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Nutrition, Bone, and Aging: An Integrative Physiology Approach

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Abstract Osteoporosis, a condition associated with significant morbidity and mortality, is prevalent in the growing elderly population. Aging is associated with characteristic changes in the complex pathways of bone remodeling and in patterns of food intake. Whereas the traditional focus of nutritional supplementation for protection of bone health has centered around calcium and vitamin D, a multitude of nutrients have been identified with effects on bone, both individually and in combination. An integrative physiology approach can assist in formulating a deeper understanding of the complex interactions of nutrition and aging with bone, with the goal of identifying modifiable risk factors for the prevention of bone loss.

Keywords Osteoporosis · Bone remodeling · Integrative physiology · Nutrition · Aging

Introduction

Osteoporosis is a widespread disease with an understanding that has evolved from a simple focus on bone loss into comprehensive clinical, translational, and academic research and practice activities. This expanded view realizes many physiologic interactions that affect bone, among which, nutritional medicine and aging play important roles. As the population grows older, the burden of fractures becomes more significant with an imperative to identify modifiable risk factors. Supplementation with calcium and vitamin D is the mainstay of nutritional intervention for bone health, but other nutrients play important roles [1–4]. The purpose of this review is to illustrate an integrative physiology representation of bone health with a specific focus on the roles of nutrition and aging. A similar representation of bone remodeling and the skeletal subsystem was formulated in a recent issue of *Current Osteoporosis Reports* [5].

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Bone Remodeling and Aging

Throughout adult life, the human skeleton undergoes a dynamic and highly coordinated process of renewal, involving coupling of bone-resorbing osteoclasts and bone-forming osteoblasts. The ability of bone to respond to external signals to repair microdamage, remove mechanically unneeded bone, and maintain calcium homeostasis is critical for survival. Skeletal injury is sensed by osteocytes embedded within bone, which undergo apoptosis [6]. This leads to a loss of osteocyte-secreted transforming growth factor-β (TGF-β) and subsequent permissive effects on osteoclastogenesis [6]. Osteocytes also express sclerostin, an inhibitor of the Wnt signaling bone formation pathway; osteocyte apoptosis reverses this inhibitory pathway [7]. Hormonal signals of remodeling include parathyroid hormone (PTH), which binds to its receptor on osteoblasts, leading to the recruitment and differentiation of osteoclast precursor cells [7].

The key osteoclastogenesis regulatory step involves the production of receptor activator of nuclear factor-κβ (NF-κβ) ligand (RANKL) by osteoblasts, which binds to the RANK receptor on osteoclast precursor cells, activating NF-κβ and promoting osteoclast differentiation [8]. Osteoclast proliferation and survival also requires the binding of osteoblast-derived macrophage colony-stimulating factor (M-CSF) to the osteoclast receptor c-fms [9]. Osteoblast production of osteoprotegerin (OPG), a soluble decoy receptor for RANKL, competitively antagonizes the binding of RANKL to RANK, thereby inhibiting osteoclastogenesis [10]. The RANKL/OPG ratio dictates the extent of bone resorption [7] and is influenced by numerous stimuli including PTH,

1,25-dihydroxyvitamin D (1,25-D), prostaglandins, and cytokines [9].

Following bone resorption, osteoblast precursor cells are recruited in response to a gradient of TGF-β1 [11] and secrete a proteinaceous bone matrix, composed of type 1 collagen and various noncollagenous proteins including osteocalcin (OCN). Unmineralized osteoid requires incorporation of calcium- and phosphorous-containing hydroxyapatite to form complete mineralized bone [9].

Aging is associated with changes in the bone remodeling process, characterized by an increase in the resorption/formation ratio, leading to a progressive loss of bone. Osteoporosis has been associated with deficient plasma levels of antioxidants [12]. Excessive generation of reactive oxygen species (ROS) beyond antioxidant capacity (oxidative stress) is associated with age-related bone loss [13]. Oxidative stress diverts the maturation of mesenchymal stem cells from osteoblastogenesis toward adipogenesis [14], suppresses osteoblastic differentiation via extracellular signal–regulated kinases, and potentiates osteoclast maturation [15]. Osteocyte apoptosis is also linked to oxidative stress, and contributes to increased brittleness of bone due to hypermineralization and inappropriate signaling of the remodeling cascade [14]. NF-κβ is an oxidative stress-responsive transcription factor and may be activated by free radicals.

Aging is also a proinflammatory state with a persistent low-grade activation of the innate immune system [16]. Inflammatory mediators, including tumor necrosis factor (TNF)-α, interleukin (IL)-1, -6, -7, and -17, and prostaglandin E2, induce expression of M-CSF and RANKL, facilitating bone resorption [15].

