CALCIUM AND VITAMIN D IN BONE HEALTH

Calcium and vitamin D supplementation is historically one of the most researched and sound nutritional practices to strengthen the bone structure in infants, children, women, men and diverse racial or ethnic groups. Based on the 2010 position statement of The North American Menopause Society adequate calcium and vitamin D intake along with balanced diet, adequate exercise, smoking cessation and avoidance of excessive alcohol intake are the most important measures to maintain bone health and prevent osteoporosis.

In one study with human volunteers the inorganic form of calcium, calcium carbonate, and an organic form of calcium, calcium citrate, produced identical 24-hour time increment in total serum calcium levels. Thus, inorganic and organic forms were equally absorbed and had equivalent bioavailability. Given the equivalent bioavailability of the two marketed products, the cost benefit analysis favors the less expensive carbonate product (1).

The effects of vitamin D and calcium cannot be separated. Vitamin D3 with calcium supplementation compared to placebo has a beneficial effect on bone mass density (BMD) in individuals with osteoporosis, and may reduce the risk of fractures (2). The risk of toxicity with “high” amounts of vitamin D intake is low. To achieve optimal vitamin D status, daily intakes of at least 1000 IU of vitamin D are required (3). Vitamin D3 is inactive biologically and needs to be changed, or hydroxylated, twice in the body to become active to 1,25-di-hydroxyvitamin D, called calcitriol. Calcitriol, a steroid hormone, is the active form of vitamin D in the body. Calcitriol mediates its biological effects by binding to the vitamin D receptor (VDR), which is located in the intestine, bone, kidney, and parathyroid gland cells to maintain calcium and phosphorus levels in the blood with the assistance of parathyroid hormone and calcitonin. The binding of calcitriol to the VDR upregulates the gene expression of transport proteins (such as calbindin), which are involved in calcium absorption in the intestine.

A little known finding is that oral bone and tooth loss are correlated with bone loss at non-oral sites. In one study tooth loss was examined in 145 healthy subjects aged 65 years and older who completed a 3-year, randomized, placebo-controlled trial of the effect of calcium and vitamin D supplementation on bone loss from the hip with the 2-year follow-up of the patients (4). During the 2-year follow-up period, 31 of the 77 subjects...
ultimately prevent the teeth loss. Mice fed bone loss in periodontal disease, and long-chain essential fatty acids may also positively associate with bone mineral density (BMD). Concentrations of DHA were measured at baseline and at 22 and 72% less alveolar (periodontal) bone loss compared with the control group. The authors of this study concluded that alveolar bone loss may be inversely related to omega-3 polyunsaturated fatty acid tissue levels, and fish oil dietary supplementation may play an important role in periodontal disease prevention and in periodontal disease management (6).

LYCOPENE AND BONE HEALTH

Our understanding of the complex role that nutrition plays in bone health is constantly evolving with increased attention given to new nutrients in addition to the archetypical examples of calcium and vitamin D. Relatively little is known about fruit and vegetable derived carotenoid consumption among postmenopausal women. Carotenoids are tetraterpenoid organic pigments split into two classes, xanthophylls and carotenes which are an important source of antioxidants and vitamin A in the diet; four carotenoids, referred to as provitamin A carotenoids, i.e. beta-carotene, alpha-carotene, gamma-carotene, and beta-cryptoxanthin can be converted in the body to vitamin A. The primary carotenoids in human serum are alpha- and beta-carotene, lycopene, beta-cryptoxanthin, lutein, and zeaxanthin.

One study investigated the relationships between serum carotenoid concentrations, fruit and vegetable intake, and osteoporosis in postmenopausal women (9). It has been found that serum lycopene concentrations were significantly lower in women with osteoporosis as compared to the healthy controls. The total fruit and vegetable intake correlated well with serum levels of lycopene, alpha-carotene, zeaxanthin and beta-cryptoxanthin. Therefore, the carotenoids and specifically lycopene that apparently is lower in women with osteoporosis as compared to healthy controls may play a beneficial role in maintaining healthy bone structure and preventing osteoporosis.

In a randomized, placebo controlled intervention study, sixty postmenopausal women supplemented with lycopene were evaluated nutritionally and in the oxidative stress parameters (10). The patients were divided into groups that received: i) regular tomato juice, ii) lycopene-rich tomato juice, iii) tomato Lyc-O-Mato® capsules, or iv) placebo capsules, twice daily for total lycopene intakes of 30, 70, 30, and 0 mg/day respectively for 4 months. The lycopene supplementation, regardless of the source of supplement, for 4 months significantly increased serum levels of this carotenoid, as compared to the placebo receiving group, and also resulted in significantly increased antioxidant capacity and decreased lipid peroxidation, protein oxidation, and markers of bone resorption. These laboratory findings suggest that postmenopausal women supplemented with lycopene may benefit significantly with increased antioxidant capacity and related decrease in bone resorption, as assessed by decrease in levels of bone resorption marker.

