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DIETARY MINERAL ELEMENTS AND THEIR ROLE IN PREVENTING OSTEOPOROSIS: A REVIEW

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ABSTRACT

In today's time, osteoporosis emerges out as one of the most common metabolic disorders which negatively acts on bones and reduces their density. Notably, more than 200 million people globally are suffering from it. This chronic bone disorder affects all age groups however the aging population is most affected and it is now becoming epidemic. Bones provide support, give protection to organs, stores minerals, and many more. The inorganic components in bone help the bone to maintain its structure. Some mineral elements act in an antagonist nature that is when their concentration is increased in enormous amounts and they stimulate bone resorption instead of bone formation while some of them stimulate osteogenesis. Each mineral element present in the bones has its own uniqueness and own impact and functions accordingly. This review paper lists out some of the mineral elements that influence the bone in remodeling and also states the underlying mechanism of action.

KEYWORDS: Osteoporosis, bone health, bone disorder, dietary minerals.

INTRODUCTION

Osteoporosis is a progressive skeletal disorder defined as low bone density, loss of bone tissues, and many more factors (**Fig.1**). According to World Health Organization (WHO), osteoporosis is where adults bone mineral density (BMD) decreases to −2.5 T-score (**Fig.2A**) or lower than that when measured with Dual-energy X-ray absorptiometry (DXA). Overall, the integrity of the bone is lost. The bones fail to remodulate properly which directly affects the carrying capacity of it and as a result, the bones become susceptible to fractures (on Osteoporosis and Prevention 2001, Clynes, Harvey et al. 2020). Till now it is also known to be a silent illness until there is a fracture which leads to some serious damage to the body and may even cause death (Cosman, de Beur et al. 2014). Scientifically it is proven that in men and women, bones generally start to deteriorate and lose their mass as they reach to the age of 30 or above (Hunter and Sambrook 2000). It has been estimated that every 1 out of 3 women and every 1 out of 5 men above aged 50 are likely to suffer from osteoporotic fractures (Kanis, Johnell et al. 2000). Oden et al. suggested a probability graph showing the fracture rates from 2010 to 2040 **(Fig. 2B**) (Oden, McCloskey et al. 2015). However, osteoporosis is preventable if self-care is taken wisely (Sinaki 2021).

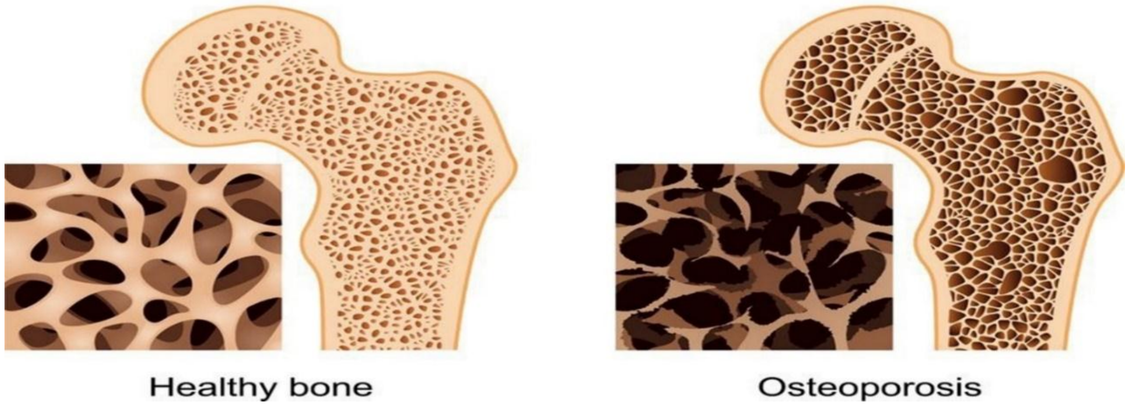

Fig. 1: Morphology of healthy bone and osteoporotic bone (https://www.spineuniverse.com /conditions/osteoporosis/osteoporosis-silent-thief).