In women, estrogen deficiency after menopause leads to a loss of osteoclast apoptosis and an increased production of cytokines and ROS, altering the RANKL/OPG ratio in favor of bone resorption [17]. Aging men sustain an increase in sex hormone–binding globulin and a steady decline in bioavailable testosterone and estradiol levels [18]. Secondary hyperparathyroidism occurs due to vitamin D deficiency, which is prevalent in the elderly, and a chronic negative calcium balance, exacerbated by estrogen deficiency [19]. Age-related declines in adrenal androgen production (dehydroepiandrosterone [DHEA] and DHEA-sulfate [S]) and in the growth hormone and insulin-like growth factor-1 (IGF-1) axis contribute to bone loss [18]. Additionally, sarcopenia and reduced physical activity occur with aging, leading to decreased skeletal loading and subsequent bone resorption [20, 21].

Relevant Nutrition and Aging Mechanisms

Aging is associated with a variety of physiologic changes that impact nutritional status and predispose to a state of malnutrition termed the "anorexia of aging" [22]. Decreased energy expenditure with aging reduces energy requirements. Food intake is often less than required needs, due to a decreased sense of smell and taste, poor dentition, decreased saliva production, and decreased variety, frequency, and pleasure of food intake. This results in a loss of lean mass and body weight. Reduced gastric acid secretion due to chronic gastritis or use of proton pump inhibitors predispose to small bowel bacterial overgrowth, a condition associated with reduced body weight and impaired nutrient absorption [23]. Increased postprandial secretion of gut hormones, cholecystokinin and peptide YY, may be implicated in delayed gastric emptying and increased satiety in the elderly [24]. Increased levels of insulin and adipose-derived leptin also contribute to hypothalamic satiety signaling [23]. Depression, dementia, drug side effects, social isolation, economic duress, and other chronic conditions contribute to a deteriorating nutritional status in the elderly [22].

Geriatric cachexia is associated with augmented proinflammatory cytokines, including TNF-α, IL-1, IL-6, serotonin, and interferon-γ [25]. These cytokines are associated with decreased appetite, reduced food intake, and subsequent weight loss in the elderly via physiologic alterations in gastrointestinal motility and acid secretion. Increased cytokines also occur due to increased production of glucocorticoids and catecholamines and decreased production of sex and growth hormones [25].

The "anorexia of aging" significantly impacts bone health via effects on hormonal axes and nutrient levels. Protein, calcium, vitamin D, and vitamin B_6 requirements are increased in the elderly, despite a decrease in caloric intake and impairment in nutrient absorption, leading to multiple deficiency states with an impact on bone health [26]. In particular, protein deficiency leads to sarcopenia and decreased skeletal loading. The nutritional effects on bone loss are compounded by age-related hormonal declines (estrogen, testosterone, IGF-1, DHEA-S) predisposing the elderly to increased bone resorption. Figure 1 summarizes the effects of aging on bone remodeling and nutrition and highlights the various interrelationships between nutrients that will be discussed below.

Nutrition and Bone Physiology

Minerals

Calcium

Calcium is a key architectural component of bone and critical for maintenance of bone health. Inadequate calcium absorption increases PTH concentration leading to increased bone resorption. The recommended dietary allowance for calcium

