

Microelements for bone boost: the last but not the least

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Summary

Osteoporosis is a major public health problem affects many millions of people around the world. It is a metabolic bone disease characterized by loss of bone mass and strength, resulting in increased risk of fractures. Several lifestyle factors are considered to be important determinants of it and nutrition can potentially have a positive impact on bone health, in the development and maintenance of bone mass and in the prevention of osteoporosis. There are potentially numerous nutrients and dietary components that can influence bone health, and these range from the macronutrients to micronutrients. In the last decade, epidemiological studies and clinical trials showed micronutrients can potentially have a positive impact on bone health, preventing bone loss and fractures, decreasing bone resorption and increasing bone formation. Consequently, optimizing micronutrients intake might represent an effective and low-cost preventive measure against osteoporosis.

KEY WORDS: osteoporosis; microelements; nutrition.

Introduction

Osteoporosis is a major public health problem affects many millions of people around the world (1). It is characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and consequent increase in fracture risk (2). More than 200 million people are presumably affected worldwide; annually there are 3.5 million new fragility fractures and this incidence will increase in the next years (3). Osteoporotic fractures are a major cause of morbidity and disability in the elderly and can lead to premature death. In addition, they impose a considerable economic burden on health services, costing many bil-

lions of dollars each year (4). Osteoporosis is a multifactorial disease and several factors, unmodifiable, such as genetic, sex, age, and modifiable such as lifestyle are considered to be important determinants of it (5). Nutrition is an important modifiable factor in the development and maintenance of bone mass and in the prevention of osteoporosis. Physiologically, bone is an active tissue constantly remodeled by concerted and coordinated interactions between osteoclasts, involved in bone resorption, and osteoblasts, which ensure bone formation and mineralization; for this continuous remodeling, an adequate supply of macronutrients and micronutrients substrate, such as vitamins and minerals, are needed to support bone remodeling. In recent years, there has been a growing interest in studies concerning the role of dietary micronutrients on bone health (6). Many of the micronutrients consumed as part of a Westernized diet can potentially have a positive impact on bone health. In the last decade major attention was focused on the role of calcium in nutritional prevention of osteoporosis, furthermore, several additional dietary inorganic minerals, also defined micronutrients, are known to be important for skeleton recently, and their intake is positively associated with bone mass (7, 8). Micronutrients play a prominent role in bone health: several minerals have direct roles in hydroxyapatite crystal formation and structure, other nutrients have indirect roles as cofactors or as regulators of cellular activity (9).

Calcium

Calcium is one of the main bone-forming minerals and 99% of the body's calcium resides in the skeleton. Calcium intake is one of the important modifiable environmental factors for the normal development of skeleton in young and the maintenance of bone mass in adult (10). Higher calcium intake has been related to higher bone mass in adults and post-menopausal women and this effect has been examined in a large number of randomized controlled trials (11-14). These trials have shown that in older people with a baseline calcium intake of 500-1000 mg/day, increasing the intake by a further 500-1200 mg/day can prevent bone loss. Studies in men showed similar effects (15). In the last decade, meta-analysis have concluded that calcium intake is a significant determinant of BMD but the magnitude of the effect is small, at about 1% of the population variance (16, 17). Recently, a meta-analysis confirms that increasing calcium intake from dietary sources slightly increased bone mineral density by 0.6-1.8% over one to two years at all sites, except for the forearm (18).

The influence of calcium supplementation on fracture risk is still a matter of debate, having reported in literature contrasting results. In fact, low calcium intake correlates with increased risk of hip fracture, but increasing intake above 750 mg/day does not correlate with progressively lower risks of hip fracture (19, 20). A recent meta-analysis indicates that dietary calcium intake is not associated with risk of fracture, and there is no evidence currently that increasing dietary calcium intake prevents fractures (21). The recommended dietary allowance of calcium ranges from 1000 to 1.300 mg/day.

Magnesium

Magnesium, an ubiquitous element in various organ systems and co-factor of hundreds of enzymes, is increasingly recognized as an important contributor to bone health. About 60% of all magnesium in the body is found in bone, where it is a structural constituent, along with calcium and phosphate; this magnesium makes up about 1% of the total bone mineral content (22). In several studies on animals, dietary magnesium restriction promotes osteoporosis, fragility, microfractures of the trabeculae and reduction of bone's mechanical properties (23); conversely, in ovariectomized rats magnesium supplementation increased osteocalcin, reduced parathyroid hormone and deoxypyridinoline, and increased bone strength and fracture resistance (24). Also in humans magnesium deficiency contributes to osteoporosis; in Framingham study magnesium intake was positively associated with bone mass density (25). Recently, the protective effect of high magnesium intake on bone quality was documented in healthy women using ultrasound measurement in calcaneus (26) and a trial shows a positive effect of magnesium supplementation on the accrual of bone mass in the hip of young women (27). Several direct and indirect mechanisms contribute to the effects of low magnesium on bone density: low magnesium can directly affect the bone by altering the structure of apatite crystals; magnesium deficiency is also associated with reduction of PTH and 1,25(OH)₂D levels and low grade inflammation and endothelial dysfunction, with a well-known relation between inflammation and bone loss (28). Dietary sources of magnesium include almonds, cashews and peanuts, raisin bran cereal, potato skins, brown rice, kidney beans, black-eyed peas and lentils. A modest supplementation with 250 mg/day of magnesium is reasonable to support bone health, and for other aspects of general health (29).