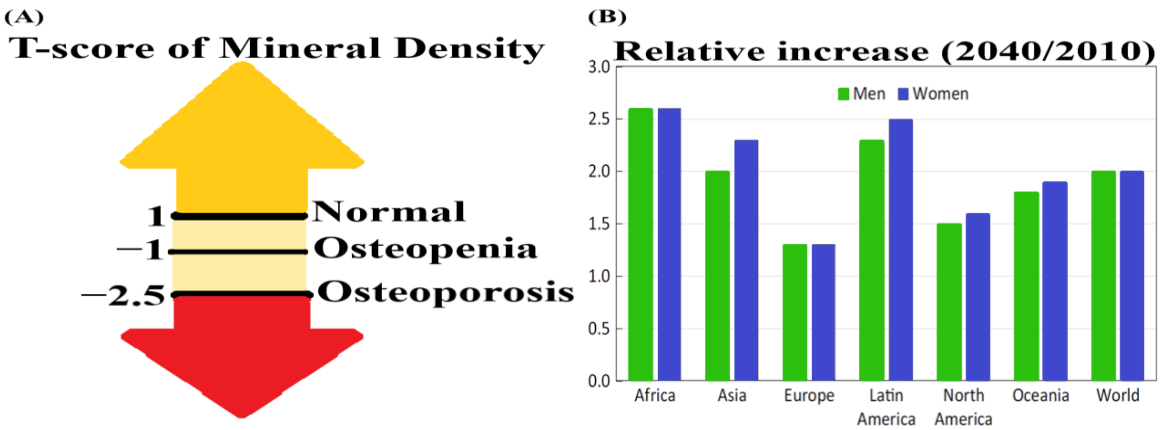

Fig. 2: (A) T-score illustrating the concentration of minerals required for strong bone. >−1: normal; −1 to−2.5 suffers from osteopenia; below−2.5 osteoporosis occurs leading to fracture. (B) Graph showing the probability of fractures in different countries men and women between the years 2010 to 2040 (Oden, McCloskey et al. 2015).

The bone itself holds an intrinsic capacity to regenerate in response to trauma during the process of repair. Moreover, bones undergo constant remodeling throughout human life

(Einhorn 1998, Bates, Yeo et al. 2018). There are widely known factors that determine the mass of bone, for instance, the factor can be genetic or endocrinal or simply nutrients (Rizzoli 2014, Viljakainen 2016). Therefore, for maintaining this continuous reorganization, bones require an adequate amount of nutrition. As far as we know, almost 65% of adult bone mass is made up of hydroxyapatite, an indissoluble salt of calcium and phosphorus and thereby making these two the major constituents of bone **(Fig. 3)**. Bones also contain some other small amounts of minerals like magnesium, fluoride, sodium, bicarbonates, and many more to maintain their health. Other than their passive roles, dietary minerals have also shown their active roles in the metabolism of bones. Even the Food and Nutrition Board (FNB) of the National Academy of Sciences, thoroughly releases new Dietary Reference Intakes (DRI) which are mainly based on the mineral requirements for optimizing health (Food and Board 1999) **(Table 1)**.

