

Review Article

Role of vitamin D in controlling Postmenopausal Osteoporosis

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Submitted: 09 February 2018

Accepted: 03 January 2019

Published: 04 January 2019

ISSN: 2333-6692

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OPEN ACCESS

Keywords

- Vitamin D
- Osteoporosis
- Brittleness
- Menopause
- Fracture

Abstract

Vitamin D plays an important role in bone growth and maintenance by enhancing intestinal absorption of calcium and influencing bone metabolism in women and improves biochemical markers for Osteoporosis. Vitamin D deficiency in adults can exacerbate osteopenia and osteoporosis, cause osteomalacia and muscle weakness, and increase the risk of fracture. Osteoporosis is a disorder having characteristic features of low bone mass and structural degeneration, promoting the development of brittleness of the bones and increasing the risk of fractures of the bones of pelvis, vertebral column and wrist. Osteoporosis is estimated to affect 200 million women worldwide - approximately one-tenth of women aged 60, one-fifth of women aged 70, two-fifths of women aged 80 and two-third of women aged 90. Since bone loss occurs without symptoms, osteoporosis is often considered a 'silent disease'. Menopausal is commonly defined by the state of the uterus and the absence of menstrual flow or "periods," but it can instead be more accurately defined as the permanent cessation of the primary functions of the ovaries. A drop in estrogens production after menopause results in increased bone reabsorption, leads to the risk of osteoporosis during menopause and decreased calcium absorption. Postmenopausal women have a higher risk of falling or fracture when they do not maintain serum 25-hydroxyvitamin D levels higher than 30 ng/mL.

INTRODUCTION

Elmer McCollum and Marguerite Davis in 1914 discovered a substance in cod liver oil, which later was called "Vitamin D". Vitamin D refers to a group of fat-soluble secosteroids responsible for enhancing intestinal absorption of calcium, iron, magnesium, phosphate and zinc. In humans, the most important compounds in this group are vitamin D₃ and Vitamin D₂. In adults, vitamin D deficiency is defined as a serum 25-hydroxyvitamin D level of less than 20 ng per mL (50 nmol per L), and insufficiency is defined as a serum 25-hydroxyvitamin D level of 20 to 30 ng per mL (50 to 75 nmol per L). The consequences of vitamin D deficiency are secondary hyperparathyroidism and bone loss, leading to osteoporosis and fractures, mineralization defects, which may lead to osteomalacia in the long term, and muscle weakness, causing falls and fractures [1,2]. Vitamin D rich dietary sources are limited and unaffordable to most Indians. Vitamin D supplements are available, but most Indians are not aware that they need additional vitamin D. additionally; the cost of these supplements is essentially prohibitive to the majority. Fortification of staple foods with vitamin D may prove to be a more viable solution towards attaining vitamin D sufficiency in India. Vitamin D deficiency is categorized into 4 groups on the basis of Serum 25-hydroxyvitamin D level [3].

1. **Severe vitamin D deficiency:** 25OHD <10 ng/ml.
2. **Moderate deficiency:** 25OHD 10-19 ng/ml
3. **Mild deficiency:** 25OHD 20-29 ng/ml

4. **Normal/optimal:** 30-80 ng/ml

VITAMIN D METABOLISM

Vitamin D can be synthesized in sufficient amounts by most vertebrates on adequate exposure of the skin to sunlight (UVB rays). It is critical that most vertebrates obtain a sufficient amount of vitamin D either from their diet or from adequate exposure of the skin to sunlight. The term "vitamin D" refers to compounds vitamin D₃ (cholecalciferol) or vitamin D₂ (ergocalciferol). Vitamin D₃ is produced in the skin on exposure to sunlight. Vitamin D₃ is derived from 7-dehydrocholesterol by ultraviolet irradiation of the skin. Vitamin D₃ is also found in animal food sources e.g., fatty fish (e.g., salmon, mackerel and tuna) cod liver oil, milk, etc. Vitamin D₂ is found in vegetal sources like sun-exposed yeast and mushrooms. Notably, most dietary sources are not sufficiently rich in their vitamin D content. Vitamin D (both forms D₃ or D₂) is a prohormone which requires two hydroxylations to finally attain its biologically active form-1,25(OH)₂D. The first hydroxylation occurs in the liver, at position C25 to form 25-hydroxyvitamin D, also known as 25(OH)D or calcidiol. 25(OH)D is the major circulating form of vitamin D. The second hydroxylation occurs at position C1α to form 1,25 (OH)₂D, also known as calcitriol. 1,25(OH)₂D is produced primarily but not exclusively in the kidneys. 1,25(OH)₂D is released in blood, where it binds to vitamin D binding protein (DBP) and reaches its target tissues to exert its endocrine functions through the vitamin D receptor (VDR). 1,25(OH)₂D is also produced in several external tissues for its paracrine and autocrine functions. Most cells in the body

