REVIEW ARTICLE

BONE IS NOT JUST CALCIUM AND VITAMIN D- A REVIEW OF ESSENTIAL NUTRIENTS REQUIRED FOR BONE HEALTH

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ABSTRACT

Bone formation is a constant procedure in which osteoblasts lay new bone and osteoclasts resorb it. Mineralization takes place at active bone formation sites where the extracellular matrix vesicles, the major sites of apatite mineral deposition, are present. Turnover of bone, which maintains its structure and integrity, has several events such as activation, resorption and osteogenesis by osteoblasts. The bone crystals proliferation depends on the presence of collagen, hormones, minerals and vitamins such as phosphorus, magnesium, calcium, zinc, fluoride, potassium, manganese, boron, copper, iron, calcium and a number of vitamins such as B,K,C,A,D, etc. Information regarding the elements involved in bone formation was retrieved through studies published up to 2017 in PubMed, Medline and other authentic search engines available in the University.

This review highlights the individual roles of specific vitamins and minerals at the respective steps of bone formation, insufficiency at all particular stages result in various bone pathologies, leading to deficiency disorders, fractures and poor friable bones. Since the role of vitamin D and calcium is well established therefore these were not included in this review.

Keywords: Osteoblasts, Osteoclasts, Vitamins, Minerals, Osteogenesis, Collagen, RANK Ligand.

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INTRODUCTION

The emergence of new data on vitamins and minerals suggests that their potential benefits for the body are beyond than what is being anticipated for the past 100 years or so. The human body, besides having many vital organs, has 270 bones,[1] many fuse during growth, leaving 206 separate bones in an adult[2]. Adult bones need constant maintenance and hence, undergo a continuous state of remodeling, which happens in a certain pattern by the two important cells osteoclasts and osteoblasts along with connective tissue blood vessels and nerves. Osteoclasts degrade the organic matrix, does the resorption of bone by removing the mineral content. Osteoblasts on the other hand, migrate to resorption site and synthesize and mineralize the new bone matrix through a process called coupling[3,4]. This process is based on series of metabolic reactions, and requires, besides calcium and vitamin D, a constant supply of many dietary nutrients including proteins, minerals like Mg, P, K, Mn, Cu, Fe, Bo, Zn, and vitamins like A, K, C, and the B complex.

Cortical bone has a network of capillaries, the intracortical canals links the periosteum and endosteum, it consists of transverse Volkmann canals and longitudinal Haversian canals[5,6]. A sufficient blood supply is essential for bone strength it transports oxygen, metabolic wastes, nutrients, minerals and oxygen required for mineralization[5-7]. During modeling the endothelial cells form a vascular channel for nutrient supply to enter from the growth plate region of cartilage and provide a site for new bone formation[5,8]. Blood vessels present at the bone remodeling site enable the coupling reaction[9,10]. The two principal components of bones are collagen and calcium phosphate that make up the individual bones of the human skeletal system. Information regarding the elements involved in bone formation was retrieved through studies published from 1990 to 2018 in PubMed, Medline and other authentic search engines available in the

University.

The theme of this review is to highlight the individual roles of specific vitamins and minerals at the respective steps of bone formation.

DISCUSSION

Our skeletal system, in early years, is the most neglected part of the body till we reach the twilight zone. Then comes the recognition of the success story of this unsung hero in shaping, storing, protecting and producing various metabolites as well as enabling the movement of the body for work and play. Like the rest of the body, bone tissues constantly break down and regenerate. It is important to understand factors that have a great influence on bone formation to maintain a healthy skeletal system. Diet of all the factors remains utmost in this endeavor. Vitamins and minerals, the naturally occurring chemical compounds, are supreme in supporting bone modelling.

A series of events occur in the remodeling of bone. It begins with the activation followed by resorption carried out by the osteoclasts, then there is breakdown and removal of bone and eventually new bone is laid by the osteoblast cells. Later there is an inactive phase. In the process of remodeling, paracrine and endocrine factors have an effect on osteoblastic and osteoclastic activities[11,12]. Preosteoclasts formation is stimulated by monocytes/macrophages[12]. Preosteoclasts then fuse and become osteoclasts[12,13]. Preosteoclasts are present in abundance on the surface of periosteum, at active growth sites[14,15].
Runx2 is an essential transcription factor which initiates the differentiation of osteoblasts and forms preosteoblasts. Growth factors, like transforming growth factor-beta (TGF-β) and insulin-like growth factor type 1 (IGF-1) contribute in the formation of new bone[16,17]. Formation and resorption of bone occurs independently.