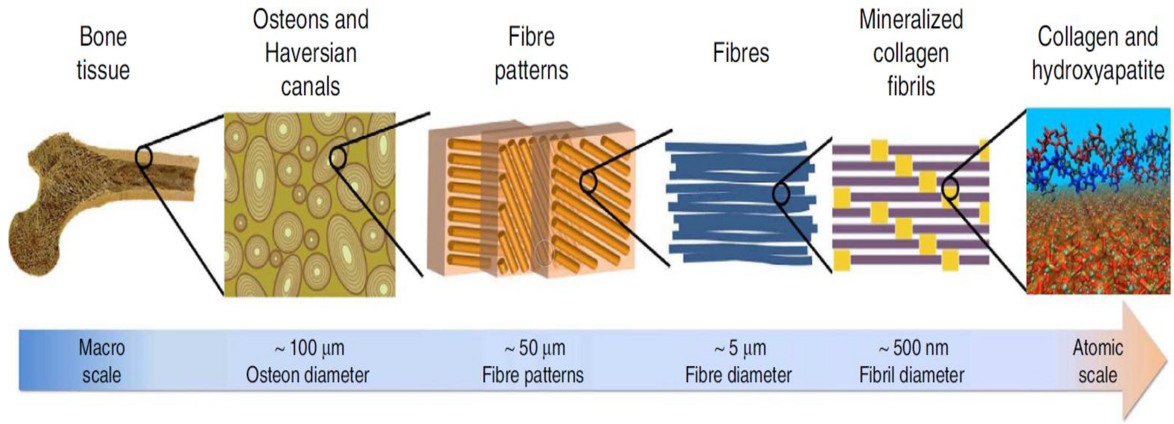

Fig. 3: Bone structure from macro size to nano size[reprinted with permission (Nair, Gautieri et al. 2013)].

Table 1: Some selected minerals elements which are found in the bone (Iyengar and Tandon 1999).

Minerals	Values (mg/kg)
Aluminium (Al)	2-67
Calcium (Ca) (%)	9-29
Cadmium (Cd)	0.02-4
Copper (Cu)	0.2-2.6
Fluoride (F)	640-6400
Potassium (K)	48-6200
Magnesium (Mg) (%)	0.01-0.4
Manganese (Mn)	0.1-8
Sodium (Na) (%)	0.3-1.4
Strontium (Sr)	48-420
Zinc (Zn)	50-260

This paper highlights some of the major mineral elements that play important role in maintaining the homeostasis of the bones and preventing it from collapsing.

Calcium

Among the numerous mineral ions, Ca^{2+} is one of the core elements that play a significant amount of biological functions and bone mineralization is one of them. More than 99% of calcium is present in the bone as the calcium phosphate complex is mainly present in teeth and bones (Bhattarai, Shrestha et al. 2020). It provides strength and core to the bone (Bronner 2001, Marino, Masella et al. 2011).

The calcium concentration in serum is regulated by some of the calciotropic hormones such as PTH (parathyroid hormone), FGF23 (Fibroblast growth factor23), calcitonin, and 1,25dihydroxyvitamin D **(Fig. 4)**. The recommended calcium intake is 1200 mg/day but studies contradict and shows older women in the United States (US) consumes less than 600mg per day (Haleem, Lutchman et al. 2008). In fact, high calcium intake is associated with a reduced risk of fractures in elders suffering from osteoporotic fractures (Heaney 2000, Huncharek, Muscat et al. 2008, Rizzoli, Bianchi et al. 2010). Precursors of osteoblast cells and osteoblasts exhibit CaSR (Calcium sensing receptor) and the importance of these receptors is highlighted by an experiment conducted by Chang et al. (Chang, Tu et al. 2008). The research showed deletion of CaSR in collagen promoters (I and II) resulted in the loss of skeletal growth. Calcium also plays a vital role in intercellular signaling. The L-type calcium channels facilitate communication of cells within osteons through gap junctions present in them. Osteons are the fundamental part of the bone that coordinates and maintains bone synthesis (Henriksen, Hiken et al. 2006). Another calcium channel which is mainly stretched activated is equally crucial for the proliferation of bone-forming cells. Apart from osteons, osteocalcin, a12-kDa non-collagenous proteins are present in bone acting as a calcium-binding protein. These proteins are vitamin K-dependent and help in bone mineralization. However, H Kaji et al. (Kaji, Sugimoto et al. 1996) experiment's revealed that extracellular calcium in high concentration results in the formation of osteoclast forming cells and stimulates bone resorption. The underlying action is governed by osteoblast cells that trigger DNA synthesis and thereby eliciting proliferating activities of osteoclast cells (Sugimoto, Kanatani et al. 1994, Asagiri and Takayanagi 2007). On the contrary, a high concentration of calcium in cytosol results in lowering of osteoclast cell capacity (Miyauchi, Hruska et al. 1990, Siddiqui, Lively et al. 2012).

