NUTRACEUTICALS FOR THE MANAGEMENT OF OSTEOPOROSIS: A REVIEW

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Abstract:

The healthy and long-term operation of several vital skeletal processes depends on bones. Vital organs like brain and bone marrow are shielded by them in addition to providing support and attachment points for muscles. In addition, bones store important minerals like phosphate and calcium and act as metabolic organs. In their lives, these tissues rebuild themselves repeatedly and hold 99 % of the calcium ions in the body. Sustaining appropriate nutritional status is crucial for maintaining optimal skeletal health. The key to maintain the maximum peak bone mass and reducing bone loss in the elderly is eating a balanced diet that meets daily calorie needs and includes necessary amounts of calcium and vitamin D. In addition to these essential nutrients, the total nutritional content of food, which includes macro and micronutrients, also affects bone health. With the exception of calcium and vitamin D, it is crucial to emphasize that there is no arbitrary relationship between various nutrients and the prevention and treatment of osteoporosis. These two elements are more likely to be absent in cases of fragile fractures. When evaluating the effects of calcium and vitamin D on osteoporotic bone quality, it is also necessary to account for additional dietary components that affect bone metabolism, such as phosphorus, magnesium, boron, manganese, zinc, and vitamins A, B, C, E, and K.

Key Words: Nutraceuticals, Bone, Minerals, Trace Elements, Vitamins.

INTRODUCTION

Bones are integral to the well-organized and lifelong functioning of various essential skeletal processes. They serve not only to support and provide attachment sites for muscles but also act as protective shields for vital organs such as the brain and bone marrow. Additionally, bones function as metabolic organs, storing crucial minerals like calcium and phosphate. These tissues constantly undergo rebuilding throughout life, serving as reservoirs for 99% of the body's calcium ions.

Composed of an organic phase featuring collagen and mucopolysaccharides for flexibility, and an inorganic mineral phase with hydroxyapatite (crystalline calcium phosphate) providing rigidity, bones also house numerous cells crucial for development and maintenance. The process of bone modeling initiates during fetal stages, reaching its peak during puberty. Subsequently, remodeling takes place to sustain optimal mineral levels in the body. Osteoclasts and osteoblasts, pivotal bone cells, play distinct roles in this remodeling process, with osteoclasts releasing minerals from bone tissue and osteoblasts replacing and mineralizing them (Appleton & Lockwood, 2006).

In essence, bones represent dynamic tissues that continually remodel to meet the body's demands. Nevertheless, any disruption in this dynamic process can lead to various bone-related issues.

Bone weakness and a higher risk of fractures are caused by osteoporosis, a crippling medical condition marked by a decrease in bone density and a breakdown of bone structure. Low bone mass factors can be broadly classified into two categories: factors that are unchangeable (genetics, age, ethnic background, height, weight, race, and age) and factors that are modifiable (hormone status, factors related to lifestyle like eating habits, drinking, and smoking trends, and regular exercise levels) (Feng & McDonald, 2011). While there are several drug classes available to treat osteoporosis, they frequently have serious side effects that include atrial fibrillation, delayed fracture healing, atypical subtrochanteric fractures, severe leg cramps, and gastrointestinal problems (nausea, vomiting, constipation, etc.). The goal of this review is to provide an overview of various nutraceutical classes that can help with osteoporosis management and overall bone health.

CLASSIFICATION

When the following factors affecting the metabolism of bone are taken into account, two main groups of osteoporosis can be identified: -

Primary osteoporosis

It can also be divided into two subgroups:

Involutional Osteoporosis Type I (Postmenopausal Osteoporosis)

Postmenopausal osteoporosis, resulting from estrogen deficiency, primarily impacts trabecular bone. Consequently, women exhibit a higher susceptibility to osteoporosis compared to men, as indicated by a ratio of 4 to 5.7.

Involutional Osteoporosis Type II (Senile Osteoporosis)

It is alternatively referred to as senile osteoporosis, associated with the decline in bone mass resulting from the aging of cortical and trabecular bones.

Secondary osteoporosis:

Secondary osteoporosis can be brought on by a variety of illnesses, drugs, and lifestyle modifications (Tümay Sözen *et al.,* 2017)

MAJOR CAUSES OF OSTEOPOROSIS

Age

One common cause of bone loss associated with age is the build-up of bone, the bone marrow fat rather than osteoblastogenesis. Mesenchymal stem cells differentiate into adipocytes instead of osteoblasts. The bone marrow must contain sufficient blood and oxygen, as well as development factors and transcription variables unique to the mesenchymal lineage, for mesenchymal stem cells to be able to differentiate into osteoblasts. Ageing modifies these favourable conditions for mesenchymal stem cell differentiation into osteoblasts and adipocytes. The nucleus lamina and matrix contain intermediate filament proteins called lamins, which are essential for regulating the growth of mesenchymal stem cells. Furthermore, normal osteoblasts exhibit a significant reduction in lamin functionality as they age (Oddom Demontiero *et al.,* 2012).

Genetic factors

Numerous genetic polymorphisms associated with osteoporosis and bone mineral density (BMD) have been successfully identified through genetic investigations. It has been determined how the vitamin D receptor gene affects BMD in individuals. One of the important genes is COLIA 1, which codes for the type I collagen alpha1 chain, an essential protein for bone structure and a prominent contender in the aetiology of osteoporosis. Furthermore, the ESR1 gene-transcribed oestrogen receptor alpha is a key player in controlling bone mass. Recessive osteoporosis may be

exacerbated by inactivating mutations in the TCIRG1 gene, which codes for the ATP6i subunit of the osteoclast-specific pump. Further genetic research has investigated the relationship between osteoporosis and the SOST gene, which produces sclerostin, and the CLCN7 gene, which encodes chloride channels that are highly expressed in osteoclasts (Stuart H. Ralston, 2007).