have VDR. Many cell types can also produce 1,25 (OH)₂D. 1,25 (OH)₂D is capable of regulating a wide variety of genes that have important functions in regulating cell growth and differentiation.

ROLE OF VITAMIN D IN SKELETAL HEALTH

Rickets, osteomalacia and osteoporosis are widely prevalent all over the world. The most well recognized function of 1,25(OH)₂D involves regulation of calcium and phosphorus balance for bone mineralization and remodeling. Without adequate levels of 1,25 (OH)₂D in the bloodstream, dietary calcium cannot be absorbed. Low calcium levels lead to an increase in serum PTH concentration, which leads to increased tubular reclamation of calcium in kidneys and resorption from the skeleton at the cost of lowering bone density. In the long term, this leads to weakened and brittle bones that break easily [4]. Approximately 40%–60% of total skeletal mass at maturity is accumulated during childhood and adolescence. Rickets results from inadequate mineralization of growing bone. Thus, it is a childhood disease and it is manifested as bone deformities, bone pain and weakness. Biochemical abnormalities consistently include hypophosphatemia, elevated alkaline phosphates levels and serum 25(OH)D levels are usually below 5 ng/mL. Chronic vitamin D deficiency in adults results in osteomalacia, osteoporosis, muscle weakness and increased risk of falls. Epidemiological support for skeletal benefits of vitamin D is well known.

SYNTHESIS AND METABOLISM OF VITAMIN D IN THE REGULATION OF CALCIUM, PHOSPHORUS AND BONE METABOLISM

During exposure to solar radiation, 7-dehydrocholesterol in the skin is converted to vitamin D₃ in a heat-dependent process. Vitamin D₂ and vitamin D₃ from dietary sources are incorporated into chylomicrons and transported by the lymphatic system into the venous circulation. Vitamin D in the circulation is bound to the vitamin D-binding protein, which transports it to the liver, where vitamin D is converted by vitamin D-25-hydroxylase to 25-hydroxyvitamin D [25(OH)D]. This is the major circulating form of vitamin D that is used by clinicians to determine vitamin D status. This form of vitamin D is biologically inactive and must be converted in the kidneys by 25-hydroxyvitamin D-1 α -hydroxylase (1-OHase) to the biologically active form-1,25-dihydroxyvitamin D [1,25(OH)₂D] [5] Serum phosphorus, calcium, fibroblast growth factor 23 (FGF-23), and other factors can either increase (+) or decrease (-) the renal production of 1,25(OH)₂D and decreases the synthesis and secretion of parathyroid hormone by the parathyroid glands. [6] 1,25(OH)₂D increases the expression of 25-hydroxyvitamin to catabolize 1,25(OH)₂D to the water-soluble, biologically inactive calcitric acid, which is excreted in the bile. 1,25(OH)₂D enhances intestinal calcium absorption in the small intestine by interacting with the vitamin D receptor-retinoic acid x-receptor complex (VDR-RXR) to enhance the expression of the epithelial calcium. 1,25(OH)₂D is recognized by its receptor in osteoblasts, causing an increase in the expression of the receptor activator of nuclear factor- κ B ligand (RANKL). RANK, the receptor for RANKL on preosteoclasts, binds RANKL, which induces preosteoclasts to become mature osteoclasts. Mature osteoclasts remove calcium and phosphorus from the bone, maintaining calcium and phosphorus levels in

the blood. Adequate calcium (Ca²⁺) and phosphorus (HPO₄²⁻) levels promote the mineralization of the skeleton.

