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Position Statement

THE USE OF VITAMINS AND MINERALS IN SKELETAL HEALTH: AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND THE AMERICAN COLLEGE OF ENDOCRINOLOGY (AACE/ACE) POSITION STATEMENT

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Running Head: Dietary supplements and bone health

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Introduction

The desire to maintain health, including bone health, into old age has led to almost one-half of the population and 70% of older adults in the United States (U.S.) (1) and up to 26% in Europe (2,3) using dietary supplements. Dietary supplements allow for randomized controlled trials (RCTs) that can assess a single nutrient. However, in nutrient studies it is difficult to account for the impact of food and food fortification on skeletal outcomes. The ability to accurately quantify the effect of an individual nutrient on bone health is confounded by methodological issues and the time lag to assess outcomes. Multiple challenges exist to define what constitutes optimal nutrition for bone health. As stated by Dr. Robert Heaney, "…the Institute of Medicine (IOM) makes recommendations concerning intakes of something like nineteen essential nutrients … for virtually all of them, there are still major unresolved questions … most fundamental, what is normal?" (4). Challenges in defining nutritional adequacy are related in part to study design. Baseline nutrient assessment can also be challenging due to variability in daily food consumption. Furthermore, the interactions between nutrients in food, rather than provision of a single nutrient as a supplement, may have important effects. Finally, it seems implausible that a single nutrient amount is optimal for all individuals regardless of gender, age, ethnicity, body size and co-morbidities. Thus, it is unrealistic to expect systematic reviews or meta-analyses to provide a simple "one-size fits all" definition of optimal nutritional status for skeletal health. Nonetheless, clinicians are commonly asked for advice regarding proper nutrient intake to maintain health. Recognizing that additional data are sorely needed, the aim of this position paper is to outline our current understanding of optimal nutrition to maximize

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bone gain, minimize bone loss and reduce fragility fracture risk until future studies provide more clarity.

Skeletal Health Throughout Life

Osteoporosis is an age-related skeletal disorder of compromised bone strength predisposing to an increased risk of fracture (5). Modifiable determinants of adult bone health, to include nutrition, influence accrual of peak bone mass and size, and nutrition may have its greatest influence on adult bone health by affecting early skeletal growth (6).

Bone growth generally tracks at a consistent trajectory during youth until puberty, when bone turnover and nutrient demand markedly increase. Depending on the skeletal site, peak bone mass occurs by the end of the second or early in the third decade of life. Supported by sufficient nutrition, bone mass and bone turnover remain relatively stable in midlife. Despite metabolic demands during pregnancy and lactation for fetal bone growth, transient changes in maternal regional or systemic skeletal turnover are without enduring consequence on skeletal integrity (7).

Menopause related estrogen deficiency leads to an increase in bone remodeling. The rate of bone resorption exceeds formation leading to microarchitectural deterioration and loss of both cortical and trabecular bone. Optimal nutrition can attenuate but not prevent age-related decline in bone strength seen in both women and men, although nutritional status can impact fracture risk with aging through non-skeletal risk factors (i.e., physical function associated with sarcopenia).

Nutrition supplies the required substrate for the cellular activity, tissue structure and function of all components of bone. The non-cellular bone tissue consists of minerals (i.e., calcium,

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phosphate and magnesium), collagen and non-collagenous proteins. Minerals strengthen the collagen-protein matrix while also serving as a source of important ions for bodily homeostasis. Thus, growth and maintenance skeletal tissue requires provision of adequate nutrients during each stage of life (8).