Stimulators and Inhibitors of Bone Resorption
Parathyroid hormone causes bone formation but can also resorb bone. It attaches to a receptor, PTH/PTHrP type 1 to activate signaling pathway, which includes the canonical Wnt-signaling pathway that has catabolic as well as anabolic effects[18]. Teriparatide is known for increasing cancellous and endocortical ossification, at sites which are actively remodeling bone. However it increases cortical porosity[19]. PTHrP 1 and its analog abaloparatide, binds to PTH/PTHrP 1 receptor, increases the markers of bone formation and resorpion, but not as much as teriparatide[20,21].

Process of resorption is primarily inhibited by substances that decrease the bone turn over, such as denosumab, bisphosphonates, and selective estrogen receptor modulators (SERMs). Various humans and animals studies with osteopetrosis proved that reduction in resorption of bone does not always have an association with reduced bone formation if the osteoclasts remain together[22-24]. A protease Cathepsin K (CatK), found abundantly in osteoclasts plays a role in degrading bone's organic matrix.

ROLE OF VITAMINS:

Vitamins being crucial nutrients are essential to perform various biochemical and physiological functions. It is important to include vitamins in our diet. Vitamins play an integral role in the formation of bone be it water soluble such as B complex and vitamin C or fat soluble such as vitamins A, D, E and K.

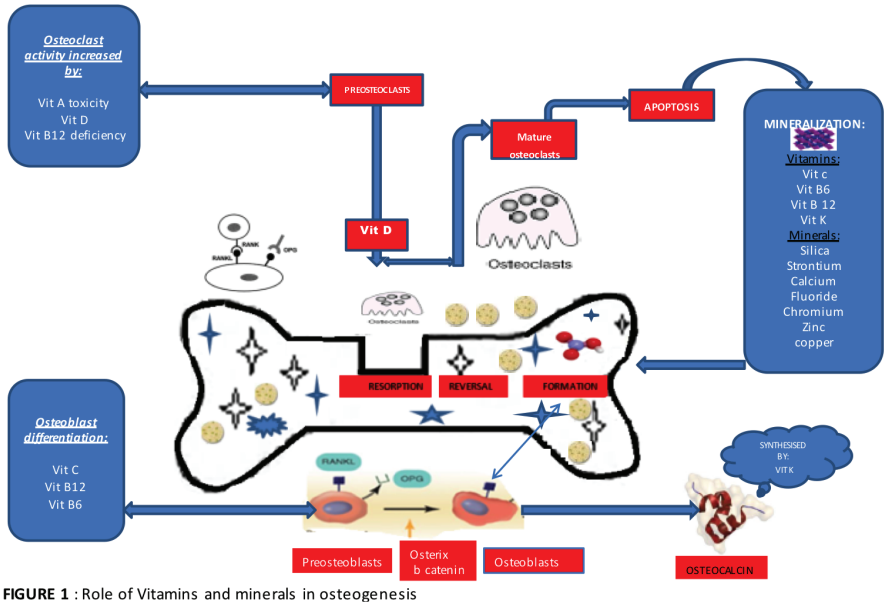

FIGURE 1 : Role of Vitamins and minerals in osteogenesis

Vitamin C (Ascorbic acid):

Ascorbic acid, a water-soluble vitamin, is well known for its antioxidant activity, scavenging reactive oxygen species (ROS) and reactive nitrogen species (RNS). In the development of bone and cartilage, Ascorbic acid, plays a major role, being an important cofactor for prolyl lysyl hydroxylase.[25-27] It is required for the differentiation of mesenchymal-derived cell types, including adipocytes[28], osteoblasts[29-32] myoblasts[33,34], and chondrocytes[35,36]. It prevents the loss of osteoblast differentiation markers (Osterix, osteocalcin, Runx2, BMP-2) and attenuates bone loss; as well as stimulates bone formation[37].The growth factor effect is regulated through stimulation of collagen matrix by Vitamin C38 which is vital for the differentiation of osteoblasts for expression of osterix[39].

The deficiency of vitamin C can compromise the proliferation of chondrocytes at the growth plate, the synthesis of matrix and can reduce osteoblasts [39,40].