Insufficient levels of vitamin D

Serum vitamin D deficiency causes parathyroid hormone (PTH) to be released, which speeds up bone resorption. But this change is not associated with a concomitant enhancement of bone formation, leading to a rise in bone resorption. PTH increases the synthesis of the protein known to bind growth factor (IGF-B), which is in charge of reducing the effect of IGF on bone cells. Because IGF is an essential growth regulator for osteoblasts, low serum vitamin D causes elevated PTH levels to suppress IGF activity (A. Deplas, 2004). Twenty percent of patients with hip fractures who had 119 bone biopsies showed signs of high bone turnover, and eighty percent of them had a serum level of 25-Hydroxyvitamin D3, a metabolite of vitamin D, below 25 nmol/L (Paul Lips, 2001).

Hormones

Estrogen plays a crucial role in maintaining bone health by interacting with high-affinity estrogen receptors in osteoclasts and osteoblasts, thereby regulating bone turnover. The onset of menopause in females is associated with a general rise in bone turnover, suggesting a diminished regulatory effect. After studying 653 French women, Garnero et al., came to the conclusion that menopause increased bone resorption overall. Moreover, low oestrogen also increases the PTH sensitivity and speeds up the rate of resorption. Additionally, estrogen deficiency heightens responsiveness to PTH, leading to an increased rate of bone resorption (Riggs *et al.,* 1998).

NUTRACEUTICALS

About 2500 years ago, the well-known Greek physician Hippocrates said, “Let food be thy medicine and medicine be thy food”. Nutraceuticals, dietary supplements, and functional foods are now the terms used to describe these. Stephen DeFelice, the chairman of the Foundation for Innovation in Medicine in New Jersey, USA, coined the term "Nutraceuticals" in the beginning.

"Nutraceutical" is a combination of the terms "pharmaceutical," which refers to a medicinal drug, and "nutrient," which refers to a nourishing food. In certain situations, nutraceuticals can have both therapeutic effects for illness and preventive benefits. They are used to promote wellness, prevent, and control symptoms, and are typically non-specific in nature (Wildman, 2016).

Minerals

Calcium

In the human body, calcium is the fifth most abundant element, after oxygen, carbon, hydrogen, and nitrogen. This divalent cation accounts for 1.9% of the mass of the organism. Teeth and bones are mechanically stiff because of the phosphate salt that comprises 99 percent of the body's calcium. Adolescence is a crucial time for getting adequate calcium intake because it affects bone mineral density (BMD) at its peak, which helps ward off osteoporosis (Matkovic, 1992). By protecting the neuromuscular system, which depends on calcium, parathyroid hormone-mediated bone breakdown can mobilise calcium from the bones to prevent osteoporosis, if the amount of calcium lost from extracellular fluid is higher than the amount swallowed through the stomach.

Throughout life, consuming enough calcium is essential to reach maximum peak bone mass and stop bone loss later on. Maintaining calcium balance is best achieved through food sources, as these also supply other vital nutrients. For those who don't get enough calcium from their diet, supplemental calcium may be an option. Exceeding the suggested daily intake of 1,200–1,000 mg, however, may have few disadvantages and may increase the risk of cardiovascular disease or kidney stones (Kränzlin, 2011). Calcium supplements include a variety of substances, including tricalcium phosphate, calcium acetate, calcium carbonate, calcium citrate, calcium citrate malate, calcium gluconate, calcium lactate, and calcium lactogluconate (Reid *et al.,* 2011). Particularly when taken with food, the calcium bioavailability from these formulations is generally comparable. The two most common types are the calcium carbonate and calcium citrate, with the former having the highest calcium content per serving. For those who are taking acid-blocking medication or are constipated, calcium citrate may be a better option. It is recommended that calcium supplements or diet be taken throughout the entire day, with a maximum of 500 mg at a meal, in order to maximise absorption (Burckhardt, 2011).

Numerous calcium supplementation products claim to offer benefits beyond those of standard calcium supplementation; however, the available data for these products is frequently either nonexistent or very sparse. Numerous calcium products also include other nutrients and vitamin D. There is no need to supplement the calcium supplement with other nutrients, even though there is a good reason to eat a product that also contains vitamin D (Guyatt *et al.,* 2002).

Healthy individuals do not gain any advantage from exceeding the recommended calcium intake. Consuming more calcium than advised is not beneficial; in fact, consistently high calcium intake could potentially be detrimental (Benjamin M P Tang *et al.,* 2007). Obtaining at least half of the required calcium from food is generally achievable for most people. In cases where individuals have a low dietary calcium intake, supplementation might be necessary, with a preference for promoting natural food sources of calcium. It's crucial to educate individuals that their required daily calcium intake, adjusted for the estimated daily calcium obtained from their diet, dictates the amount they should consider supplementing (Heike A. Bischoff-Ferrari *et al.,* 2005).

Adequate calcium intake to counteract obligatory losses is crucial for preventing a reduction in bone mass, a significant factor contributing to osteoporosis. It is especially important to ensure recommended calcium levels are met during the adolescent years (10-18), a period marked by rapid growth. Bones serve as the body's calcium reserve, playing dual roles in bone formation and resorption, which involves the transfer of minerals from the blood to the bone (Beth Bryles Phillips *et al.,* 2011).

During pregnancy, maintaining an optimal calcium intake is essential as fetal growth occurs from 10 weeks of gestation until the baby reaches full maturity. Calcium is a fundamental element for healthy bone formation, and the development of the fetus's bones relies on the mother's dietary calcium intake. Similarly, during lactation, women require increased calcium to support both their own bone health and the growth of the baby's bones (Reid *et al.,* 2008).