Zinc

Zinc is a cofactor in many metalloenzymes and is an extremely important element from the point of view of bone health; skeleton contains a large proportion of the total body burden of zinc (30). In experimental animal models, zinc deficiency has been associated with altered osteoblastic activity and decreased synthesis of collagen, chondroitin sulfate, and alkaline phosphatase (7); it is also observed that zinc inhibited loss of bone mass in ovariectomized rats and similar beneficial effects of zinc in rats with low calcium intake (31, 32). The importance of zinc in bone metabolism has been recognized in humans. A study showed the mean concentrations of serum zinc were significantly lower in osteoporotic women than in either osteopenic or normal women (33). One study showed that serum zinc level in patients with bone fractures was significantly lower than normal range and supplementation with zinc had positive effect on callus formation (34). A recent study showed that the mean dietary intake of magnesium, zinc and calcium in post-menopausal women with low bone density were significantly lower than recommended dietary allowance (35). Zinc plays a pivotal role in the regulation of bone homeostasis. Many zinc-related proteins are found to involve in the regulation of cellular function in osteoblasts and osteoclasts. Zinc stimulates cell differentiation, cell proliferation, and mineralization in osteoblasts through gene expression of various proteins including type I collagen, alkaline phosphatase, and osteocalcin (36). Furthermore, zinc inhibits osteoclastic bone resorption suppressing osteoclast-like cell formation, inhibits action of RANKL in pre-osteoclasts and stimulates gene expression of OPG in osteoblastic cells (36). Zinc is found in a wide variety of foods including red meat, lamb, shell fish, seeds, nuts, dairy products, poultry and beans. The recommended daily minimum intake of zinc is 12 mg and for bone health 15 mg is recommended (37).

Manganese

Manganese is distributed in tissues throughout the body, including bone; manganese activates phosphatases, kinases, decarboxylases and glycosyltransferases, also is a constituent of some enzymes (38). In recent decades research has uncovered the special role manganese plays as a co-factor in the formation of bone cartilage and bone collagen, as well as in bone mineralization (39). Multiple studies in rats have shown diets lower in manganese prevent cartilage formation and produce osteopenia, as result of an imbalance between osteoblastic and osteoclastic activity (40). In humans it has been reported that osteoporotic subjects have low serum manganese level (41), furthermore, in a randomized, controlled, two-year trial, a supplement containing manganese, copper and zinc in combination with a calcium supplement was found to be more effective than the calcium supplement alone in preventing spinal bone loss (42). The skeleton abnormalities could be due to a reduction in proteoglycan synthesis secondary to a reduction of manganese dependent glycosyltransferases; recently, in manganese deficient rats it has been reported an alteration in synthesis of IGF-1, involved in regular bone formation (43). Dietary sources of manganese include cereals, nuts, pineapples, beans, mollusks, dark chocolate, cinnamon, and tea. The Recommended Daily Allowance of manganese is 1.8 mg/day for women and 2.3 mg/day for men; relative to bone health, adequate intake of manganese has not been established.

Boron

The trace mineral boron is a micronutrient with diverse and vitally important roles in metabolism. Recent data from animal and human studies suggest boron may be important for mineral metabolism and prevention of osteoporosis (44). There is evidence that compositional and functional properties of bone, as well as mineral status required for bone health, are affected by boron status with a worsening under circumstances of boron deprivation (45-47). In animals, supplemental boron as boric acid has been shown to increase bone strength (48-50) and two studies published recently (51, 52) found that healing of the alveolar bone, a ridge of compact bone that contains the tooth sockets on the maxillae and mandible, was inhibited in boron deficient rats. In two human studies, boron deprivation was associated with decreased plasma calcium and calcitonin and increased urinary calcium excretion (45, 46). The mechanism by which boron acts on bone has not yet been established; it has been shown to enhance collagenase and cathepsin D activity in fibroblasts that modulate the turnover of extracellular matrix, allowing for changes in composition, structure, and strength of bones (53). Beneficial effects on bone metabolism can due in part to the roles it plays in both producing E₂ and in increasing its biological half-life and that of vitamin D (54). The Recommended Daily Allowance of boron has not been established; however, a study of postmenopausal women reported that 3-4 mg/die of boron for a period of one year improved bone mineral density (55), thus, it is reasonable supplement diet by consumption of foods rich in boron such as prunes, raisins, dried apricots, or avocados.