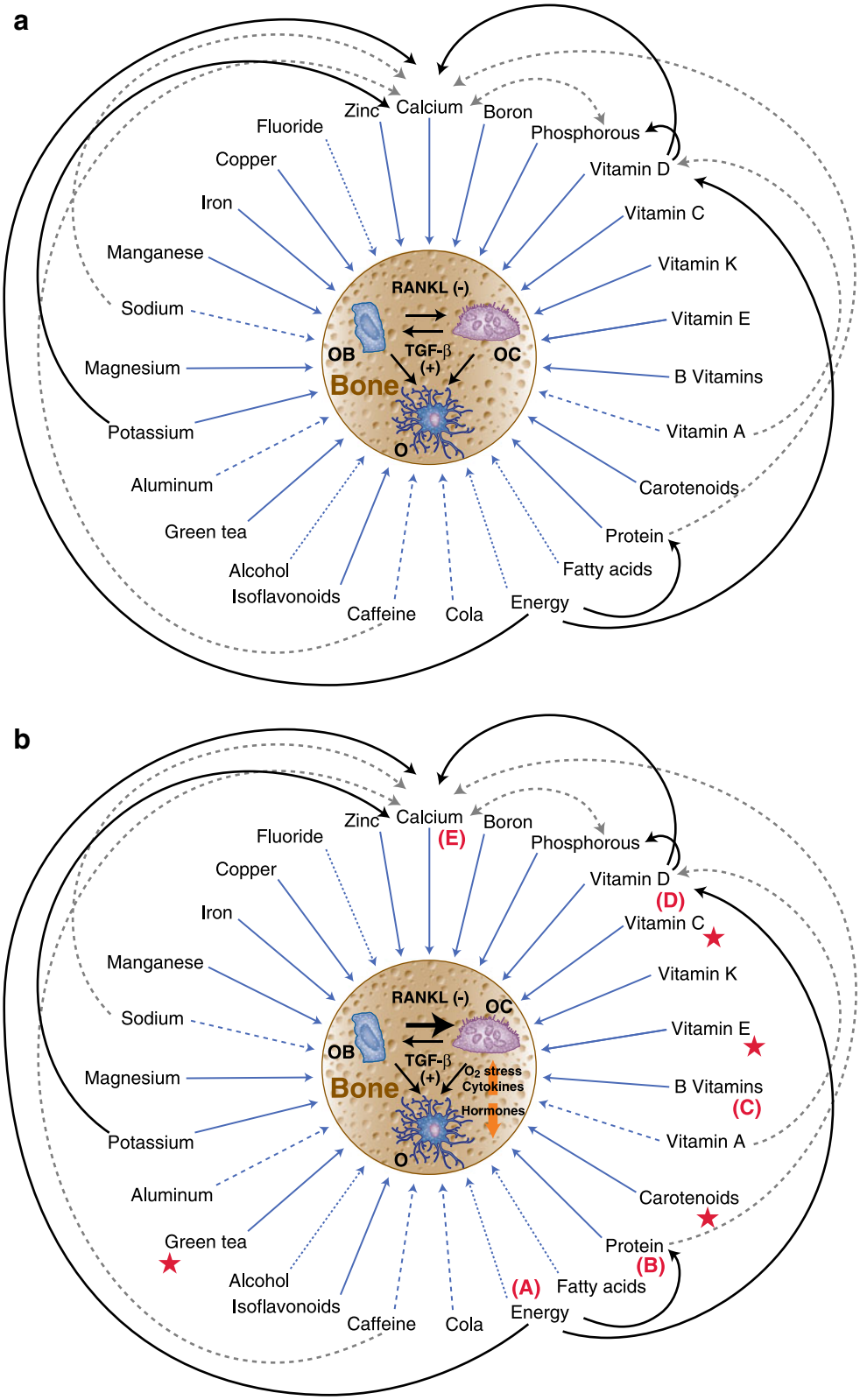

Fig. 1 Comparison of the various relationships that nutrients have on bone. **A** Depicts the effects that nutrients have on bone and with each other in a young person. **B** Shows the changes that occur with aging, predisposing to an excess of bone resorption, including increases in oxidative stress and cytokine production and decreases in hormone production (estrogen, testosterone, IGF-1, DHEA-S). **a** Decreased energy intake occurs due to impaired senses of smell, taste, and saliva production, as well as changes in gut hormones resulting in an overall negative energy state that worsens bone metabolism. **b** Decreased protein intake leads to sarcopenia, decreased skeletal loading, and decreased IGF-1, which in turn weakens bone. **c** Increased rates of B vitamin deficiencies occur with aging. **d** Increased rates of vitamin D deficiency occur with aging. **e** Calcium decreases with aging from a variety of sources including estrogen deficiency, vitamin D deficiency, and decreased intake. *Asterisk* indicates requirements for nutrients with antioxidant capacity may be heightened with aging due to increases in oxidative stress; *solid line* indicates positive effect; *dashed line* indicates negative effect; *dotted line* indicates mixed positive/negative effect. DHEA-S—dehydroepiandrosterone sulfate; IGF-1—insulin-like growth factor-1; O—osteocyte; OB—osteoblast; OC—osteoclast; RANKL—receptor activator of nuclear factor-κβ ligand; TGF-β—transforming growth factor-β

is 1,000 mg/day for younger adults and 1,200 mg/day for women over the age of 50 years and men over the age of 70 years [27].

The positive effect of calcium supplementation on bone mineral density (BMD) has been well established [28, 29]. However, the efficacy of calcium in preventing hip fractures

and for improved BMD to serve as a surrogate measure for fracture risk reduction has recently been called into question [30]. In a 2007 meta-analysis of randomized controlled trials, Bischoff-Ferrari et al. [31] showed that calcium monotherapy had no effect on nonvertebral fractures and a 64% greater hip fracture risk. A meta-analysis by Tang et al. [29] initially reported a 12% risk reduction in total fracture rate with calcium supplementation, but a re-analysis of the data showed an increased risk of hip fracture with calcium monotherapy [32, 33].

Calcium-carbonate or -citrate therapy may negatively affect bone mineralization by reducing phosphate absorption and the critical calcium-phosphate product [34]. This disadvantage of calcium therapy is mitigated by concomitant use of vitamin D, which increases renal phosphate reabsorption. Moreover, calcium-rich foods are also good sources of phosphorus and may not predispose to an increased fracture risk [31].