Optimal calcium intake remains crucial during the adolescent period as well, given that a person's height is significantly influenced by dietary calcium. Therefore, it is advisable to include calcium-rich foods such as milk and dairy products, millets like ragi, animal products, and green leafy vegetables in the diet.

Magnesium

Magnesium (Mg) is a common intracellular cation that is found throughout the human body. It is second in abundance to potassium. Adults contain 20–28 g of it, of which 39% are found in intracellular compartments, 60% are found in bones, and 1% or less are found in extracellular fluids. In varied amounts, almost every food contains magnesium. It is found in leafy vegetables at a concentration of 30–60 mg/100 g, where it forms the pyrrolic structure of chlorophyll. Greater amounts are found in legumes (80–170 mg/100 g), nuts (130–264 mg/100 g), and whole-grain foods (up to 550 mg/100 g in wheat bran). When grains are refined, more than 80% of the magnesium is removed (white bread contains only 15 mg/100 g). High amounts (80 mg/100 g in ready-to-drink form) are found in coffee. Lower magnesium contents (20–70 mg/100 g) are found in fruit that is dried, potato, and foods derived from animals (meat, fish, milk, and derivatives). The average concentration of magnesium in water, as reported on the labels of 150 bottled waters included in the INRAN-SCAI 2005–06 survey, ranges from 1 to 109 mg/L, depending on the source. Certain components of the diet affect the bioavailability of magnesium; the phytates calcium, phosphorus, and long-chain fatty acids reduce absorption, but the effect of oxalic acid is still unclear (Gabriella Peron *et al.,* 2021).

As a result, the advantages of taking magnesium may be outweighed by the effects of other nutrients. Cooking also reduces the bioavailability of food; on the other hand, when particular nutrients are present, such as protein, fructose, inulin, and fruit- and galacto-oligosaccharides, bioavailability increases. Particularly if it comes to bone health, magnesium is crucial.

A magnesium deficiency may have direct effects on bone health (by lowering osteoclasts, increasing osteoblasts, and reducing bone stiffness) as well as indirect effects (by interfering with PTH and vitamin D, promoting inflammation and oxidative stress, and ultimately resulting in bone loss). As a cofactor involved in the synthesis and stimulation of vitamin D, magnesium is essential for maintaining the body's homeostasis. This reciprocal relationship between the two nutrients improves intestinal absorption of magnesium (Jeanette A. M. Maier *et al.,* 2013)

Phosphorus:

Phosphorus serves a number of physiological purposes and is essential to human health. It forms a major portion of the phospholipid bilayer, the sugar-phosphate backbone of nucleic acids, and the hydroxyapatite found in bones and teeth ($Ca_{10}(PO_4)_6(OH)_2$), all of which contribute to the

structural makeup of cell membranes. Furthermore, phosphorus is essential for the metabolism of energy because it is a component of molecules like GDP, ATP, GTP, and ADP. It also supports intracellular cell signalling and the maintenance of the acid/base balance. Approximately 85% of the phosphorus in the body is found in bone mineral, and the remaining 15% is found in soft tissues, including 1% in extracellular fluid.

In children, phosphorus deficiency can cause stunted growth and rickets; in adults, it can cause osteomalacia. Nonetheless, because phosphorus is present in so many different foods and is easily absorbed by humans, dietary phosphorus deficiency is extremely uncommon in humans. Hypophosphatemia cases usually affect otherwise healthy people and are related to specific situations, such as malnutrition, refeeding syndrome, or inadequate parenteral nutrition. Most often, a kidney's reabsorption defect causes phosphorus deficiency. A number of genetic disorders that result in elevated levels of phosphaturic hormones such as PTH or fibroblast growth factor-23 (FGF23) or defects in the renal tubular sodium phosphate co-transporters, which are responsible for phosphate reabsorption, can cause various renal hypophosphatemias, which are characterised by low plasma phosphate and a decreased tubular maximum reabsorption rate of phosphate (TmP). Oral phosphate supplements are often used in the treatment of these conditions (Vorland et al., 2017).

The relationship between calcium and phosphorus levels is significant because these minerals share close connections in tissues (like hydroxyapatite) and hormone regulation, in addition to influencing each other's absorption in the GI tract. Elevated dietary phosphorus has been shown in animal studies to consistently have negative effects on bone-related outcomes; although less consistently, human data also suggests that high phosphorus intake has an independent effect on unfavourable bone-related outcomes. According to recent research, increased consumption of phosphorus from inorganic phosphate additives, which are absorbed quickly, has a negative impact on bone metabolism (Draper et al., 1972).

Fluoride

The presence of fluoride in bone can replace the hydroxyl groups in the hydroxyapatite crystal, resulting in the formation of less soluble fluoroapatite and increasing the size of the crystallisation. Although fluoridating water for drinking has long been used to prevent dental

caries, there are positive as well as negative impacts that fluoridation can have on bone health (Yiming Li *et al.,* 2001). Increased bone mineral density, or BMD, has been reported in populations exposed to 1 ppm fluoridated water, which lowers the overall risk of fracture. On the other hand, fracture risk increases with a fluoride concentration in water that is higher than 4.32 ppm. The rationale for using fluoride supplements in fracture prevention stems from the fact that elevated fluoride levels also stimulate osteoblast activity (Lehmann *et al.,* 1998). Research using high fluoride salt concentrations (>50 mg/d) have produced conflicting findings regarding the prevention of fractures. On the other hand, there seems to be an increase in BMD at the lumbar, femoral neck, and spine and a decrease in the risk of vertebral fracture at lower doses (11–20 mg/d). This implies that while moderate levels of fluoride in water and supplements may be beneficial for bone health, excessive amounts of fluoride can lead to the development of very large crystals, which makes bones fragile and brittle (Riggs *et al.,* 1990).

