

# Nutrition and osteoporosis prevention and treatment

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## ABSTRACT

**Introduction:** Osteoporosis falls among the major general health issues, specifically in the elderly, and is a widespread disease these days. According to various studies, good nutrition plays a significant role in osteoporosis prevention and treatment. The aim of this study was to conduct an extensive literature review on the effects of different nutrients to understand how macronutrients, micronutrients, and non-nutritive substances affect bone health. **Methodology:** To find relevant studies, the main keyword "osteoporosis" was searched in combination with "zinc," "vitamin K," "phosphorus," "vitamin D," "calcium," "lipid," "protein," and "phytoestrogens" in PubMed (MEDLINE), Web of Science, SID, and Iran Medex databases. **Findings:** The most important element for bone health is calcium, which has a direct link to the bone mass density (BMD). In the case of calcium deficiency, high phosphorus content can damage bone tissue. The acceptable ratio of phosphorus to calcium is 0.5-1.5:1. Vitamin D is another important nutrient for bones; serum levels of vitamin D less than 20 ng/ml reduce bone density and increase the risk of fracture. High protein intake results in calcium excretion and loss of bone mass. In addition, calcium deficiency increases the risk of osteoporosis, specifically in the elderly. According to the literature, there is an inverse correlation between saturated fats and BMD. Vitamin K and magnesium deficiencies are correlated with BMD reduction and increased risk of osteoporosis. Copper and zinc are used as co-factors in the formation of collagen and elastin, and in mineralization of bone. As a result, deficiency of these elements may disrupt the process of incorporating minerals into the bone matrix. **Conclusion:** Good nutrition may play a significant role in osteoporosis prevention and treatment. Indeed, a healthy diet containing calcium (1,200 mg/day); vitamin D (600 IU); and certain amounts of protein, magnesium, and vitamin K can contribute greatly to bone health.

**Key words:** Osteoporosis, Nutrition, Calcium, Vitamin D

## INTRODUCTION

Osteoporosis is among the major health issues, specifically in the elderly. It is one of the main causes of morbidity and mortality in this group of people<sup>1,2</sup>. In addition, it imposes a profound financial burden on the healthcare system every year<sup>3</sup>. Today, because of the rapid growth of the elderly population, osteoporosis has become an epidemic in some societies<sup>4</sup>. According to the definition of the World Health Organization, osteoporosis is a systematic skeletal disease, characterized by the loss of bone mass density (BMD) and damage to the microstructure of bone tissue, leading to increased bone vulnerability and risk of fracture<sup>5,6</sup>. Although osteoporosis can affect all bones, the wrist bones, lumbar vertebrae, and pelvis are more vulnerable to it<sup>7</sup>. There are different and, sometimes, contradictory reports about the prevalence and incidence of osteoporosis in different societies. These reports contain differences in definitions, BMD measurement techniques, location of density measurement, and research population. On

average, the prevalence rates of osteoporosis in men and women over 50 years old have been reported as 1:3 and 1:8, respectively, indicating a higher risk of osteoporosis in women<sup>8</sup>. Typically, the annual bone turnover is 0.2-0.5% between ages 40 and 45 years<sup>1</sup>. Osteoporosis is a multi-factor disease in which genetics, age, gender, race, weight, and consumption of certain medications (e.g., corticosteroids and thyroid hormones), as well as some diseases (rheumatoid arthritis and gastrointestinal disorders), can affect the BMD and consequently bone health.

Lifestyle is among the most important factors that impact bone density. Factors such as physical activity, exercise, nutrition habits, and alcohol/tobacco consumption are correctable and, thus, have been taken into consideration as important. According to different studies, good nutrition plays a significant role in osteoporosis prevention. In this regard, the most important nutrients are calcium and vitamin D. In addition, paying attention to nutrition is an important component in the treatment and rehabilitation

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of osteoporosis patients. In contrast, poor nutrition can slow down the recovery process and increase the risk of bone fracture. Devoting extra attention to micronutrients, such as calcium and vitamin D, has led to awareness of other micronutrients with an important role in bone health<sup>9</sup>.

The goal of this study was to conduct an extensive literature review on the effects of different nutrients, specifically macronutrients (e.g., protein and fat) and micronutrients (e.g., calcium, vitamin D, phosphorus, vitamin K, magnesium, and zinc), and a non-nutritive substance (phytoestrogens) on bone health. The aim of the analysis was to provide good diet solutions for osteoporosis prevention and treatment.