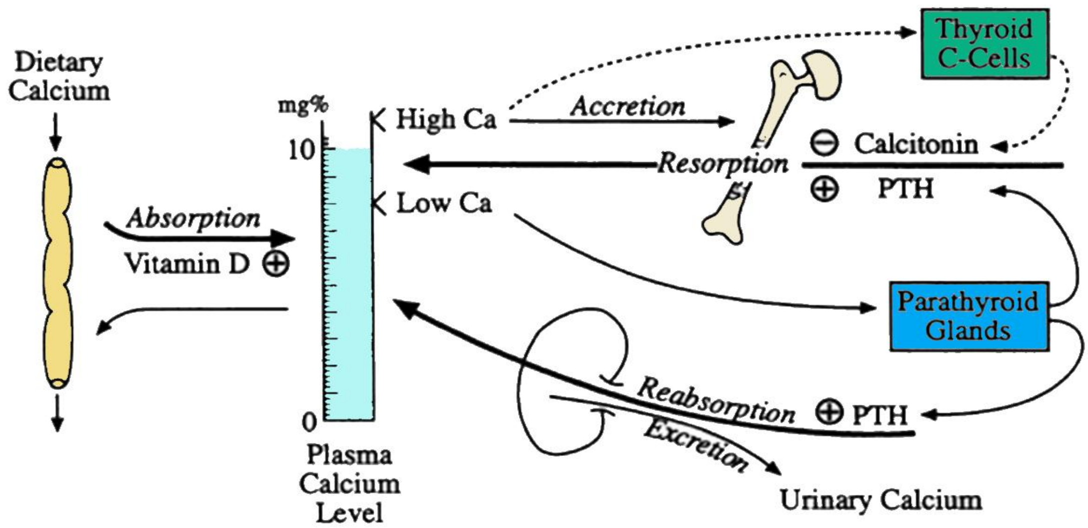

Fig. 4: Role of the parathyroid gland and thyroid cells in calcium homeostasis (http://www2.csudh.edu/nsturm/CHE452/20_Calcium%20Homeostasis16.htm).

Table 2: Some clinical studies on calcium-rich mineral water in different conditions.

Experiments conducted in earlier days	**Acute effect of calcium intake in bone metabolism**
1. Guillemant et al,. (Guillemant, Le et al. 2000) experimented on 12 healthy men and they were given water containing calcium (172mg Ca in 0.5 L water).	The study revealed that there was a progressive reduction in marker collagen I cross-linked telopeptide (CTX)
2. Cepollaro et al. (Cepollaro, Orlandi et al. 1996) demonstrated one-year consumption of a low calcium diet in 45 early staged postmenopausal women.	The wrists 45 women group showed a significant downfall in bone mass / BMD.
3. Costi et al. (Costi, Calcaterra et al. 1999) studied the regular consumption of calcium water in 255 menopausal women (both pre and post)	The sample analysis showed that calcium-rich water significantly maintained the bone density of the vertebra, especially in postmenopausal women.
4. Aptel et al. (Aptel, Cance-Rouzaud et al. 1999) showed data of 4434 osteoporotic women and data also states that those women were provided with 100mg of calcium daily.	The observation concluded that daily intake of calcium increased the bone density of the neck region by 0.5% in women aged above 75 years.

Fluorine

Since the last decade, Fluoride ions used in a concentration of 10-20mg daily in the form of medication have shown a positive effect on bone density, especially in trabecular bone (Pak, Sakhaee et al. 1997, Vestergaard, Jorgensen et al. 2008). Due to its narrow "therapeutic window" and to avoid fluorosis, only up to 50-120g/L of it is allowed in the blood serum. Pak et al. Pak, Sakhaee et al. 1997) successfully treated osteoporotic patients with 20-25 mg of fluoride tablets daily for four consecutive years and showed that 233 patients treated with it showed up to 70% lower spinal fracture rate. It has also been seen that in low doses of fluoride each year there is a 3 to 5% increase in vertebral bone density (Ringe, Kipshoven et al. 1999). The mechanism of fluoride action can be understood by an experiment conducted in ROS17/2.8 rat's osteosarcoma cells by Qu H et al. (Qu and Wei 2006). The result of the experiment showed that the fluoridated hydroxyapatite Stimulates the proliferation and osteoblastic cell attachment of osteosarcoma cells. Another experiment demonstrated that fluoride anions adapt the environment of bone tissues and substitute the hydroxyl group of hydroxyapatite compound and it changes the crystalline structure of it (Posner 1996). All together fluoride salts within their dosage limit increase bone formation and do not affect bone resorption (Chavassieux, Boivin et al. 1993).

