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Review Article

An Insight into the Role of Vitamins other than Vitamin D on Bone

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Abstract

Vitamins are essential micronutrients for normal development. Great emphasis has been placed on vitamin D for bone development and maintenance. However, other vitamins also influence bone health. While some of them are more beneficial to bone and increase bone mass by increasing bone formation, calcium deposition and stimulate osteoblastogenesis, higher concentrations of others have deleterious effects causing fragile bones and increasing the risk of fractures. Knowledge about the effects of these vitamins will help in better maintenance of bone. This review focuses on the information available on vitamins A,B,C,E and K on bone health. Existing information supports vitamin C and K to play a role in bone formation and calcification. Vitamin E in low amounts and some of the B vitamins may also be beneficial to bone. There is very limited data supporting the favorable effects of vitamin A.

Keywords: Vitamin A; Vitamin B; Vitamin C; Vitamin E; Vitamin K; Bone

Abbreviations

ALP: Alkaline Phosphatase; αTF: α tocopherol; BMC: Bone Mineral Content; BMD: Bone Mineral Density; BMP: Bone Morphogenetic Protein; COX2: Cyclooxygenase 2; FN: Femoral Neck; G-CSF: Granulocyte Colony Stimulating Factor; IGF-I: Insulin Like Growth Factor I; IL: Interleukin; MTHFR: Methylenetetrahydrofolate reductase; NFAT: Nuclear Factor Activated T Cells; OVX: Ovariectomized; PTH: Parathyroid Hormone; PPAR: Peroxisome Proliferator-Activated Receptor; PGE: Prostaglandin E; PUFA: Polyunsaturated Fatty Acid; RAR: Retinoic Acid Receptor; RXR: Retinoid X Receptor; RA: Retinoic Acid; RANKL: Receptor Activated Nuclear Factor Kappa Ligand; SVCT: Sodium Dependent Vitamin C Transporter; IEC-6: Small Intestine Epithelial Cells; SD: Sprague Dawley; TGF: Tumor Growth Factor; TRAP: Tartrateresistant Acid Phosphatase

Introduction

An individual's well-being is dependent on several factors such as: diet, physical activity, availability of resources etc. Among diet, the balance in intake of macronutrients such as carbohydrates, proteins, lipids and micronutrients like vitamins and minerals is important. Vitamins form some of the most essential micronutrients. They are implicated in many diseases that can be reversed by supplementing or limiting the intake of vitamins.

Vitamins are divided into water soluble (B vitamins, C) or fat soluble (vitamins A, D, E, K) depending on their solubility. Their categorization also refers to the mode by which they are absorbed in the body after digestion. Water soluble vitamins are absorbed with the help of sodium dependent transporters, while fat soluble vitamins follow the fat absorption pathway and are packed in chylomicrons for delivery to the organs. The availability and storage of these vitamins is dependent on ones intake. They serve as important catalyst for many enzymatic activities; are converted to essential compounds required for normal metabolism or they can activate and deactivate important signaling pathways. Therefore, adequate vitamin intake is necessary for normal development of all the different organ systems, in an individual, including the skeletal system.

Bone is an active organ undergoing modeling and remodeling throughout life. During childhood and adolescence, bone modeling takes place helping the bones to grow. Throughout this period, bone formation is dominant and needs balanced nutrients to increase bone mass. After attaining peak bone mass, the skeletal system is maintained by bone remodeling and bone resorption increases, steadily decreasing bone mass with age. Several vitamins play a role in building bones and maintaining them through the years. An imbalance or decrease intake of these vitamins can negatively impact the bone remodeling process by increasing bone resorption. When bones do not get the nourishment required for normal growth and development, they are weak and are easily susceptible to fractures putting individuals at risk of developing osteoporosis. Osteoporosis is a medical condition that is seen in one out of two women and one out of four men [1]. People diagnosed with osteoporosis have low bone mass and fragile bones that breaks with minor trauma. In women, bone loss is accelerated during menopause and post menopause. However, close to half the trabecular bone is lost in women and men before the age of 50 [2].

Bone formation and resorption are sequestered events involving many different proteins. Bone formation is accomplished by osteoblasts. Osteoblasts differentiate from bone marrow stem cells (mesenchymal stem cells) under the influence of growth factors(insulin-like growth factor I (IGF-I)), cytokines (Interleukin (IL) -18 (IL-18)), several transcriptional regulators (homeodomain proteins, surfactant proteins, Runt homology domain transcriptional factors), hormones (estrogen, parathyroid hormone (PTH), vitamin D), prostaglandin E_1 (PGE_1), on costatin M, adrenomedullin and leptin [3]. Mature osteoblasts first form the collagen matrix and then

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Table 1: Sources of the various vitamin B compounds [7-9].