## METHOD

Searches were carried out using the PubMed (MEDLINE), Web of Science, SID, and Iran Medex databases, with the main keyword “osteoporosis,” in combination with “zinc,” “vitamin K,” “phosphorus,” “vitamin D,” “calcium,” “lipid,” “protein,” and “phytoestrogens,” among articles published between 2000 and 2017. The reference list of articles deemed relevant to the review was also further evaluated. This database searching identified 625 articles, all of which were in English. After the screening step, 70 relevant clinical articles were assessed for eligibility. Of these, 30 poor articles were excluded, and the remaining ones were reviewed and prioritized according to the validity of methods, clarity of results, and recency of data.

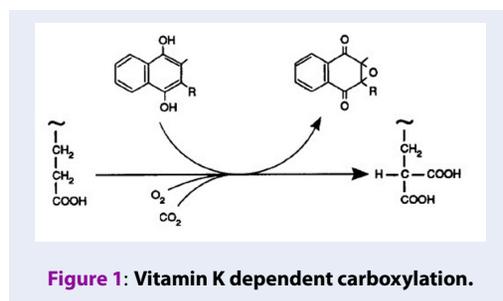


Figure 1: Vitamin K dependent carboxylation.

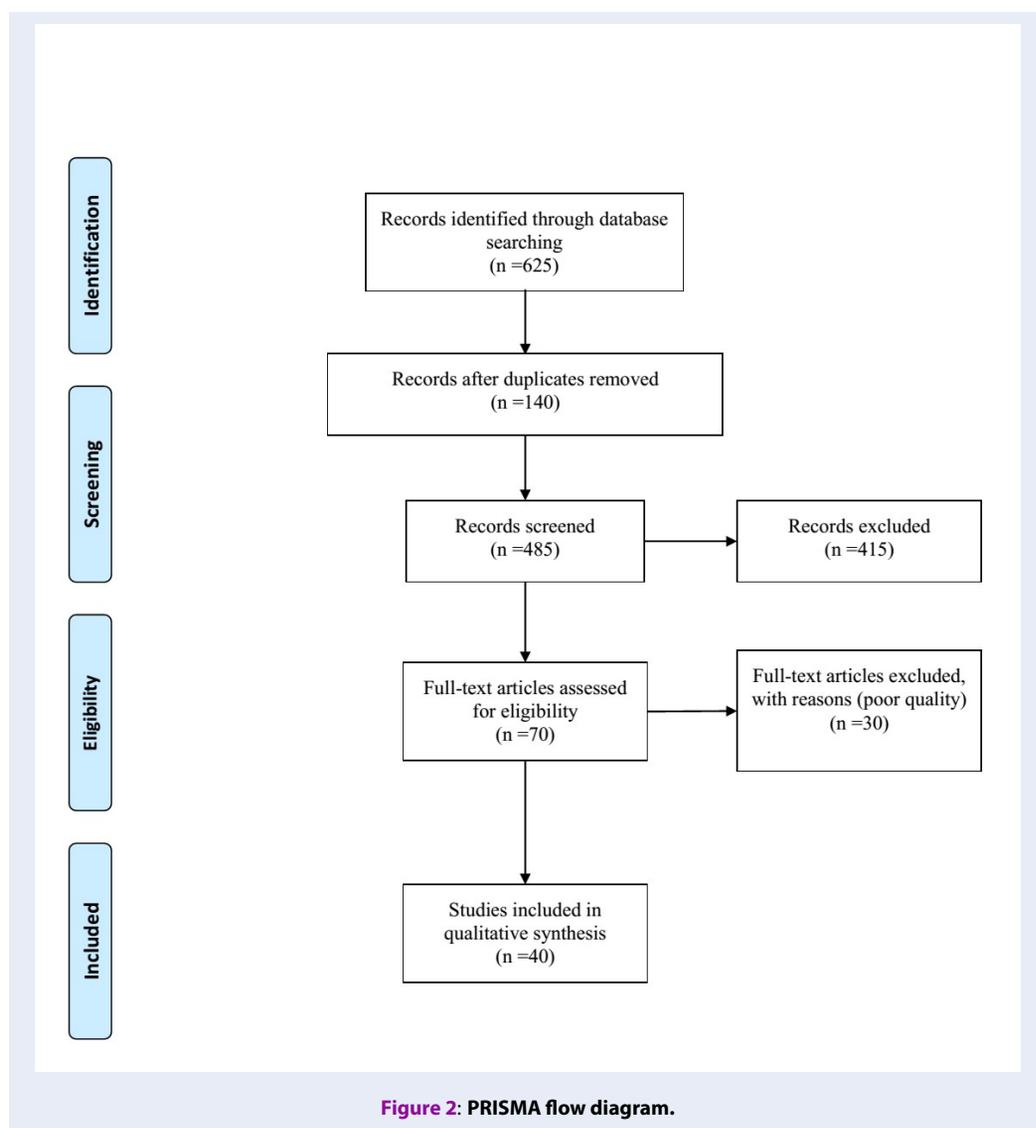
## MACRONUTRIENTS AND OSTEOPOROSIS

### Protein

Despite several studies on the effects of the type and amount of protein intake on bone metabolism, findings are still contradictory. According to studies, high protein intake can result in increased urinary excretion of calcium, negative calcium balance, and loss of