Strontium

Strontium (Sr) ion acts as an osteoclast inhibitor which prevents bone resorption. This inhibiting characteristic is seen in monkeys and rodents (Matsumoto 1988, Marie, Hott et al. 1993). Sr ions play a crucial role in stimulating the mesenchymal stem cells of bones to differentiate into osteoblast (Zeng, Guo et al. 2020, Chen, Udduttula et al. 2021).Yang et al. discovered that strontium activates the Wnt/β-catenin canonical pathway to differentiate mesenchymal stem cells (MSCs). (Yang, Yang et al. 2011) Another study reports that Sr represses the osteoclastic activity through the NF-κB pathway.Zhu et al. (Zhu, Hu et al. 2016) demonstrated through RT-PCR that the Strontium coupled with Calcium (SrCl2) suppresses the osteoclast genes like c-fos, cathepsin-K, MMP-9, TRAP.

Copper

Copper is a trace element however deficiency of it leads to fractures, osteoporosis, and fragile bones (Dollwet and Sorenson 1988, Sarazin, Alexandre et al. 2000). It influences osteogenesis, mineralization of skeletal bones. A copper-dependent enzyme, Lysyl oxidase (LOX), also known as protein lysine 6-oxidase that catalyzes the conversion of lysine to reactive aldehyde and plays a vital role in cross-links of collagen fibrils, increasing the core strength of the extracellular matrix proteins and making it stronger and flexible. Studies on animals showed a deficiency of $Cu2^{+}$ leads to weakening of bone strength (Jonas, Burns et al. 1993). Studies on post-menopausal women showed that 2.5-3 mg of copper per day increases bone density as well as it decreases bone loss (Strause, Saltman et al. 1994, Eaton-Evans, Mcllrath et al. 1996). Copper is also a ubiquitous element like other iron and zinc and higher concentration may lead to severe problems.

Magnesium

Magnesium is also proved to be a great contributor to the health of bone (Vormann 2003, Launius, Brown et al. 2004, Rude, Singer et al. 2009). In the human body, magnesium is present in a good quantity, and in the bone, almost 50-60% of 25gm is situated in bones (Martin 2002). Studies showed that deficiency in magnesium ion in the bone leads to loss of skeletal growth, osteoporosis, and impaired bone formation (Vormann 2003, Rude, Gruber et al. 2005, Rude, Gruber et al. 2006, Rude, Singer et al. 2009). Magnesium supplements show actual benefits to bone. A data collected from Israel showed that there has been a significant increment in bone density of women suffering from osteoporosis after taking 250mg of magnesium on regular basis (Stending-Lindberg, Tepper et al. 1993).

Silicon

Silicon is one of the essential minerals which is accelerates osteogenesis independent of vitamin D levels. A study presented by Jugdao et al. (Jugdaohsingh, Calomme et al. 2008) supports the presence of silicon in bones. The research was conducted in Sprague Dawley rats. The below table and a graph depict the concentration of silicon in female adult rats **(Table 3) (Fig. 5)**.

Table 3: Different element concentration in the adult female humeral bone of rats.

Minerals	Mean (SD)
Si	16.39 (3.80) µg/g
B	1.59 (0.13) µg/g
Mn	0.421 (0.020) µg/g
Cu	0.858 (0.176) µg/g
Zn	231.8 (14.6) µg/g
Mg	4.22 (0.25) mg/g
K	1.71 (0.21) mg/g
P	100.8 (4.0) mg/g
Ca	210.9 (3.5) mg/g