Zinc

Zinc is normally distributed by the body as follows: roughly 57% is found in muscle, 29% in bone, 6% in skin, 5% in liver, 1.5% in brain, and 0.1% in blood plasma (Janet C. King *et al.,* 2000). Because zinc is so important for the growth and development of the skeleton, a lot of research has been done to look at how zinc affects osteoblast activity (Kunio Ishikawa *et al.,* 2002; Ikuyo Tsukamoto *et al.,* 2011). Zinc has been consistently shown to promote osteoblast proliferation in animals as well as in primary and established cell models. Zinc has also been consistently shown to increase alkaline phosphatase (ALP) activity, both *in vivo* (In-Sook Kwun *et al.,* 2010) and *in vitro* (Dimai *et al.,* 1998) in organ cultures. Furthermore, a biphasic dose response has been observed in the impact of zinc on osteoblast proliferation, ALP activity, and other osteogenic processes. Zinc has a limited range of beneficial effects on osteoblast activity (1–50 μM); doses above this range inhibit osteogenic activity, while doses below it have no appreciable effect (Cerovic *et al.,* 2006).

Copper

To maintain the strength of connective tissues, support skeletal mineralization, and shape bone structure, copper is essential. Lysyl oxidase, an enzyme that contains copper, is essential for cross-linking collagen fibrils, which increases the mechanical toughness of proteins and aids in

the growth of strong, flexible connective tissue. Research conducted on animals suggests that a copper deficit may result in weakened bones. Furthermore, two years of copper supplementation was associated with a decrease in bone loss in postmenopausal and perimenopausal women in human studies (C.R.Paterson *et al.,* 1993).

The recommended copper levels were ascertained using a variety of indicators, including platelet copper concentration, serum ceruloplasmin activity, plasma copper concentration, and superoxide dismutase activity (Strause *et al.,* 1994). Depletion-repletion studies provide the basis for the recommended dietary allowance (RDA) for copper, which is 900 mg/day for adults and is set with the intention of preventing deficiency. However, greater consumption levels (2.5–3 mg/day) in pre-menopausal and post-menopausal women have been associated with increased bone mineral density and decreased bone loss.

Boron

Boron is not a necessary nutrient, there are no set recommended intakes for borate. It can be found in a wide range of foods, including dried goods, legumes, nuts, eggs, milk, wine, and vegetables (like potatoes and avocados). Despite this, a sizable portion of people routinely take in less than 1 mg of boron daily, and it is still unclear what the clinical implications of this low intake are. Although the daily requirement for boron is still unknown, most diets typically contain 1.5–3 mg of boron per day (Forrest H Nielsen, 2008). A lot of multivitamins and mineral supplements offer 3-9 mg. Rapid variations in urinary boron excretion with alterations in boron intake were noted in a small study, suggesting renal involvement in homeostatic regulation. Although some research indicates that taking 3 mg of boron daily may benefit bone, there are not enough controlled trials to draw that conclusion. In a postmenopausal woman's study, 3 mg/day of boron supplementation decreased the amount of calcium lost in the urine. On the other hand, high boron intakes could result in higher excretion of riboflavin B2. It is advised to think about getting boron from foods like fruits, vegetables, and legumes because they are known to provide benefits related to bone health (Barbara Sutherlan *et al.,* 1998).

Manganese

As a cofactor for several enzymes in bone tissue, manganese is essential for the biosynthesis of mucopolysaccharides during the creation of the bone matrix. Manganese-deficient animals show

alterations in growth, bone structure, and IGF metabolism. Over the course of two years, postmenopausal women who were supplemented with manganese in addition to calcium, copper, and zinc saw a larger increase in bone mass than those who only took calcium supplements (Michael S. Cleg *et al.,* 1998).

Potassium

Along with the other nutrients present in vegetables and fruit, consuming a high potassium diet helps to create an alkaline environment. Thus, less skeletal salt will be required to regulate the endogenous acid created by acid-forming food items like meats (Tucker *et al.,* 1999). Foods high in potassium may prevent osteoporosis by retaining calcium in the bones, which could otherwise be used to maintain a normal pH. Studies reveal a favourable association between potassium consumption and total bone mineral density (BMD) in women going through menopause, as well as with BMD in the forearm and hip in older adults (Lernann *et al.,* 1991). Furthermore, reductions in bone resorption, an increase in bone formation, an improvement in calcium balance, and a decrease in urinary calcium excretion have all been shown in clinical trials involving potassium bicarbonate supplementation. On the other hand, elevated bone resorption has been associated with low consumption of potassium (Jacob Lemann *et al.,* 1993).

Iron

Enzymes involved in the formation of the collagen bone matrix require iron as a cofactor. These enzymes, which include lysyl and prolyl hydroxylases, are essential to the processes that come before the copper-dependent enzyme lysyl oxidase catalyses crosslinking. Furthermore, iron functions as a cofactor for 25-hydroxycholcalciferol hydroxylase, an enzyme that is essential for converting vitamin D into its active form and affecting the absorption of calcium. Rats with adequate iron levels have larger bones and greater mechanical strength than animals lacking iron. While no statistically significant associations have been found between human iron status and bone health, a trend was noted in females' serum ferritin levels and bone mineral density (BMD) at the radius (Ilich-Ernst *et al.,* 1998). The purpose of the most recent revision to the Recommended Dietary Allowance (RDA) for iron is to prevent iron deficiency and ensure that people with varied diets have adequate stores of iron. There is currently no evidence connecting human bone health to a particular level of iron intake.