bone mass in both young and old people<sup>10</sup>. This is mainly due to the acidic environment created by protein metabolism, specifically animal proteins, in the human body. This acidic environment is created because of sulfur-containing amino acids and the production of acidic equivalents<sup>11</sup>. In fact, it is argued that the bones release ions, such as calcium carbonate, to neutralize this acidic environment, leading to increased urinary excretion of calcium and to BMD loss<sup>12</sup>. In addition, other studies have shown that although animal proteins have sulfur-containing amino acids, they are more effective than vegetable proteins in reducing the risk of pelvic fractures<sup>13</sup>. However, other studies have suggested that low protein intake is a risk factor for osteoporosis, and is correlated with low BMD<sup>14</sup>. Low protein intake also increases the risk of fracture in the elderly<sup>15</sup>.

Conversely, increased protein intake by different mechanisms can positively affect bone health through the absorption of calcium, through increased secretion of insulin-like growth factor 1 (IGF-1), and promotion of lean body mass<sup>16,17</sup>. Some studies have shown that increased protein intake improves calcium absorption<sup>18,19</sup>; however, other studies have rejected this correlation. Increased protein levels can also affect liver products and growth factor function<sup>20</sup>. Because IGF-1 can increase the density and strength of bones<sup>21</sup>, proteins can contribute to bone mass maintenance through the production of IGF-1<sup>22</sup>. Some cross-sectional studies have shown a positive relationship between protein intake and BMD, whereas other studies have not reported such correlations<sup>23</sup>. Observational studies by Michaelsson *et al.*<sup>24</sup> and Lacey *et al.*<sup>25</sup> have shown that among the hospitalized elderly, women receiving 1 g/kg of protein had greater BMD in their lumbar vertebrae, femoral neck, and thigh-bone than women receiving a smaller amount of protein. As a result, Rapuri *et al.* have recommended the intake of 1 g/kg of protein, which is slightly higher than the standard recommendation (0.8 g/kg) for maintenance of bone health<sup>26</sup>. In a study by Meyer *et al.*, the authors did not find any significant correlation between protein intake and the risk of pelvic fracture. However, increased protein intake in people with calcium deficiency was shown to increase the risk of pelvic fracture<sup>27</sup>. According to a meta-analysis conducted to investigate the relationship of protein intake and bone health, a weak correlation was observed between protein intake and bone mass in lumbar vertebrae; however, this relationship was not observed in the pelvic bone. Therefore, increased protein intake has little impact on bone health; however, this effect does not necessarily reduce the risk of bone fracture in the long term<sup>12</sup>.



## Fat

There are several lines of evidence showing that the type and amount of dietary fat can significantly affect bone health. It has been observed that there is an inverse relationship between the intake of saturated fatty acids (SFA) and BMD. The proposed mechanisms for this phenomenon include:

1. SFA decreases the membrane fluidity of intestinal epithelia cells, thereby reducing the uptake of calcium by small intestinal brush border cells.
2. An SFA-enriched diet inhibits bone mineralization.
3. It has been shown that SFA suppresses the differentiation of rat bone marrow mesenchymal stem cells.

4. According to some reports, oxidized lipids increase osteoclast cell differentiation (bone resorbing cells). Therefore, people who eat an SFA-enriched diet (mostly from animal fats) are more at risk for osteoporosis

Among non-saturated fatty acids, the ratio of omega-3 to omega-6 plays an important role in the regulation of osteoblast and osteoclast activities. According to studies, prostaglandin E2, leukotriene B4, interleukin-1, and tumor necrosis factor are all capable of increasing bone mineral incorporation<sup>28</sup>. Omega-6 fatty acids are known to increase the production of eicosanoids and cytokines, whereas omega-3 fatty acids inhibit their production<sup>29</sup>. In addition, omega-3 fatty acids increase the absorption

of calcium and decrease its urinary and fecal excretion<sup>30</sup>. Despite significant progress in the treatment of cardiovascular diseases and osteoporosis, these diseases are still the major causes of mortality among the aging population<sup>31</sup>. Recent evidence suggests that they share a common etiological factor in that hyperlipidemia not only is correlated with atherosclerotic plaque but also results in osteoporosis, following a similar biological mechanism that includes lipid oxidation<sup>32</sup>. Animal studies have revealed that a high-fat diet has a destructive impact on bone health because some fatty acids induce bone destruction. The following mechanisms mediate those effects: calcium absorption changes, prostaglandin synthesis, formation of osteoblasts, and lipid oxidation. Despite reliable results from broad animal studies *in vitro*, there are scant studies in humans in this regard. Results from studies on women were consistent with those from animal studies, indicating that the amount of fat intake is positively associated with risk of fracture but inversely correlated with bone density<sup>27</sup>.