Calcium supplements, without coadministered vitamin D, have also been recently implicated in increased cardiovascular risk by predisposing to vascular calcification. Bolland et al. [35••] performed a meta-analysis of randomized placebo-controlled trials and determined a hazard ratio of 1.31 (95% CI, 1.02–1.67; P=0.035) for myocardial infarction with calcium supplements versus placebo. This meta-analysis has been questioned because it relies on unpublished data and the findings are not generalizable to the standard of care: combined treatment with calcium and vitamin D.

Potassium

Potassium, found in many fruits and vegetables, has been postulated to have a positive effect on bone based on its coexistence with bicarbonate. A high-potassium diet may protect bone by decreasing the dietary acid load, obviating the need for bone resorption to provide buffer when renal mechanisms are overwhelmed [36]. In vitro and animal studies have shown an effect of acidosis on osteoclast activation [37]. Studies in humans on low potassium and high-acid diets resulted in increased urinary calcium excretion [38, 39]. Observational studies have linked a diet low in net endogenous acid production (NEAP) and high in potassium, with improved markers of bone turnover [40] and higher BMD [41]. However, data from a small intervention study with potassium citrate did not show a reduction in bone turnover or an increase in BMD [42]. The "acid–base theory" has been seriously questioned by Fenton et al. [43••] in a recent systematic review and meta-analysis that showed a lack of causality of dietary acid load on bone loss.

Other Minerals

Magnesium deficiency has been associated with lower hip BMD in postmenopausal women [44]. Magnesium is an important structural component of bone [1] and regulates PTH secretion via binding to the calcium-sensing receptor [45]. Magnesium deficiency may lead to increased cytokine and free radical production, activation of NF-κβ, and enhanced bone resorption [46]. Short-term magnesium supplementation in postmenopausal women decreases intact PTH and urinary deoxypyridinoline levels and increases serum OCN levels [46].

High sodium intake is associated with calciuria [47] and had been linked to a greater decline in BMD in observational studies [48]. There is a lack of data on the causal relationship of sodium intake and fracture risk.

Fluoride is incorporated in bone as fluoroapatite and has a stimulatory effect on osteoblasts leading to an increase in BMD. High fluoride exposure is linked to osteosclerosis, characterized by dense and brittle bone with an increased fracture risk [49].

Aluminum toxicity has been associated with impaired deposition of calcium, phosphorous, and magnesium and loss of BMD in animal studies [50]. Possible effects of aluminum on the production and secretion of PTH and 1,25-D have been considered [50].

Several other trace elements are required for bone matrix formation and mineralization (manganese, zinc, and iron), collagen crosslinking (copper), and steroid hormone formation (boron) [1]. Further evidence is needed to establish a role for supplementing these elements specifically for bone health.

Vitamins

Vitamin D

Vitamin D is a fat-soluble vitamin that can be produced in the skin after sun exposure or ingested in the diet, particularly as fatty fish or fortified foods. Vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol) are transformed by the liver into 25-hydroxyvitamin D (25-D) and by renal 1α-hydroxylase into the active 1,25-D form. 1,25-D binds to the widely distributed vitamin D receptor (VDR), which interacts with DNA response elements on target genes after forming a heterodimer with the retinoid X receptor (RXR) [51]. Inadequate levels of vitamin D lead to reduced intestinal calcium absorption, secondary hyperparathyroidism, impaired mineralization, and increased bone resorption. Vitamin D deficiency is prevalent in the elderly, particularly in nursing home residents, and has been associated with an increased rate of frailty [51], impaired muscle function, and falls [52]. Some epidemiologic studies have supported an association between vitamin D deficiency and mortality; possible mechanisms include effects on DNA repair, protection from oxidative stress, and immune regulation [51].

Current recommendations for vitamin D intake are 600 IU/day for adults and 800 IU/day for men and women

over the age of 70 years [27]. Whereas the 2010 Institute of Medicine report [27] advocated a lowering of the cutoff for 25-D sufficiency from 30 to 20 ng/mL in healthy individuals, this practice has not been widely accepted and is not applicable for patients with bone disease. Furthermore, a recently published clinical practice guideline by the Endocrine Society endorses traditional 25-D cutoffs: sufficient (30–100 ng/mL), insufficient (20–29 ng/mL), and deficient (<20 ng/mL) based on data correlating normalization of PTH with correction of vitamin D deficiency [53]. Whereas vitamin D monotherapy has not been consistently shown to decrease fracture risk, combined calcium and vitamin D therapy has proven to be beneficial for hip fracture risk reduction [54, 55••].