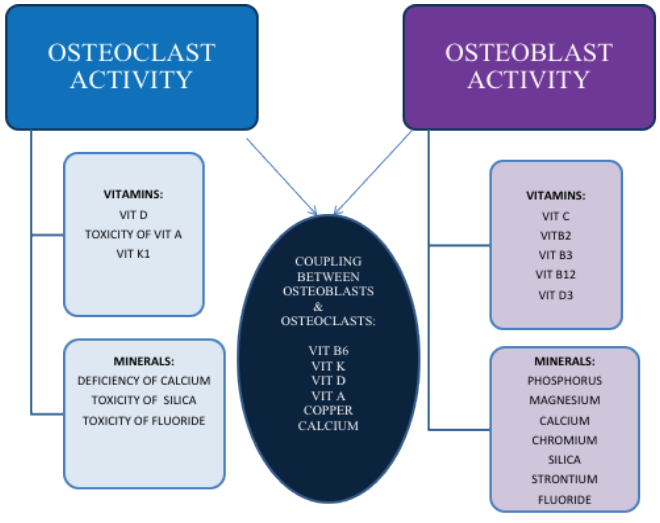

Figure 2: Vitamins & Minerals required in remodeling of bone

B VITAMINS:
The B vitamins function as cofactors for the enzymatic processes that are a part of energy-releasing pathways for carbohydrates, fats and proteins. Research reveals the importance of B vitamins in bone health with a focus on B6, B12 (cobalamin), B9 (folate) as cofactors for the enzymes required for DNA metabolism and the remethylation of homocysteine[41-44].

VITAMIN B3 (NIACIN):
Vitamin B3 (Niacin) is required in the form of two active coenzymes, nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP). The major role of NAD is concerning DNA processing, cell differentiation, and mobilizing calcium, providing substrates vital for all these processes[45]. The role of NAD in bone is through its action in calcium signaling. From the intracellular stores calcium is released under its influence of NAD and binding and opening to a class of calcium channels called ryanodine receptors which are present in membranes of organelles[46].

In addition to calcium signaling, NAD is a precursor of cyclic Adenosine diphosphate ribose[46].

VITAMIN B6 (PYRIDOXINE):
The role of B6 in the formation of bone is to provide a substrate for ALP (alkaline phosphatases)[47] to facilitate the coupling of bone cells, osteoclasts and osteoblasts with the help of G6PD (glucose 6-phosphate dehydrogenase)[48] hence B6 deficiency causes an increase in bone cavities, weakens bone, reduces trabecular number and thickness and decreases new bone formation[49].

VITAMIN B9 FOLATE:
Vitamin B9 folate is involved in the methylation of DNA, RNA, proteins and phospholipids providing methyl group in the nucleotide synthesis. Folic acid is also required in the metabolism of homocysteine hence, deficiency leads to increased serum levels of homocysteine resulting in hyperhomocysteinemia[47] which may promote inflammatory processes via oxidative stress[50]. Also the accumulated amount of homocysteine[51] binds to the collagen and deposits in the bone which activates osteoclastic processes decreasing bone strength and compromising osteoblastic activity[52]. Overall altering the biochemical and anatomical characteristics of bone.

VITAMIN B12 COBALAMIN:
Cyanocobalamin (B12) is linked to the action of two enzymes, l-methylmalonyl-coenzyme A (CoA) mutase and methiononine synthase[53].

B12 is directly involved in proliferation of osteoblasts and activity of alkaline phosphatase[54]. The homocysteine to methionine metabolism described above involves methionine synthase which is a Vitamin B12 dependent enzyme. Thus to prevent osteoporosis and ensure proper bone health supplementation of B12 in addition to Folic acid is crucial.[51]

VITAMIN K:
Vitamin K is essential for bone strength and it regulates bone remodeling. During the process of mineralization in bone formation synthesis of osteocalcin is Vitamin K dependent. It is hypotheses that vitamin K introduces calcium binding sites during mineralsation on the matrix vesicle. Matrix vesicle (MVs) is different from the plasma membrane possessing a distinctive composition of lipid and protein which helps in the facilitation of initialization of process of mineralization at the matrix front hence, calcium crystallizes here and bone structure is laid on. The function of vitamin K is to carboxylate Glutamate residues, introducing calcium binding sites during the posttranslational modification. Vitamin K along calcium and vitamin D increases bone health. Since, bioavailablity of vitamin K is better hence; its affects are long lasting, imparting greater bone strength[55].

VITAMIN A:
Most of the biological actions of vitamin A are controlled by all-trans-retinoic-acid. The bone resorptive effect is dependent on osteoclastogeneic cytokine RANKL[56]. Vitamin A increases mRNA and consequently expression of RANKL protein. The function of vitamin A is to bind to

osteoprotegrin (OPG), inhibiter of RANKL and consequently increase the expression of RANK/RANKL interaction between osteoblastic and osteoclastic cells. Toxicity of vitamin A may lead to an increase in osteoclastic activity resulting in bone fragility.