## MICRONUTRIENTS AND OSTEOPOROSIS

### Calcium

Undoubtedly, calcium is the most important nutrient for bone health. This is because 99% of the calcium requirement of the body is stored in the bones. In general, 67% of the bones is made of mineral, specifically in the form of hydroxyapatite. The remaining 33% is made of organic substances, specifically collagen. The recommended amount of calcium depends on age (1,000 mg/day for men and women, and 1,200 mg/day for people over 50 years)<sup>27</sup>. When calcium intake is insufficient, serum calcium levels start decreasing, causing a series of consequences. First, increased secretion of parathyroid hormone (PTH) results in the resorption of bones and release of their content to the blood, which inhibits the reduction of the serum calcium level. Continuation of this phenomenon decreases BMD and increases the risk of osteoporosis<sup>33</sup>. Among the total of 139 articles published since 1975 on the relationship of calcium intake and bone health, 52 articles have been interventional studies with controls, of which 50 articles have reported that calcium intake increases BMD during the growing age, decreases BMD loss in the elderly, and reduces the risk of bone fracture. Three-fourths of the 86 observational studies also indicate a positive correlation between calcium intake and bone health. In general, this evidence reveals the important role of calcium in bone health<sup>34</sup>. In response to calcium deficiency, the body reduces bone mass with the help of

a bone degradation mechanism to maintain the ionized calcium level of extracellular fluid.

Calcium deficiency is associated with many other consequences. Dietary calcium deficiency is a major cause of childhood rickets in developing countries<sup>35</sup>. Calcium plays a significant role in osteoporosis prevention because the calcium level is directly related to BMD and bone health. Nevertheless, calcium is not adequate for bone health because vitamin D deficiency is an important factor in increasing calcium uptake by the intestines. This phenomenon lowers the absorption of calcium and results in reduced bone mass and increased risk of osteoporosis<sup>36</sup>. In addition, lactose increases the uptake of calcium in the intestines. Glucose and fructose have similar effects on calcium uptake, and thus may have a role in increasing calcium level and decreasing the risk of osteoporosis<sup>34</sup>. Although the majority of studies have addressed the effectiveness of calcium supplementation in postmenopausal women, there is a limited number of studies showing the effectiveness of calcium supplementation for young men and premenopausal women<sup>35</sup>. Before menopause, BMD remains relatively constant in women, but it starts decreasing immediately afterwards. Therefore, because the intake of calcium and vitamin D is highly effective at achieving peak BMD, dietary or pharmacological intake of these substances can prevent excessive BMD loss after menopause<sup>37</sup>. The main dietary source of calcium is dairy; nevertheless, those who do not receive adequate dietary calcium, for example, because of lactose intolerance, can use commercial supplements, such as acetate, lactate, gluconate, citrate, and calcium carbonate, among which the latter has the highest absorbability.

### Vitamin D

Almost 90% of the vitamin D requirement for the body is made in the skin from exposure to sunlight, and a small amount of vitamin D is supplied from foods<sup>38</sup>. Vitamin D synthesis in the skin decreases under the effect of ultraviolet radiation or by aging, which is due to decreased duration of exposure to sunlight and skin production performance<sup>15</sup>. It seems that vitamin D deficiency is a widespread problem among the elderly in all countries except the US, where foods are fortified with vitamin D<sup>39</sup>. Although there is no consensus about the vitamin D requirement for the body, all scientists consider a serum level lower than 20 ng/mL as an ideal level to define vitamin D deficiency<sup>40</sup>. However, some scientists define this