Vitamin	Source
Vitamin B_1 (Thiamine)	Found in cereals (rice, wheat, maida, rava, poha, etc.) breads, fortified cereals and pasta, pulses or lentils (dals such as moong dal, masoor dal, chana dal etc), legumes (whole pulses such as whole moong, channa, chowli, rajmah), dark green leafy vegetables such as spinach, fenugreek, lettuce, cabbage, asparagus etc. soy foods, whole grains like wheat germ, fish, egg, milk, meat, pork ham etc, nuts such as almonds and pecans. *Daily value: 1mg for men; 0.8mg for women.*
Vitamin B_2 (Riboflavin)	Some of the best sources of riboflavin are chicken, fish, eggs, legumes (like peas and lentils), milk and milk products such as yogurt and cheese, nuts, green leafy vegetables like spinach, broccoli, asparagus, and fortified cereals also supply significant amounts of riboflavin to the diet. *Daily value: 1.3mg for men; 1.1mg for women.*
Vitamin B_3 (Niacin)	It is found in chicken, salmon and in fishes like canned tuna – they are an excellent source of niacin. Vegetarians can get their source of niacin from legumes, pasta and whole wheat. *Daily value: 17mg for men; 13mg for women.*
Vitamin B_6 (Pyridoxine)	Foods like potatoes, beans, red meat, poultry, eggs and fortified cereals contain are very high in vitamin B6. *Daily value: 1.4mg for men; 1.2mg for women*.
Vitamin B_5 (Pantothenic Acid)	Yogurt and avocado are both excellent sources of pantothenic acid, but it is also available in a wide variety of foods such as legumes including lentils and split peas, sweet potatoes, mushrooms and broccoli. *Daily Value: 4-7 mg for adults.*
Vitamin B_7 (Biotin)	Liver and egg yolks are the richest dietary sources of biotin, but fortunately this B vitamin is well distributed throughout the food supply, so it is doubtful that anyone eating a balanced, varied diet will experience a deficiency. Salmon, pork and avocado are good sources; most fruits and vegetables contain a little biotin, as do cheeses and grain foods. *Daily value: 30-100 mg for adolescents and adults.*
Vitamin B_9 (Folate, folic acid, or folacin)	To remember which foods are high in folate, remember that the word folate has the same root as the word foliage. Leafy greens such as spinach, fenugreek, turnip greens, asparagus, etc and other fresh fruits and vegetables are all excellent sources of folate. Liver, dried beans and other legumes, and orange juice are good sources of this vitamin. So are fortified bread, rice, and cereals. *Daily value: 0.2mg for adults.*
Vitamin B_{12} (Cobalamin)	Animal foods are the only natural source of vitamin B12. It is found naturally in fish, red meat, poultry, milk, milk products, cheese, and eggs. But, many products, including soy products and cereals, are fortified with B12 so it is widely available in the food supply. Other good natural sources include shellfish, such as clams, mussels and crab, fin fish and beef. *Daily value: 0.0015mg for adults.*

with the help of osteocalcin start the mineralization process [3]. On the other hand, cells involved in bone resorption, are multinucleated cells called osteoclasts and differentiate from hematopoietic cells. Their differentiation takes place under the influence of several cytokines (IL-1, IL-6, IL-7, and tumor necrosis factor-α (TNFα), hormones (PTH, estrogen and vitamin D) and prostaglandin E_2 (PGE_2). These cells, dissolve the matrix proteins [4] and release the minerals from the bone leading to cavities and increasing the fragility of the bone [3].

This review focuses on the influence of vitamins on bone health. Articles were collected from Pubmed and Medline databases. The keywords used were: vitamin A and bone, retinoic acid (RA) and bone, vitamin B and bone, thiamine and bone, riboflavin and bone, vitamin B_3 and bone, vitamin B_5 and bone, vitamin B_6 and bone, vitamin B_7 and bone, vitamin B_9 and bone, vitamin B_{12} and bone, vitamin C and bone, vitamin E and bone, and vitamin K and bone. As the role of vitamin D on bone health is very well established, this review focuses on the influence of other vitamins on bone strength, bone mineral density (BMD), micro architecture and pathways of bone.

