Association of Vitamin D 3 Deficiency and Osteoporosis. Review

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Abstract

Osteoporosis is a condition in which bone growth and loss are out of balance. Vitamin D is one of the most important vitamins for bone metabolism and mineralization. Circulating 25-hydroxyvitamin D levels below 20 ng/mL (50 nmol/L) are considered deficient, and this condition is becoming increasingly common across the world. This review covers all aspects of vitamin D metabolism, vitamin D deficiency consequences, and vitamin D supplementation effects on musculoskeletal health in older individuals. According to current research findings, Vitamin D deficiency has been related to osteoporosis, poor bone mineral density, and muscle problems as well as falls and fractures. Osteoporosis falls and fractures can all be prevented by long-term administration of vitamin D and calcium. When it comes to osteoporosis, fracture risk is our primary concern yet vitamin D therapy has no consistent influence on fracture prevention unless calcium is also provided (particularly in frail populations living in care homes).

Keywords: Osteoporosis, vitamin D, bone mineral density, BMD.

الخلاصة

هشاشة العظام هي حالة يكون فيها نمو العظام وفقدانها غير متوازن. يعتبر فيتامين دال من أهم الفيتامينات في استقلاب العظام وتمعدنها. تعتبر مستويات 25-هيدروكسي فيتامين دال التي تقل عن 20 نانوغرام / مل (50 نانومول / لتر) متدنية، وقد أصبحت هذه الحالة شائعة بشكل متزايد في جميع أنحاء العالم. تغطي هذه المراجعة جميع جوانب استقلاب فيتامين (دال)، وعواقب نقص فيتامين (دال)، وآثار مكملات فيتامين (دال) على صحة الجهاز العضلي الهيكلي لدى الأفراد الأكبر سنًا. وفقًا لنتائج الأبحاث الحالية، ارتبط نقص فيتامين (دال) بهشاشة العظام وضعف كثافة المعادن في العظام ومشاكل العضلات وكذلك السقوط والكسور. يمكن منع حدوث هشاشة العظام والكسور عن طريق تناول فيتامين دال والكالسيوم على المدى الطويل. عندما يتعلق الأمر بهشاشة العظام، فإن خطر الكسر هو شاغلنا الأساسي، لكن العلاج بفيتامين (دال) ليس له تأثير ثابت على الوقاية من الكسور ما لم يتم توفير الكالسيوم أيضًا (خاصة في الفئات الضعيفة التي تعيش في دور الرعاية).

Introduction

When bone density is reduced, synovial membrane inflammation and cartilage degradation take place, the joints become more susceptible to fracture. Osteoporosis is a degenerative, progressive joint condition that causes widespread fragility and increased fracture risk. [1]. Biologically active vitamin D is 1,25 dihydroxy vitamin D, which is essential for bone mineralization because it produces the proper microenvironment. Vitamin D deficiency is frequent in both adults and children, despite consuming vitamin D-enriched foods or taking vitamin D pills. Vitamin D [25(OH)D] deficiency is connected to secondary hyperparathyroidism, which results in accelerated bone turnover and loss, which increases the risk of fracture. In the treatment of osteoporosis, calcium and vitamin D play a key role. According to numerous studies, Bone mass and muscle function can be improved with adequate vitamin D and calcium intake. Osteoporosis and fractures can also be avoided with regular use of these products. Getting at least 1200 milligrams of calcium and 800 international units (IU) of vitamin D daily is suggested [2].

Vitamin D Metabolism and action

In terms of bone and muscle health, Vitamin D's role in calcium and phosphate absorption and metabolism cannot be overstated. Ergocalciferol and cholecalciferol are two forms of vitamin D, which can be found in foods. It's important to note that vitamin D2 is derived from plants, whereas vitamin D3 is produced by the skin after exposure to UVB light. To make pre-vitamin D3, 7-DHC, a cholesterol-based pre-cursor compound must be activated by UVB radiation. [3]