**Table 1: Characteristics and details of the studies used in this review**

Micronutrient	Effect on BMD	Mechanism
Calcium	Increase	When calcium intake is not enough, serum calcium level starts decreasing, causing a series of consequences. First increased secretion of parathyroid hormone (PTH) results in the resorption of bones and release of their content in blood, which inhibit the reduction of serum calcium level.
Vitamin D	Increase	Vitamin D deficiency results in the secondary hyperparathyroidism, increased bone turnover, bone loss, reduced minerals. Newly formed bone matrix in adults is not mineralized. This phenomenon results in the development of osteomalacia. With respect to the children, vitamin D deficiency causes rickets through disruption of cartilage calcification
Phosphorus (high intake or inadequate intake)	Decrease	Low intake of phosphorus or its negative balance can result in reduced performance of osteoblasts, but increased osteoclast activities, and thus bone turnover. In general, what is more important than the role of phosphorus intake in bone health is the intake ratio of phosphorus to calcium, which should be 0.5-1.5:1.
Vitamin K	Protective effect	Evidence show that low serum non-carboxylated osteocalcin and phyloquinone are directly correlated with low BMD and increased risk of bone fracture caused by osteoporosis.
Magnesium	Increase	Magnesium deficiency can result in endothelial dysfunction that causes damage to bone health. In addition, magnesium deficiency leads to greater release of inflammatory cytokines and then bone remodeling and osteopenia. since magnesium has mitogenic impact on osteoblasts, its deficiency inhibits cellular growth and results in the formation of larger and perfect hydroxyapatite crystals. So, osteoporosis, expands and trabecules microfractures are appeared. Magnesium deficiency indirectly affects bone structure though the regulation of PTH level and serum 1,25(OH)2D3 level, which finally results in hypocalcemia.
Zinc	Increase	Zinc also stimulates the formation of bone osteoblasts, and prevents bone resorption by osteoclasts. Zinc also has a structural role in the bone matrix. This element, as a cofactor of alkaline phosphatase, stimulates bone mineralization.
Copper	Increase	The role of copper in bone metabolism can first be connected to copper-related enzyme, called lysyl oxidase that is essential for the formation of chemical bonds derived from lysine in collagen and elastin. Copper has a key role in bone resorption, which is done through superoxide dismutase enzyme, in which copper acts as a cofactor
<b>Macronutrient</b>	<b>Effect on BMD</b>	<b>Mechanism</b>
protein	contraversial	1. Increased protein intake by different mechanisms can positively affect bone health through the absorption of calcium, and increased secretion of insulin like growth factor 1 (IGF-1) as well as lean body mass. 2. High protein intake results in increased urinary excretion of calcium, negative calcium balance, and loss of bone mass in both young and old people <sup>10</sup> . This is mainly due to the acidic environment created by protein metabolism
SFA	decrease	1. SFA decreases the membrane fluidity of intestinal epithelia cell, and thus reduces the uptake of calcium by small intestinal brush-border cells 2. An SFA enriched diet inhibits bone mineralization. 3. Oxidized lipids increase osteoclast cell differentiation.
Non-SFA	increase	1. Omega-6 fatty acids increase the production of eicosanoids and cytokines that are capable of increasing bone mineral feeding. 2. Omega-3 fatty acids increase the absorption of calcium and decrease its urinary and fecal excretion
<b>Non-nutritive substances</b>	<b>Effect on BMD</b>	<b>Mechanism</b>
phytoestrogen	increase	first, through the activation of estrogen receptors causing the increased activation of osteoblasts, and second, through increasing the production of insulin-like growth factor 1 (IGF-1)

deficiency level as 30 ng/mL and consider any vitamin D level lower than that as an important risk factor<sup>41</sup>. The current recommendation for vitamin D intake is 10 µg/day in people aged 50-70 years and 15 µg/day in older people. Nevertheless, studies have shown that a higher dose of this vitamin (800-1,000 IU/day) may have good effects on bone health<sup>42</sup>. Indeed, vitamin D plays an important role in calcium and phosphorus homeostasis; its deficiency results in secondary hyperparathyroidism, increased bone turnover, bone loss, reduced minerals, and pelvic and other fractures<sup>15</sup>. With respect to children, vitamin D deficiency causes rickets through disruption of cartilage calcification. The newly formed bone matrix in adults is not mineralized. This phenomenon results in the development of osteomalacia<sup>33</sup>.

Vitamin D is hydroxylated in the liver to form 25-hydroxy-vitamin D<sup>43</sup>. This substance is then converted into hydroxylated 1,25(OH)D<sub>3</sub>. The hydroxylation in the liver is activated by PTH and inhibited by phosphate. In addition, 25(OH)D<sub>3</sub> limits biological activities<sup>44</sup>, whereas the active form of vitamin D [i.e., 1,25(OH)<sub>2</sub>D<sub>3</sub>] increases plasma calcium and phosphorus levels by affecting the kidneys, intestines, and bones. Binding of 1,25(OH)<sub>2</sub>D<sub>3</sub> to its receptors in the intestines results in the synthesis of proteins in the intestinal cells that are involved in the transportation of calcium from the intestinal tract to the blood. These vitamin D receptors exist in other organs, such as bones, muscles, the pancreas, and the hypophysis<sup>19</sup>. The presence of 1,25(OH)<sub>2</sub>D<sub>3</sub> in bone stimulates osteoblasts, thereby increasing the production of osteocalcin and alkaline phosphatase, and decreasing the production of type 1 collagen. The presence of 1,25(OH)<sub>2</sub>D<sub>3</sub> also improves bone resorption *in vitro*. The production of 1,25(OH)<sub>2</sub>D<sub>3</sub> is controlled directly by serum calcium and phosphate levels, and indirectly by calcium through the reduction of serum levels of PTH<sup>20</sup>. Reduced synthesis of 1,25(OH)<sub>2</sub>D<sub>3</sub> results in a slight reduction of the serum calcium level, which increases the serum PTH level<sup>45</sup>. Secondary hyperparathyroidism is known as the main mechanism that causes vitamin D deficiency, leading to pelvic fracture. Several studies have reported the increased serum level of PTH in the elderly, which has been related to vitamin D deficiency<sup>46</sup>. This negative relationship between 1,25(OH)<sub>2</sub>D<sub>3</sub> and PTH has been observed in not only the elderly but also postmenopausal women aged 45-65 years<sup>47</sup>.

