

## Osteoporosis, Its Pathophysiology and Effect of Nutraceuticals

Zeenat Ara<sup>1</sup>, Sandeep Pandey<sup>2</sup>, Shatakshi Pant<sup>3</sup>, Ramesh Mani Tripathi<sup>4</sup>,  
Devarshi Rastogi<sup>5</sup>, Shah Waliullah<sup>6</sup>

<sup>1,3,5</sup>Department of Orthopaedic Surgery, <sup>2,4</sup>Department of Biochemistry, King George's Medical University, Shahmina Road, Chowk, Lucknow, Uttar Pradesh, India, <sup>6</sup>Additional Professor, Department of Orthopaedic Surgery, King George's Medical University, Shahmina Road, Chowk, Lucknow, Uttar Pradesh, India.

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### Abstract

Osteoporosis a classical age related disease that effects women more in comparison to men. Albright and colleagues were first proposed the hypothesis that estrogen deficiency is related to osteoporosis. Its a condition related to bone fragility resulting from micro-architectural deterioration and decreased bone mass, Nowadays typical Western diet (high in protein, salt and refined, processed foods) combined with an increasing sedentary lifestyle mainly contribute to the increasing incidence of osteoporosis in the elderly. Mediterranean diet (MD), proved very beneficial in chronic diseases and fragility related fractures. Thus for management of osteoporosis proper lifestyle is plays major role. Healthy, well-balanced nutrition can play an important role in the prevention and pathogenesis of osteoporosis, and in support of pharmacological therapy. Calcium plays major role in proper bone health.

**Key Words:** Osteoporosis, Spinal cord Injury, BMD, Fragility, Taurine, RANKL and osteoprotegerin.

### Introduction

Osteoporosis, a systemic skeletal disease that is characterized by the loss of bone mineral density (BMD) and bone mechanical strength (BMS), it leads to fragility related fractures in the wrist, hip, and spine. Nowadays Osteoporosis is major public health problem associated with aging. Bone density and bone quality mainly defines the strength of bone. There is a clear correlation between each standard deviation (SD) decrease in bone mineral density and the risk of fracture. Nowadays osteoporosis is a common health issue, and after ischemic heart disease, dementia, and lung cancer (IOF 2021) it is the

fourth most burdensome chronic disease. Although, a higher prevalence of osteoporosis has been most common in postmenopausal women. According to the International Osteoporosis Foundation (IOF), one-third of females and one-fifth of males will suffer once in their lifetime from fragility related fractures<sup>[1]</sup>. Age, dietary habits, menopause, long-term glucocorticoid therapy, inherited osteoporosis (osteogenesis-imperfecta), etc are the common risk factors that are related in the progression of this disease<sup>[1]</sup>. Two common type of osteoporosis, on the basis of their known cause are primary osteoporosis most common in postmenopausal women, and secondary osteoporosis, with defined etiological mechanisms.

**Corresponding Author:** Shah Waliullah, Additional Professor, Department of Orthopaedic Surgery, King George's Medical University, Shahmina Road, Chowk, Lucknow, Uttar Pradesh, India.

**E-mail:** shahwali2008@gmail.com

**Contact No:** +91-9335716350

Primary osteoporosis is characterized into two types i.e. 1 and 2, Primary osteoporosis is also known as postmenopausal osteoporosis (Type 1), bone loss mostly occurs due to estrogen deficiency, Type 2 or senile osteoporosis results from systemic senescence<sup>[2]</sup> Nowadays currently employed therapies for the treatment of osteoporosis is bisphosphonates, denosumab (anti-RANKL monoclonal antibody), teriparatide (parathyroid hormone-PTH), and vitamin D supplementation exhibit the ability to modulate immune mediators. In case of postmenopausal women, there is an imbalance between RANKL and osteoprotegerin (increased RANKL and reduced osteoprotegerin), due to estrogen deficiency that leads to net bone loss, this similar imbalance occurs in rheumatoid arthritis, myeloma bone disease, and osteolytic metastatic bone disease; and subjects suffering from prostate cancer who are receiving androgen deprivation therapy, subjects of breast cancer who are on aromatase inhibitors therapy have also imbalance between RANKL and osteoprotegerin levels and are also osteoporotic. RANKL is targeted by Denosumab a fully human monoclonal antibody<sup>[3]</sup>. By binding to RANKL, this drug prevents the maturation and differentiation of preosteoclasts and promotes apoptosis of osteoclasts, thus it almost suppress bone resorption process. In one of the pivotal phase 3 clinical trial Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months (FREEDOM) in postmenopausal women with osteoporosis showed that denosumab administration is effective and prevented vertebral, non-vertebral, and hip fractures<sup>[4]</sup>. There was a close relationship between femoral neck BMD change and fracture risk reduction<sup>[5]</sup>, Denosumab had showed long term continuous effect atleast upto 10 years in preventing vertebral and non-vertebral fracture, and improving lumbar and proximal femoral BMD<sup>[6]</sup>. Elevation in BMD of 1/3 radius consisting of mainly cortical bone almost in a linear fashion due to denosumab, but this continuous increment in radial BMD was not seen in subjects who are receiving oral bisphosphonates<sup>[7]</sup>. These findings reveal that in comparison to bisphosphonates, denosumab has potent effects on both trabecular & cortical bones. Denosumab possess Anti-fracture effect on its long term use different from those of bisphosphonates.