Calcium

Calcium and phosphorus represent the two principal minerals that form hydroxyl apatite, the major component of bone. The dairy food group is most associated with bone health, with recommended intake of two to three servings a day. Dairy products contain calcium, phosphorus, magnesium, potassium and protein, and milk consumption has been positively associated with bone health. Adolescent girls who ingest greater amounts of calcium have a higher bone mineral density (BMD), and children and adults consuming low calcium diets are at risk of osteoporosis and fractures (9-11). Few clinical trials assess the effects of calcium supplementation on BMD and fracture risk independent of vitamin D administration. Two RCTs of calcium supplementation in elderly women reduced bone turnover and decreased bone loss (12,13). A Cochrane meta-analysis reported calcium alone was not superior to vitamin D alone in preventing fractures in postmenopausal women and older men (14). However, several meta-analyses show that calcium given with vitamin D reduces vertebral and non-vertebral fracture risk (15,16), consistent with vitamin D's action to improve gastrointestinal (GI) absorption of calcium and ensure adequate bone mineralization.

Calcium supplementation has been reported to increase the risk of cardiovascular (CV) disease in cohort studies, clinical trials and meta-analyses of previously completed trials (17-19). However, these findings have not been validated in recent studies. A large prospective study of

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over 9,000 participants taking up to 1,000 mg of calcium daily and followed for ten years demonstrated no increased risk of CV mortality (20). An updated meta-analysis of RCTs, prospective cohort studies and case-control studies reported no CV outcome risk in individuals consuming dietary or supplemental calcium up to 2,000-2,500 mg/day (21). The National Osteoporosis Foundation and the American Society for Preventative Cardiology stated that calcium intake not exceeding 2,000-2,500 mg/day should be considered safe from CV risk. The AACE/ACE clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis recommend sufficiency of both calcium and vitamin D as part of the treatment regimen (22). A patient's total calcium intake should be assessed from both the diet and any supplement use, and the total daily amount of calcium should not exceed 1,200-1,500 mg. Studies suggest that it is most prudent to obtain calcium from food sources and to use supplements only as needed to reach the recommended total calcium intake.

Non Calcium Minerals

Approximately 85% of the body's phosphorus is found in bone. Phosphate is plentiful in most foods, particularly in processed foods and sodas. Phosphate homeostasis occurs primarily by renal phosphate excretion through the effects of parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF-23)/Klotho. Phosphate is readily absorbed in the gut, enhanced to some extent by 1,25-dihydroxyvitamin D. Insufficient phosphate intake can lead to impaired bone mineralization and rickets or osteomalacia, although inadequate intake is rarely a concern, except for persons experiencing starvation. Data suggest increased dietary phosphate intake is associated with increased PTH and FGF-23 levels and increased bone resorption (23). However, excessive phosphate consumption does not interfere with calcium absorption if there is

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adequate calcium intake (24) and does not seem to be associated with a lower BMD (25). Inaccurate estimates of dietary phosphate intake, the association of inorganic acid load with dietary phosphate, and the presence of a circadian rhythm of serum phosphate are all factors that might affect nutrient study of phosphate (26). Phosphate supplementation in otherwise healthy adults is not recommended and may be detrimental to bone, particularly in those with compromised renal function or low calcium intake.

Magnesium, an intracellular cation and cofactor for multiple enzyme systems, is necessary for both calcium and potassium homeostasis. Although found widely in foods, 48% of the U.S. population consume less than the recommended daily amount (RDA) of magnesium (27). Magnesium homeostasis is primarily regulated by the kidneys, and deficiency may occur from renal causes (diuretics, diuresis, tubular necrosis, etc.) or GI malabsorption. Hypomagnesemia may impair osteoblast function, decrease PTH and 1,25-dihydroxyvitamin D production or action, and increase osteoclast activation (27). Effects of magnesium supplementation on BMD are variable. A Women's Health Initiative (WHI) Study analysis by food questionnaire found hip and whole body BMD significantly related to magnesium intake, although fracture risk was unchanged except in women at the highest quintiles of magnesium intake (28). At present, there is no evidence to support routine magnesium supplementation in otherwise healthy adults.