Selenium

Selenium, a trace element found in bones that influences bone metabolism, is less prevalent than boron, iron, zinc, and copper in bones. Skeletal muscles have the highest percentage of selenium in the body (27.5%), followed by bone (16%). Lack of selenium has been linked to osteoarthropathy in KBD patients and low bone mass in male rats. This is because selenium deficiency negatively impacts the biosynthesis of multiple antioxidant selenoproteins, which in turn affects bone metabolism (Regina Ebert & Franz Jakob, 2007).

Sufficient intake of selenium seems crucial for the proliferation and differentiation of osteoclasts and osteoblasts, primarily through the regulation of reactive oxygen species (ROS). Research indicates that extracellular signal-regulated kinases, ERK1/2, play a role in mediating the inhibitory impact of hydrogen peroxide on osteoblast differentiation. Treatment with selenium has demonstrated its ability to safeguard bone marrow stromal cells from the suppressive effects of hydrogen peroxide on osteoblastic differentiation by hindering oxidative stress and inhibiting ERK activation. Conversely, a decrease in selenoprotein expression correlated with elevated ROS levels, contributing to pathologically intensified signalling and heightened osteoclast activity (Moreno-Reyes *et al.,* 2001).

Silicon

Due to its ability to bind to glycosaminoglycans, silicon is essential for the formation of cross-links between proteoglycans and collagen. Although silicon is found in many different body tissues, bone and other connective tissues like skin, hair, arteries, and nails have the highest concentrations of silicon. According to in-vitro studies, silicon stimulates osteoblast differentiation and type 1 collagen synthesis. Rat studies have demonstrated that biological levels of silicon improve calcium incorporation in bones relative to silicon-deficient rats, highlighting the critical role of silicon in the formation of bones (Reffitt *et al.,* 2003).

Between 20 and 50 mg of silicon are typically consumed daily by people in North America and Europe. In China and India, where grains, fruits, and vegetables make up a large amount of the diet, people consume more silicon daily—between 140 and 200 mg. Interestingly, in comparison to other parts of the world, these regions also show the lowest rate of hip fractures. Diets higher

than 40 mg/day of silicon have been positively associated with higher femoral bone mineral density than diets lower than 14 mg/day (Charles T. Price *et al.,* 2013).

Strontium

The interactions of strontium with bone tissue are dependent on biological processes involving calcium because of the close physical and chemical similarities between strontium and calcium. Plasma, extracellular fluids, soft tissues, and the skeleton all contain accumulations of both elements (Marie *et al.,* 2001). Strontium's rate of incorporation into bone is almost the same as calcium's. Nonetheless, the results of studies in which postmenopausal osteoporosis patients received strontium ranelate point to a variable distribution of this element in bone tissue. Compared to cortical bone, trabecular bone has a higher concentration of strontium, which may be explained by a higher surface area-to-volume ratio or a faster rate of trabecular remodelling (D. Marx, *et al.,* 2020).

Strontium affects bone tissue in two ways. First off, it promotes the growth and differentiation of osteoblasts, which in turn promotes the production of new bone tissue. Higher expression levels of osteogenic genes, including Runx, ALP, BSP, and BGP, are indicative of this. Additionally, strontium increases osteoblast survival by promoting the formation of bone matrix proteins within osteoblasts and inhibiting apoptosis (Zuzana Saidak & Pierre J. Marie, 2012). On the other hand, strontium promotes apoptosis and inhibits osteoclast development and differentiation, which ultimately results in a decrease in bone resorption.

Vitamins

Vitamin A

Provitamin A (beta-carotene) and retinol are the two main categories of fat-soluble dietary compounds that are included under the umbrella term "Vitamin A." It is important for maintaining immune system integrity, growth, reproduction, and eye health. It has been known since the early 1940s that a vitamin A deficiency has a significant impact on bone health and can result in many abnormalities (Edward Mellanby, 1941). Vitamin A deficiency in growing animals was shown by Mellanby's research to disrupt both osteoclastic and osteoblastic activity. This resulted in irregular growth of the spine and basioccipital bone, as well as severe

neurological complications. Remarkably, more research showed that these vitamin A deficiency-related alterations in bone are reversible (Edward Mellanby, 1947). When the animals received vitamin A, their osteoclasts and osteoblasts were reactivated. This allowed the excess bone that had accumulated or not been absorbed during the deficiency period to be removed, restoring normal bone structure.

Moreover, a high dietary vitamin A intake was negatively correlated with bone mineral density (BMD) in the hip, spine, and entire body. This effect remained even after controlling for factors like body mass index, energy intake, degree of physical activity, smoking status, and oestrogen use (Hakan Melhus *et al.,* 1998).

B Vitamins

The B vitamins, thiamin, riboflavin, and niacin, have roles in energy metabolism that indirectly affect bone metabolism, even though they may not have a direct impact on it. Niacin has demonstrated a positive correlation with BMD at the calcaneus in premenopausal women, and riboflavin has been associated with bone health in Japanese women. In addition, hip fracture patients consumed substantially less thiamin than age-matched controls (Satoshi Sasaki & Ryoko Yanagibori, 2001).

The enzyme ornithine decarboxylase, which is critical for osteoblast NADPH concentrations, requires vitamin B6 as a cofactor. Vitamin B6 may have an effect on how vitamin K affects bone metabolism because of NADPH's role in the vitamin K cycle. Vitamin B6 deficiency may impair bone mechanical performance, according to animal studies. In humans, vitamin B6 intake was significantly lower in those with hip fractures than in those without fractures (M. Lumbers *et al.,* 2001).

As a coenzyme, folic acid helps transfer one-carbon units in several processes essential to the metabolism of amino acids and nucleic acids. A significant correlation was found between changes in radial bone mineral content (BMC) and folate in a 4-year clinical trial of postmenopausal women (Freudenheim *et al.,* 1986).

