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Editorial

FRUIT AND VEGETABLES AND BONE: THE OPPORTUNITIES AND CHALLENGES AHEAD

Osteoporosis, a global health problem, is increasingly significant as people live longer and the world's population grows[1]. Prevention and treatment of osteoporosis and its complications are essential socioeconomic priorities, calling for the development and implementation of strategies, in particular nutritional approaches and policies.

Increasing scientific evidence links high fruit and vegetable intake to more favourable bone health parameters in adults and in children/adolescents (cf. Steer & Goldberg article). This data is largely epidemiologic in nature.

While these findings are very encouraging, full elucidation of the underlying mechanism(s) of action is required. Fruit and vegetables are rich sources of nutrients and bioactive constituents for which various lines of evidence exist for effects on bone metabolism and bone mass (cf. Coxam & Horcajada articles). Fruit and vegetables also contribute to a lower potential renal acid load, which may have a positive impact on calcium and bone metabolism (cf. Steer & Goldberg article). Use of new tools such as microarray, proteomics and metabolomics may help enhance our understanding of the impact of fruit and vegetables to bone health.

It is possible that not all fruit or vegetables are equal in terms of the beneficial effects on bone, and the dose-response is unclear. These knowledge gaps need to be addressed before specific guidelines are formulated in relation to fruit and vegetables and bone health.

These recent findings on a beneficial effect of fruit and vegetables on bone health highlight the need for further investigation into a causal relationship, including intervention trials in human subjects. Until results emerge, recommending a diet high in fruit and vegetables is undeniably a prudent public health strategy.

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Fruit and vegetables: potential role in building better bones

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Global incidence of and risk for osteoporosis

In countries such as North America, Europe and Australasia it is estimated that 1 in every 3 women and 1 in every 10 men aged 55 years and over suffer from osteoporosis. Osteoporosis means 'porous bones' and describes the thinning of the inner honeycomb structure of bones which leads to an increase in bone fracture risk. Fractures are most common at the wrist, spine, and hip. Globally, around 1.7 million hip fractures occur each year; this is expected to increase four fold by 2050[1]. Hip fracture rates are highest in Caucasian women living in temperate climates, slightly lower in women from Mediterranean and Asian countries and lowest in women living in Africa[2]. The lifetime risk of fracture in women aged over 50 years is greater than the risk of breast cancer and cardiovascular disease[3]. As the incidence of fracture increases with age in both sexes, osteoporosis also becomes a major problem for older men too. In countries with high fractures rates, 20% of symptomatic spine fracture and 30% of hip fractures occur in men[4].

Osteoporotic fractures are a major cause of morbidity. Fractures often result in loss of mobility and long-term functional incapacity which leads to loss of independence. In some cases, fractures can lead to premature death. As well as the huge personal cost to the individual, it is estimated that the associated annual health costs for osteoporotic fractures in Europe is over 13.9 billion Euros.

Diet, fruit and vegetable intake, and risk for osteoporosis

Bone health is influenced by genes, hormonal status and lifestyle factors such as levels of physical activity, smoking and dietary intake. Diet is an important, modifiable risk factor for osteoporosis in later life. It is well known that an adequate intake of dietary calcium and vitamin D status is important for bone health. However, fruits and vegetables are emerging as another important food group.

In an ancillary study of the Dietary Approaches to Stop Hypertension (DASH) trial, men and women (aged 23-76 years) who consumed a diet rich in fruit and vegetables over three months had significantly lower markers of bone turnover[5]. Several other observational studies also demonstrate this association in more specific age groups. In a cross-sectional study, intakes of zinc, magnesium, potassium, fibre and vitamin C were associated with higher bone mass in premenopausal women[6]. These relationships were independent of factors such as weight, height, total energy intake, smoking and physical activity. In older adults (69-93 years) in the Framingham Osteoporosis Study, those who had a diet rich in fruit and vegetables had significantly higher bone mineral density than individuals whose diets were lower in fruit and vegetables and higher in confectionery[7].

The observational data for younger people is slightly less consistent, although the trends are in a similar direction. McGartland et al. found that higher intakes of fruit resulted in higher heel bone mineral density in girls aged 12 years but not boys[8], whereas Valanparast et al. found that fruit and vegetables significantly predicted total body bone mineral content in boys but not girls aged 8-20 years[9].