Fluoride is naturally present in soil and water and consequently found in the food chain. Fluoride is absorbed completely in the GI tract. Fluoride absorption drops to 50-80% when complexes form with proteins, calcium and other minerals. Approximately 95% of bodily fluoride is found in the bones and teeth, and fluoroapatite is antimicrobial and strengthens

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dental enamel. Fluoride stimulates bone formation at low doses, and although the mechanism is unclear, possible means include increasing osteoblast number and function (29). At a dose of 75 mg/day, bone may become abnormally mineralized and susceptible to fracture (30), and skeletal fluorosis has developed from excessive consumption of fluoride in tea (31). Conversely, although 25 mg twice daily dosing of slow-release fluoride showed some success to increase BMD and reduce vertebral fractures (32,33), a meta-analyses reported no benefit for reducing vertebral fractures and an increased non-vertebral fracture risk after four years of treatment (34). Thus, although controversial, fluoride supplementation is not recommended for skeletal health.

Strontium is also a naturally occurring mineral in soil and water. Strontium has chemical similarity to calcium, but is found primarily on the surface of bone apatite crystals and only a small amount replaces calcium within the crystal lattice. Strontium results in a reduced calcium and increased carbonate content of the apatite crystal, thereby enlarging the crystal lattice size. Strontium is rapidly incorporated into bone and reduces bone resorption while modestly stimulating bone formation. Strontium increases BMD related to effects on bone turnover, but due to physicochemical consequences of replacing calcium within the lattice structure (35) may not improve bone strength. There is no evidence of bone toxicity or impaired mineralization at low doses, but strontium has induced osteomalacia in animals, and there may be increased susceptibility in persons with renal failure (36). Strontium is approved outside the U.S. for the treatment of osteoporosis and is reported to decrease the incidence of vertebral and non-vertebral fractures (37,38). However, due to lack of data on bone health, and concerns of

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severe cutaneous drug reactions and increased CV events, strontium supplementation is not recommended for skeletal health.

Boron is a trace element found naturally in plants, and a diet consuming fruits, leafy vegetables, nuts and legumes is high in boron. Boron does not seem to have a clear biochemical function in humans (39), but may have a role in reproductive and bone health in animals (40). Boron may stabilize and extend the half-life of vitamin D and estrogen and increase the renal retention of calcium and magnesium, but there is insufficient data to recommend supplementation for skeletal health (41).

Sodium intake increases urinary calcium excretion, thereby potentially increasing the risk for kidney stones and bone loss (42, 43). An association of sodium intake with decreased hip (44) or spine BMD (45) is reported, but an analysis of WHI data did not find any association between sodium intake and BMD or hip fracture risk independent of calcium intake (46).

Vitamin D

Vitamin D is present only in small amounts in food, and is primarily produced in the skin upon exposure to ultraviolet B radiation (47) and hypovitaminosis D is common when dietary intake is low or poorly absorbed and sun exposure is limited. Vitamin D plays a major role in active GI transport of calcium and may improve muscle function and balance, thereby reducing fall risk (48), and important for patients with osteoporosis as falls cause ≥90% of hip fractures. Furthermore, vitamin D might also improve the BMD response to bisphosphonates (49, 50). As a result of all these skeletal effects, multiple medical organizations recommend optimizing vitamin D status as a core component in the treatment of osteoporosis. Defining “vitamin D inadequacy” is extremely controversial. RCTs evaluating nutrients are often confounded when

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"low" nutrient status is not established since nutrients reach a threshold effect in which greater amounts do not provide enhanced physiologic effects (51). As such, providing vitamin D to volunteers who are vitamin D replete should not be expected to demonstrate beneficial effects. Another major confounder is variability of the 25-hydroxyvitamin D [25(OH)D] assay. Despite being the best determinate of bodily vitamin D status (52), substantial variability between 25(OH)D assays and laboratories persists (53). The Office of Dietary Supplements Vitamin D Standardization Program (VDSP) facilitates standardization of the intra-assay variability and bias of 25(OH)D measurements, recommending a 10% coefficient variability (C.V.) for clinical laboratories (54). It is important to appreciate this assay variability. For example, a 25(OH)D laboratory result of 30 ng/mL meeting the 10% C.V. VDSP recommendation means that the "true" value is between 24 and 36 ng/mL (55). Such variability in 25(OH)D results represents a major challenge to meta-analysis of RCTs (56).