It is a cofactor for proteins related to osteoblasts, such as osteocalcin and bone alkaline phosphatase, vitamin B12 is essential for maintaining osteoblast function. Furthermore, vitamin

B12 plays a crucial role in iron metabolism, which is linked to the development of bones. Studies conducted in-vitro suggests that osteoblast activity is reduced by a vitamin B12 deficiency. Studies show that people with insignificant or deficient vitamin B12 status have a greater risk of osteoporosis than people with normal levels (Dhonukshe-Rutten *et al.,* 2003).

To avoid deficiencies, thiamin, riboflavin, and niacin have recommended dietary allowances (RDAs). Regarding vitamin B6, the main goal is to keep the concentration of plasma pyridoxal phosphate at a sufficient level. The most recent recommended daily allowance (RDA) for folate is determined by measuring the amount of folate present in red blood cells at various levels of folate intake, which is correlated with liver folate stores. The RDA for Vitamin B12 seeks to maintain serum B12 levels and haematological status (Tucker *et al.,* 2005). There is, however, insufficient data to determine whether the suggested dosages of these B vitamins are suitable for achieving the best possible bone health.

Vitamin C

The vital vitamin ascorbic acid, which the body is unable to produce, is essential for the hydroxylation of proline and lysine. The formation of stable collagen triple helixes, which in turn supports healthy bone growth, depends on this process (Wolf *et al.,* 2005).

BMD in the hip and spine was found to positively correlate with vitamin C intake in the Postmenopausal Estrogen/Progestin Interventions Trial. The amount of calcium consumed through diet had an impact on this association's strength, but it was unaffected by the consumption of other nutrients. Not all studies came to the same conclusion, despite certain ones confirming the association between BMD and dietary vitamin C intake (K. Michaelsson *et al.,* 1995).

Vitamin C intake and BMD did not appear to be significantly correlated in the Women's Health Initiative Study. However, higher vitamin C intakes were associated with a more pronounced positive effect of hormone treatment on BMD at different skeletal sites (S. L. Hall & G. A. Greendale, 1998). The Framingham Osteoporosis Study found a correlation between male nonsmokers' vitamin C intake and femoral neck bone mineral density. It's interesting to note that, in contrast to the results of the after menopause Estrogen/Progestin Interventions Trial, the

relationship was significant only for men who consumed low amounts of calcium—not for those who consumed large amounts (Sahni *et al.,* 2008).

Both dietary and supplemental vitamin C intake were associated with less BMD loss in the radial shaft, hip, and spine over a 4-year follow-up period. This correlation was more pronounced in men who consumed low amounts of calcium and vitamin E, and it was more significant in those who got their vitamin C from food rather than supplements

Vitamin D

Calciferol, another name for vitamin D, is a fat-soluble vitamin that is produced in the skin when exposed to sunlight. It can be consumed naturally or as supplements (ergocalciferol, or vitamin D2) in either form (Dennehy & Tsourounis, 2010). The two hydroxylation reactions that these different forms of vitamin D go through in the liver and kidneys result in 1,25 dihydroxyvitamin D (1,25(OH)2D), which is the biologically active form of calcitriol (Vaibhav Kumar Maurya & Manjeet Aggarwal, 2017). About 80–90% of vitamin D is produced by sun exposure through dermal synthesis (Ghishan & Kiela, 2017).

By controlling intestinal calcium absorption, bone and renal calcium resorption, and PTH synthesis, this vitamin affects bone health both directly and indirectly. It also contributes to skeletal mineralization and is essential for preserving the ideal levels of phosphorus and calcium in the blood (John A Sunyecz , 2008). Furthermore, taking supplements of vitamin D greatly increases muscle and bone strength, which lowers the risk of fractures and falls (Araceli Muñoz-Garach *et al.,* 2020).

Egg yolks, fatty seafood, cod liver oil, and breakfast cereals are foods high in vitamin D. By standard guidelines, to support antiosteoporotic treatment, the ideal amount of 1,25(OH)2D ought to be at least ≥20 ng/mL, and for those at higher fracture risk, ≥30 ng/mL (A. Capozzi, *et al.,* 2020). Even though eating a healthy diet is important, getting enough vitamin D from food alone can be difficult because there aren't many sources, which means supplements are frequently required (Theodore Troupis *et al.,* 2017).

Lack of vitamin D affects the body's immune system, inflammation, and muscle function, increasing the risk of autoimmune disorders and nonskeletal chronic diseases. Elderly people

who have low vitamin D levels are more likely to fracture their hips, and high vitamin A levels can lower vitamin D's bioavailability by 30% (Lorincz *et al.,* 2009).

Vitamin D deficiency is a common occurrence in obese people, suggesting a possible role for adipose tissue in lowering serum vitamin D levels. It's been proposed that fat-soluble vitamin D may be stored as body fat, which would lower its bioavailability in obese people (S. Migliaccio *et al.,* 2019). As a result, higher vitamin D dosages may be necessary for obese people to return their serum levels to normal. Vitamin D supplementation has been shown to be effective in treating obesity and its associated co-morbidities (Young Jin Tak & Sang Yeoup Lee, 2021).

Vitamin E

There are two forms of Vitamin E, a vital fat-soluble vitamin that is essential for its antioxidant properties: tocopherol and tocotrienol. Recently, tocotrienol has attracted more scientific attention because of its strong antioxidant properties (Kathleen M. Fairfield & Robert H. Fletcher, 2002). Numerous in-vitro and animal studies have demonstrated the critical role that oxidative stress—which is typified by an excess of free radical formation—plays in osteoblast and osteocyte apoptosis, osteoclastogenesis, and ultimately, bone resorption. Additionally, nuclear factor-kappa B, a regulator of osteoclast differentiation that affects bone resorption and remodelling, is activated by oxidative stress, which increases bone resorption (Kim *et al.,* 2006).