Water Soluble Vitamins

There are two water soluble vitamins – vitamin B complex and vitamin C. Both vitamin B complex and C are not stored in the body and have to be supplemented in the diet regularly. They are absorbed with the help of sodium dependent transporters [5].

Vitamin B complex

B Vitamins are composed of 8 compounds: vitamin B_1 (thiamine), vitamin B_2 (riboflavin), vitamin B_3 (niacin), vitamin B_5 (pantothenic acids), vitamin B_6 (pyridoxine, pyridoxal, pyridoxamine), vitamin B_7 (biotin), vitamin B_9 (folic acid), vitamin B_{12} (cobalamine) [5]. Off these, thiamine prevented malformations of the palate related to teratogony [6]. Studies on the direct effects of thiamine on bone are lacking. Sources of the different B vitamin are listed in Table 1 [7-9].

In vitro studies using Vitamin B_2 (riboflavin) in MC3T3 cells, which can be differentiated to become osteoblasts, have shown to enhance the differentiation process [10]. Osteoclastogenesis was also decreased by riboflavin through the expression of osteoprotegrin which is secreted by the osteoblastic stromal cells [10]. In patients with elevated homocysteine, due to MTHFR C677T polymorphism, riboflavin was not associated with fracture risk [11] especially in the femoral neck [12].

In vitro studies using vitamin B_3 (niacin and niacin amide) have shown no effect on the bone mineral content (BMC) in male leghorn chicken, and it also decreased bone strength [13,14]. This may be because niacin can stimulate oxidative stress in bone marrow cells [15] – a factor that stimulates bone resorption. However, in diabetic mice, niacin supplementation improved blood flow after ischemia [16] which may be beneficial to bone health.

Limited studies have reported the effects of vitamin B_5 (pantothenic acid) on bone. Deficiency of this vitamin changed the osteogenesis in the tibia of rats, in a time dependent manner. Reports concluded that, longer deficiency caused more damage to the tibia [17,18]. Additionally, longer periods of pantothenic acid deficiency, led to decreased osteoblast proliferation, osteogenesis and increased trabecular bone resorption which led to loss of trabeculae [17].

The effects of vitamin B_6 (pyridoxine, pyridoxal and pyridoxamine), on bone health, has been reported in a few *in vivo* studies. Studies on male Wister rats showed that vitamin B_6 deficiency decreased cross-link intermediates and impaired crosslink formation [19]. Similar effects were also reported in chick embryo. When treated with vitamin B_6 antagonist there was decreased cross-linking of collagen supporting vitamin B_6 supplementation during pregnancy [20]. In addition, vitamin B_6 deficiency decreased alkaline phosphatase (ALP), bone healing and tibial strength [21].

Vitamin B_7 (biotin) deficiency affects bone formation. In broiler chicken, vitamin B_7 deficiency decreased periosteal bone apposition, bone formation rate, osteoid perimeter and IGF-I [22,23]. Biotin may require riboflavin to maintain tibial BMD, strength and stiffness as demonstrated in young turkey chicks [24].

Vitamin B_9 (folic acid and folate) is well known for their effects on

Table 2: List of sources, serving size, and vitamin C content in foods [7-9].

Source	Serving Size	Vitamin Content (mg)
Guava, raw	½ cup	188
Red sweet pepper, raw	½ cup	142
Red Sweet pepper, cooked	½ cup	116
Kiwi fruit	1 medium	70
Orange, raw	1 medium	70
Orange juice, ¾ cup	¾ cup	61-93
Green pepper, sweet, raw	½ cup	60
Green pepper, sweet, cooked	½ cup	51
Grapefruit juice	¾ cup	50-70
Vegetable juice cocktail	¾ cup	50
Strawberries, raw	½ cup	49
Brussel sprouts, cooked	½ cup	48
Cantaloupe	¼ medium	47
Papaya, raw	¼ medium	47
Kohlrabi, cooked	½ cup	45
Daily value: 90 mg for men; 75 mg for women		

the nervous system. In the rat embryo skull bone, folic acid decreased TGFβ1 and TGF-1 expression [25]. Otherwise, there is no evidence that folic acid directly affects bone. However, when adequate amount of folate is not consumed, there is decreased BMD and trabecular thickness in the vertebra of postmenopausal women which can be reversed with folate supplementation [26,27]. Additional studies, showed that folic acid could reduce the accumulation of aluminum in organs such as bone, kidney and brain, thereby, reducing the toxicity [28].