Based on this background of uncertainty, systematic reviews find vitamin D supplementation with daily doses of $\geq$800 International Units (IU) to reduce hip and non-vertebral fractures (57, 58). A reasonable clinical approach is a vitamin D intake of ≥1,000 IU/day for adults age $\geq$50, as vitamin D inadequacy is common in those with a low BMD or prior fragility fracture. AACE/ACE clinical practice guidelines recommend vitamin D sufficiency be defined as serum 25(OH)D ≥30 ng/mL, based on an increased prevalence of secondary HPT below this level (22). The IOM reviewed virtually the same evidence base and recommended 25(OH)D $\geq$20 ng/mL to define vitamin D sufficiency (52). The level that constitutes "high" vitamin D status is similarly controversial. A conservative upper level, based upon 25(OH)D values achieved by highly sun-exposed young adults is 50-60 ng/mL (59). Reasonable approaches to vitamin D assessment and

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treatment include an initial measurement of 25(OH)D in patients at risk of deficiency, or alternatively, vitamin D supplementation and subsequent 25(OH)D measurement 3-4 months later to assess dose adequacy. The amount of vitamin D required to correct deficiency and reach target levels varies among individuals due to not yet well-understood factors, to include obesity and ethnicity (60). Use of huge single doses of vitamin D is not recommended as limited data find this approach to paradoxically increase falls and fracture risk (61). It is essential that vitamin D replacement of deficient states be followed by maintenance dosing (e.g., 1,000-2,000 IU/day), recognizing that higher doses may be needed in patients with obesity or malabsorption.

Other Vitamins

Vitamin A is known to influence bone content. Vitamin A is derived from retinol ingested as either retinyl esters (animal source foods) or carotenoids (fruits and vegetables) and is metabolized to active compounds such as 11-cis-retinal important for vision and all-trans-retinoic acid which is the primary mediator of biological actions of vitamin A. The role retinoids play in regulating osteoclastogenesis remains unclear. In a small cross-sectional study, vitamin A levels showed a negative correlation with BMD, but this association disappeared when a multivariate analysis was applied to include other antioxidants (62). Plasma retinol levels and carotenoids tested in ambulatory women were found to be associated with lower hip BMD and consistently lower in those with osteoporosis (63). Some studies suggest that moderate intakes of retinol (64) and increased circulating retinol levels (65) may increase fracture risk, whereas others have found no effect on hip BMD (66) or fractures (67,68). In a randomized study of 998 adults, lower fracture risk was suggested with increasing plasma total carotenes after long-term

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supplementation, but no association was found between plasma retinol levels and fracture risk (69).

Vitamin K is a cofactor of γ-carboxylase and is essential for γ-carboxylation of osteocalcin, a major noncollagenous bone matrix protein important in bone mineralization. Undercarboxylated osteocalcin (ucOC) lacks structural integrity and its ability to bind to hydroxyapatite is impaired (70). Observational studies suggest diets low in vitamin K are associated with increased fracture risk in older adults (71). However, a recent review of RCTs to assess the impact of fortified foods on bone outcomes assessed both before and after supplementation found only two studies of vitamin K and just one study with folate food fortification, with no effect from folate and inconsistent effects noted with vitamin K (72). One RCT found no effect of vitamin K fortified milk when compared to calcium, but was <4 months duration and only assessed markers of bone turnover in young premenopausal women (73). The second RCT included postmenopausal women consuming calcium and vitamin D fortified dairy with or without vitamin K (74). After one year, the vitamin K groups had significantly lower serum ucOC ratios and urine deoxypyridinoline bone turnover levels. Significant increases in total body BMD occurred in all treatment groups, with better increases in spine BMD observed only in the vitamin K groups after controlling for 25(OH)D levels and dietary calcium intake. There are two naturally occurring vitamin K forms; phylloquinone (K1) is the major dietary form (especially green leafy vegetables), whereas menaquinone-4 (K2) is the main tissue form, to include bone. Vitamin K2 is synthesized by gut bacteria, but is also present in some foods (fermented soy beans, cheese and curds). A two year RCT with vitamin K1, vitamin D and calcium or their combination was studied in postmenopausal women without osteoporosis. The