### Phosphorus

It seems that the intake of the recommended amount of phosphorus (700 mg/day) does not have any negative impact on bone homeostasis. However, a high

intake of phosphorus, specifically when it is associated with a low intake of calcium, can be harmful. In contrast, an adequate intake of phosphorus is essential for bone formation during the growth ages because low serum phosphate levels limit the formation and mineralization of bone<sup>48</sup>. In addition, low serum phosphorus levels can be regarded as an indicator of malnutrition, which is a risk factor for osteoporosis and fracture. Low intake of phosphorus or its negative balance can result in reduced performance of osteoblasts, but increased osteoclast activity and, thus, higher bone turnover<sup>49</sup>. In general, what is more important than the role of phosphorus intake in bone health is the intake ratio of phosphorus to calcium, which should be 0.5-1.5:1<sup>50</sup>. A study in the US and Canada showed satisfactory intake of calcium in children and adolescents; however, the intake of calcium in adults, specifically young women, was poor. Although the dietary ratio of calcium to phosphorus was satisfactory in these regions (1:16), low intake of dairy foods, along with excessive consumption of foods rich in phosphorus or with added phosphorus, can increase this ratio to over 1:2. This increase can subsequently heighten the risk of osteoporosis<sup>51</sup>. In fact, the ratio of calcium to phosphorus, rather than the calcium or phosphorus content alone, is a determining factor in bone health and a predictor of osteoporosis. Thus, adequate levels of dietary calcium and phosphorus are very important for the health of bones<sup>52</sup>.

In a study of the relationship of age and serum phosphorus levels in women, a significant correlation was observed between the phosphorus serum level, age, and osteoporosis. In fact, fat and phosphorus levels increased in postmenopausal women<sup>53</sup>.

### Vitamin K

The vitamin K requirement of the body is supplied from two sources, but mainly from phyloquinone (K<sub>2</sub>), which exists in plant foods. The remaining vitamin K requirement is produced by intestinal bacteria. The carboxylation of protein depends on vitamin K as a cofactor in this process. After translation, this microsomal enzyme becomes responsible for the conversion of special glutamyl to gamma-carboxy glutamic residue found in a few proteins<sup>54</sup>.

### VITAMIN K-DEPENDENT CARBOXYLATION

Vitamin K is an essential coenzyme for the gamma-carboxylation that occurs in bone proteins, such as osteocalcin<sup>29</sup>. There is evidence showing that vitamin

K may have a protective effect on age-related BMD loss. Vitamin K deficiency results in the synthesis of non-carboxylated osteocalcin. Evidence shows that low serum non-carboxylated osteocalcin and phylloquinone are directly correlated with low BMD and increased risk of bone fracture caused by osteoporosis<sup>55</sup>. In a well-known cohort study by nurses, the increased risk of pelvic fracture in women was attributed to the lack of dietary phylloquinone intake<sup>27</sup>. The Framingham cohort study showed that low intake of phylloquinone was associated with increased risk of pelvic fracture in the elderly. Despite this, no correlation was observed between the intake of phylloquinone and BMD<sup>29</sup>. In a study conducted on 155 healthy postmenopausal women aged 50-60 years to determine the effect of phylloquinone, it was found that the intake of phylloquinone decreased the likelihood of femoral neck osteoporosis by 35% in the case group, as compared with the control group<sup>29</sup>.

### Magnesium

Magnesium is essential for the function of many key organs and has an important role in the physiology of humans and other mammals. The presence of magnesium is vital in bone and teeth structures and has a role in more than 300 enzymes as a cofactor, including binding to ATP for kinase reactions, permeability of excitable membranes, and neuromuscular transmission. Despite these significant tasks, the physiology and homeostasis of magnesium continue to remain largely unknown. The majority of the human population does not receive adequate dietary magnesium<sup>56</sup>. In the US, three-fourths of the population has magnesium deficiency. More than half of the body magnesium requirement (60%) is stored in the bones, and the remaining 30-40% is stored in skeletal muscles and soft tissues, while only 1% is stored in bodily liquids<sup>57</sup>. Magnesium is an intracellular cation, and thus serum magnesium level is not a good predictor of magnesium level in the body. Because of this, many patients visiting medical centers are unaware of their low magnesium levels<sup>56</sup>. Magnesium deficiency can result in endothelial dysfunction that damages bone health. In addition, magnesium deficiency leads to greater release of inflammatory cytokines, and subsequently bone remodeling and osteopenia<sup>55</sup>. In addition, because magnesium has a mitogenic impact on osteoblasts, its deficiency inhibits cellular growth and results in the formation of larger and perfect hydroxyapatite crystals<sup>58</sup>. From this, osteoporosis is facilitated, via induction of bone fragility and weakness, limited bone formation and expansion, and the