Vitamin B_{12} (cobalamine) can act on both osteoblasts and osteoclasts [29-31]. Its deficiency decreased bone mass by stimulating osteoclastogenesis mainly by increasing methyl malonic acid and homocysteine [29]. It also influenced ALP secretion in patients' deficient with vitamin B_{12} and decreased BMD [30-34]. In vegetarians decreased intake of vitamin B_{12} increased bone turnover [35] which may lead to net loss of bone.

Decreased consumption of vitamin B_{12} and folic acid decreased BMD in older men which led to greater bone loss [26,36,37]. One of the functions of vitamin B_{12} and B_6 is to regulate homocysteine. Hyperhomocysteinemia is caused by deficiency of folate and B_{12} [38]. For every mmol/l of homocysteine there is 4% increase in fracture risk [32,39]. Universally, homocysteine is associated inversely with BMD, as it reduced BMD in older women [33,40-44]. Increased homocysteine and low vitamin B_{12} were significantly associated with high levels of bone turnover markers and increased fracture risk [45]. High concentrations of homocysteine may also interfere with the cross linking of collagen, thereby, decreasing the stability and strength of collagen network [46]. Additional evidence showed that homocysteine may increase osteoclast formation and activity [46-48], bone turnover [44] and bone marker levels [44]. Due to plasma homocysteine levels association with osteoporosis [49], it has been suggested that levels of circulating homocysteine can be used as a marker of fragility in females>75 years of age [44]. In male rats, however, there was no change in the BMD in the tibia, although there was decreased blood flow to the bone and reduced biochemical properties [50]. Homocysteine is reported to bind with collagen resulting in decreased bone strength [32,51]. Supplementation with folic acid, vitamins B_{12} and vitamin B_6 effectively reduced homocysteine levels [46].

Except for vitamin B_3, other vitamin B compounds are beneficial to bone health. It was interesting to note that there were scanty reports on vitamin B_1 and bone. Vitamin B_{12} and B_6 plays a major role in lowering homocysteine levels, thereby reducing osteoclast activity and decreasing bone turnover.

Vitamins C (ascorbic acid)

Vitamin C is absorbed in the small intestine into the brush border cells using the sodium dependent vitamin C transporter (SVCT) proteins. When this transporter is overexpressed, it is able to increase mineralization and calcium deposition. It is also reported to help with the bone marrow stromal cells to differentiate into osteoblasts as knockdown of this transporter inhibitedosteogenesisin these cells [52]. In bone marrow aspirates from athymic BALB/C ru mice with subcutaneous implant, ALP and calcium deposition on scaffolds increased [53] with vitamin C supplementation. A list of the sources, serving sizes and recommended daily value of vitamin C is given in Table 2 [7,9].

In male Sprague Dawley (SD) rats, there was increased bioavailability of calcium as corbate compared to calcium acetate [54]. In female guinea pigs, lower intake of vitamin C was associated with decreased collagen synthesis resulting in lower levels of collagen, ALP and osteocalcin [55,56]. Decreased intake of vitamin C also increased bone turnover and reduced transition of salts to the crystalline form [57], whereas, long term deficiency of vitamin C, decreased skeletal maturation and showed bone abnormalities in female guinea pigs [58]. Total deprivation of vitamin C in guinea pigs led to destruction of the proximal tibia with micro fractures. Additionally, damage to the diaphysis led to Genu Varums (bow legs) [59]. Treatment with vitamin C restored the tibia and formation of trabecular bone at the growth cartilage by sub periosteal thickening [59] and development of trabecular callus. However in dogs, vitamin C supplementation did not modify BMC [60] and the tibial breaking strength or egg shell thickness in hens also was not altered due to vitamin C supplementation [61]. Inversely, in chicks, it is reported that ascorbic acid may be involved in mobilizing calcium and phosphorus soon after injection but had no effect on bone resorption or the bone formation process [62].

Vitamin C deficiency accelerated bone loss and increased fractures, in the femur of senescence marker protein 30 knockout mice [63]. It is known to help in the differentiation of osteoblasts and deficiency promotes osteoblasts to transition into adipocytes [63]. It may accomplish this by upregulating the expression of proximal proliferator-activated receptor gamma (PPARγ) [63] which is an important cofactor required for the hydroxylation of collagen and is necessary for osteoblast proliferation [64]. ALP expression is also dependent on as corbate levels. It influenced collagen organization to form the protein matrix for the deposition of minerals [64]. In addition, it is established that vitamin C deficiency inhibits calcification process [64].

Table 3: List of sources, serving size, and vitamin A content in foods [7-9].

