bone can replace the hydroxyl groups in the hydroxyapatite crystal to form the less soluble fluoroapatite, which increases the crystallization size. Drinking water fluoridation has been long used in the prevention of dental caries, but may also positively or negatively affect bone. Greater BMD has been reported in populations with fluoridated water at 1 ppm,[56] with a decrease in overall fracture risk.[57] However, >4.32 ppm fluoride in water increases the risk.[56] High fluoride concentrations also stimulate osteoblast activity, and this has been the rationale for using fluoride supplements in fracture prevention. Studies using high levels of fluoride salts (>50 mg/d) have found inconclusive results in the prevention of fractures.[58,59] However, lower levels (11–20 mg/d) appear to decrease vertebral fracture risk and increase spine, lumbar, and femoral neck BMD.[60,61] This suggests that excessive fluoride may lead to very large crystals and bone may become brittle and more fragile but lower levels of fluoride in water and in supplements could be beneficial to bone.

The AI for fluoride was based on estimated intakes that have been shown to reduce the occurrence of dental caries most effectively without causing the unwanted side effect of dental fluorosis.[21] These levels (3 mg/d in women and 4 mg/d in men) have been shown to lower fracture risk and increase BMD in adults.[56,62]

ZINC

Zinc is needed for osteoblastic activity, collagen synthesis, and alkaline phosphatase activity. Low serum zinc levels and excessive urinary zinc excretion appears to be related to osteoporosis,[63,64] but the data is not yet conclusive. The elderly population may be at higher risk of zinc deficiency since this group has low serum zinc values.[65] A 2-y clinical study in postmenopausal women, calcium supplementation plus zinc, copper, and manganese resulted in greater gain in bone compared to calcium alone.[66] Zinc supplementation has also shown to improve height gain[67] and bone and collagen synthesis[68] of growth retarded children.

Since a sensitive indicator of zinc nutritional status is not readily available, the RDA for zinc was based on a number of different indicators of zinc nutritional status and represents the daily intake likely to prevent deficiency in nearly all individuals in a specific age and gender group.[69] The reported intake level of zinc associated with increases in BMD in postmenopausal women is higher (15 mg/d)[66] than the current RDA (8 mg/d in women and 11 mg/d in men).

COPPER

Copper influences bone formation, skeletal mineralization, and the integrity of the connective tissue. Lysyl oxidase, a copper-containing enzyme, is essential for cross-linking of collagen fibrils, thereby increasing the mechanical strength of the protein and forming strong, flexible connective tissue. Copper deficiency has been shown to decrease bone strength in animal studies.[70] In humans, copper supplementation for 2 years was associated with a reduction in bone loss in perimenopausal[71] and postmenopausal women.[66]

A variety of indicators were used to establish the recommended levels for copper, including plasma copper concentration, serum ceruloplasmin activity, superoxide dismutase activity, and platelet copper concentration.[69] The RDA for copper reflects the results of depletion-repletion studies and was based on the prevention of deficiency (900 mg/d for adults). However, higher levels (2.5–3 mg/d) have been associated with greater BMD and lower bone loss in pre and post-menopausal women.[66,71]

BORON

Boron may play role in bone health through the formation of steroid hormones, and therefore, it may be involved in the prevention of calcium loss and bone demineralization. It has been shown that boron supplementation markedly reduces the urinary calcium and magnesium excretion, increases serum levels of estradiol,[72] and increases calcium absorption,[73] in peri- and postmenopausal women. In college age females, boron supplementation was shown to be related to BMD.[74] Boron has also been related to vitamin D function by stimulating growth in vitamin D deficient animals and alleviating perturbations in mineral metabolism that are characteristic of vitamin D deficiency.[75]

No recommended levels have been set for boron, only upper limits of intake (20 mg/d).[69] Because no data are available on the adverse effects of very high intakes of boron in humans, animal studies were used to extrapolate the upper limit. These studies were based on the effects of high boron intakes on reproductive and developmental function. The level of boron intake associated with gains in bone was about 3 mg/d[73] well below this limit.

MANGANESE

Manganese is needed for the biosynthesis of mucopolysaccharides in bone matrix formation and is a cofactor for several enzymes in bone tissue. Manganese deficient animals have

alterations in IGF metabolism, growth, and bone.[76] Manganese supplementation, along with calcium, copper, and zinc resulted in greater gain in bone compared to calcium alone in post-menopausal women over a 2 year period.[66] More studies are needed to determine the impact of manganese supplementation alone on bone.