Vitamin K

Vitamin K, a fat-soluble vitamin, is found as vitamin K_1 (phylloquinone) in green leafy vegetables and vitamin K_2 (menaquinone) in intestinal bacteria. Vitamin K_2 supplementation has proven efficacious for osteoporosis, culminating in its designation with level B evidence at the pharmacologic dose for therapy by the World Health Organization Scientific Group [56]. Vitamin K is a cofactor for γ-carboxylase, which converts glutamic acid residues on OCN to γ-carboxy glutamic acid, allowing OCN to bind to hydroxyapatite. Vitamin K deficiency or warfarin use leads to abnormal undercarboxylated OCN [57]. Another possible mechanism of action of vitamin K on bone is as a transcriptional regulator of bone-specific genes via steroid and xenobiotic receptors favoring expression of osteoblastic markers [58].

Randomized controlled trials of vitamin K_1 or K_2 supplementation have consistently demonstrated decreased levels of undercarboxylated OCN in the treatment groups, inconsistent effects on total OCN levels, and no significant changes of bone turnover markers [57]. Of three studies that assessed fracture as an outcome, two showed a reduced fracture risk [59, 60] and although the third and largest study did not demonstrate benefit [61], a post hoc analysis of patients with a prior history of five or more vertebral fractures did demonstrate a reduced fracture risk. The lack of benefit on markers of bone turnover may reflect the fact that vitamin K serves to improve bone quality via its effect on OCN rather than through BMD.

Vitamin C

Vitamin C (L-ascorbic acid) is an essential water-soluble vitamin found primarily in fruits and vegetables. As a potent antioxidant, vitamin C can scavenge free radicals, preventing activation of NF-κβ and bone resorption [62]. Vitamin C also acts as a cofactor in the enzymatic hydroxylation of proline and lysine residues, a required step for collagen to assume its proper structural role in bone [63].

Observational studies have found positive correlations between vitamin C intake and hip fracture reduction in current or prior smokers [64, 65]. A possible explanation for this relationship is the increase in oxidative stress associated with smoking, potentially allowing for a greater benefit from antioxidants such as vitamin C. One recent randomized controlled trial in 90 elderly subjects tested dual supplementation with 500 or 1,000 mg of vitamin C plus 400 IU of vitamin E versus placebo for 1 year [66]. Hip BMD significantly increased in the group receiving high-dose vitamins C and E [66]. Markers of antioxidant status correlated with BMD [66].

B Vitamins

B vitamins and homocysteine have been studied with respect to bone health. Homocysteine metabolism requires the presence of vitamin B_6, vitamin B_{12}, and folate; deficiency of any of these vitamins can lead to elevations in plasma homocysteine. Homocystinuria, a rare autosomal-recessive disorder causing elevated plasma homocysteine levels and severe vaso-occlusive disease, is associated with osteoporosis [67]. Hyperhomocysteinemia in the general population has been associated with a two- to fourfold increase in fracture risk [68, 69], but studies of homocysteine and BMD are inconsistent [67]. It is unclear whether the causal connection between homocysteine and bone is direct or indirect, involving a B vitamin deficiency/insufficiency. For instance, vitamin B_{12} deficiency in the setting of pernicious anemia has been associated with an increased rate of bone loss [70]. In addition, vitamin B_6 acts as an essential coenzyme for lysyl oxidase, a collagen crosslink precursor.

Sato et al. [71] studied folic acid (5 mg) and vitamin B_{12} (1,500 μg) supplementation versus placebo over 2 years in a population of Japanese individuals with hemiplegia secondary to stroke and with baseline values of high plasma homocysteine (mean 19.9 μmol/L) and low serum folate (mean 5.4 nmol/L). The intervention group showed an 80% and 76% reduced risk of hip fracture and total fracture, respectively, and no change in metacarpal BMD [71]. Herrmann et al. [72] studied folic acid (2.5 mg), B_{12} (0.5 mg), and B_6 (25 mg) supplementation versus placebo in 47 subjects with osteoporosis for 1 year, with no significant change in bone turnover markers or BMD.

Vitamin A and Carotenoids

Vitamin A has been associated with negative effects on bone health. Retinol, the active form of vitamin A, is obtained from foods of animal origin, especially liver and dairy products, or via fortified foods or supplements.

Carotenoids, plant-derived pigments such as β-carotene, can be conditionally converted to retinol in the setting of vitamin A deficiency [3], and also play a role as antioxidants.

In humans, vitamin A toxicity can induce hypercalcemia and impaired bone remodeling [73]. Chronic use of synthetic retinoids has been associated with decreased BMD, suppressed bone turnover, and hyperostosis [74]. Animal studies have shown that retinoic acid suppresses osteoblast activity, stimulates osteoclastogenesis, and antagonizes the action of vitamin D [73].

