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Review

Osteoporosis and mineral nutrition. A literature review

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Summary. Osteoporosis is a disease affecting millions of people in the world. The work consists in a review of data on the main nutrition-related minerals. The following minerals have been analyzed: calcium, phosphorus, potassium, magnesium fluoride, sodium, iron, silicon, zinc, copper, manganese and strontium.

Key words: osteoporosis, mineral, nutrition

Introduction

Osteoporosis is a progressive disease which leads to the depletion in the bone structure with loss of bone mineral density (BMD) increasing the risk of fractures over the years. In the United States, adults in these conditions over 50, are more than 12 million and 40 million adults are also at high risk of developing osteoporosis because of a low BMD.

In Italy are estimated 3.5 million osteoporotic women and 1 million men. In addition, there are 250.000 fractures due to osteoporosis each year, of which 80.000 hips and 70.000 femurs. It is important to note that patients with fracture of the proximal femur show, within a year, a mortality rate of 15-30% (1).

Osteoporosis is characterized by low BMD and shows a deterioration of the microarchitecture with trabeculae smallness, reduced mineralization and is associated with an increase in cortical porosity (2). The BMD is the result of a balance between bone resorption due to osteoclasts and bone formation due to osteoblasts, during an ongoing remodelling process. During the growth of children bone formation requires a balance in favour of bone growth and the achievement of peak bone mass until they reach the adult state where the BMD tends to remain relatively stable. With aging the activity of osteoclasts increases compared to that of osteoblasts and this leads to a loss of bone mass (3).

Measurement of bone mineral density

The most widely used method is the DXA (dual energy absorbed x-ray absorptiometry) based on the different X-ray absorption of soft tissues and bone. DXA provides the measurement of BMD in specific locations such as the hip and spine and the bone mineral density is expressed as g/cm². These measures are compared with an healthy population (normally healthy Caucasian women at their bone mass peak) considered as a standard; a score (T-score) lower than -2,5 SD is defined as osteoporosis, between -2,5 and -1 is considered as "low bone mass" and a T-score higher than -1 is considered normal.

BMD and risk of fracture

The measurement of BMD to define the state of osteoporosis is important because there is an inverse relationship in adulthood between BMD and fracture risk. A meta-analysis of 12 cohorts in different pop-

ulations show that, using DXA in the femoral neck, BMD is a strong predictor of subsequent fractures in both men and women (4).Vertebral compression fractures may lead to curvature of the spine that can cause chronic pain and disability and are more common in women than men (5). Age-related reduction in bone density, associated with falls due to decreased muscle strength, loss of balance, arthropathies, decreased vision, use of drugs, increases the risk of fractures (6).

As shown in the Framingham Osteoporosis Study (FOS), in the elderly, in women there are many important risk factors associated with bone loss such as age, low weight, a weight loss, while the use of estrogen appears to be a protective factor. In men bone loss appears to be associated with smoking. Surprisingly both in men and in women physical activity, intake of caffeine and calcium or serum concentration of 25-OH Vit.D aren't associated the loss of bone mass (7)

On the contrary the Rotterdam study with older adults, bone loss is associated with low weight and smoking in both men and women while the calcium intake is protective in men but not in women (8). In another study done with 9516 older female patients it was found that the risk of fracture associated with previous fractures, is associated with high weight, poor health care, hyperthyroidism, treatment with benzodiazepines, caffeine intake and sitting for more than 4 hours per day (9).

Nutritional factors in BMD and fracture risk

Bone is a living tissue with a constant remodelling and appears dependent on a wide variety of nutrients. The nutrients in foods as principal minerals, clearly associated with bone status are listed in Table 1.

Minerals

The bone matrix is composed of calcium, phosphorus, protein, magnesium and other minerals contained n traces. In the past calcium was thought to be the only nutritional factor for bone health; nowadays others diet components allows to understand bone health (10).