Calcium and phosphate metabolism and absorption are both aided by the lipid-soluble prohormone vitamin D. D2 (ergocalciferol) and D3 (cholecalciferol) are the two forms of vitamin D. (cholecalciferol). D2 vitamin supplements are usually available in fortified foods, whereas D3 vitamin is created through skin exposure to UVB light (ultraviolet B) from the sun. Sunlight's UVB rays activate 7-dehydrocholesterol (7-DHC), a cholesterol precursor compound found mostly in the epidermis, to create pre-vitamin D3 [3, 4]. Pre-vitamin D3 isomerizes to vitamin D3, which is then transferred to the liver or kidney to be hydroxylated by 25-hydroxylase and 25(OH)D3-1-hydroxylase to produce the physiologically active 1,25(OH)2D3. With the help of the vitamin D receptor (VDR) and the retinoid X receptor (RXR) in a complex, 1,25(OH)2D3 may now exert its effects in target tissues[4]. To facilitate calcium absorption in the digestive tract and the pancreas, the binding of 1,25 (OH)2D3 to VDR/RXR and subsequent binding to VDR increases the synthesis of calcium binding proteins such as calbindin-D9K and calbindin-D28K. Even though it's classified as a vitamin, the hormone-like effects of vitamin D may surprise some people. This vitamin helps to maintain a healthy calcium and phosphorus balance by increasing intestinal calcium absorption and decreasing renal excretion of calcium. When blood calcium levels fall below the optimum range (2.25-2.5 mmol/L), it helps prevent rickets and osteomalacia by encouraging bone mineralization and resorption [5][6][7].

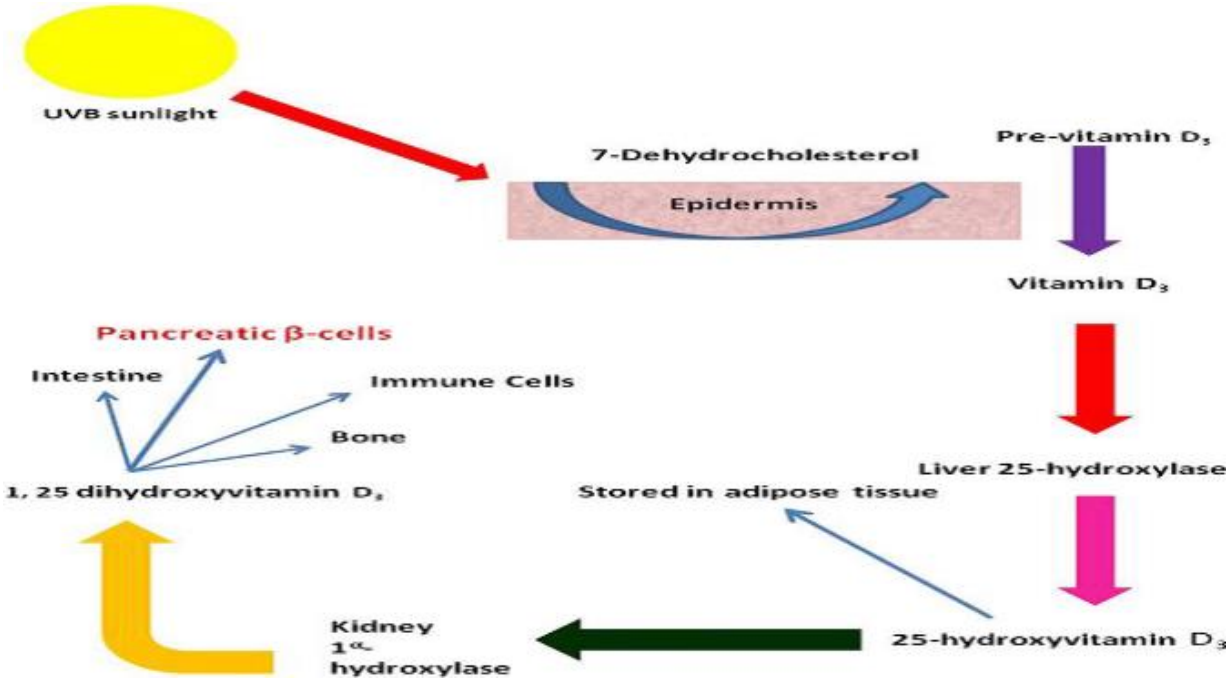

Figure 1. The biosynthesis of vitamin D [3].