Sources	Serving Size	Vitamin Content (IU)
Liver, beef, cooked*	3 oz.	27,185
Liver, chicken, cooked*	3 oz.	12,325
Carrot juice, canned*	½ cup	22,567
Carrots, boiled*	½ cup slices	13,418
Spinach, frozen, boiled*	½ cup	11,458
Kale, frozen, boiled	½ cup	9558
Carrots, raw	7 ½ in	8666
Vegetable soup, canned, chunky, ready-to-serve	1 cup	5820
Cantaloupe	1 cup cubes	5411
Spinach, raw	1 cup	2813
Apricots with skin, juice pack	½ cup	2063
Daily value: 5000IU for adults and children age 4 and older		

*high in retinol activity equivalents.

In postmenopausal women, BMD decreased in response to lower vitamin C intake in a dose dependent manner, however, there was no such effect in males [65]. Another study reported a 3% increase in BMD at the ultra-distalmidshaft, radii, hip and lumbar spine in postmenopausal women [66]. It also increased ALP and enhanced collagen synthesis as well as stimulated procollagen [66]. Short term (7 weeks) vitamin C supplementation in children (boys) did not show any changes in biochemical markers like pyridoxiline and deoxypyridoxiline [67].

Fluoride toxicity in monkeys and copper toxicity in rabbits were attenuated by supplementation with vitamin C [68,69]. Vitamin C and Zinc positively influenced bone geometry, size and strength in children [70].

Overall, vitamin C is required for osteoblast differentiation and is important for bone formation. It is also an anti-oxidant, therefore, may act by reducing oxidative stress and positively influencing bone.

Fat Soluble Vitamins

All fat soluble vitamins are absorbed along with fatty acid and delivered to the liver as fatty acid. It is dependent on bile salts and can be transported in chylomicrons. These vitamins are stored in the body just like fatty acids.

Vitamin A (retinoids)

Vitamin A consists of a group of compounds – retinal, retinyl ester, retinol and RA [5]. Vitamin A can affect the translational processes in cells and nuclear receptors like retinoic acid receptor (RAR) and retinoid X receptor (RXR) help in this process. The sources, serving sizes and recommended intake of vitamin A and pro vitamin A are listed in Table 3 [7,9].

RA treatment of growth plate chondrocytes, induced annexins II, V and VI to form Ca^{2+} channels and influx calcium into the cells. It also stimulated the release of ALP to initiate mineralization [71]. In addition, RA stimulated chondrocyte differentiation by upregulating the expression of bone morphogenetic protein (BMP) [72]. In human and murine cells, RA inhibited Receptor Activator of Nuclear Factor kappa-B Ligand (RANKL) stimulated osteoclast differentiation [73] and in the fish, Atlantic cod, RA decreased bone resorption [74]. On the other hand, there are also reports that RA decreased BMP2 expression thereby stimulating osteoclastogenesis [75] and induced bone loss. Interestingly, it has been used as a method to induce bone loss in female rats [76]. There are also reports showing reduction of mineralization with RA supplementation [77] and RA has a negative effect on the oral bone mass in rats [78].

One of the receptors, retinoic acid receptor γ (RARγ) is a potent inhibitor of osteoclastogenesis as it decreased nuclear factor activated T cells (NFAT) activation, granulocyte colony stimulating factor (G-CSF) and RANKL, and also increased bone formation [79]. Carotenoids from fruits and vegetables act through the anti-oxidant pathway to reduce bone resorption [80].

Vitamin A supplementation in female rats, increased BMD but decreased trabecular area with no change in cortical thickness or stiffness and levels of osteocalcin [81]. In IEC-6 cells, vitamin A supplementation up regulated ALP [82]. Vitamin A can also promote bone formation through the BMP2/7 heterodimer [83]. It is also reported that vitamin A supplementation in postmenopausal women, had no age related increase in risk for fractures or any changes in BMD [84] and the mechanical properties of the bone [85]. However, the beneficial effect of vitamin A is more in the trabecular bone than the cortical bone in aged rats [85]. When vitamin A is consumed with polyunsaturated fatty acids (PUFAs) they act on different pathways and while vitamin A can cause malformations, PUFAs increased bone formation independent of each other [86].

However, some reports concluded that supplementation with vitamin A did not show any beneficial or detrimental effects in humans and animal models. In women, decreased intake of vitamin A did not have a detrimental effect on bone [84] and in men, short term supplementation with vitamin A did not influence bone turnover [87]. Similarly, studies on dogs supplemented with vitamin A also did not show any detrimental effects on bone [88].