Research has shown that vitamin E inhibits the synthesis of collagen in a variety of rodent tissues. On the other hand, contradictory research indicates that vitamin E can increase the amount of hydroxyproline in the liver of rabbits and partially restore the synthesis of collagen in primary cultures of avian epiphyseal chondrocytes (Bruce A. Watkins *et al.,* 1996). Vitamin E injected intramuscularly protects chondrocyte membranes during maturation and differentiation in nursing lambs. It is suggested that vitamin E reduces the production of free radicals and lipid peroxidation, which prevents cartilage resorption and protects chondrocyte membranes (Maiorano *et al.,* 1999).

The relationship between vitamin E and increased bone mass as well as lower risk of fracture in humans seems to be mediated by smoking habits and is mainly due to the antioxidant qualities of vitamin E (Xu *et al.,* 1995).

Vitamin K

The enzyme γ-carboxylase, which is essential for the γ-carboxylation of glutamic acid residues in proteins, including osteocalcin, the main noncollagenous protein in bones, requires vitamin K as a cofactor (Szulc *et al.,* 1996). Higher levels of under carboxylated osteocalcin, a less functional form seen in patients with osteoporotic fractures, are caused by insufficient vitamin K.[100] Low vitamin K intake has been linked to decreased BMD or an increased risk of fractures, according to population studies (Booth *et al.,* 2003). On the other hand, vitamin K supplementation increases bone formation and decreases under carboxylated osteocalcin, urinary calcium excretion, and bone resorption (Feskanich *et al.,* 1999). Accurate estimation of vitamin K requirements is hampered by inadequate data and an incomplete understanding of physiological significance, despite the availability of multiple indicators for evaluating vitamin K status. Therefore, suggested intake levels (90 mcg/ day for women and 120 mcg/ day for men) are lower than levels linked to ideal vitamin K and bone health because they are based on data from healthy individuals (Braam *et al.,* 2003). According to recent reports, these effects are seen in women who consume vitamin K at the lowest quartile.

Proteins

Proteins are complex molecules that serve a variety of purposes in the body. Depending on the amount and source of protein consumed—high-protein versus low-protein diets, plant-based versus animal—bone health may benefit or suffer from protein intake (Robert P Heaney & Donald K Layman, 2008). Through several mechanisms, including (a) its significant contribution to the organic bone matrix, (b) its regulation of insulin-like growth factor 1 (IGF-1) levels, and (c) its potential influence on calcium metabolism, dietary protein has a significant impact on skeletal health. Furthermore, proteins are essential to bone composition, making up approximately 50% of bone volume and 30% of bone mass. Dietary protein intake has an impact on how the body metabolises bone (Robert P Heaney, 2002).

Often called "complete" proteins, animal-derived proteins can be found in meat, fish, poultry, eggs, and dairy products. These proteins have an adequate amount of essential amino acids. Variations in the composition of amino acids, such as reduced levels of lysine, cysteine, or methionine, may result in a less optimal nutritional profile for vegetable proteins derived from

sources such as legumes, tofu, soy, tempeh, seitan, nuts, and seeds (Philip J Atherton *et al.,* 2020). A variety of processes, including the partial support of osteoblast growth and differentiation through insulin secretion stimulation by alanine, lysine, arginine, leucine, and glutamine, are suggested by in-vitro studies as ways in which amino acids may affect bone health (A. D. Conigrave *et al.,* 2008). The production of nitric oxide (NO) and type I collagen synthesis are positively impacted by lysine and arginine, indicating potential applications in the prevention of osteoporosis (J. Yang *et al.,* 2010).

Bioactive peptides, which are particular protein fragments produced during gastrointestinal digestion by enzymatic proteolysis, have also drawn attention in recent decades. Through the modification of osteoblast functions and the activation of signalling pathways, these peptides have a direct impact on bone regulation (M. Fini *et al.,* 2001).

RDA FOR INDIANS:

Even among normal, healthy individuals, nutrient requirements can vary significantly (distributed) from person to person. Two characteristics of the requirements distribution are used to extract a single value for the requirement. The estimated average requirement (EAR) is the median of this distribution; the RDA is 97.5% of the distribution. It is not advised to use the RDAs to calculate nutrient deficiencies or to plan menus for parties or individuals. EARs typically account for 80% or more of RDA. Furthermore, it is anticipated that the distribution of dietary intake and nutrient requirements will overlap in a healthy population. Additionally, when RDA is used as the reference, the population as a whole move above and beyond the requirements and a sizable portion may be at the Tolerable Upper Limit (TUL).

Table I: RDA for Indians

Age group	Category of work (kg)	Body weight	Protein (g/d)	Cholesterol (mg/d)	Ca (mg/d)	Mg (mg/d)	Iron (mg/d)	Zinc (mg/d)	Vit B1 (mg/d)	Vit B2 (mg/d)	Vit B3 (mg/d)	Vit B6 (mg/d)	Vit B9 (µg/d)	Vit B12 (µg/d)	Vit C (mg/d)	Vit A (µg/d)	Vit D (IU/d)
Men	Sedentary	65	54	130	1000	385	19	17	1.4	2.0	14	1.9	300	2.5	80	1000	600
	Moderate								1.8	2.5	18	2.4					
	Heavy								2.	3.	23	3.1					