Vitamin D deficiency and optimal vitamin D levels

The excess concentration of 25(OH)D in the blood is 1000 times that of serum 1,25(OH)D3, creating a storage facility comparable to that for steroid hormones. Clinicians have chosen to use 25(OH)D to measure vitamin D levels [8]. Vitamin D adequacy is most accurately measured by serum 25(OH)D3 concentrations. however, there is no strong evidence that these amounts are attained. Formerly, a blood level of 25-hydroxy vitamin D (25(OH)D) less than 10 ng/mL (25nmole) was considered to be vitamin D deficiency [9]. It was determined through an intensive study in 2011 that 25(OH)D concentrations of 20ng/ml and above are necessary for good bone health, according to the Institute of Medicine (IOM) [10].

Vitamin D deficiency was classified by the United States Endocrine Society as a blood level of 25(OH)D of less than 20 ng/ml, 21–29 ng/mL as insufficiency, and 30 ng/ml as sufficient for maximum musculoskeletal health, with an optimum vitamin D level of 30-50 ng/ml [11]. These definitions were adopted by the International Osteoporosis Foundation, National Osteoporosis Foundation, American Association of Clinical Endocrinologists, and the American Geriatric Society [12].

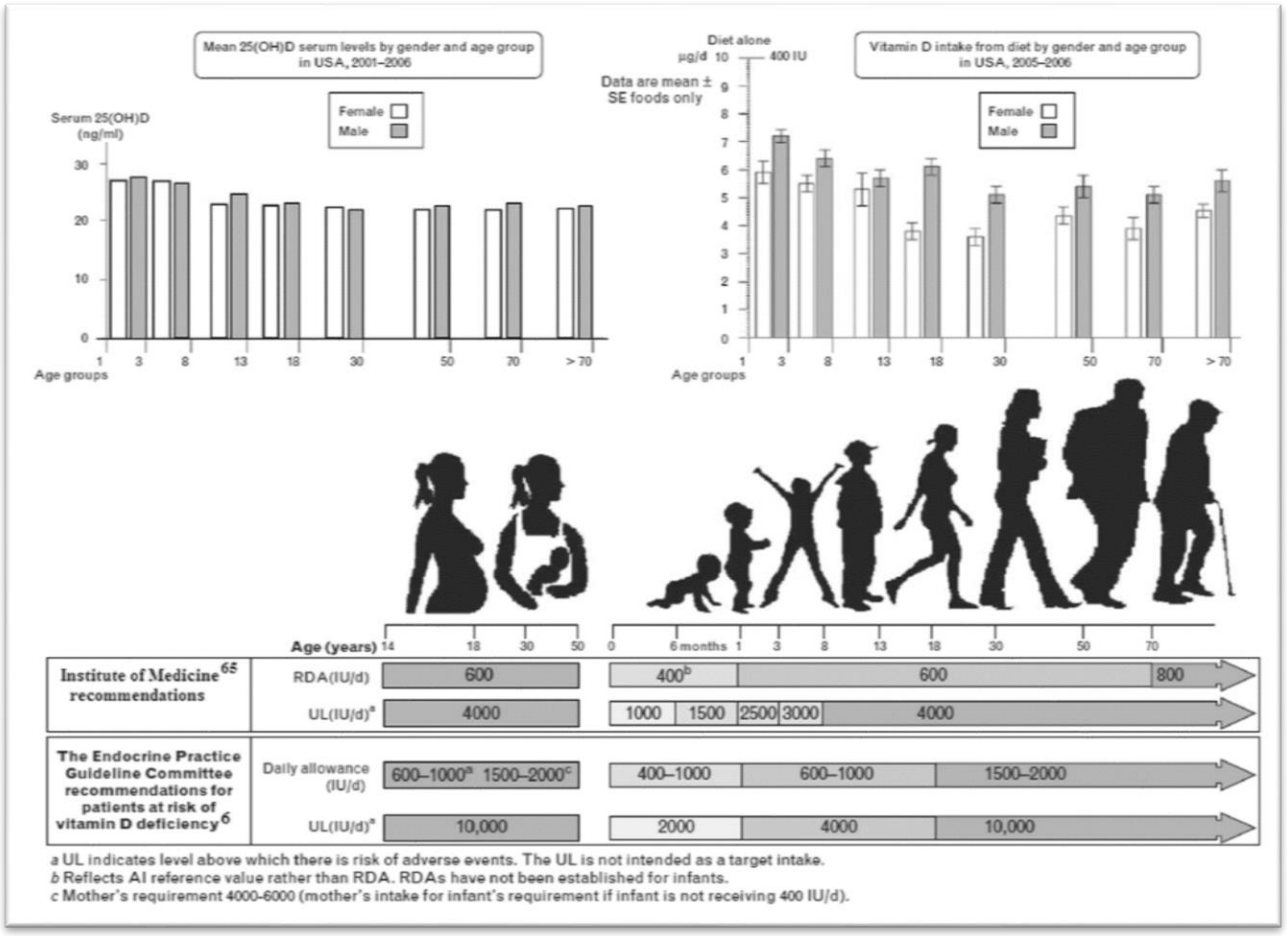

Fig. 2. Serum 25-hydroxyvitamin D levels in children and adults in the United States. Approaches to diagnosis, treatment, and prevention of vitamin D insufficiency [13].

Vitamin D Deficiency Causes:

Many situations might cause vitamin D deficiency [14].
1. Decreased dietary intake and/or absorption.

Malabsorption disorders, such as celiac disease, short bowel syndrome, gastric bypass, inflammatory bowel disease, chronic pancreatic insufficiency, and cystic fibrosis, can cause vitamin D deficiency, which can lead to a lack of vitamin. Elderly people are more likely to suffer from an oral vitamin D deficiency [15].

2. Reduced exposure to the sun.

Vitamin D is mostly absorbed by the skin through exposure to sunshine, with the rest coming from the food. At least 20 minutes of sunshine every day with at least 40% of the skin exposed is necessary to avoid vitamin D deficiency. "Formal" phrasing As we grow older, our skin's ability to synthesize vitamin D declines. Those with darker skin have lower levels of cutaneous vitamin D production. Vitamin D deficiency can occur as a result of insufficient sun exposure, which is