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group with combined vitamin K, vitamin D and calcium had significant changes in serum vitamin K1 (+157%), ucOC (-51%), 25(OH)D (+17%) and PTH (-11%) with BMD improvement at the radius but no other skeletal sites (75). A review of eight small RCTs (n= 63 to 241 subjects) of 1-2 years duration showed that menatetrenone, a synthetic vitamin K2, decreased serum ucOC, increased spine BMD, and reduced the incidence of vertebral fractures (70). Although vitamin K antagonists (VKAs) decrease serum bone turnover markers, their link with osteoporosis and fractures remains controversial. A meta-analysis of cross-sectional and longitudinal studies assessed patients treated with VKAs compared to healthy controls or those with a medical illness (76). Compared with healthy controls, only a single study showed significantly lower spine BMD in the VKA group, and findings in the longitudinal studies were not significant. Currently, there is not enough evidence to recommend the use of vitamin K supplements for skeletal health.

There is conflicting evidence of the role of vitamin E on bone health. The most abundant vitamin E isomer present in food and most widely distributed in the body is α-tocopherol (αTF). Supplementation generally shows positive effects in various animal models of osteoporosis, but high-dose αTF may be detrimental to bone. Possible reasons αTF may be harmful to bone include interference with the effects of vitamin K on bone, blocking other vitamin E isomers beneficial to bone, and its role as a pro-oxidant. Observational studies to assess the skeletal effects of αTF have generally been positive (77). However, several limitations are involved in the interpretation of these studies. The WHI Observational Study and Clinical Trial reported the association between the amount of vitamin E consumed, the αTF level and78) BMD (78) and neither serum vitamin E nor other antioxidant levels were associated with hip BMD. Due to the

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heterogeneity of these studies, no recommendation for vitamin E supplementation can be made for bone health.

Vitamin C is found naturally in fruits and vegetables and is a common fortification in cereals and juices due to its low toxicity. However, the prevalence of deficiency in the U.S. is reported as 6% (79). Human studies generally showed a positive relationship between vitamin C and bone health, although some suggest that the relationship may be U-shaped, more prominent in certain subgroups and different between dietary and supplemental forms of ascorbic acid (80, 81). Many of these observational or cross-sectional studies used varied methods to assess vitamin C intake, and differ in effect size and statistical significance. In contrast, the large WHI study found no association between dietary intake, total intake or serum levels of vitamin C and BMD (78). In addition, the NHANES III survey found inconsistent outcomes between vitamin C status and BMD among 13,080 U.S. adults; positive among premenopausal women, nonlinear for men, and negative in postmenopausal women with no history of smoking or estrogen use (82). Longitudinal study outcomes from the Framingham Osteoporosis Study, using dietary questionnaires to assess vitamin C intake, found mixed results for BMD outcomes over four years and no association with fracture risk, although significantly fewer hip and nonvertebral fractures occurred in the highest versus lowest tertile of intake (83). Two small six and twelve month RCTs noted positive but different spine and hip BMD effects (84,85). Taken together, the majority of studies have found either positive trends or significant effects of vitamin C on skeletal health. Vitamin C is known to play a role in collagen formation, bone matrix development, osteoblast differentiation and in limiting bone resorption, but the exact effect that vitamin C may have on bone density is presently unknown (78,80).