After denosumab treatment, At sites of bone with microcracks or deteriorated strength RANKL expression by osteoblasts and osteocytes is expected to increase, so after 4 to 6 months, there is possibility of bone remodelling especially where RANKL expression is high. But it needs more future research. As RANKL-induced bone resorption is inhibited by denosumab so patients should be supplemented with enough vitamin D or calcium or both, otherwise there will be a chance of hypocalcemia, especially during the first week after administration. The adverse effect of Denosumab is that it is associated with an increased risk of atypical femoral fracture; and osteonecrosis of the jaw. After discontinuation of Denosumab treatment with other anti-resorptive drugs is must as after discontinuation, of this drug there is a rapid increase in bone turnover resulting in a rapid loss of bone and a possible increase in fractures<sup>[8]</sup>

### Consideration of targets in osteoporosis

The WHO criteria for determining Osteoporosis is as follows: T score must be  $-2.5$  or below, standard deviations (SD) as assessed by dual-energy X-ray absorptiometry (DXA), Excess mortality rate (8 to 36%), within 1 year because of hip fracture is more common in men than women<sup>[9]</sup> additionally, hip fractures are followed by a 2.5-fold increased risk of future fractures<sup>[10]</sup> Almost long-term nursing home care, is required in case of 20% of hip fracture patients, but only 40% fully regain their pre-fracture level of independence, Initially majority of vertebral fractures are clinically silent, oftenly these fractures are mostly associated with symptoms such as pain, disability, deformity, and mortality<sup>[11]</sup>

According to the UK National Institute for Health and Care Excellence (NICE), all women aged 65 and above, all men aged 75 and above, and younger patients with risk factors should receive osteoporosis risk assessment. BMD (Bone Mineral Density), is the gold standard investigation method of Osteoporosis.

Due to aging population Osteoporosis has rapidly increased in Taiwan including the rest of Asia, Asians and Caucasians are the two races that are considered at high risk for osteoporosis. In Taiwan the epidemiology of osteoporosis might be different from that of the Western world or the other parts of Asia due to rapid aging. Incidence of

Osteoporotic fractures have geographic variations due to racial differences in skeletal size. With growing age incidence of osteoporosis and fracture associated with it also increases<sup>[12]</sup>, The hip is the most common fracture site in both sexes in old age.

The T-score: T score is calculated by subtracting the bone mass value (BMD) of the subject from the reference value of normal subject of 30 years of age (YN), at this age bone mass is at maximum and the risk of fractures at maximum. The obtained value is divided by the standard deviation (SD).

**T-score = (BMD - YN) / SD**

**Intranasal Calcitonin in osteoporosis:** Calcitonin a naturally occurring peptide hormone which decrease the activity of specific receptors present on osteoclasts and suppress their activity, thereby reducing bone loss. Salmon calcitonin is the most popular product of recombinant & synthetic variants of calcitonin that was introduced in the market. Because of its convenience of administration, it is mostly administered as an intranasal spray at a single daily spray providing 200 IU of the drug. Calcitonin therapy is used along with calcium and vitamin D supplementation<sup>[13]</sup>, In case of osteoporotic vertebral fractures, calcitonin treatment helps in diminishing body Pain and is usually reserved for patients with vertebral crush fractures and also for those patients who are not candidates for the other available osteoporosis treatments. Whereas there are few side effects of calcitonin like rhinitis, epistaxis and allergic reactions.