Calcium

Calcium is the largest mineral of bone tissue and about 99% of calcium in an adult is contained in the bone in the form of hydroxyapatite. Although growing children are thought need more calcium intake than adults, studies on children supplemented with calcium provided conflicting data. A review by Wosije et al. concluded that calcium contributes to an higher BMD primarily on the cortical bone and was more effective in low calcium consuming people and in pubertal rather than pre-pubertal children (11). In another review on 2859 children who were supple-

Table 1

Mineral	Daily value°	Foods
Calcium	1000-1200 mg	Milk,yogurt and cheese. Small or canned fish edible bones (sardines, salmon) Calcium set tofu Fortified soy milk
Magnesium	240 mg	Whole grains and whole grain cereals (wheat bran, wheat germ, brown rice, quinoa, otmeal, raisin bran, shredded wheat)
Potassium	3900 mg	Baked potato, sweet potato, tomato paste,tomato sauce Mature beans (kidney beans, white beans, soy beans, lima beans, lentils) Yogurt milk Fish (halibut, rockfish, cod, trout) Winter squash Orange juice Banana

° Italian Society Of Human Nuitrition SINU 2014 in adults

mented with calcium it was found that supplementation has a small effect on upper limb BMD but no effect on the femoral neck or lumbar spine. Furthermore, there is no evidence that sex, calcium, puberty, ethnicity and physical activity may affect bone mass and calcium supplementation in children does not reduce the risk of fracture (12). Another review demonstrates that calcium supplementation in adults leads to an improvement in bone condition, ameliorates bone growth and reduces fractures due to bone loss during ageing (13).

A follow up study focused on calcium and vitamin D supplementation for 3 years period in older men and women showed that BMD benefits were lost 2 years after the end of the supplementation (14).These studies seem to demonstrate that calcium supplementation does not influence the final state of the bone mass and does not reduce the risk of fracture except in those cases where the basal calcium level was low. It may be that calcium intake with the diet may be more effective than calcium supplementation. A follow-up analysis demonstrates that low intake of milk during childhood and adolescence is associated with a significantly lower BMD and doubles the risk of fractures in women over the age of 50 (15). Studies with calcium-enriched foods have shown beneficial effects on the bone. In one study, spinal bone loss was significantly lower in premenopausal women who used food that increased calcium intake from 900 to 1500 mg per day compared to a control group (16). In another study, 3 portions of yoghurt per day were provided and significant reductions were found in urinary excretion of bone turnover markers in older women (17). A recent study on 6-month effects of kefir treatment in 40 osteoporotic patients showed that BMD increases, the serum beta c-terminal telopeptide of type 1 collagen decreases, serum osteocalcin increases, PTH increases after treatment, but decreases in control group: Authors concluded that kefir therapy is associated with bone turnover and increases bone BMD in osteoporotic patients at 6 months (18).The calcium contained in foods like milk and yoghurt seems to be more effective than supplementation because it comes along with other important nutrients including vitamin D, protein, potassium and magnesium

Phosphorus

Phosphorus is essential for the bone but taking too much phosphorus in combination with low calcium can lead to reduced calcium bioavailability and boost bone loss. The phosphorus intake deficiency in older adults seems to be due to malnutrition, intestinal malabsorption or prolonged use of phosphorus-binding medicines including antacids (19). In general, the population tends to exceed the amount of phosphorus intake. In a study in the United States, average phosphorus intake was 1123 mg/day for women and 1550 mg/day for men, with a recommended intake of 700 mg/day, while calcium intake was 883 mg/day in women and 1038 m /day for adult men with a recommended intake of 1200 mg for both women and men (20).

Excess phosphorus forms chemical complexes with calcium and interfere with calcium intake. This leads to lowering of serum calcium level, increasing PTH production , lowering production of 1.25 $(OH)_2D$ and calcium absorption in the intestinal tract and consequently releasing calcium from the bone (21). One of the main sources of phosphorus intake is the cola drinks. A study in teenage girls has shown that cola consumption leads to an increased risk of fracture (22). Women who consume daily cola have a significantly lower hip BMD than those consuming less than once a week (23). From these studies, it seems likely that prolonged consumption of large amounts of phosphoric acids directly affect BMD causing small/moderate BMD loss.