Manganese deficiency has not been documented in humans eating natural diets, therefore, the AI was based on average dietary intakes of manganese in healthy individuals.[69] Levels higher than the AI (1.8 mg/d in women and 2.3 mg/d in men) are associated with gains in BMD (5 mg/d).[66]

POTASSIUM

A high potassium intake, along with other nutrients present in fruit and vegetables, promote an alkaline environment, thereby reducing the demand for skeletal salts to balance the endogenous acid generated from acid producing foods, such as meats. By preserving calcium in bones, which might otherwise be mobilized to maintain normal pH, potassium rich foods may help prevent osteoporosis. Studies have shown a positive association between potassium intake and total BMD in perimenopausal women[49] and with hip and forearm BMD in the elderly.[50] Moreover, clinical trials with potassium bicarbonate supplementation has shown a decrease in urinary calcium excretion, improved calcium balance, decreased bone resorption, and increased bone formation,[77,78] while low potassium intakes increased bone resorption.[49]

The new potassium recommendations are 3500 mg/d for ages 1–3 y, 3800 mg/d for ages 4–8 y, 4500 mg/d for ages 9–18 y, and 4700 mg/d for ages 19 and older. These levels would benefit bone since the study by Tucker et al. showed that subjects consuming the highest quartile of potassium intake, about 3494–3999 mg/d, had significantly greater trochanter BMD in men and women compared to the lower quartiles.[50]

IRON

Iron acts as a cofactor in enzymes involved in collagen bone matrix synthesis. Such enzymes are prolyl and lysyl hydroxylases, essentials in steps before crosslinking by the copper-dependent enzyme lysyl oxidase. Iron is also a cofactor in 25-hydroxycholcalciferol hydroxylase, which is involved in transforming vitamin D to active form, thereby affecting calcium absorption. Iron-deficient animals have lower bone mass and mechanical strength compared to iron-replete rats. In humans, no significant associations have been detected between bone and iron status, however, a trend was observed in girls between BMD at the radius and serum ferritin.[79]

The RDA for iron was recently revised and was based on the prevention of iron deficiency and maintenance of adequate iron stores in individuals eating a mixed diet.[69] No iron intake level has yet been related to bone in humans.

VITAMIN D

Vitamin D is a critical nutrient for optimal bone health because it maintains serum calcium levels by increasing calcium absorption efficiency. Vitamin D insufficiency is associated with increased risk of hip fractures, especially in the elderly, due to less efficient skin synthesis and intestinal absorption, reduced sun exposure and intake.[80,81] Hypovitaminosis D is now a major worldwide public health problem, even in young adults[82] Several randomized, controlled trials have shown that vitamin D supplementation, along with calcium, decreases bone loss and fracture incidence in the elderly.[38,83] Vitamin D supplementation alone has also shown to protect against bone loss at the femoral neck[84] and at the spine[85] in elderly women. However, no additional benefit to bone has been reported when vitamin D in addition to calcium is given, rather than calcium alone in Caucasian postmenopausal women[86] and in African–American post-menopausal women[87] with normal serum 25-hydroxyvitamin D levels.

The AI for vitamin D was set at the intake that will maintain adequate serum 25-hydroxyvitamin D levels for individuals in the population group who have limited but uncertain sun exposure and stores, multiplied by a safety factor of 100% for those unable to obtain sunlight, which prevents the seasonal fluctuations. These levels were set at 200 mg/d for individuals younger than 50 y, 400 mg/d for 51–70 y, and 600 for >70 y.[21] A requirement of this nutrient is a very active area of research. Recently, an 18-y prospective study reported that vitamin D intakes of about 500 IU (12.5 μg), within the AI level, were related to 37% lower fracture risk in postmenopausal women.[88]

VITAMIN K

Vitamin K is a cofactor of γ-carboxylase, an enzyme necessary for the γ-carboxylation of glutamic acid residues in proteins, including osteocalcin, the principal noncollagenous protein of bone. Vitamin K deficiency increases undercarboxylated osteocalcin, a less fully functional form, and detected in osteoporotic patients.[89] Population studies have also shown an association between low vitamin K intake and lower BMD or higher fracture risk.[90,91] Conversely, vitamin K supplementation reduces undercaboxylated fractions of osteocalcin, urinary calcium excretion, and bone resorption and increases bone.[92,93]

Various indicators have been used to assess vitamin K status; however, they do not provide an adequate basis on which to estimate vitamin K requirements due to incomplete understanding of the physiological significance and lack of data. Therefore, intake levels for vitamin K were based on reported data on consumption levels of healthy individuals.[69] These levels (90 mcg/d in women and 120 mcg/d in men) are lower compared to the levels relating vitamin K and bone health. Recent reports demonstrated that women consuming the lowest quartile of vitamin K intake (<109 mcg/d) had the lowest BMD and highest fracture risks compared to those in the highest quartiles of intake.[90,91]

VITAMIN C

Vitamin C is a cofactor in the hydroxylation of lysine and proline, and therefore is required in the cross-linking of collagen fibrils in bone. Vitamin C stimulates alkaline phosphatase activity, a marker for osteoblast formation. Several studies have reported a beneficial effect of vitamin C intake on BMD in children,[94] early post-menopausal women consuming at least 500 mg of calcium,[95] and in post-menopausal women.[96]