Estrogen deficiency promotes the number of osteoclasts cells whereas declines the number of osteoblast cells leading to an unbalanced activity of the basic multicellular unit in favour of bone resorption<sup>[14]</sup>, This concept is now well accepted that estrogen deficiency is involve indirectly in bone resorption via the release of bone-active cytokines. These osteoclastogenic cytokines are inflammatory cytokines, that describes the role of interactions of the immune system and bone tissue also in the pathophysiology of osteoporosis. Levels of Proinflammatory cytokines such as TNF, IL-1, IL-6, or IL-17 mostly elevated in the first ten years after menopause this finding strength there role in causing osteoporosis<sup>[15]</sup>. In osteoporosis T-cells are major source of proinflammatory cytokines.

In case of any inflammation, immune system cells such as T cells, B cells, macrophages or dendritic cells, become activated and began to produce inflammatory cytokines, that plays vital role or act as mediators in osteoimmunology<sup>[16]</sup>, Among these cells, T cells are major stimulators of osteoclastogenesis as they increase the production of bone absorbing cytokines such as TNF- $\alpha$  and RANKL; thus activated T cells are suggested to play major role in progression of osteoporosis<sup>[16]</sup>.

**Osteoporosis after spinal cord Injury:** After Injury in case of SCI bone loss begins Immediately and is mostly affected by age, immobilization, bed rest, and a lack of gravity environment<sup>[17]</sup>, Regions rich in cancellous and cortical bones have reduced bone mineral density nearly 4% and 2% per month respectively, One of the studies on 41 SCI subjects have shown that 25 subjects WHO's criteria for osteoporosis (61%), whereas eight subjects were osteopenic (19.5%) and normal values were recorded only in 8 subjects (19.5%)<sup>[17]</sup>

In SCI Subjects bone loss in the epiphysis part of bone is almost double that of diaphysis 50% & 60% loss in the epiphysis region of femur and tibia respectively, whereas 35% and 25%, respectively in the diaphysis region of both femur and tibia, this study also demonstrated that loss of bone in between both the compartments of trabecular and cortical bone occurs through different mechanism i.e. due to a decrease in trabecular, bone loss occurs in the epiphysis bone. Because of endocortical resorption, bone loss happens in the diaphysis. In contrast, cortical bone density is maintained in the diaphysis region of bone<sup>[17]</sup>, Another study with the help of p QCT have shown that in case of complete paraplegics with a high and low neurological level of injury (thoracic D4-D7) and low (thoracic D8-D12), bone loss in the trabecular bone at the tibia was 57.5% vs 51%, in high vs low paraplegics, respectively. Whereas cortical bone loss was 3.6% and 6.5%, respectively. This data indicates that during the first year of paralysis the most affected bone is trabecular bone in comparison to cortical bone<sup>[17]</sup>. In case of SCI physical activity is very compulsory because it helps in increasing bone mass, As due to muscular activity blood flow increases in bone, thus Bone vasculature is also increased, And

due to physical activity femoral blood flows almost doubles, due to exercise metabolic activity also changes in SCI Subjects thus blood flow in bones is enhanced and thus SCI-associated osteoporosis can be positively affected by physical activity via enhanced bone metabolism and regeneration.