CONSEQUENCES OF VITAMIN D DEFICIENCY

Vitamin D deficiency can be asymptomatic, but may also cause several problems including:

- Osteomalacia
- Osteoporosis
- Rickets:
- Pre-eclampsia
- Depression
- Craniotables (abnormal softening or thinning of the skull)
- Muscle aches and weakness
- Increased risk of fracture
- Muscle twitching
- Light-headedness
- Periodontitis

PREVENTION AND TREATMENT

Unprotected sun exposure is the major source of vitamin D for both children and adults. Provision of vitamin D from sunlight is as follows: For Indian skin tone, minimum “direct sun exposure” required daily is more than 45 min to bare face, arms and legs to sun’s UV rays (wavelength 290–310 nm), especially between the hours of 10 am to 2 pm. Full-body sun exposure producing slight pinkness in light skinned persons results in vitamin D production equivalent to ingesting 10,000-25,000 IU [7,8]. Vitamin D supplementation by annual injection or oral tablets increases 25-hydroxyvitamin D levels, suppresses parathyroid hormone, increases bone mineral density and reduces falls over the following year. Oral vitamin D₃ is the treatment of choice in vitamin D deficiency

POSTMENOPAUSAL OSTEOPOROSIS

Osteoporosis mostly affects postmenopausal women and substantially increases their risk of fracture. Fractures associated with osteoporosis (fragility fractures) have a major impact on quality of life, mortality, and health care costs. Osteoporosis is a disease characterized by low bone mass and deterioration of bone tissue. This leads to increase bone fragility and risk of fracture, particularly of hip, spine and wrist. Osteoporosis is often known as the silent thief because bone loss occurs without symptoms. The decline of ovarian function at menopause results in decreased production of estrogen and a parallel increase in FSH levels. The combined effects of estrogen deprivation and raising FSH production cause a marked stimulation of bone resorption and a period of rapid bone loss, which is central for the onset of postmenopausal osteoporosis [9] several risk factors are implicated in favoring postmenopausal bone loss. Important nonmodifiable predictors of bone demineralization are age, sex, period of amenorrhea [10,11] and parental history of fracture [12] Important modifiable factors are dietary calcium intake [13] low body mass index [14,15], smoking [16,17] reduced physical

Table 1: WHO criteria for the diagnosis of Osteoporosis.

BMD T Score	Diagnosis
T- Score ≥ -1	Normal
T-Score -1 to -2.5	Low bone mass (Osteopenia)
T- Score ≤ -2.5	Osteoporosis

activity [18] and high alcohol intake [19,20] Osteoporosis is more common clinical problem in India and in throughout the world. Majority of the post-menopausal women and aged population are affected. [21] Menopausal is commonly defined by the state of the uterus and the absence of menstrual flow or “periods”, but it can instead be more accurately defined as the permanent cessation of the primary functions of the ovaries. [22]

MECHANISM OF POST MENOPAUSAL OSTEOPOROSIS

The female reproductive system plays a major role in regulating the acquisition and loss of bone by the skeleton from menarche through senescence (14). Estrogen deficiency increases the rate of remodeling and the volume of bone that is resorbed and decreases the volume of bone that is formed resulting in bone loss and structural decay after menopause (15). Postmenopausal osteoporosis is related to the loss of gonadal function. The quantity and quality of the bone after menopause decreases rapidly resulting in an increased risk of fractures (3,4). Estrogens are known to play an important role in regulating bone homeostasis and preventing postmenopausal bone loss (1). Therefore, onset of menopause after 30 year of age the estrogen level will decline leads to increase rate of resorption and decrease bone mass. Estrogen level stimulates a protein that is known as OPG (Osteoprotegerin) and OPG inhibit the activity of RANK ligand (Receptor activator or nuclear factor K) RANKL works like a signaling molecules for osteoclast regulation [23] Osteoclast is a type of bone cells responsible for bone resorption and bone remodeling. So in case of increase in bone resorption loss of bone mineral density (BMD) occur and this leads to finally osteoporosis.