The RDA for vitamin C was recently increased to 75 mg/d in women and 90 mg/d in men.[97] It is still based primarily on the prevention of deficiency, rather than the prevention of chronic disease and the promotion of optimum health. However, intakes higher than the RDAs have been related to better bone health. In postmenopausal women greater BMD was reported as vitamin C intake from supplements increased from 0, 500 and 1000 mg/d.[96]

VITAMIN A

Vitamin A is essential in the bone remodeling process because osteoblasts and osteoclasts have nuclear receptors for retinoic acid. Vitamin A deficiency in animals leads to morphological changes in bone by increasing bone thickness. However, excess vitamin A intakes from retinol and serum retinol are related to lower BMD and higher fracture risk,[98,99] but low intakes as well.[100]

The latest RDA was based on the amount needed to ensure adequate stores of vitamin A in the body to support normal reproductive and immune function, gene expression, and vision.[69] It has been shown recently that vitamin A intake close to current recommendations (2333 IU in women and 3000 IU in men) is associated with peak BMD and bone maintenance.[100]

B VITAMINS

Although the B vitamins, thiamin, riboflavin, and niacin, do not have a direct role on bone metabolism, these may be important indirectly by their role in energy metabolism. Riboflavin has been associated with bone in Japanese women.[101] Niacin has been also found to be positively related to BMD at the calcaneus in pre-menopausal women.[102] In addition, thiamin intake was found significantly lower in hip fracture patients compared with age-matched counterparts.[103]

Vitamin B_6 is an essential cofactor for the enzyme ornithine decarboxylase, which is involved in osteoblast NADPH concentrations. NADPH is essential for the vitamin K cycle; therefore, it is possible that vitamin B_6 could modulate the effects of vitamin K on bone metabolism. Studies in animals show that vitamin B_6 deficiency appears to impair bone mechanical performance. In humans, hip fracture patients had significantly lower vitamin B_6 intake compared to those without fractures.[103]

Folic acid acts as a coenzyme mediating the transfer of one-carbon units in a variety of reactions critical to the metabolism of

nucleic and amino acids. A 4-yr clinical trial in postmenopausal women found folate significantly correlated with changes in radius BMC.[104]

Vitamin B_{12} is important for osteoblast function, by acting as a cofactor on osteoblast-related proteins, such as bone alkaline phosphatase and osteocalcin. Vitamin B12 also is involved in iron metabolism, which is also involved in bone formation (above). In vitro studies have shown that vitamin B_{12} deficiency suppressed activity of osteoblasts. Studies have shown that osteoporosis occurred more often among men and women with marginal or deficient vitamin B_{12} status compared to those with a normal status.[105,106]

The RDA of thiamin, riboflavin, and niacin was set to prevent deficiency. For vitamin B_6, requirements were set by primarily to maintain an adequate plasma pyridoxal phosphate concentration. For folate, the most recent RDA was based primarily on the adequacy of red blood cell folate concentrations at different levels of folate intake, which have been shown to correlate with liver folate stores. For vitamin B_{12}, the RDA was set to maintain the hematological status and serum B_{12} values. There is little evidence to determine the appropriateness of these B vitamins' recommended levels for optimal bone health.

CONCLUSIONS

Bone is strongly influenced by the intake of several nutrients. Not only the traditional nutrients related to bone, e.g. calcium, protein, phosphorus, magnesium, vitamin D, and fluoride, are important in bone health, but also several other vitamins and minerals. The recommended levels of many of these nutrients are not optimal for bone health. Several recent epidemiological studies and clinical trials have reported higher intake levels of some of these nutrients for building bone mass, preventing bone loss and fractures, and decreasing bone resorption and/or increasing bone formation. Such nutrients include zinc, copper, manganese, vitamin K, and vitamin C. Other nutrients, including iron, boron, thiamin, riboflavin, niacin, vitamins B_6 and B_{12}, and folate need to be further studied to assess the appropriateness of the current recommendations to bone health.

These nutrients are found in a variety of foods. Dairy products provide ample calcium, as well as protein, vitamin D, phosphorus, potassium, magnesium, and zinc. Calcium is also found in green leafy vegetables, such as bok choy, broccoli, collard, and kale, which also provide magnesium, potassium, boron, vitamins K, A, and C. Fruits and vegetables provide magnesium, boron, vitamins K, A, and C. In addition, they promote an alkaline environment, thereby reducing the demand for skeletal salts to balance the acid generated from meats. Legumes and whole-grain products provide phosphorus, potassium, magnesium, manganese, zinc, copper, and vitamin K. In addition, beef, fish, or poultry, and nuts and seeds are good sources of protein, zinc, magnesium, copper, phosphorus, manganese, and iron.

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