Copper

Copper is an essential trace mineral that has only recently been found to play an important role in bone health maintenance. Studies in animals showed rats fed a copper deficient diet had re-

duced bone mineral content and reduced bone strength (56). In humans severe copper deficiency is known to cause skeletal abnormalities, for example, osteoporosis is associated with malabsorption of copper in Menkes' disease (57). Elderly patients with fractures of the femoral neck were found to have significantly lower serum copper levels than age and sex matched controls (58). Post-menopausal women with a high dietary calcium intake combined with a high serum copper level had a greater lumbar bone density than women with low calcium intake and low serum copper (59). In a 2-year double-blind, placebo controlled study, bone loss in post-menopausal women given combined calcium and copper, manganese and zinc supplements was significantly less than in the placebo group and in groups taking the trace mineral or calcium alone (60). The role of copper in bone formation, skeletal mineralization and integrity of the connective tissue is still not fully understood. As a general enzymatic cofactor, it activates lysyl oxidase which induces the formation of lysine crosslinks in collagen and elastin (61), removes bone free radicals as a cofactor of antioxidant enzymes (62), directly inhibits osteoclastic resorption (63). Dietary copper is available in a wide variety of foods including meats, seafood, nuts and grains. The recommended daily intake of copper adequate for bone health in adults is 0.9 mg/day (64).

Silicon

Silicon, the most abundant mineral on earth, appears to have a beneficial role in bone health and formation (65). Severe dietary silicon deprivation in growing animals appears to cause abnormal growth and defects of the connective tissues (66, 67). In recent studies, supplementation with silicon in ovariectomised rats reduced bone resorption and bone loss and increased bone formation and bone mineral content (68, 69). In humans, two epidemiological studies have reported that increase silicon intake correlated with increased bone mineral density for men, premenopausal women, and postmenopausal women on hormone replacement therapy (70, 71). Other studies showed in osteoporotic subjects silicon supplementation resulted in increased bone volume (72) and increases in femoral and lumbar spine BMD (73). A recent study on osteopenic and osteoporotic subjects, shows silicon supplementation induced a trend for increased bone formation markers in serum and a slight significant increase in femoral BMD (74). Mechanisms of health silicon effect on bone are not clear but it has been suggested silicon involvement in the radical-dependent prolyl-hydroxylase pathway (75) during type I collagen formation. Others have suggested a structural role in the cross-linking and stabilization of collagen and glycoaminoglycans (76); furthermore orthosilicic acid stimulates human osteoblasts and osteoblast-like cells to secrete type I collagen and other markers involved in bone cell maturation and bone formation (77). Dietary sources of silicon include whole grains and cereals, carrots and green beans. Recent epidemiological findings suggest that intakes near 25 mg/d might promote bone health (78).

Iron

Iron is essential in oxygen transport and participates in many enzymatic systems in the body, with important roles in collagen synthesis and vitamin D metabolism. Iron-deficient rats have been shown to have poorly mineralized skeletons and pathological changes in the microarchitecture of trabecular bone (79). In healthy populations the relationship between iron status and bone metabolism is controversial. Results show positive correlation between serum

ferritin and BMD in elderly men but not in women (80). In contrast, there was a negative correlation in women older than 45 years of age (81), and no association between BMD and either transferrin saturation or ferritin in men (82). Buyukbese et al. (83) did not observe differences in ferritin levels between osteoporotic postmenopausal women and controls. Different mechanisms by which iron deficiency affects bone have been suggested. On the one hand, there is the role of iron as an essential cofactor for hydroxylation of prolyl and lysyl residues of procollagen. On the other hand, there is its participation in vitamin D metabolism through the cytochromes P450. Furthermore, hypoxia related to anemia is a major stimulator of bone resorption, inducing osteoclastogenesis (84). Relative to bone mineral density, adequate intake of iron has not been established.

Selenium

Selenium is an essential nutrient and plays critical roles in a variety of physiological processes as constituent of selenoproteins which function as antioxidative scavengers and it has been reported that selenium inadequacy can influence bone metabolism (85). In animal studies, deprivation of this micronutrient increased bone resorption and changed bone microarchitecture with a reduction in BMD and bone volume (86, 87). Similarly, studies in humans founded that selenium status was inversely related to bone remodeling and positively correlated with BMD in post-menopausal women (88). A case-control study found selenium intake to be inversely associated with reduced risk of osteoporotic hip fracture (89). These effects can be explained by inhibiting oxidative stress, in fact, adequate selenium intake appears to play an essential role in osteoclast/osteoblast cell proliferation and differentiation enhancing osteoblastic differentiation by the reduction of free radicals (90).

The main sources of selenium for nutrition are wheat, red meat and sea food with a recommended daily allowance of 55 µg/day (91).

Conclusion

Osteoporosis is a multifactorial disease and nutrition is an important modifiable factor in the development and maintenance of bone mass and in the prevention of osteoporosis. There are potentially numerous nutrients and dietary components that can influence bone health, and these range from the macronutrients to micronutrients. With regard to bone health, there has been a growing interest not only in the traditional nutrient related to bone as calcium and vitamin D but also in micronutrients. Epidemiological studies and clinical trials showed micronutrients can potentially have a positive impact on bone health, preventing bone loss and fractures, decreasing bone resorption and increasing bone formation. The micronutrient needs for optimizing bone health can be easily met by a healthy diet that is high in fruits, vegetables and sea food with a modest intake of meat. Consequently, optimizing micronutrients intake might represent an effective and low-cost preventive measure against osteoporosis.

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