common in which is common in institutionalized persons or in long-term care facilities. Regular sunscreen users have a less effective exposure to the sun [16].

3. Decreased endogenous synthesis.

People with cirrhosis or other forms of chronic liver illness have problems with 25-hydroxylation, which results in a deficiency in active vitamin D3. Hyperparathyroidism, renal failure, and a deficit in 1-alpha hydroxylase can all affect 1-alpha-25-hydroxylation. [17]

4. Increased hepatic catabolism

Hepatic p450 enzymes are activated by medications such as phenobarbital, dexamethasone, nifedipine, spironolactone, clotrimazole, and rifampin, which degrade vitamin D [18]

5. End organ resistance

Hereditary vitamin D resistant rickets are an example of vitamin D end organ resistance. As initially used by Albright *et al*. in 1937, the term 'vitamin D-resistance rickets' refers to the kind of rickets that requires high levels of vitamin D in order to recover. Rickets (Vitamin D dependent rickets (DDR) II, an autosomal recessive variant of vitamin D dependent rickets, with less than 50 reported afflicted families. It was found that rickets was a common affliction among the patients who were the children of consanguineous couples. 1,25-dihydroxy vitamin D has shown varying degrees of resistance, and some patients appear to be responding well to treatment. [19]

6-The microbiota of the gut

In the context of the gut microbiome, the term refers to bacteria that dwell in the human digestive system and are symbiotic with the body. As a result, they have a role in regulating a wide range of bodily functions and are linked to a number of illnesses. Inducing apoptosis, slowing bone resorption or encouraging osteoblast proliferation and maturation are all ways in which gut microorganisms might help build bone mass and treat osteoporosis [20]. Many metabolic activities and hormone development, such as sex steroid production are influenced by the gut flora and play a critical part in the turnover of the skeleton. Serotonin and vitamin D metabolism are also regulated by the microbiome, which affects bone health. Calcium channel activity, calcium absorption and bone calcification are all controlled by vitamin D which plays a vital role in bone metabolism. Vitamin D and calcium absorption in the intestines alter as people become older. Osteoporosis can be caused by a lack of calcium and vitamin D absorption in the intestines [21]