Potential mechanisms for fruit and vegetable intake and reduction in risk for osteoporosis

It is not entirely clear how fruits and vegetables might have positive effect on bone. There are likely to be several plausible mechanisms. Humans eat foods that produce and consume hydrogen ions that affect acid-base balance. Foods such as cereals, dairy products and meat are associated with a higher dietary acid load relative to alkali forming foods such as fruit and vegetables. The tight control of extracellular fluid between a pH of 7.35 and 7.45 is essential for survival and it has been known for several decades that alkaline bone mineral contributes to the maintenance of the body's pH. The skeleton acts as a buffer by liberating calcium from bone that is ultimately excreted in urine. Diets rich in fruit and vegetables may result in a more alkaline extracellular fluid which, in theory, reduces the need to draw on skeletal calcium supplies. In the DASH study, increasing fruit and vegetable intake from 3.6 to 9.5 portions a day decreased urinary calcium excretion from 157 mg/d to 110 mg/d[10].

The positive effect of fruits and vegetables on bone health may not be entirely due to the effect on acid-base balance. Fruit and vegetables are also rich sources of vitamins C, K1 and beta-carotene. Vitamin C plays a role in collagen formation and plays a regulatory role in osteoblast differentiation. Vitamin C and beta-carotene are antioxidants. Oxidative stress has been shown to be negatively associated with bone mineral density in men and women[11]. In an observational study a significant positive association was found between fruit and fruit juice (a major source of vitamin C) and bone mineral content in boys aged 16-18 years[12].

Osteocalcin plays a role in the calcification of bones. Vitamin K1 is essential for the alpha-carboxylation of osteocalcin, this allows the protein to function properly. The richest source of vitamin K1 is green leafy vegetables. Population studies have shown that low dietary or circulating vitamin K are associated with low bone mineral density. Supplementation of postmenopausal women (n=45) with low bone mineral density with 80 µg of vitamin K1 daily for 12 months resulted in an increase in alpha-carboxylated osteocalcin to similar levels observed in women with normal bone mineral density[13].

Conclusion

Osteoporosis presents a growing public health problem and the associated personal and health care costs are considerable. Fruit and vegetables are already a key part of public health strategies across Europe to reduce the risk of cancer and CVD[1]. Emerging evidence of the protective effect of this food group on bones adds to the case for initiatives to encourage greater consumption of fruit and vegetables.

However, more research is also needed to elucidate the mechanisms of action and perhaps most importantly, into effective methods to increase consumption among a population who need more than just research to persuade them to eat more fruit and vegetables.

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Polyphenols from fruit and vegetables and bone health

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Evidence for the role of polyphenols in preventing degenerative diseases, such as cancer, cardiovascular diseases or osteoporosis is emerging. Due to their antioxidant and anti-inflammatory potency, those molecules may actually help limit the damage associated with aging. However, the health effects of those micronutrients, although abundant in our diet, depend on both dietary intake and their bioavailability. Bioavailability differs from one polyphenol to another, possibly explaining why the most abundant are not necessarily those carrying the highest biological activity in target tissues, and are not necessarily the most likely to exert protective health effects.

Polyphenols found in fruit and vegetables

Several thousand polyphenols have been identified in plants, of which several hundred are found in edible plants. They are classified as phenolic acids, flavonoids, stilbenes and lignans, with respect to the number of phenol rings that they contain. Actually flavonoid molecules represent one of the most interesting classes of biologically active compounds with health-related properties. They are divided into 6 subclasses : flavonols (onions, kale, broccoli, blueberries...), flavones (mainly found in parsley and celery), anthocyanins (red wine, cereals and fruit), flavanols (catechins present in apricots, green tea and chocolate and proanthocyanidins found in grapes, peaches, apples, pears but also in several beverages), flavanones (citrus fruit) and isoflavones (found almost exclusively in leguminous plants, mainly soya).

Dietary intake in humans

Fruit and beverages (tea and red wine) constitute the main sources of polyphenols, but in most cases, they contain complex mixtures of these compounds, which unfortunately are often poorly documented. This may explain in part why dietary intake of one isolated polyphenol or of one subclass remains difficult to estimate. However, it has been well accepted that humans ingest around 1 gram of polyphenols per day (Scalbert & Williamson, 2000).