### Role of Nutrition in Osteoporosis

Nutrition plays major role in prevention and treatment of Osteoporosis. Calcium & Vitamin D plays major role as studies have proved that higher calcium uptake at various stages are associated with higher BMD.<sup>[18]</sup> In postmenopausal women, who are consuming calcium and vitamin D have least chances of bone loss. decrease bone turnover and reduced chances of nonvertebral fractures<sup>[19]</sup>, Potassium plays major role in calcium homeostasis particularly in the urinary conservation and excretion of calcium. Therefore there is increase in urinary calcium loss if the subject is on low Potassium diets. Vegetables, fruits, legumes, and milk are richest source of Potassium and it tends to have alkaline ash characteristics. There have been some studies relating the Net Endogenous Acid Production (NEAP) to potassium intake and bone density<sup>[20]</sup>, Consumption of high salt diet increases loss of calcium through urine, Research has suggested that in postmenopausal women if they consume high salt diet then rate of bone resorption increases over a 4-week period, but consuming high potassium as potassium citrate changes this adverse event<sup>[20]</sup>, Consumption of fruits & vegetables rich in potassium was associated with higher baseline BMD and less bone loss<sup>[21]</sup>, One of the study by demonstrated the relationship between the serum Vitamin K1 level in postmenopausal osteoporotic women, women and BMD, in their study the enrolled 23 postmenopausal osteoporotic women, and in 15 postmenopausal healthy control women using ELISA, whereas Lumbar Spine BMD was assessed, and they observed that in postmenopausal osteoporotic women in comparison to normal healthy controls The mean serum vitamin k1 level was significantly lower (mean=0.794 vs 3.61 ng/ml,  $P < 0.0001$ ), and concentration of serum Vitamin K1 was positively correlated with BMD of Lumbar spine among postmenopausal osteoporotic women ( $R=0.533$ ,  $p = 0.009$ ), and in postmenopausal healthy control ( $R=0.563$ ,  $p = 0.02$ ). Thus their findings reveal

that Vitamin K1 may contribute in Bone Mineral density and thus it can be established as therapeutic diagnosing biomarker in post-menopausal osteoporosis.

Nutrient	Recommended dietary allowance	Median intake
Vitamin D	600-800 IU	150-300 IU
Calcium	1000-1200mg	735 mg
Magnesium	320-420mg	243 mg
Silicon	*40 mg for bone health	21 mg
Vitamin K	90-120ugm	70-80 umg
Boron	*3 mg for bone Health	1mg
Vitamin C	75-90 mg	103 mg
Copper	0.9 mg	1.1mg
Zinc	8-11mg	9.6 mg
Manganese	1.8-2.3 mg	2.8 mg

### Common Nutrients for Bone Health

**Taurine and osteoporosis:** Osteoporotic subjects possess lower serum taurine level in comparison to healthy subjects<sup>[22]</sup>, lower taurine level in urine is a marker of post-menopause and osteoporosis where taurine levels in urine were decreased 1.9 fold in post-menopausal women with osteoporosis compared to pre-menopausal women with normal BMD<sup>[23]</sup>, Taurine levels can be elevated by using drug bisphosphonates in osteoporotic subjects. One of the study on ovariectomized mice has shown that treatment with alendronate sodium, a bisphosphonate elevates taurine levels from  $467.6 \pm 116.0 \mu\text{M}$  to  $669.2 \pm 127.6 \mu\text{M}$ <sup>[24]</sup>, Supplements that can be used to treat osteoporosis.

Supplement	Rationale	Safety
Taurine	Involved in intracellular calcium homeostasis and assists with absorption of vitamin D and vitamin K	3000mg a day (Shao Aet al 2008)

Continue .....

Supplement	Rationale	Safety
Calcium	assists with bone formation	600 mg of calcium is taken from calcium carbonate twice a day. The National Osteoporosis Foundation holds adequate calcium intake is 1200 mg/day for women 51 and older (Cosman F et al 2014)
Vitamin D3	promotes absorption of calcium	2000 IUs of vitamin D3 would be taken a day. The Institute of Medicine (US) has set the Tolerable Upper Level Intake for vitamin D at 4000 IUs for adults. (Institute of Medicine (US) 2011)
Vitamin K MK-7	needed for bone to bind calcium	No toxicity has been observed with vitamin K MK-7 supplementation which is better absorbed than other kinds of vitamin K [88]. Approximately 2 mg of MK-7 would be taken a day. (Marles RJ et al 2017).

In the United state of America the recommended dose for Vitamin D supplementation is 400 IU for adults aged between 51 and 70 years & and for 70+ the recommended dose is 600 IU, whereas dose recommended by the Commission of the European Communities is 400 IU daily for people over 65 years<sup>[25]</sup>, 2000 IU/day is set as an acceptable upper limit for vitamin D intake, The “no observed adverse event level” is 10,000 IU daily and the “lowest observed adverse event level” is 40,000 IU/ day<sup>[26]</sup>. Vitamin D intoxication level is still unknown, but is likely to be considerably higher than the above mentioned doses. Whereas supplementation of high dose carries a risk of hypercalcaemia that impaired Kidney function. High calcium intake, hypercalcaemia, idiopathic hypercalciuria, sarcoidosis, overproduction of vitamin D metabolites, reduced vitamin D binding and hyper responsivity to vitamin D are some of the predisposing factors that express vitamin D intoxication<sup>[27]</sup>,