The prevalence of Vitamin D deficiency in population

Vitamin D deficiency and insufficiency are becoming an increasing problem in Asia. Fish, beef, fortified dairy products, eggs, liver and sundried mushrooms are the most common sources of vitamin D in Asia. Saturated fats are high in vitamin D but public health campaigns have lately made an attempt to encourage individuals to consume less of them. Additionally the lack of time available for meal preparation and consumption during a regular weekday may worsen the condition. [22]

Vitamin D insufficiency has been discovered to be more prevalent among young people in China and Thailand than previously thought [23]. Vitamin D deficiency is defined as fewer than 30 nmol/L, insufficiency as 30–49.9 nmol/L and adequate as higher than 50 nmol/L as stated by the Chinese Gerontological Society's Osteoporosis Committee. [24].

In the Middle East, population-based research is rare. Vitamin D insufficiency and rickets are common in the Middle East, despite the region's abundance of sunlight. Serum 25(OH)D levels were from 25 to 50 nmol/L in most surveys, with lower values in females than males depending on clothing style. Middle East vitamin D insufficiency rates ranged from 30 to 90 percent based on the research type, country, age group and test used. According to a recent thorough analysis [25]. Around 64% of persons in the Qatar Biobank had low levels of vitamin D (less than 20 ng/ml) with males having somewhat lower levels than women. Men in the Middle East have been shown to have greater vitamin D levels than women in previous research. When it came to vitamin D deficiency, women outnumbered men in a Saudi Arabian sample of 10,709 people [26]. According to a Bahraini and Lebanese study, females had lower mean blood vitamin D levels than males [27].