Estrogens are responsible for bone maturation and maintenance of bone mineral density throughout life. Due to hypoestrogenism, the risk of osteoporosis increases during menopause. A drop in estrogen production after menopause results in increased bone resorption and decreased calcium absorption [24].

ESTROGEN HAS THREE FUNDAMENTAL EFFECTS ON BONE METABOLISM

1. Inhibition and activation of bone remodeling and the initiation of new basic multicellular units (BMUs)
2. Inhibition, differentiation and promotes of osteoclasts, therefore bone resorption reduces
3. Prevents apoptosis of osteoblastic cells, therefore bone formation is maintaining at the cellular level [25].

The main effect of estrogen is inhibition of bone remodeling, likely via the osteocyte. Estrogen also inhibits bone resorption, by direct effects on osteoclasts, although effects of estrogen on

osteoblast/osteocyte and T cell regulation of osteoclasts likely also play a role [26]. Estrogen deficiency associated with a gap between bone resorption and formation, likely due to the loss of the effects of estrogen on decreasing osteoblast apoptosis, oxidative stress, osteoblastic NF- κ B activity [27].

DIAGNOSIS AND PREVENTION OF OSTEOPOROSIS

The most widely method used for the diagnosis of osteoporosis is dual energy x-ray Absorptiometry (DEXA). This scan is the most reliable method in this method all women 65 years old and older be routinely screened for osteoporosis. Patients lie on exam table for approx 5 minutes while exam is performed. Therefore, by this method Measures bone mineral density, approximation of bone mass and best predictor of fracture risk.

FRACTURE RISK ASSESSMENT TOOL (FRAX)

In 2008, the World Health Organization released a Fracture Risk Assessment tool (FRAX). This is available at www.shef.ac.uk/FRAX and incorporates clinical risk factors and femoral neck BMD in determining fracture risk. It estimates the 10-year probability for hip fractures and major osteoporotic fractures for an untreated person.

THERAPEUTIC STRATEGIES OF POSTMENOPAUSAL OSTEOPOROSIS

The two main pharmacological approaches to osteoporosis are the anti catabolic and anabolic therapy, which helps in maintenance of bone density, reduce fracture rates and decrease bone resorption [28,29] and stimulate new bone formation [30,31]. The anticatabolic agents comprise Bisphosphonates and other non-hormonal drugs like etidronate, alendronate, risedronate, and zoledronic acid. Bisphosphonates accumulate in the mineral phase of bone and reduce OC activity by inhibiting farnesyl pyrophosphate synthase [32]. They can be administered orally (daily, weekly, or monthly) or (quarterly or yearly). Selective Estrogen Receptor Modulators (SERMs) are drugs which act in a similar way to estrogen on the bone, helping to maintain bone density and reduce fracture rates specifically at the spine The only anabolic agent currently available is teriparatide [33]. Calcium and vitamin D supplements can be of benefit for older people to reduce the risk of hip fracture. Parathyroid hormone stimulates new bone formation and significantly, increases bone mineral density and reduce fracture rates. Hormone replacement therapy (HRT) is estrogen replacement for women at the menopause, which help maintain bone density and reduce fracture rates for the duration of therapy. Calcitonin injectable and nasal spray is approved by the FDA for the treatment of postmenopausal osteoporosis. Calcitonin is an endogenous polypeptide hormone that inhibits osteoclastic bone resorption.

MANAGEMENT OF POSTMENOPAUSAL OSTEOPOROSIS

The Indian Menopausal Society has developed guidelines for the management of postmenopausal osteoporosis. It has divided women according to years (less than 5 years and more) since menopause. Menopause with less than 5 years and no risk factors require only primary preventive measures like improved nutrition, lifestyle modification, adequate vitamin D and calcium,

Table 2: Research highlights related to role of vitamin D in controlling Postmenopausal osteoporosis.