To, use vitamin D and calcium specifically in case of postmenopausal women is not compulsory or any major precaution, but it has been reported that if there is decrease in levels of 25(OH)D then there is increased chances of prevalence of albuminuria, which is a risk factor for progression of chronic kidney disease<sup>[28]</sup>, Another major cause of osteoporosis is Cigarette smoking, as we know Nicotine is the only chemical among the 4,700 chemicals found in the tar phase of cigarette smoke, various studies have proved the major role of Nicotine in causing osteoporosis as it is the only chemical that confirmed its deleterious effect on bone remodeling as it inhibits osteoblast activity and growth and promotes osteoclastic activity and it also induces oxidative stress as proved by many in vitro and in vivo animal studies<sup>[29]</sup>, and this chemical also activates NF- $\kappa$ B-signaling pathway thus indirectly involve in osteoclast differentiation, and it also elevates the proinflammatory cytokines IL-1 and IL-6 in animal model<sup>[29]</sup>, High dose of vitamin E a group of potent, lipid-soluble, chain-breaking antioxidants proved beneficial in suppressing nicotine-induced elevation of IL-1 and IL-6, (Tocotrienol), where astocopherol had no significant effects on both cytokines thus in both forms of vitamin E Tocotrienol proves to be more effective in comparison to tocopherol in terms of its action on bone resorbing cytokines thus Tocotrienol is more effective in reducing bone loss and inflammation<sup>[29]</sup>,

Zinc has anabolic effect on bone metabolism because bone act as a zinc sink, zinc is released during skeleton breakdown and it is reincorporated into the skeleton, the vertebral calcium/ zinc ratio is inversely related to age in case of human, it suggest that in comparison to calcium, zinc is more conserved in later life. Zinc is present in the mineral component of bone hydroxyapatite, it may be complex with fluoride; and both zinc and the zinc-fluoride complex may improve the crystallinity of apatite, In case of osteoporosis subjects, level of zinc is found lower in their skeleton. Zinc is a marker of bone resorption as studies have proved that in postmenopausal women, urinary zinc concentration is very high, since women with osteoporosis excrete over than 800 ug zinc/g creatinine in urine<sup>[30]</sup>, Trace mineral supplementation proves very beneficial in with or without calcium in postmenopausal women as it exerts its beneficial

impact on bone mineral density<sup>[30]</sup>, Both invitroin vivo studies have proved anabolic effect of zinc on bone metabolism as supplementation of zinc sulfate (5 and 10 mg Zn/kg body weight) for 3 days produced dose dependent increases in the contents of zinc, deoxyribonucleic acid (DNA), collagen and calcium, and the activity of alkaline phosphatase in the femoral diaphysis (cortical bone) of weanling rats<sup>[30]</sup>, one of the interesting study by Park HM<sup>[31]</sup>, showed that high dietary intake of calcium from plant source reduces the risk of osteoporosis and help in increasing bone mineral density in postmenopausal Korean women, thus it is concluded from their study that Vegetables might be a best source of calcium, vitamins and other minerals that exerts beneficial impact on bones. Another important nutraceuticals is curcumin as it prevents inflammation and oxidative stress, one of the controlled clinical trial by Hatefi M et al<sup>[32]</sup>, on 100 subjects with spinal cord injury in order to assess the effects of curcumin on biochemical markers of osteoporosis and BMD, he demonstrated that administration of curcumin significantly inhibited the bone loss in patients with spinal cord injury and improved densitometric parameters at the lumbar spine, neck of femur and hip bone. Studies have shown that Curcumin Treatment revealed positive effect on certain Serum bone markers such as bone Alkaline Phosphatase, serum osteocalcin, serum CTX and procollagen type I N propeptide (PINP) in chronic spinal cord injury patients.

### Conclusion

As we know nutritional supplementation is easy to administer and nutritional needs for optimizing bone health can be easily fulfilled by healthy diet with adequate calcium and vitamin D intakes through dairy or calcium fortified foods. Different minerals and vitamin has different properties like some acts as antioxidant, some acts as anti-inflammatory etc, the beneficial impact of various nutrients have been proved by many studies but most of them were done on animal model so it needs human trial to proves its efficacy.

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