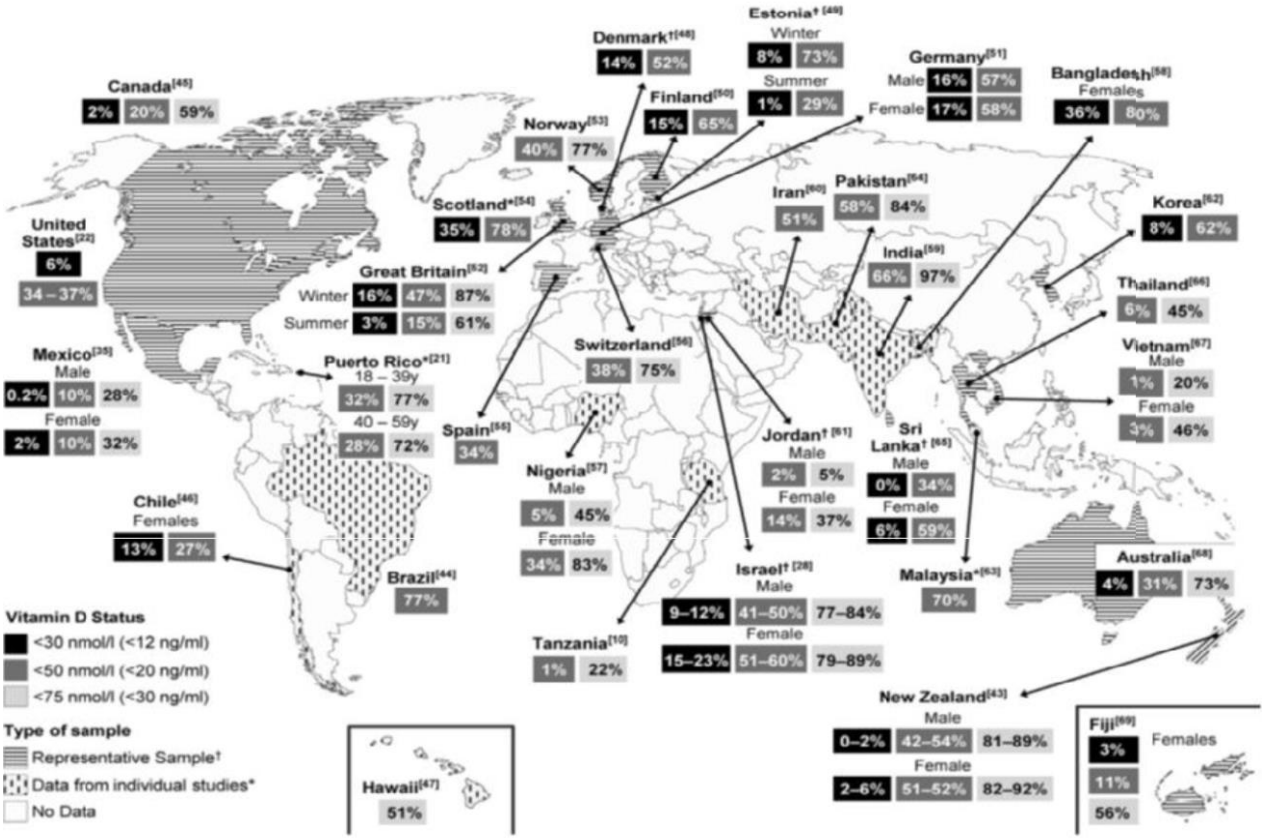

Figure. 3 Prevalence of vitamin D deficiency in adults worldwide [28].

Association of osteoporosis with vitamin D deficiency

This condition (osteoporosis) is the most common bone disease in the world and has been related to decreasing of bone strength and increasing fracture risk. Vitamin-D and Calcium (Ca/VitD) insufficiency is a key risk factor of osteoporosis along with postmenopausal estrogen decrease, old age, and inactivity. Bone resorption by osteoclasts are controlled by vitamin D to maintain equilibrium in the urinary and digestive systems. Vitamin D deficiency and a lack of calcium delivery lead to an increase in bone resorption which lowers bone mass and quality. Around 3 billion people in the globe are thought to be deficient in vitamin D. The number is expected to climb as a result of demographic shifts, insufficient dietary vitamin-D and calcium intake in the elderly and reduced intestinal absorption of calcium and endogenous production of vitamin-D [29]. Osteoporosis is frequently misdiagnosed until the patient has their first fragility fracture and even then, 80–90% of patients do not receive appropriate treatment. Calcium and vitamin D are essential for bone health. Among the elderly with osteoporosis, a lack of supply is common [30].

Bone loss in vitamin D deficient patients: pathophysiology

Activated vitamin D metabolite 1,25(OH)2D opens stomach calcium channels, stimulates calcium-binding protein production in intestinal cells and so enhance the absorption of calcium and phosphates. As a consequence, the ideal circumstances for bone mineralization are established. As long as there is adequate calcium and vitamin D in the diet, the mineralization is an automatic process. 1,25(OH)2D levels decrease when vitamin D intake is inadequate. This results in a reduction in bone mineralization because calcium is less accessible for this purpose. Parathyroid hormone will accelerate the hydroxylation of 25(OH)D to 1,25(OH)2D in the kidney (PTH). Bone turnover and loss are caused by elevated blood levels of PTH [31]. It's possible that the new steady state will allow serum 1,25(OH)2D levels to return to normal while increasing bone resorption. Osteoporosis can result from long periods of vitamin D deficiency (Fig. 4).
Osteoid tissue in high turnover bone is more than in normal bone because of the increased surface remodeling (not yet calcified bone). Bone with a higher concentration of minerals, such as bone that has been mineralized tends to be less dense. Because osteons have a shorter lifespan than other bone tissue, mineral deposits can persist for up to two years after formation. When vitamin D deficiency is long-term and chronic, the amount of osteoid tissue builds up to more than 5% resulting in osteomalacia. Lips *et al.* identified significant bone turnover in 20% of individuals with hip fractures but no overt osteomalacia in 119 bone biopsy samples [32]. A blood 25(OH)D level of less than 25 nmol/l was found in nearly 80 percent of the patients in Paul Lips' investigation. Osteoid volume, thickness, surface and number of osteoid lamellae were all shown to vary widely in 19 series of hip fracture patients with hyperosteoidosis. Osteomalacia's prevalence ranged from 0% to 12 % [31].