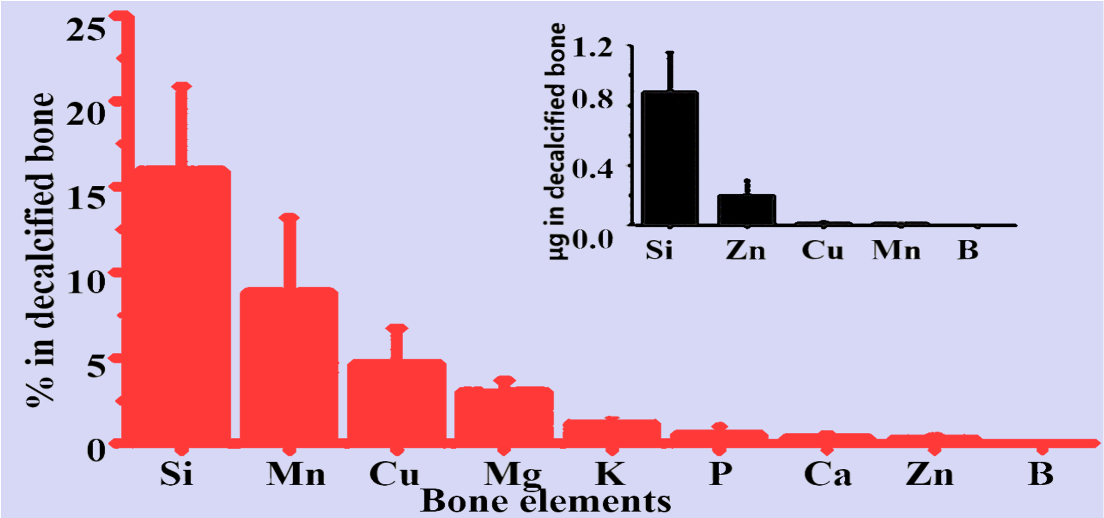

Fig. 6: Distribution of various minerals in the decalcified femoral bone of adult female rat.

Intake of supplements enriched with Si is associated with enhanced BMD (Eisinger and Clairet 1993, Jugdaohsingh, Tucker et al. 2004, Macdonald, Hardcastle et al. 2012). In collagen synthesis too, Si plays a pivotal role as a co-factor for the collagen enzymes (Carlisle, Berger et al. 1981, Reffitt, Ogston et al. 2003) and simulates osteoblast differentiation (Reffitt, Ogston et al. 2003).

It also enhances the incorporation of calcium in the bone (Hott, de Pollak et al. 1993, Seaborn and Nielsen 2002). A study illustrating the bone volume in cancellous bone changed in women suffering from osteoporosis and administration of silicon parenterally and orally with 16.5mg and 27.5mg respectively for 3 months and 4 months showed an increase in the volume (Schiano, Eisinger et al. 1979).

Iron

Iron is another essential element for bones. Research in both *in vivo* and *in vitro* shows that iron plays a crucial role in the homeostasis of bone and deficiency of iron actually hampers this homeostasis. But more than the advantages of the element, studies reported more on the adverse effects. For instance, overload of iron leads to some serious conditions such as osteoporosis, thalassemia, renal failure (Jian, Pelle et al. 2009). As stated earlier, there are only a few studies supporting iron in maintain bone density, and Katsumata et al. (Katsumata, Katsumata-Tsuboi et al. 2009) study is one of them. The experiment demonstrated that due to low concentration of serum1,25-dihydroxycholecalciferol, insulin-like growth factor-I, andosteocalcin, the regulation and bone markers are disrupted which results in increased bone resorption than bone formation.

Boron

Boron is not considered as an essential element but there are plenty of studies showcasing the advantages of the element on the bone (Newnham 1994, Armstrong and Spears 2001, Naghii, Torkaman et al. 2006, Nielsen 2009). Deficiency of the element itself does not result in adversity but instead, it is associated with loss of chondrocyte density found within the growth plate of bone. Deprivation of boron also leads to increase calcium excretion, loss of magnesium, and many more elements which were involved in bone mineralization (Armstrong and Spears 2001, Nielsen 2008). Boron supplements improve bone minerals and increase bone calcification as well as decrease calciuria (Hunt 1996, Devirian and Volpe 2003, Nielsen, Stoecker et al. 2007, Nielsen 2008). All studies are indicating that deficiency of boron leads to lowering of osteogenesis mechanism as well as it somehow impairs the repair system of bone (Newnham 1994, Gorustovich, Steimetz et al. 2008). Somehow data supports the action of boron with steroid hormone particularly 17-estradiol. It illustrates that boron contributes the steroid hormone with more concentration and function and thereby it increases the volume of trabecular bone (Sheng, Taper et al. 2001). Moreover, the element enhances the absorption of other mineral elements like calcium, magnesium. Boron also improves the efficacy and increases the vitamin D concentration (Hunt 2012).