appearance of trabecular microfractures<sup>16</sup>. Reduced magnesium levels increase the release of free radicals, which may damage the skeletal muscle structure, specifically their sarcoplasm reticula and mitochondria<sup>59</sup>. Moreover, magnesium deficiency indirectly affects bone structure through the regulation of PTH levels and serum 1,25(OH)<sub>2</sub>D<sub>3</sub> levels, which finally result in hypocalcemia. Because magnesium acts as a cofactor in the creation of PTH, a low magnesium level decreases the secretion of PTH, which results in 1,25(OH)<sub>2</sub>D<sub>3</sub> deficiency<sup>16</sup>. Magnesium can intervene with calciotropic hormone function, and is known as a neutralizer of calcium. It seems that the ratio of magnesium to calcium is a determining factor in bone physiology and pathology. A study showed that the ratio of serum and hair levels of calcium to magnesium is a good index for the measurement of BMD<sup>60</sup>. Various small epidemiological studies have reported that high magnesium intake is associated with high BMD in the elderly<sup>61</sup>. In addition, small clinical trials have shown that magnesium supplementation in people with low magnesium levels has had a positive impact on reduced BMD<sup>62</sup>. In a study conducted in Israel, a group of postmenopausal women received magnesium supplements (250-750 mg/day) for 24 months. It was observed that the BMD in trabecular bones increased by up to 8%, and BMD loss was reduced in 87% of cases<sup>63</sup>. Despite this, existing evidence with respect to magnesium supplements is inadequate, and results from observational and interventional studies into the relation of magnesium and bone health are not definitive. According to a recent study, high intake of magnesium is associated with the risk of forearm fracture<sup>64</sup>.

### Zinc

Zinc is an essential growth element. This element acts as a cofactor in the synthesis of AND and ANR polymerase, and enzymes involved in the production of proteins. Zinc is part of the structure of more than 200 enzymes and seems essential for the normal synthesis of collagen and bone mineralization<sup>65</sup>. Animal studies have shown that zinc deficiency is associated with abnormal bone growth and mineralization<sup>66</sup>. The strong correlation between the zinc content of bone and high BMD can demonstrate the important role of zinc in bone health<sup>67</sup>. Inadequate bone growth is very common under the condition of zinc deficiency during the growth period in animals and children<sup>68</sup>. Reduced growth is a feature of acrodermatitis enteropathica, an autosomal recessive disorder that reduces the zinc level in neonates<sup>69</sup>. Studies with rats have shown that serum zinc deficiency

reduces zinc density in the thigh bone, consequently decreasing trabecular bone density and causing bone turnover<sup>70</sup>. Moreover, zinc has a structural role in the bone matrix. Bone minerals are composed of hydroxyapatite crystals that include a zinc-fluoride combination. Zinc also stimulates the formation of bone osteoblasts and prevents bone resorption by osteoclasts. Thus, zinc is essential for osteoblastic activities; it directly causes the activation of aminoacyl tRNA synthesis and stimulates cellular protein synthesis. This element, as a cofactor of alkaline phosphatase, stimulates bone mineralization<sup>71</sup>. Studies of rat bone marrow have shown that zinc inhibits bone resorption by preventing the formation of osteoblast-like cells<sup>72</sup>. According to these reports, the low intake of zinc is associated with low BMD in women; in addition, women with osteoporosis have had lower plasma zinc levels and greater urinary excretion of zinc<sup>73</sup>. An epidemiological study showed that the risk of fracture was significantly greater in men with lower zinc intake than in those with high zinc intake<sup>74</sup>.

### Copper

Severe copper deficiency results in skeletal problems. Studies have shown that osteoporosis is related to Menkes syndrome<sup>75</sup>, which genetically disrupts the intake of copper in the body. The role of copper in bone metabolism can first be connected to the copper-related enzyme called lysyl oxidase. This enzyme is essential for the formation of chemical bonds derived from lysine in collagen and elastin<sup>76</sup>. Animal studies have shown that the activity of this enzyme is stimulated in response to increased dietary intake of copper<sup>77</sup>. Copper plays a key role in bone resorption, which is done through the superoxide dismutase enzyme, in which copper acts as a cofactor. Superoxide dismutase is an antioxidant enzyme formed with zinc and copper atoms. The role of these two elements is the neutralization of antioxidant radicals that are produced during bone resorption by osteoclasts. Studies of animals with inadequate copper intake have shown that copper deficiency inhibits osteoclast activities but does not affect osteoblast activities<sup>78</sup>.