Another intervention study has examined the influence of individual carotenoid intake on the risk of bone fracture in elderly men and women (11). The intake of alpha-carotene, beta-carotene, beta-cryptoxanthin, lycopene, lutein and zeaxanthin on the frequency of hip fracture and non-vertebral osteoporotic fracture was evaluated in 370 men and 576 women with a mean age of 75. The study population completed a food frequency questionnaire in 1988-1989 and were monitored for hip fracture until 2005 and nonvertebral fracture until 2003. A total of 100 hip fractures occurred over 17 years of follow-up. Subjects with the highest total carotenoid intake had significantly lower risk of hip fracture, and subjects with higher lycopene intake had significantly lower risk of hip fracture and non-vertebral fracture. A non-significant protective trend was observed for total beta-carotene intake for hip fracture alone. No significant associations were observed between the incidence of fractures and levels of intake of alpha-carotene, beta-cryptoxanthin, or lutein and zeaxanthin. These results suggest a protective role of lycopene and several other carotenoids for bone health in older adults.

The relationships of dietary intakes of retinol and carotenoids were examined in an Anglo-Celtic Australian population of 68 men and 137 women (12). Bone mass of total body and lumbar spine were positively related to lycopene intake in men, and to lycopene and lutein/zeaxanthin intake in premenopausal women. In addition, a positive association of lumbar spine bone mass with dietary beta-carotene intake was observed in postmenopausal women. No relationship was found between dietary retinol intake and bone mineral status. The finding of this study suggests that fruit, vegetable consumption and dietary carotenoid intake has a beneficial effect on bone health. 

VITAMIN K2

The nutritional role of menaquinones or vitamin K2 is increasingly recognized and

BONE HEALTH
distinguished from the biological role of vitamin K1 or phylloquinone (13). Epidemiological studies show that dietary intake of natto, a traditional food in Japan prepared from fermented soy-beans which contains significant amount of menaquinone-7 (MK-7), reduces the risk of bone mass loss and/or age related decline in bone tensile strength. Vitamin K2, especially MK-7 form, with the half life in plasma significantly longer compared to phylloquinone, plays an important role as a co-substrate for the enzyme gamma-glutamyl carboxylase which carboxylates glutamic moiety of certain biologically important proteins (13). Vitamin K2 is responsible for carboxylation and activation of osteocalcin, which is specific to bone gamma-carboxy-glutamic acid protein synthesized by bone building cells osteoblasts. The bone is constantly remodeled and the remodeling is mediated by two cell types, osteoblasts (bone building) and osteoclasts (bone resorption). Osteoblastic bone formation and osteoclastic bone resorption are reflected in levels of bone metabolism markers, e.g. intact osteocalcin, carboxylated osteocalcin, under-carboxylated osteocalcin and bone alkaline phosphatase, an enzyme involved in bone mineralization. Bone resorption can also be evaluated by measuring the urinary free and total pyridinoline, a molecule that cross-links deposits in the bone via carboxylated osteocalcin, while it has the opposite effect on the circulatory system by preventing receptor activator of NF-kB (RANK) and activate nuclear factor kappa beta (NF-kB). Activation of NF-kB, often referred to as “master switch” of inflammation, is a necessary step for proliferation of osteoclasts and osteoporosis. Therefore by occupying the receptor activator of NF-kB (RANK), vitamin K2 sequesters RANK receptor and prevents further steps leading to formation of osteoclasts or osteoclastogenesis and excessive bone destruction – osteoporosis. In principle the described action of K2 is anti-inflammatory and similar to the mechanism of natural anti-inflammatory compounds boswellic acids, i.e. acetyl-keto beta-boswellic acid (AKBA) prevents receptor activator of NF-kB ligand (RANKL) signaling, NF-kB activation and osteoclastogenesis (18) (Figure 1). A new paradigm emerges in nutritional support of healthy skeletal system which i) makes bone health an integral part of a general health and wellbeing; ii) advocates use of multiple synergistic nutrients; iii) takes into account a complex interaction between nutrients, e.g. nutrients affecting bone and cardiovascular health; iv) considers role of nutrients modifying the inflammatory processes in bone physiology and pathology; and v) recognizes that deficiencies in nutrients other than calcium maybe responsible for poor bone structure and performance.

REFERENCES

1) HEANEY R.P., DOWELL M.S., BIERMAN J., HALE C.A., BENDICH A.
2) CRANNEY A. et al. Effectiveness and Safety of Vitamin D in Relation to Bone

![Figure 1 – NF-kB role in osteoclastogenesis](image-url)