Phosphorus

Phosphorus is an essential mineral anion that is found everywhere in the human body and 85% of it is present in the bones mainly coupled with calcium forming hydroxyapatite, a major structural constituent of bone, and the rest of the phosphate remains as condensed calcium phosphate (Farrow and White 2010, Serna and Bergwitz 2020). Deficiency in phosphorus hampers the calcification of epiphyseal growth plate (Hunter, Arsenault et al. 1991). All these years studies illustrate that deficiency of calcium disrupts the bone homeostasis but the fact is, the main factor behind some major bone illness such as rickets, osteomalacia is phosphate (Amanzadeh and Reilly 2006, Tiosano and Hochberg 2009, Marks, Debnam et al. 2010). A high concentration of phosphate acts negatively on osteoblasts and causes the death of these cells but osteoblasts secrets fibroblast growth factor 23 that regulates the phosphate level in cells.

Zinc

Zinc is one of the transition metals that is found throughout the body. According to many studies conducted *in vivo*, deficiency of zinc is related to osteopenia, abnormal bone formation (Ma and Yamaguchi 2000, Cho, Lomeda et al. 2007, Kim, Baek et al. 2009, Seo, Cho et al. 2010). Other symptoms show impaired calcification, defective skeletal development (Beattie and Avenell 1992). Studies also revealed that supplements containing Zn help bone to produce new cells, proving higher mass to the bone, and at the same time, it reduces bone resorption (Yamaguchi and Kishi 1996, Ovesen, Møller-Madsen et al. 2001, Hadley, Newman et al. 2010, Nagata and Lönnerdal 2011, Dermience, Lognay et al. 2015). As stated earlier, Zn positively acts by alleviates differentiation of osteoblast cells and acts inversely on osteoclast cells by decreasing the resorption capability of the bone. There has been plenty of evidence supporting the Zn element as an important mineral in bone metabolism. At the same time, it shows great similarity with other growth factors like insulin-like growth factor1 in terms of its effect (Ovesen, Møller-Madsen et al. 2001). There are many enzymes too that are zinc-dependent such as alkaline phosphatase, collagenases that influence the metabolism of bones and defects that arises when zinc concentration is disturbed (Yousef, El Hendy et al. 2002, Yamaguchi 2010). There are many zinc finger transcriptional factors that help the bone to differentiate and they do so by regulating their gene expressions such as runt-related transcription factor, odd skipped related2 transcription factor (Kawai, Yamauchi et al. 2007, Yamaguchi, Goto et al. 2008, Kwun, Cho et al. 2010). In another hand, zinc prevents osteoclast differentiation by suppressing the RANKL and tumor necrosis factor-like processes (Fong, Tan et al. 2009, Yamaguchi 2010).

CONCLUSION

The bones act as a framework for the human body that permits free movement and provides structure to the body. There are plenty of mineral elements present in the environment and in the bone itself that regulates its homeostasis and as well as maintain its microarchitecture. These elements solely act according to their concentration. Some elements in higher concentration show their proper function while others show in a lower concentration. As reviewed in this paper, food with proper mineral supplements is also very necessary to maintain bone health. All these years, mineral supplements consumed parenterally and orally have proved that it keeps the bone in its healthy state by replenishing the minerals, and moreover, it has proved to be the simplest practice to keep ourselves safe from bone disorders like osteoporosis. There are numerous reasons behind this bone fragility and fractures but now the drugs with minerals infused in them can cover any deficiency occurring in bones. The advanced technology today has enabled us to know about most of the actions of these minerals still deep research and knowledge are required in this field to discover all the cons and pros of the elements. Therefore in this review we have highlighted the importance of some mineral elements in bone health.

Competing interests

The authors declare that they have no competing interests.

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