## NON-NUTRITIVE SUBSTANCES AND OSTEOPOROSIS

### Phytoestrogens

In the past, it was believed that estrogen was created only in animals. Later, it was found that plants are also capable of producing estrogen-like molecules called phytoestrogens<sup>79</sup>. Phytoestrogens are plant compounds with an estrogen-like chemical structure

and a similar impact on the bone tissue. Phytoestrogens show estrogen-like activities and, due to structural similarity, have a high tendency to combine with the estrogen receptor beta<sup>78</sup>. They are among the most important isoflavones. Soy and flaxseed proteins are the most common sources of phytoestrogens<sup>80</sup>. In recent years, several studies have been conducted on soy isoflavones and their effects not only on sexual hormone metabolism but also on other biological activities, including reduced cholesterol level, risk of cancer, and protection of bone health<sup>81</sup>. In terms of mechanisms, evidence shows that isoflavones not only reduce bone resorption but also increase the formation of bone tissue at the same time. In a study of postmenopausal women, it was found that urinary excretion of deoxypyridinoline decreases with increased intake of soy protein. Deoxypyridinoline in urine is an indicator of bone resorption<sup>82</sup>. Isoflavones increase bone formation at least in two ways: first, through the activation of estrogen receptors, causing the increased activation of osteoblasts<sup>83</sup>, and second, by increasing the production of IGF-1<sup>84</sup>. Studies have shown that IGF-1 increases osteoblastic activity in humans and has a direct relationship with BMD<sup>85</sup>. In a six-month-long study on postmenopausal women, the subjects were divided into three groups; the first and second groups received 90 mg and 56 mg of isoflavones, respectively, while the third group did not receive isoflavones at all. It was observed that those who received the highest amount of isoflavones had a greater BMD level (2.2%) in the vertebral column area, as compared with the control group<sup>86</sup>. Despite this, further prospective interventional studies with longer implementation and larger sample size are required to determine the effect of phytoestrogen-enriched diets on bone mass loss and reduced risk of fracture.

### Osteoporosis and Nutritive Status in Iran

There are no accurate statistics on the prevalence of osteoporosis in Iran. In a study conducted in Tehran on a group of women aged 40-60 years, the prevalence of osteoporosis among postmenopausal women was reported as 23.1% and 4.6% in the vertebral column and femoral neck areas, respectively. These findings indicated a low prevalence of osteoporosis in this city<sup>87</sup>. Another study by Mojibian *et al.* in postmenopausal women in Yazd reported the prevalence of osteoporosis in the femoral and vertebral column regions as 43.03% and 20.5%, respectively<sup>88</sup>. Another study in Mashhad showed the prevalence of osteoporosis (35.7%) and osteopenia (38.9%) in the lumbar

vertebrae of women aged 50-80 years<sup>89</sup>. This difference in the prevalence of osteoporosis and osteopenia in different societies can be due to different reasons, including differences in lifestyle, age of subjects, measuring instruments, BMD, race, and BMD measurement region<sup>90</sup>.

Quantitative studies in Iran have addressed the nutritional status of patients with osteoporosis. A study conducted in the northwest region of Iran showed a significant difference between dietary intake of nutrients and the recommended dietary allowance<sup>91</sup>. For example, adequate intake of calcium, vitamin D, and vitamin K was observed only in 7.2%, 3.1%, and 42.3% of cases, respectively<sup>92</sup>. Nevertheless, further studies in different parts of the country are required.

## CONCLUSION

In general, having good nutrition plays a very significant role in osteoporosis prevention and treatment. In other words, people can greatly improve their bone health by observing the following simple recommendations: in addition to the recommended intake of calcium (1,200 mg/day) by the elderly over 70 years old, it is recommended they take at least 600 IU (ideally 800-1,000 IU) of vitamin D. Paying attention to adequate intake of calcium and vitamin D should not result in the neglect of other nutrients and dietary compounds. Other important micronutrients for bone health, such as magnesium, vitamin K, and potassium, can be supplied by having a healthy diet containing large portions of fruits and vegetables (at least five servings per day). In addition to diet, living a good lifestyle by avoiding high-risk behaviors (e.g., excessive use of tobacco and alcohol) and by including adequate physical activity can assure bone health.

## ABBREVIATIONS

**BMD:** Bone mass density

**SFA:** Saturated fatty acids

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## AUTHOR'S CONTRIBUTIONS

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The authors declare that they have no competing interests.

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