Effects of polyphenols on bone health

Mechanisms are poorly understood

While it is established that calcium, vitamin D and micronutrients are essential for bone health, considerable research has also taken place to investigate the role of other compounds in food, in particular polyphenols (mainly flavonoids), which may modulate bone metabolism. However, when compared to other diseases or metabolism, little is known about the effects of polyphenols on bone health, with the exception of soy isoflavones. Evidence of protective effects of isoflavones in humans has been established in observational and intervention studies. Indeed, in Japanese women, consumption of soybeans is associated with greater bone mineral density. Moreover, several animal studies (rodents) have demonstrated the efficacy of supplementing of the diet with genistein, daidzein (aglycon or glycosides) or feeding soy proteins in preventing bone loss induced by ovariectomy. Those effects were attributed to the estrogen-like activity of isoflavones and their potency to bind estrogen receptors, explaining in part why those molecules were considered as possible alternative treatment to prevent osteoporosis. However, the mechanisms involved in these protective effects are poorly documented and not well understood, but available in vitro studies suggest that several mechanisms of action on bone may be considered. Finally, in humans, some intervention studies have shown prevention of bone loss in postmenopausal women with 80-90 mg isoflavones / day while others did not. Nevertheless, in practice, consumption of soy products is relatively low in Western countries as compared to the Asian population whose average daily intake is 20-40 mg/day. Thus, nutritional prevention of osteoporosis based essentially on soy-rich diet (with classic calcium and vitamin D intake) may be limited in Western countries and has led some researchers to focus on other polyphenols which may modulate bone metabolism.

Epidemiological evidence

Some epidemiological studies have suggested associations between consumption of fruit and vegetables and prevention of osteoporosis. Fruit and vegetables contain flavonoids, which are the most abundant polyphenol in our diets. Thus, these anti-oxidant flavonoids may be partially responsible for some of the positive links found between fruit and vegetable intake and higher bone mineral density in adults and children. Several animal studies have shown that consumption of some flavonoids inhibit ovariectomy induced bone loss in rats. For example, rutin, a quercetin glycoside found mainly in onions, but also resveratrol (present in red wine), phloridzin (apples) or euloropein (olive oil) were able to protect bone density when added to the diet. The flavanone hesperedin, found abundantly in citrus fruits, especially oranges, has been shown to inhibit bone loss in ovariectomized mice and rats while citrus juice consumption has recently been demonstrated to prevent bone loss in male orchidectomized rats. One interesting point is that hesperidin is much more abundant than isoflavones in the Western diet. Intakes range from 35-50 kg of orange per person per year. Indeed, in Finland, the flavonone consumption was estimated to be 28.3 mg hesperetin/day (contributing to 50% of total flavonoid intake), closer to the consumption of isoflavones by Asian women. Thus, these molecules, as well as other plant micronutrients may offer a good opportunity for nutrition research to investigate and develop new strategies for osteoporosis prevention.

Finally, consumption of green tea has been associated with higher bone mineral density in humans, suggesting an effect of catechins. The effects of these polyphenols have yet to be assessed in intervention studies.

Despite all evidence shared by animal studies, the mechanisms of action that explain the effects of flavonoids on bone remain unknown due to the difficulty of conducting well-designed studies. Indeed, the metabolites present in blood, resulting from digestive and hepatic processes, usually differ from the native compound and are not all known or available.

Conclusion

Human studies are needed to provide clear evidence of protective effects of polyphenols on bone health, where their potency on fracture risk prevention to date has not been evaluated.

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Vitamins from leafy vegetables and bone health

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Targeting nutrition as a possible way to achieve optimal bone health

The World Health Organisation has identified osteoporosis as the second leading health care problem after cardiovascular diseases. The hallmark of osteoporosis is bone fragility. It affects some 200 million people, and the number of sufferers is expected to increase steadily as the human race experiences a progressive lengthening of life expectancy.

There is an overwhelming body of evidence indicating that nutrition is an important modifiable factor in the development and maintenance of bone mass. Although most studies have focussed on the effect of calcium and milk products on bone accrual, the role of vegetables and fruit in the diet is emerging, suggesting complementary lines of prevention. Indeed, the cause of osteoporosis is multifactorial. Oxidative stress induced by reactive oxygen species plays an important role as well in the pathophysiology of primary osteoporosis, and has been positively associated with the risk of fracture. This provides a rationale for investigating the role of dietary antioxidants in osteoporosis, which can act as free radical scavengers. Even though there was a lack of relation between plasma levels of vitamin and mineral antioxidants and bone mineral density in the Women's Health Initiative trial, antioxidant intake such as ß-carotene, vitamin E or vitamin C has been shown to be lower in osteoporotic women and was even associated with reduced risk of fracture in smokers in the UTAH study. Thus, it is worthwhile to consider specific foods, like leafy vegetables which are typically rich in phytochemicals such as carotenoids, and high in vitamins C, B, E and K, and the mineral calcium, while being low in calories.