Sr. No.	Sources	Author/ date	Title	Methodology		Major findings	Conclusions
				Treatment	Treatment		
1.	Age and Ageing	Harwood et al., 2004	Comparison of different calcium and vitamin D supplementation regimens in Postmenopausal women after hip fracture	They taken 150 with age 67-92 years Within 7 days of surgery of hip fracture divided in 4 groups as following. 1.N=38 Injected Vitamin D 2.N=36 Injected Vitamin D + oral calcium 3.N=39 Oral vitamin D + Calcium 4.N=37 Control (no treatment).	Patients were seen in a dedicated clinic 3, 6 and 12 months after their fracture. Deaths, falls and new fractures were ascertained. Biochemical measurements and BMD were repeated after 12 month	Patients were seen in a dedicated clinic 3, 6 and 12 months after their fracture. Deaths, falls and new fractures were ascertained. Biochemical measurements and BMD were repeated after 12 month	Mean 25-hydroxy-vitamin D increased and mean parathyroid hormone was suppressed in all the actively treated groups
2.	Journal of Bone Metabolism	Kim et al., 2014	Vitamin D Status and Response to Initial Vitamin D Supplementation in Korean Postmenopausal Women with Osteoporosis	Women (N=52) with osteoporosis They were recommended to be exposed to sun light for more than 30 min a day. Subjects were divided into 3 groups according to serum 25-hydroxy-vitamin D3 (25-[OH] D3) status: 1. N=36 Deficiency (≤ 20 ng/ml) treated with 1800-2,000 IU/day of Cholecalciferol 2. N=12 Sufficiency (≥ 30 ng/ml) 3. N=4 Insufficiency (20-30 ng/ml) Both group received (1,000 IU/day)	They compared 25-(OH)D levels at baseline and after vitamin D supplementation for 3 months	About 44% of vitamin D deficient patients did not attain the optimal level of serum 25-(OH)D despite recommended daily intake of vitamin D to 1,000 IU in patients with osteoporosis. Follow-up of serum 25-(OH)D levels may be required for vitamin D supplementation in vitamin D deficient patients with osteoporosis.	Postmenopausal women have a higher risk of falling or fracture when they do not maintain serum 25-(OH) D level higher than 30 ng/mL . 88.9% of patient attained optimal 25(OH)D levels by doubling the recommended daily amount of vitamin D to 2,000 IU.
3.	The Journal of Clinical Endocrinology & Metabolism	Lips et al., 2013	A Global Study of Vitamin D Status and Parathyroid Function in Postmenopausal Women with Osteoporosis.	N=7705 2 years postmenopausal women 1. Substudy I patient- BMD at the femoral neck or lumbar spine was lower than t-score - 2.5 2. Substudy II patients had one moderate or two mild vertebral fractures regardless of BMD	Fasting blood samples were obtained at baseline. Fasting blood samples were again obtained after 6 months of treatment with vitamin D3 (400-600 IU/day), calcium (500 mg/day) and placebo	The increase in serum 25OHD and the decrease in serum PTH after treatment were greater when baseline serum 25OHD was lower	Treatment with vitamin D3 and calcium in the postmenopausal women increased serum 25(OH)D3 and decreased serum PTH significantly
4.	American Journal of Clinical Nutrition,	Holick et al., 2012	Prevalence of Vitamin D Inadequacy among Postmenopausal Women Receiving Osteoporosis Therapy	N =1536 women aged 55 year and above postmenopause for minimum of 2 year receiving osteoporosis medications. All calcium, vitamin D and multivitamin supplements taken within 3 months before the study visit were recorded	Single blood sample was collected to assess 25(OH) D3, calcium, intact PTH, phosphorus, albumin, creatinine, magnesium, alkaline phosphatase and total bilirubin concentrations	Prevalence of 25(OH) was significant higher in subject who takes less than 400 IU/day. There was significant negative correlation between serum PTH concentration between serum PTH concentration and 25(OH)D	Supplemental use of vitamin D less than 400 IU/d independently and significantly associated with vitamin D inadequacy

5.	Journal of Mid-life Health,	Bener and Saleh, 2015	Low vitamin D and bone mineral density with depressive symptoms burden in menopausal and postmenopausal women	A multi-stage sampling design was used and a representative sample of 1436 women aged 45-65 years postmenopausal women were included diagnosed with of major depression	BMD (g/m ²) was assessed be measured. Data on body mass index (BMI serum 25-hydroxyvitamin D were collected. The Beck Depression Inventory (BDI) was administered for depression purposes	Diminished low vitamin D is correlated with BMD and depressive symptoms may be a risk factor for reduced BMD in postmenopausal-women. more than 80% of the women experience physical or psychological symptoms in the years when they approach menopause.	This study revealed that there was a strong association between vitamin D level and BMD in Arab womenduring the menopausal and post-menopausal period.
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and proper exercise. However, menopause since more than 5years and with diagnosed osteoporosis requires active medical treatment.