A prospective cohort study within the Nurses' Health Study, showed a significantly increased risk of hip fracture in the highest quintiles of retinol and total vitamin A intake, but no significant association with β-carotene intake [75]. In the Women's Health Initiative, an increased risk for total fracture was seen only when a high vitamin A intake was associated with a low vitamin D intake (≤11 μg/day or 440 IU) [73]. It is possible that the negative effect of vitamin A on bone is more clinically relevant in situations of vitamin D deficiency, because vitamin A inhibits vitamin D effects on bone [76]. The vitamin D and RXRs bind to target genes as a VDR-RXR heterodimer and may be modulated by levels of retinoic acid [76, 77].

Carotenoids, which cannot contribute to vitamin A toxicity due to the controlled conversion step, do not appear to carry the same negative potential on bone as retinols, and have been associated with improved fracture risk, most likely due to their other role as antioxidants [78].

Macronutrients

Protein

Traditionally, high protein intake was thought to be detrimental to bone health, but recent data have shed light on the important relationship between protein and bone. Increased protein intake is known to promote urinary calcium excretion, leading to hypercalciuria. Previously, a high protein diet characterized by a large sulfur content and acid-generating ability was thought to be harmful to bone, because the increased urine calcium was presumed to be of bone origin [79]. However, short-term studies using calcium isotopes have confirmed that higher protein intake leads to hypercalciuria via increased intestinal calcium absorption rather than through losses of mineral from bone [80]. Protein intake is also associated with preservation and accumulation of skeletal muscle mass, a key determinant of BMD [81]. Additionally, protein intake correlates with levels of IGF-1, a growth factor with anabolic effects on bone mass in adults [82].

Several epidemiologic studies have supported the above findings by showing significant positive associations between protein intake and BMD or decreased fracture risk. Darling et al. [83••] published a systematic review and meta-analysis of protein supplementation and bone health including 19 randomized controlled trials. This analysis showed a small positive impact of protein supplementation on lumbar spine BMD and no significant interaction with fracture rate. Studies comparing animal and vegetable sources of protein have conflicting results; higher sulfur content in meat-derived protein and a typically lower daily intake of protein in vegetarians may be contributing factors [79].

Total Energy (kcal)

Low caloric intake is associated with detrimental effects on bone. An extreme version of caloric restriction, anorexia nervosa, is frequently associated with osteoporosis and osteopenia. Starvation and depleted fat stores result in decreased leptin levels acting on the hypothalamus. In females with anorexia, leptin-induced changes in the hypothalamic-pituitary axis impair gonadotropin-releasing hormone pulsatility and suppress the secretion of gonadotropins, particularly luteinizing hormone, leading to anovulation, hypoestrogenism, and amenorrhea [84]. Hypogonadotropic hypogonadism is seen in males with anorexia nervosa. Decreased IGF-1 production with growth hormone resistance, hypercortisolism, and a low T3 state are other endocrine consequences of anorexia; all have adverse effects on bone physiology, promoting bone resorption and impairment of compensatory bone formation [85]. The bone disease of anorexia nervosa is compounded by the failure of adolescents to achieve peak bone mass and by poor nutrition, including calcium and protein deficiencies.

Milder forms of caloric restriction have also been linked to bone loss and may operate through similar mechanisms but on a lesser scale. A cross-sectional study of 52 nonobese women classified by daily caloric intake at 100%, 80%, or 55% of the recommended minimum daily requirement demonstrated a 10% lower femoral BMD in the extremely low caloric intake (55%) group ($P<0.05$) and a nonsignificant trend toward lower spine BMD compared with the other two groups [86]. What is not clear is how much of this calorie-bone effect is due specifically to an energy deficit versus the negative effects of other coexistent nutritional deficiencies.

Whereas excessive energy intake leading to an overweight/obese body composition was once believed to have a protective effect on BMD, a new understanding has recently emerged. Obesity is characterized as a systemic inflammatory state, with increased secretion of cytokines known to upregulate RANKL and facilitate osteoclastogenesis [87]. When adjustments are made for lean versus fat mass for a particular body weight, increased body fat is inversely associated with BMD in premenopausal women and has no effect in men and postmenopausal women [87]. A possible

explanation for the protective effect of adiposity in the latter two groups involves the more significant contribution of fat-aromatized estrogen on increasing the low total body estrogen levels in men and postmenopausal women compared with the high baseline levels of estrogen seen in premenopausal women.

Fatty Acids

High saturated fatty acid consumption has been associated with an increased risk of hip fracture in a cohort of postmenopausal women in the Women's Health Initiative [88]. Data on omega-3 and omega-6 fatty acids have been inconsistent, but a potential benefit through their anti-inflammatory properties has been postulated.