									3	2							
Women	Sedentary	55	45.7	130	1000	323	29	13.2	1.4	1.9	11	1.9	220	2.5	65	840	600
	Moderate								1.7	2.4	14	1.9					
	Heavy								2.2	3.1	18	2.4					
	Pregnant women	55 + 10	+9.5 (2nd trimester) + 22 (3rd trimester)	175	1000	385	40	14.5	2.0	2.7	2.5	2.3	570	0.25	15	900	600
	Lactation 0-6 months		16.9	200	1200	325	23	14	2.1	3.0	5	0.26	330	1	50	950	600
	Lactation 7-12 months		13.2							2.9		0.17					
Infants	0-6 months	5.8	8.1	55	300	30	-	-	0.2	0.4	2	0.1	25	1.2	20	350	400
	6-12 months	8.5	10.5	95	300	75	3	2.5	0.4	0.6	5	0.6	85	1.2	27	350	400
Children	1-3 Years	11.7	11.3	130	500	135	8	3.0	0.7	0.9	7	0.9	110	1.2	27	390	600
	4-6 Years	18.3	15.9	130	550	155	11	4.5	0.9	1.3	9	1.2	135	1.2	32	510	600
	7-9 Years	25.3	23.3	130	650	215	15	5.9	1.1	1.6	11	1.5	170	2.5	43	630	600
Boys	10-12 Years	34.9	31.8	130	850	270	16	8.5	1.5	2.1	15	2.0	220	2.5	54	770	600
Girls	10-12 years	36.4	32.8	130	850	255	28	8.5	1.4	1.9	14	1.9	225	2.5	52	790	600
Boys	13-15 years	50.5	44.9	130	1000	355	22	14.3	1.9	2.7	19	2.6	285	2.5	72	930	600
Girls	13-15 Years	49.6	43.2	130	1000	325	30	12.8	1.6	2.2	16	2.2	245	2.5	66	890	600
Boys	16-18 years	64.4	55.4	10	1050	405	26	17.6	2.2	3.1	22	3.0	340	2.5	82	1000	600
Girls	16-18 years	55.7	46.2	130	1050	335	32	14.2	1.7	2.7	17	2.3	270	2.5	68	860	600

Note: kg-kilogram, g/d- gram/day, mg/d-milligram/day, µg/d- microgram/day, IU/d-International Units/day, Ca- Calcium, Mg-Magnesium

Table II: **Recommended Intakes for Other Minerals and Trace Elements**

Minerals/Trace Elements	**Recommended Intake**
Phosphorous	1000mg/d
Sodium	2000mg/d
Potassium	3500mg/d

Copper	2mg/d
Manganese	4mg/d
Chromium	50µg/d
Selenium	40µg/d

Note: kg-kilogram, g/d- gram/day, mg/d-milligram/day, µg/d- microgram/day

Table III: Tolerable Upper Limit (TUL) for Nutrients

Age group	Category of work (kg)	Protein (PE ratio)	Ca (mg/d)	Mg (mg/d)	Iron (mg/d)	Zinc (mg/d)	Vit B3 (mg/d)	Vit B6 (mg/d)	Vit B9 (µg/d)	Vit C (mg/d)	Vit A (µg/d)	Vit D (IU/d)
Men	Sedentary	<40%	2500	350	45	40	35	100	1000	2000	3000	4000
	Moderate											
	Heavy											
Women	Sedentary	<40%	2500	350	45	40	35	100	1000	2000	3000	4000
	Moderate											
	Heavy											
	Pregnant women	<30%	2500	350	45	40	-	-	1000	2000	3000	4000
	Lactation 0-6 months	<40%	2500	350	45	40	-	-	1000	2000	3000	4000
	Lactation 7-12 months	<40%										
Infants	0-6 months	<15%	-	-	40	4	-	-	-	-	600	1000
	6-12 months	<15%	-	-	40	5	-	-	-	-	600	1500
Children	1-3 Years	<15%	1500	65	40	7	-	-	-	350	600	2500
	4-6 Years	<15%	2500	110	40	12	-	-	-	550	900	3000
	7-9 Years	<15%	2500	110	40	12	-	-	300	800	900	3000
Boys	10-12 Years	<15%	3000	350	40	23	-	-	600-800	1050	900	4000
Girls	10-12 years	<15%	3000	350	40	23	-	-	-	1300	1700	4000
Boys	13-15 years	<15%	3000	350	45	34	-	-	-	1550	2800	4000
Girls	13-15 Years	<15%	3000	350	45	34	-	-	-	1800	2800	4000
Boys	16-18 years	<15%	3000	350	45	34	-	-	-	1950	2800	4000
Girls	16-18 years	<15%	3000	350	45	34	-	-	-	2000	2800	4000

Note: kg-kilogram, g/d- gram/day, mg/d-milligram/day, µg/d- microgram/day, IU/d-International Units/day, Ca- Calcium, Mg-Magnesium.

The distribution shifts to the right with RDA as the mean (ICMR, 2020). The Indian Council of Medical Research (ICMR) committee recommendations for RDA, other minerals and TUL are given in the Table I, Table-II and Table III

CONCLUSION

Optimal skeletal health relies significantly on maintaining proper nutritional status. Attaining maximum peak bone mass and minimizing bone loss in the elderly hinges on adhering to a well-balanced diet that fulfils daily caloric requirements, incorporating essential daily doses of calcium and vitamin D. Beyond these crucial nutrients, the overall nutritional composition of food, encompassing both macro- and micronutrients, also plays a role in influencing bone health.

It is important to stress that there is no arbitrary relationship between different nutrients and the prevention and treatment of osteoporosis, except calcium and vitamin D. Frailty fractures are more likely to occur when these two components are lacking. It is necessary to take into account additional dietary elements that affect bone metabolism, such as phosphorus, magnesium, boron, manganese, zinc, and vitamins A, B, C, E, and K, when assessing the effects of calcium and vitamin D on osteoporotic bone quality. Even though there is potential for these nutrients to prevent and treat osteoporosis, more investigation and data are needed.

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