DIETARY TIPS FOR OSTEOPOROSIS

Green leafy vegetables such as fenugreek, cabbage, broccoli and spinach are excellent sources of calcium. Spinach is also an excellent source of vitamin K that helps boost the bone mineral density. Nuts as almonds and walnuts contain a generous amount of potassium that can help prevent the loss of calcium through urine. Walnuts are also rich in omega-3 fatty acids that slow down the rate of bone loss. Dates are a particularly good source of calcium and manganese and help to improve the bone mineral density. Potassium-rich fruits like apple and banana. Potassium is necessary to boost your immune system and prevent calcium loss from your body. Milk is an excellent source of calcium and vitamin D. Take regular, weight-bearing exercise. Good bone building exercises include running, skipping, aerobics, tennis, and brisk walking.

- Consume daily at least three portions of milk and dairy produce with reduced fat content.
- Choose vegetables with high calcium content (broccoli, cabbage)
- Eat fish at least once a week
- Limit consumption of foods and drinks high in phosphates
- Use spices in place of salt to enhance flavor
- Eat vegetables and fruit five times daily
- Limit consumption of foods high in oxalates, phytates
- Ensure sufficient intake of vitamin D (fish, livers, milk), vitamin K (leafy vegetables, livers, fish) and vitamin C.
- Maintain a balanced diet to achieve adequate calcium and vitamin D intake. Drink mineral water with high calcium content.
- Avoid smoking and high intakes of alcohol.

RDA FOR OSTEOPOROSIS

The National Osteoporosis Foundation recommends a vitamin D intake of 800-1000 IU per day. The recent Institute of

Medicine guidelines recommend a vitamin D intake of 600 IU for women age 51-70 and 800 IU for those over age 70. For women over age 50, the recommended daily calcium is 1200 mg (diet plus supplements) [34].

PREVALENCE

1 out of 8 males and 1 out of 3 females in India suffers from osteoporosis, making India one of the largest affected countries in the world. (Osteoporosis foundation factsheet) Osteoporosis is estimated to affect 200 million women worldwide - approximately one-tenth of women aged 60, one-fifth of women aged 70, two-fifths of women aged 80 and two-thirds of women aged 90 [35] Approximately 1.6 million hip fractures occur worldwide each year and by 2050. This number could reach between 4.5 million and 6.3 million. Asian females are more prone for osteoporosis, though women from other races are also at high risk of developing this disease. Globally osteoporosis causes more than 8.9 million fractures annually, resulting in an osteoporotic fracture in every 3 sec. In a more recent study from Delhi, 808 postmenopausal females with a mean age of 57.67 ± 9.46 years were evaluated. Osteoporosis was present in 42.5% of females and osteopenia in 44.9% of females [36].

CONCLUSION

Vitamin D supplementation with Calcium is beneficial in increasing bone density in elderly women who have suffered a hip fracture. Treatment with vitamin D₃ and calcium increased serum 25(OH)D₃ and decreased serum PTH. Serum concentrations of at least 20 -30 ng/ml are necessary to maximize intestinal calcium absorption and minimize perturbations in PTH and calcium. Teriparatide treatment induced increase in spine BMD and bone formation markers in postmenopausal women with established osteoporosis. Diminished low vitamin D is correlated with BMD and depressive symptoms may be a risk factor for reduced BMD in menopause or postmenopausal women. In postmenopausal women, as estrogen decline RANK ligand expression increases. Elevated RANK ligand level lead to increase osteoclast formation, function and survival. Greater osteoclast activity increases bone loss and can ultimately leads to fracture [37].

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Cite this article

Singh A, Raghuvanshi RS (2019) Role of vitamin D in controlling Postmenopausal Osteoporosis. *J Endocrinol Diabetes Obes* 7(1): 1118.