Leafy vegetables are a rich source of micronutrients that may be important for bone health

Nearly one thousand species of plants with edible leaves are known. Leafy vegetables most often come from short-lived herbaceous plants and share a great deal with other vegetables in nutrition and cooking methods. Basically, 100g of lettuce will provide 30% of the recommended dietary allowance (RDA) for folic acid, 18% for provitamin A and 10% for vitamin C. 200g of spinach will bring about 3% of the RDA for folic acid and half of the RDA for vitamin C.

Micronutrients and bone health

Carotenoids: Conflicting research suggests a potentially complex relationship with vitamin A and bone: a low bone mineral density (BMD) and an increased risk of hip fracture have been observed in women with a high dietary intake. Conversely, observational studies have revealed that non-supplemented subjects with higher dietary intake of retinol (derived from both retinoids from animal food and carotenoids contained in vegetables and fruits) lose less bone with age than subjects with a lower intake. Moreover, in free-living elderly women, plasma levels of retinol and of all carotenoids tested have been consistently lower in osteoporotic than in controls. This suggests a bone sparing effect of retinol, to which the provitamin A activity of some carotenoids might have contributed.

B Vitamins: Current research indicates that increased dietary intake of folic acid along with the elimination of unhealthy lifestyle practices, will lower plasma levels of homocysteine (Hcy), a sulfur-containing intermediate product in the metabolism of the essential amino acid methionine. Certain forms of Hcy may cause damage through oxidative effects and negative protein interactions.

Regarding bone, an elevated level of Hcy is not only a risk factor but also a factor in abnormal bone metabolism. Indeed, genetic hyperhomocysteinemia is associated with skeletal abnormalities and osteoporosis (LASA, Rotterdam and Framingham studies).

Many studies lend support to the idea that raising B-vitamin status might be beneficial to bone, because they are involved in the metabolism and clearance of Hcy.

Reduced levels of markers for bone formation have been reported in vitamin B12-deficient individuals. In the same way, both men and women with levels of vitamin B12 lower than 148 pm have lower BMD. Hip fracture patients have been shown to a reduced vitamin B6 and folate intake, as well. A recent double blind placebo-controlled intervention trial demonstrated that a Hcy-lowering therapy with 5 mg folate and 1.5 mg vitamin B12 impressively reduced the hip fracture rate in hemiplegic stroke patients (10 fractures per 1000 patients against 43 in the placebo group).

Vitamin C: Vitamin C is a known potent antioxidant that could reduce harmful effects of free radicals. Other mechanisms through which it may contribute to BMD are speculated to be related to its role in collagen formation of bone matrix, its effect on osteoblast growth or its role in promoting calcium absorption.

Vitamin E: Plasma vitamin E concentrations have been found to be lower in osteoporotic women. Among current smokers, there is an association between low intakes of dietary vitamin E and increased risk of fracture. It has been shown to reduce pain in RA patients as well, possibly by decreasing pro-inflammatory cytokines and lipid mediators.

Vitamin K: Vitamin K, usually associated with leafy vegetables is an important factor in proper blood clotting and bone metabolism, and has emerged as a potential protector against osteoporosis. Vitamin K mediates the alpha carboxylation of glutamyl residues on several bone proteins, notably osteocalcin. It exhibits antioxidant properties, as well. This may explain why cumulative epidemiological evidence suggests that subclinical vitamin K deficiency contributes to age-related bone loss and osteoporosis fractures. Moreover, low doses of phylloquinone (1 mg/d) have been demonstrated to exert protective effects on BMD in postmenopausal women.

Conclusion

Fruit and vegetables may have a potential promise for targeting the prevention of postmenopausal osteoporosis by maintaining or improving bone mass of human subjects. Thus, any dietary and behavioural recommendations targeted to the global health of the population should take a comprehensive consideration of their potential bone sparing properties.