Other Dietary Factors

Isoflavonoids

Isoflavonoids are diphenolic compounds structurally and functionally similar to estrogen and can be found in soy foods and other legumes. These phytoestrogens (e.g., genistein, daidzein, and ipriflavone) may harbor a potential bone-protective effect. Observational studies show higher soy intake in Asian compared with Western diets [89], and lower rates of hip fracture in Asian women compared with Caucasians [90].

Isoflavonoids have been proposed to act as selective estrogen receptor modulators due to their higher affinity for estrogen receptor-β (ERβ) in bone than for estrogen receptor-α (ERα) in reproductive tissues, but overall bind more weakly to these receptors than 17β-estradiol [91]. Concern needs to be taken in studying the safety of isoflavonoid supplementation for bone health due to the known risks of hormone replacement therapy: increased risk for breast, endometrial, and ovarian cancer, cardiovascular disease, venous thromboembolism, and stroke. A recent meta-analysis of randomized controlled trials, including data on 1240 postmenopausal women, showed a 2.38% increase in spine BMD after 6 to 12 months of isoflavone extract supplementation compared with placebo, but no effect on hip BMD [92].

Alcohol

Although alcoholism is a risk factor for osteoporosis, moderate alcohol intake has been associated with improved BMD and a decreased risk of fracture. Berg et al. [93] performed a systematic review and meta-analysis showing a J-shaped relationship of alcohol with hip fracture; those consuming 0.5 to 1 drink per day had the lowest risk and consumers of two or more drinks had the highest risk. A linear relationship was seen with femoral neck BMD and alcohol consumption [93]. The mechanism of alcohol's protective effect on bone has been suggested to involve an increase in serum estradiol [94].

Resveratrol, a polyphenol found in grapes and red wine, has been increasingly studied for its osteogenic and anti-adipogenic properties. Resveratrol affects mesenchymal stem cell maturation by decreasing adipogenesis and facilitating osteoblast differentiation via activation of SIRT1, a sirtuin protein implicated in longevity, and through inhibition of peroxisome proliferator-activated receptor-γ [95]. Resveratrol has also been shown to interact with ERα and ERβ, augment Wnt signaling, and promote bone formation [95].

Caffeine

Epidemiologic studies have correlated increased caffeine intake in postmenopausal women with negative effects on bone; no effects are seen in young women [96]. In the Framingham Study, hip fracture risk was significantly increased by the consumption of ≥2.5 units of caffeine per day [97]. Caffeine increases urinary and fecal calcium losses, which can be offset by increased calcium intake. Caffeine, a known inhibitor of cyclic AMP phosphodiesterase, is also thought to inhibit osteoblast proliferation, modulate osteoclastogenesis via RANKL/OPG expression, and be antagonized by estrogen [96]. A possible explanation for the effects of caffeine on older and not younger women relates to the differing estrogen levels in the two populations [96].

Cola

Cola drinks have been associated with decreased BMD. In the Framingham Osteoporosis Study, daily cola drinkers had a mean hip BMD 4% to 5% lower than infrequent cola drinkers [98]. In addition to their caffeine content, cola contains phosphoric acid, which may interfere with intestinal calcium absorption [2]. All types of soft drinks tend to displace milk in the diet and may negatively affect bone by decreasing calcium intake.

Green Tea

Whereas epidemiologic studies of the benefits of tea consumption on BMD and fracture risk have been inconsistent, increasing in vitro and animal study data have shown a link between green tea polyphenols (GTPs) and bone health [99]. Epigallocatechin gallate, the most abundant and well-studied GTP, demonstrates antioxidant and anti-inflammatory properties and has been associated with an increase in osteoblastogenesis and osteoclast apoptosis in vitro [99]. Human studies will be necessary