Potassium

Potassium promotes calcium retention by the kidney, neutralizes the load of dietary acids and may therefore protect calcium loss from the bones. Potassium administration increases the serum concentration of osteocalcin and decreases the excretion of urinary hydroxyproline (24). Several studies have shown positive and protective association between potassium intake and bone health. In premenopausal women, a difference of 8% in femoral BMD was observed between the highest and the lowest quartile of potassium intake (25). In the elderly, potassium and, in general, alkaline-producing dietary contribute to maintenance of BMD (26). In another study with older women, higher baseline urinary potassium concentration is as-

sociated with a total BMD greater than 4% and trabecular BMD greater than 11% at 5 years (27). Some authors have pointed out that the modern diet is very deficient in potassium (on average 2500 mg versus 3900 mg recommended daily) and contains excess of sodium (about 4000 mg to 1200-1500 mg daily recommended) (28). This combination seems to have a particularly negative effect on the bone.

Magnesium

Magnesium plays an active role in crystallization because it is important in the formation of hydroxyapatite and can promote bone hardness (29). The magnesium concentration in the bone is significantly lower in women with osteoporosis than in normal ones (30). In observational studies, magnesium intake is significantly and positively associated with BMD and protects against bone loss (31). In a US study, the median magnesium intake ranged from 177 mg/die in African American women to 326 mg/die among non-Hispanic white men (32). In some studies has been shown the benefit of magnesium intake in bone mass growing in adolescent girls (33), in suppression of turnover markers in young men (34) and in preventing bone loss in osteoporotic women (35). For these reasons this mineral element, often underestimated, is important in maintaining and promoting bone health.

Sodium

Sodium intake is generally higher than the recommended dose of 1500 mg per day against an average intake of 4000 mg for men and 2800 in the United States (36) although the situation is similar in Italy. This leads to greater elimination of calcium from the kidneys. Some studies have shown that every 1000 mg of sodium over the recommended value leads to an increase in calcium loss with urine (37) and consequently to a lower BMD. Balanced optimum intake to protect the bone mass is between 1000 mg and 2000 mg of sodium per day. The effect of sodium may also depend on the potassium intake. A metabolic study found that in postmenopausal women giving 5175 mg of sodium per day increased urinary calcium and N-telopeptide, whereas in those that additionally sodium was given potassium citrate had a decrease in urinary calcium and no increase in N–telopeptide (38). Dietary Approaches to Stop Hypertension (DASH), a diet rich in fruits, vegetables, low-fat dairy products and therefore a potassium-rich diet, reduces serum markers of bone turnover reducing serum osteocalcin and PTH, in the control group (39). In another study with postmenopausal women whose sodium was reduced to less than 2000 mg/ ay for 6 months, calcium excretion of calcium and turnover markers decreased (40). However, another study shows no adverse event on BMD of 3000 mg/day of sodium compared to 1500 mg/day when participants were given adequate calcium and vitamin D intake (41). In another study involving 69.735 postmenopausal women studied over an average of 11,4 years, there is no association between sodium consumption and BMD at hip or lumbar spine, as well as with fracture risk, and concludes that sodium intake recommendations are unlikely for a significant development of osteoporosis(42).

Fluoride

Fluoride has long been known to prevent dental caries and has been added for long time to many water supplies. Fluoride replaces the hydroxyl group in the hydroxyapatite by forming fluorapatite. It has been shown that fluoride appears in the bone in the form of large crystals and increases BMD but decrease elasticity (43). In a randomized sodium fluoride study in postmenopausal women with osteoporosis, BMD spine increase but also increases the risk of vertebral fractures (44). In a meta-analysis of 25 studies, fluoride treatment increases BMD of the hip and spine, but there is no effect on the risk of fracture. The protective effect was seen at low doses (≤20 mg/day) (45). In another study comparing the bone structure of the common individuals in municipalities with or without fluoride water, it is shown that there is no difference in the physical characteristics of the bone in both groups (46).