Another vitamin A compound, retinol has a negative effect on bone as it decreased BMD in mice and rats [89-94]. Increased intake of retinol increased bone fragility and fracture risk at different sites including the femur neck, Ward's triangle, trochanter region of the proximal femur, lumbar spine [93,95]. In cases where there is decreased vitamin D, increased intake of retinol further increased fracture risk [96]. However, retinol with retinol binding protein 4 showed decreased osteoclast activity in humans (males) [97]. Early studies have shown that decreased vitamin A increased osteoblast activity [98].

In addition, there are studies that have reported several negative effects on bone, especially when vitamin A was given to children. Problems reported include building of fontanelle, increase in intracranial pressure, anoxia, drowsiness, instability followed by brain damage [99,100]. Dhem et al. have reported several other detrimental effects of vitamin A supplementation including lesions in the endocortical surface of the tibia, cavities and demineralization on the periosteal surface and cancellous bone, enlargement of Haversian canals [77,91,101] and hypervitaminosis A which is associated with long bone fractures [77,91]. High intake of cod liver oil also increased the risk of fractures [102].

Table 4: List of sources, serving sizes, and Vitamin E content in foods [7-9].

Source	Serving Size	Vitamin Content (mg)
Sunflower seeds, dry roasted	1 oz.	7.4
Sunflower oil, high linoleic	1 Tbsp.	5.6
Cottonseed oil	1 Tbsp.	4.8
Safflower oil, high oleic	1 Tbsp.	4.6
Hazelnuts (filberts)	1 oz.	4.3
Mixed nuts, dry roasted	1 oz.	3.1
Turnip greens, frozen, cooked	½ cup	2.9
Tomato paste	¼ cup	2.8
Pine nuts	1 oz.	2.6
Peanut butter	2 Tbsp.	2.5
Tomato Puree	½ cup	2.5
Tomato sauce	½ cup	2.5
Canola oil	1 Tbsp.	2.4
Wheat germ, toasted, plain	2 Tbsp.	2.3
Daily value: 30IU for adults and children above age 4.		

Although vitamin A has shown some bone protective effects by up-regulating BMP, and RAR inhibited osteoclastogenesis, there are many reports indicating that consuming high levels of this vitamin may be deleterious to both long and parietal bones.

Vitamin E (tocopherols)

Vitamin E consists of the tocopherols and tocotrienols. Each of them include4 vitamers but α tocopherol (αTF) is the biologically active form and has been studied very extensively. Table 4 lists the sources, caloric content with the recommended daily value intake of vitamin E [7,9].

Vitamin E levels have been directly related to the bone status in humans as osteoporotic subjects have less circulating vitamin E levels [103,104]. Many *in vivo* studies have reported the benefits of αTF. Supplementation with αTF increased mineralizing surface, bone formation rates and strength of bones in OVX rats [105,106]. In addition, it also decreased osteoclast surface at medium dose as well as in low doses and reduced oxidative stress [107-109]. In postmenopausal rat model, trabecular bone volume, trabecular number increased and trabecular separation decreased with αTF supplementation [106,107]. Biochemical markers like ALP, osteocalcin and IGF-I expression increased with αTF [108,110] and decreased TRAP. In male rats αTF prevented bone loss due to disuse of hind limb by decreasing cyclooxygenase – 2 (COX-2) [111]. Older mice showed increased yield stress, ultimate load and stiffness of bone [110], however this effect was not seen in younger mice with αTF supplementation. However, the effect of vitamin E is site specific as it positively correlates with BMD in the spine and not in the long bones [112]. Young (6 months old) and old (24 months old) C57Bl/6 mice when fed vitamin E showed increased bone strength and matrix protein with no change in BMD. This effect was more in older mice than younger mice. There was also decreased PGE_2 and increased IGF-I formation [110]. In female rats, vitamin E also increased calcium content [113] and also increased calcium availability and decreased certain free radical production; however, αTF did not improve calcium in the bone [114]. The beneficial effects of vitamin E are attributed to the tocotrienols in the vitamin E mixture used in the study. The ratio of vitamin E to lipids is significantly associated with decreased BMD of the lumbar spine of in postmenopausal women [115,116]. Moreover, αTF may modulate γTF by reducing its levels and affect bone formation [115].

Table 5: List of sources, serving sizes, and Vitamin K content in foods [7-9].