Table 1 Summary of effects of various nutrients on bone remodeling

Nutrient	Positive (+) vs. negative (−) effect on bone health	Action on bone
Minerals:		
Calcium	+	Incorporated as hydroxyapatite
		Adequacy prevents secondary hyperparathyroidism
Phosphorous	+	Incorporated as hydroxyapatite
Potassium	+	Decreases urinary calcium excretion
		Contributes alkali (unclear benefit)
Magnesium	+	Structural component of bone
		Deficiency increases cytokine production
Sodium	−	Inducer of calciuria
Fluoride	+/−	Incorporated as fluoroapatite
		Increases BMD, but in excess causes brittle bone
Aluminum	−	At toxic levels impairs mineralization
Manganese	+	Bone matrix formation
Zinc	+	Bone matrix formation
Iron	+	Bone matrix formation
Copper	+	Collagen crosslinking
Boron	+	Steroid hormone formation
Vitamins:		
Vitamin D	+	Increases intestinal absorption of calcium and phosphorous
Vitamin K	+	γ-carboxylation of OCN
		Transcriptional regulator of bone formation
Vitamin C	+	Antioxidant
		Collagen hydroxylation
Vitamin E	+	Antioxidant
B vitamins (B_6, B_{12}, folate)	+	Collagen crosslinking
Vitamin A	−	Inhibits osteoblasts, activates osteoclasts
		Antagonizes vitamin D
Carotenoids	+	Antioxidant
Macronutrients:		
Protein	+	Increases intestinal calcium absorption and increases calciuria
		Increases muscle accumulation
		Increases IGF-1
Energy (kcal)	+/−	Hormonal effects on hypothalamus
		Associated with other nutritional deficiencies
		In excess (obesity) inducer of osteoclastogenesis
Fatty acids	+/−	Possible anti-inflammatory effect for omega-3
Other factors:		
Isoflavonoids	+	Estrogen agonist on bone
		Associated with increased IGF-1
Alcohol	+/−	Positive in moderation: increase in serum estradiol
		Resveratrol: facilitate osteoblast proliferation, inhibit adipogenesis
		Negative in alcoholism: poor nutrition, increased falls, liver disease
Caffeine	−	Increases calciuria and fecal calcium losses
		Inhibits osteoblasts, stimulates osteoclasts, may be antagonized by estrogen
Cola	−	Phosphoric acid: interferes with intestinal calcium absorption
		Displaces milk from diet: decreased calcium intake
Green tea	+	Antioxidant, anti-inflammatory, promotes osteoblastogenesis and osteoclast apoptosis (in excess may lead to skeletal fluorosis)

BMD bone mineral density; *IGF-1* insulin-like growth factor-1; *OCN* osteocalcin

Table 2 Nutrient-nutrient interrelationships with subsequent effects on bone health

Nutrients	Relationship
Calcium–vitamin D	Vitamin D is required for calcium absorption
	Consistent benefit on fracture reduction seen only with dual therapy
Calcium–phosphorous	Both minerals required for mineralization
	Calcium supplements may inhibit phosphate absorption
	Phosphoric acid in cola may inhibit calcium absorption
Vitamin A–vitamin D	Vitamin A may antagonize the action of vitamin D
Calcium–protein Calcium–sodium Calcium–caffeine	Inducers of calciuria
Calcium–potassium	Inhibitor of calciuria
Potassium–magnesium–vitamin C–carotenoids–vitamin K	Nutrients found in fruits and vegetables
	Positive effects of fruits and vegetables; may be difficult to distinguish individual positive effects
Energy–protein Energy–calcium	Energy deficiency commonly coexists with other deficiencies
Energy–vitamin D	Negative effect of energy deficiency may be difficult to isolate

to elucidate the potential role of green tea in preventing bone loss. Other components of tea interacting with bone include isoflavonoids, caffeine, and fluoride. Excessive tea consumption has been associated with skeletal fluorosis and osteosclerosis [100].

Conclusions

Traditional reductionist approaches leave many unanswered questions about bone health. The classical model of bone remodeling can be investigated as components of the skeletal subsystem; however, many physiologic factors such as aging and nutrition, to name a few, and the role they play in bone homeostasis, would be incompletely understood at best. Instead of focusing on component parts, an integrative whole-body physiologic approach considers the many recognized organ-level subsystems and environmental stressors having direct and/or indirect effects on bone remodeling.

Recursive patterns of complexity govern the various spatiotemporal scales of multiorgan physiology. By meticulously unraveling the molecular and physiologic level mechanisms involved with bone remodeling, nutrition, and aging, complex whole-body physiology may be parsed out in a way that uncovers vulnerable and potential therapeutic targets. So how might this occur? As proposed in previous papers [5, 101], a potential solution involves complex mathematical tools, such as graph theory, network analysis, and analytical inference. Using these methods will help determine the overall behavior of complex nonlinear dynamic systems, such as human physiology. The complexity of these multi-scalar interactions can be overwhelming, and thus, we hypothesize that using this approach may help elicit some of the uncertainties about how nutrition and aging affect bone. In turn, this may help promote the development of innovative therapies for investigation.

Given the burden of morbidity and mortality associated with osteoporosis, particularly in the elderly population, the ability to identify some modifiable risk factors is desirable and worth further study. As outlined above, a variety of nutrients have been linked to bone remodeling (Table 1) and interact with each other (Table 2) and bone in a complex manner. Calcium and vitamin D supplementation may not be the only dietary recommendations appropriate for patients with or at risk for bone loss. The use of vitamin K supplementation has been fairly well studied and should be considered, in addition to recommendations of increased protein and fruit and vegetable intake, moderate alcohol intake, and avoidance of high sodium, caffeine, cola, or excess vitamin A. The bone-protective roles of certain phytochemicals, including resveratrol, isoflavonoids, and green tea polyphenols, need to be further elucidated. Further research, including large randomized controlled trials as well as a systems approach, are necessary to identify the usefulness of these nutritional interventions.

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