ROLE OF MINERALS:
PHOSPHORUS:
Phosphorus regulates proteins and produces energy by phosphorylation. In bones phosphorus is present in the form of Hydroxyapetite in combination with calcium and hydroxyl ions, forming a crystalline structure imparting strength to the skeleton. In order to build and maintain a strong bony structure Ca/P ratio between 1.67 and 1.5 is required. In case of calcium deficiency the hydroxyapatite has a structure solely occupied by phosphate or hydrogen phosphate, HPO_4^{2-}, anions and this can result in toxicity.[55]

MAGNESIUM:
Magnesium is required for the strength and firmness of bones. Magnesium stimulates the production of calcitonin from the thyroid gland which helps to regulate levels of calcium and phosphate in bones and blood. It is required to convert vitamin D into its active form. Magnesium deficiency can result in resistance of vitamin D.[57] Alkaline phosphatases require magnesium for the formation of calcium crystals, hence low levels of magnesium will form abnormally shaped crystals. Bones act as a reservoir of magnesium. Calcium and magnesium work synergistically, so deficiency of even one of them will affect the metabolism of the other. If one is taking calcium but is deficient on magnesium then it will result in deposition of calcium in soft tissues.[58]

SILICA:
Silica supplements tend to increase bone collagen by cross linking collagen strands, hence, strengthening connective tissue matrix. It has a direct affect on the rate of mineralization, especially when the levels of calcium are decreased in the body. Silica traces are seen at active sites of bone mineralization. It binds with Calcium, and initiates the process of calcification to maintain strong flexible bones.[59]

ZINC:
Zinc is required to form a matrix of collagen proteins on which calcium phosphorus compound is laid which is required for mineralization of bone. Zinc is required to produce enzymes that help in diminishing and recycling residues of bone proteins. Zinc is present at bone repair sites, hence it helps in absorption of Calcium and bone healing[59].

COPPER:
Copper being a cofactor for many enzymes, such as Lysyl oxidase, by its activity in connective tissues, forms collagen and helps in giving mechanical strength to the bone The function of this enzyme is to introduce cross linking active sites in collagen and elastin during post translational modification by oxidation at some sites of the lysine and hydroxylysine amino acids[60].

POTASSIUM:
The protein rich foods on metabolism can lead to excessive production of endogenous acid which is mobilized by base from the skeleton and hence can be a contributor in decreasing in bone mass especially during the advancing age.

Potassium bicarbonate has been found at low dose can help in neutralizing the endogenous acid, improving the balance between calcium/phosphorus, reducing osteoclastic activity and hence increasing osteoblasticity.[61]

STRONTIUM:
Strontium has a high affinity for bone and is thought

to play a critical role in bone health. It tends to migrate to the sites where active remodeling is taking place and promotes mineralization of the bones and teeth. There are about 320 mg of strontium in the body, with 99% of this located in the bones and teeth. Strontium is capable of replacing a small proportion of calcium in the calcified crystals of bone and teeth. As it appears, strontium adds strength to these tissues, making them more resistant to breakdown. Strontium also appears to draw extra calcium into the bone.[62]

FLUORIDE:

A trace element which has an effect on bone mineral, bone cells and bone architecture. Fluoride is substituted with the hydroxyl group in hydroxyapatite, forming fluorapatite. Fluoride causes retardation of mineralization and the mineral produced is then less prone to dissolution altered[63-65]. Toxicity of fluoride can inhibit the synthesis of type I collagen and decreases the cross linking of collagen. It has an influence on the proteoglycan structure[66] and matrix metallo-proteinases[67].

By researches it has been proved that an increase in the formation of fluoroapatite weakened the protein-hydroxyapatite interfaces

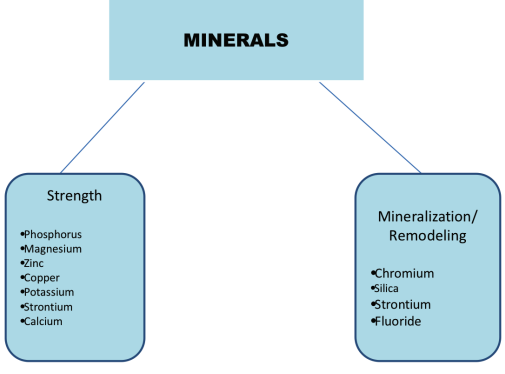

Figure 3: Classification of Minerals according to their role in bone formation.

CONCLUSION

The major contributors of bone remodelling are vitamins and minerals discussed above. These predominantly help in the formation of collagen matrix on which bone is laid. Lack of awareness in Pakistan is a leading cause of Osteoporosis and other acquired and congenital bone diseases. Poor nutrition, sedentary lifestyles, low socioeconomic status together has an effect on bone health. The International Osteoporosis Foundation, in its Asia-Pacific Audit, now warns that by 2050, 87.2m people will be over 50 years of age, and vulnerable to osteoporosis.

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