Source	Serving Size	Vitamin Content (cg)
Brussel sprouts	½ cup	460
Turnips greens, raw, chopped	1 cup	364
Broccoli	½ cup	248
Lentils, dry	½ cup	214
Cauliflower	½ cup	150
Kale, cooked	½ cup	150
Spinach, raw, chopped	½ cup	149
Garbanzo beans, dry	½ cup	132
Swiss chard	½ cup	124
Daily value: 75µg for men and women		

In lower concentrations, αTF can protect bone and at high concentrations is detrimental to bone as they can interfere with the function of vitamin K and other isoforms of vitamin E [117-119]. Moreover, the source of vitamin E may also make a difference [109].

Vitamin K

Vitamin K includes two compounds – vitamin K_1 (Phylloquinone) and K_2 (Menaquinone). The major function of vitamin K is to promote coagulation of blood but recently there is evidence that it is also involved in maintaining bone health [120,121] by increasing bone formation and reducing bone resorption [122]. Table 5 has the list of sources and serving size with the daily value for vitamin K [7,9].

Vitamin K is implicated in carboxylating a couple of proteins that are involved in the bone formation process - matrix Gla proteins and osteocalcin [123-125]. Matrix Gla protein has high affinity to calcium and functions as a modulator of calcium availability [126]. Osteocalcin is a protein secreted by osteoblasts and is an important bone biochemical marker associated with increase in bone formation [127-129]. Age related decrease in γ carboxylation of osteocalcin takes place [130].

Several studies have shown that osteocalcin is under carboxylated and does not mobilize the calcium for mineralization, thereby, decreasing bone formation and vitamin K supplementation attenuated this effect by carboxylating osteocalcin [131,132], therefore, is beneficial to bone [133].

Many *in vivo* studies on animal models have shown the benefits of vitamin K supplementation. Male rats, supplemented with menaquinone, showed decreased under carboxylated osteocalcinalong with increased mineral crystallinity and hardness in the tibiae [134]. OVX rats, fed vitamin K, showed higher bone strength and decreased risk of fractures in the tibia and femur by increasing trabecular bone volume [135,136] trabecular number and decreasing trabecular separation, osteoclast number/bone surface and osteoclast surface/bone surface [137]. Vitamin K also promoted bone

healing in a rodent model of osteotomy [138]. In gastroectomized SD rats, vitamin K_2 supplementation attenuated the decrease in ultimate force and increased stiffness of the femoral diaphysis [139]. Male orchidectomized rats, showed increased bone MAR, BFR, BV/TV and BV [140-142] and improved trabecular micro architecture with vitamin K supplementation [132]. Similar benefits of vitamin K supplementation on the trabecular structure and bone volume in tail suspended rats [143] was also reported.

Children with better vitamin K status had increased bone mass [144]. In early menopausal women, under caroboxylated osteocalcin was negatively associated with BMD in the total hip, femoral neck, and lumbar spine [145,146]. Elderly institutionalized men and women are recommended to consume higher amounts of vitamin K than the recommended adequate intake to maintain skeletal health [147]. In healthy postmenopausal women, supplementation of vitamin K_2, significantly, decreased loss in vertebral height and increased bone strength, BMC and BMD in the lumbar spine, femoral neck and hip bone geometry [148-151]. Biochemical markers of bone metabolism like serum under carboxylated osteocalcin decreased and γ carboxylated osteocalcin increased, with vitamin K supplementation [152,153]. Healthy women in the ages of 30-88 years showed decreased under carboxylated osteocalcin especially in older women, among the cohort studied [154]. However, another study reported decreased bone turnover in both the young and elderly, when supplemented with vitamin K [155]. A direct relationship between BMD and lower concentrations of phylloquinone in postmenopausal women was also reported [156]. Plasma phylloquinone levels were inversely associated with N- terminal telopeptide and under carboxylated osteocalcin in girls (3-16 years of age) [157]. Interestingly, decreased vitamin K intake decreased BMD in female but not in males [158]. Vitamin K also induced IL-1α, PGE_2 [159] in patients with femur neck fractures or lower BMD had decreased levels of circulating vitamin K [160,161]. Vitamin K supplementation also protected bone by modulating bone turnover during space flight [162] and osteoporotic patients with vitamin K_2 supplementation showed increased lumbar BMD [163].