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Macronutrients and Isoflavones

Protein is a major nutrient essential for collagen synthesis in bone (86). Current IOM guidelines for dietary protein are 0.8 g/kg (87), although maintenance of muscle mass and bone strength was not an endpoint for these RDA requirements. A meta-analysis of cross-sectional studies suggests either no association or a small positive association between protein intake and BMD (88). Several studies found inconclusive evidence linking dietary protein intake with fracture risk (89). The prospective Iowa Women's Health Study reported a decreased relative risk of hip fracture across increasing quartiles of animal protein intake, compared to vegetable protein, in postmenopausal women (90). The prospective 5-year Canadian Multicentre Osteoporosis study showed that low protein intakes (<12% of total calories) were associated with almost double the risk of fragility fracture in postmenopausal women and men aged $\geq$50 years compared to higher ($\geq$15% of total calories) protein consumption (91). The protein source was a determinant of BMD but not fracture risk, whereby greater dairy protein intake was associated with higher BMD compared to plant-based protein. It has been hypothesized that a high protein (i.e., acid-based) diet is associated with hypercalciuria from bone resorption. However, a recent review concluded that the dietary acid hypothesis is not supported by current evidence (92). In addition, a protein and calcium interaction has been identified suggesting increased dietary protein associated with decreased fracture incidence with calcium intakes >800 mg/day, whereas the effect appears reversed during lower calcium intake (93). The balance of evidence suggests that adequate protein intake is an important modifiable risk factor associated with reduced risk of fragility fracture.

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Flavonoids are lipid-soluble polyphenols widely distributed in plants and may act as chemical messengers and antioxidants. Isoflavones are “natural” or “phyto-estrogens” (e.g., bioactive compounds that bind to the estrogen receptor) found in various plants and foods, most notably soybeans. Tea flavonoids have been suggested to protect against bone loss, but epidemiologic studies have shown mixed results of habitual tea consumption on BMD and fracture risk, and the results from clinical trials are limited (94). There has been increasing interest in whether isoflavones can promote bone health and ameliorate bone loss (95) but studies are conflicting regarding a positive BMD effect (96). There is little support for the use of isoflavone supplements in Western countries due to inconclusive evidence that these compounds improve BMD or decrease fracture risk (97-99).

Trace Elements

Trace elements ae essential for the growth, development and maintenance of body tissues, including bone. Many over-the-counter supplements containing trace elements are advertised as beneficial for bone health and prevention of bone loss, but to date there are no long-term high-quality based studies that show fracture risk reduction. A recent meta-analysis found lower serum levels of zinc, copper or iron in patients with osteoporosis than healthy controls (100). In a small cross-sectional study, patients with bone loss were found to have significantly lower serum levels of zinc and copper, although no differences were observed in those with osteopenia and osteoporosis (101). In postmenopausal women, plasma and red blood cell trace element concentrations were not significantly different between those with and without osteoporosis for zinc, copper, manganese and selenium (102). A study in postmenopausal women reported a positive association of serum zinc with BMD, but no correlation to serum

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levels of copper or selenium (103). In contrast, the 6-year prospective Osteoporosis and Ultrasound Study found that higher selenium levels associated with lower bone turnover markers and greater BMD in postmenopausal women both at study baseline and 6-year follow up (104). Although trace elements are necessary for normal bone development (105), their efficacy in the treatment of osteoporosis remains unclear.

Summary

As defined by the World Health Organization and the Food and Agricultural Organization of the United Nations, fortification refers to "the practice of deliberately increasing the content of an essential micronutrient, that is, vitamins or minerals in a food, irrespective of whether the nutrients were originally in the food before processing or not, so as to provide a health benefit with minimal risk to health" (106). Food fortification has the advantage of delivering essential nutrients to large segments of the population without requiring radical changes in food consumption patterns. Foods used as fortification vehicles vary from country to country, but they generally include cereals and cereal-based products, milk and dairy products, fats and oils, tea and other beverages and condiments. Certain types of fortification are more accurately called enrichment when micronutrients lost during processing are added to back to food. Debate surrounds the benefits of individual high-dose micronutrient supplementation among well-nourished individuals, and this is true also for skeletal health. Given the study limitations limiting our current knowledge, provision of excess nutrients beyond their threshold of benefit may not produce a greater response. Three critical nutrients for bone health are calcium, vitamin D and protein, and diets that are inadequate in one may well be inadequate in other nutrients important to skeletal health. Otherwise, optimal nutritional status for bone health is

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best obtained by consuming a healthful diet and will likely not be met by single nutrient supplementation.

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