Iron

Iron is an important cofactor for hydroxylases in the formation of collagen. The lack of iron intake and, conversely, an iron overload, are negatively associated with BMD. An iron overload in patients with genetic hemochromatosis and African hemosiderosis is associated with low BMD (47). Rats with a poor iron diet, shows impairment in bone morphology, strength and

density and decreases serum osteocalcin (48). Studies in postmenopausal women show that higher iron intake is associated with a higher BMD (49, 50). In contrast, other studies show that there is no association between iron status and BMD in women (51)

Silicon

Silicon is important for the formation of collagen and glycosaminoglycan in the bone and cartilage by influencing the formation of the organic matrix. Silicon is also one of the major ions in osteogenetic cells. Orthosilicic acid is the form that is absorbed by the diet and appears to be associated with bone formation by increasing the synthesis of type I collagen and stimulation of osteoblasts (52). Chicks fed with a silicon-free diet have abnormal bone formations (53), while silicon addition to the impoverished rats diet, causes less osteoclast production, increases bone formation, decreases bone turnover, and increases BMD (54). Few studies have been made in men but silicon seems to have shown a protective action. In a study the silicon added diet showed a positive association at hip sites in men and premenopausal but not in postmenopausal women (55). French patients with osteoporosis show an increase in trabecular bone volume with silicon treatment (56) and femoral BMD increases in women with osteoporosis by silicon intramuscular injection over fluoride, magnesium and control (57). All these findings show that high silicon intake may have a protective effect on BMD even if further studies are needed.

Zinc

Zinc influences the bone for its role in nucleic acids and protein metabolism (58). Low zinc concentrations in serum and bone have been observed in patients with osteoporosis (59). In animals zinc increases alkaline phosphatase and DNA synthesis that stimulates bone formation (60). Although study debate still exist, intake of calcium, copper and zinc, seems to show a benefit in BMD preservation in post-menopausal women (61).

Copper

Copper is a co-factor of the lysil oxidase catalyzing the cross-linking of lysine and hydroxyproline in collagen.

Animals to which copper has been removed from diet show a reduction in bone strength (62) and a greater bone loss with aging (63). In women, copper plasmatic concentration is correlated to BMD in lumbar spine (64). In a controlled study in men, an increase in activity of bone resorption markers has been shown, ranging from a diet rich in copper (6 mg/day) to a poor (0.7 mg/day) and this is reversible by returning to a copper-rich diet (65)

Boron

Boron intake can protect the bone by decreasing calcium, phosphorus and magnesium loss and increasing the serum concentration of estradiol (66). In rats, the lack of boron alters trabecular bone and reduces the strength demonstrating the importance of boron in the cortical force and microstructure of the bone (67). However, there are currently no randomized studies on humans.

Manganese

Manganese can contribute to the good bone mineral state. In rats a manganese supplement leads to an increase BMD in the lumbar vertebrae and increases serum osteocalcin suggesting that manganese contributes to bone formation (68). In a study with postmenopausal women who received daily copper and calcium zinc supplements for 2 years, there was evidence that there was less bone mass loss and BMD increase compared to a control group (69).

Strontium

Strontium has similar characteristics to calcium. Strontium ranelate doses of 1 to 2 grams per day for 2 years increase BMD in postmenopausal women by 2-3% compared to placebo (70) and reduce the risk of vertebral and non-vertebral fractures (71).A meta-analysis of two clinical trials shows that strontium ranelate is associated with 31% reduction in osteoporosis femoral neck and with reduction of 40% of vertebral fractures as well. (72). Biopsies of the bone show that strontium is predominantly organized in new bone deposits and cross-link collagen and bone quality is preserved (73). Strontium ranelate is approved for the treatment and prevention of osteoporosis in Europe but in 2014 the European Medicines Agency's Pharma-

covigilance Risk Assessment Committee (PRAC) has recommended that strontium ranelate should no longer be used to treat osteoporosis due to severe cardiovascular side effects (extensive vascular calcifications).

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