Vitamin K when supplemented with alendronate increased total and trabecular BMD at the distal metaphysis of the femur, in mice. It also increased the strength of the bone [164]. Combined treatment with risendronate and vitamin K prevented glucocorticoid induced bone loss and decreased bone formation and bone erosion in rats [165-167]. In addition, when OVX rats were given vitamin K in combination with bisphosphonates, pretreatment with vitamin K improved the strength, BMD, BMC and trabecular structure in the femur [168,169]. OVX rats with, vitamin K_2 and Raloxifene showed greater strength in the femoral neck [170]. Vitamin K supplementation may also reduce drug induced osteoporosis [155].

Although there are many studies showing the benefits of vitamin K on bone, there are some studies that did not show any benefits. Early menopausal women did not show any benefits with vitamin K supplementation for 1 year [171]. Six months of vitamin K supplementation did not show any significant increase in BMD in pre and perimenopausal women [172]. In OVX rats, vitamin K did not change the BMD in the distal femur [173]. This may be due to the short term treatment or the concentration of vitamin K given to the subjects or there might have been drug/nutrient interactions.

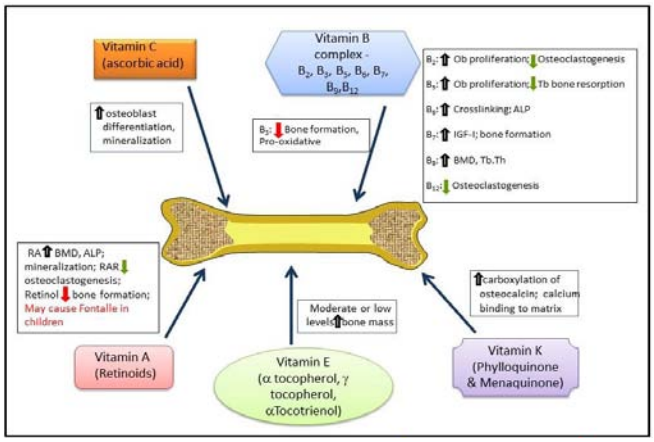

Figure 1: Text Here.

There is ample evidence to show that vitamin K is essential for the carboxylation of osteocalcin and improves calcium deposition in the matrix. Therefore, adequate vitamin K is necessary to maintain the mineral content and strength in bones.

Combination of Vitamins on Bone

Combination of vitamins C and E partially prevented bone destruction due to heparin [174]. αTF interacts with vitamin K and other vitamin E isomers to increase pro-oxidative effects. Vitamin D and K may have synergistic effects [175-177]. Decreased vitamin E and C increased fracture risk in smokers [95,103]. No influence of vitamin E supplementation on BMD of the lumbar and femoral neck (FN) has also been reported in postmenopausal women [178].

Conclusions

In summary, among the water soluble vitamins, research supports that vitamin C was most beneficial to bone. This may be because it is a potent anti-oxidant and can help in osteoblast differentiation. Of the different B vitamins, riboflavin, B_6, biotin, folic acid and B_{12} had a positive influence on bone metabolism. This may be by different mechanism such as: inhibition of osteoclastogenesis by decreasing in IGF-I levels, and interfering with the cross linking of proteins. Combination of B vitamins like folic acid, B_{12} and B_6 is probably more effective in inhibiting the action of hyperhomocysteinemia. However, vitamins B_3 had a negative effect on bone because of their pro oxidative effects. Of the fat soluble vitamins, vitamin K and E influenced bone formation positively, while vitamin A has been reported to have more deleterious effects on bone especially when given in high concentrations during infancy and childhood. So far, based on the available literature, after vitamin D, vitamin K supplementation is the most promising. Vitamin K in combination with several bisphosphonates increased BMD and strength of long bones. Further studies should be conducted to see if vitamin K can maintain bone mass with decreased concentrations of bisphosphonates. This will reduce the side effects of bisphosphonates considerably. Moreover, as pretreatment with vitamin K before bisphosphonates improves the strength, BMC and BMD, it may also benefit individuals after withdrawal of bisphosphonate treatment. Vitamin K may also help diabetic patients, where the matrix is compromised. However, more detailed studies on the effects of various vitamins have to be

conducted to elucidate the actual benefits of the different vitamins in maintaining bone health. The concise effects of vitamins are summarized in Figure 1.

An important fact to note is that most of the studies reporting the effects of vitamins in humans are self reporting surveys. A better understanding of the benefits of vitamins may be obtained by interventional controlled studies. It is also important to remember that each vitamin has a recommended intake, which should be taken into consideration to decrease any undesirable side effects and may help maintaining healthy bones. But most importantly, interactions of drugs and other nutrients with vitamins should be carefully studied before any vitamin supplementation is taken.

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