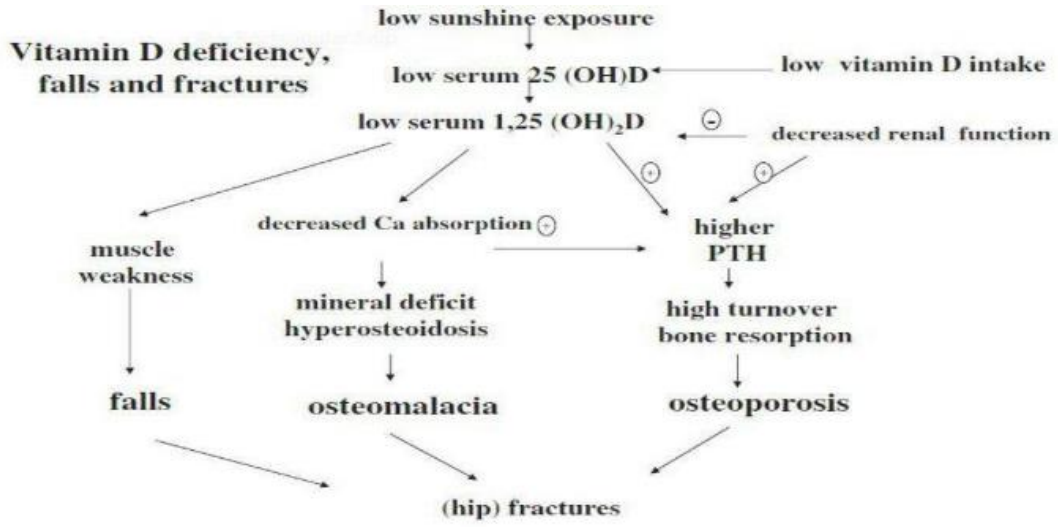

Fig. 4 The pathophysiologic pathways from vitamin D deficiency to osteoporosis [33].

Vitamin D and Bone Mineral Density (BMD)

Indirectly, 1,25(OH)D can stimulate bone mineralization by increasing phosphate availability and gastrointestinal absorption of calcium. If we don't get enough vitamin D, we only absorb 10–15% of our calcium and 60% of our phosphorus. 1,25(OH) D binding to the vitamin D receptor (VDR) enhances gastrointestinal absorption of calcium and phosphorus by 30–40% and 80%, respectively [34].

Cross-sectional studies have found a correlation between blood 1, 25 hydroxy vitamin D and hip bone mineral density. The BMD variations of 330 older female were studied for the presence of a blood 25-hydroxyvitamin D threshold. Lower than 30 nmol/L, there was a positive relationship between BMD and blood 25 hydroxy vitamin D levels but the correlation was not significant above this level. This research found the femoral neck BMD was 10% or 5% less than normal when 25-hydroxyvitamin D levels in the blood were 20 or 10 nmol/L [35]. There was a positive correlation between hip bone mineral density and blood 25 hydroxy vitamin D levels in middle-aged British women (45–65 years) and elderly New Zealand women (65+ years) [9].

Bischoff-Ferrari *et al*. [36] discovered that blood levels of 25-hydroxyvitamin D were linked to BMD in Black, White and Mexican-American women and men with the highest density occurring at 40 ng/mL or above. Vitamin D deficiency in adults was studied in southern China by Wat *et al.* [37]. Sixty two percent of those tested had 25 hydroxy vitamin D levels less than or equal to 30 ng/mL, and 6.3% had increased levels of the parathyroid hormone. Despite the fact that individuals with vitamin D levels < 30 ng/m had decreased BMD, In the spine and hip, only age, gender, and PTH were found to be BMD predictors but not 25(OH)D levels. In secondary hyperparathyroidism, the result of vitamin D deficiency, is ubiquitous and a key risk factor for bone mass loss, falls, and fractures. Even among postmenopausal osteoporotic Belgian women who were taking vitamin D supplements, Neuprez *et al.* revealed that vitamin D deficiency was common. 25(OH)D deficit was found in 15.9, 43.1, 87.5 ,91.3% of those who had cutoffs of 30, 50, 75, and 80 nmol/L. In terms of age-related increases in PTH (r = 0.16), 25-hydroxyvitamin D blood levels (r = 0.07, P 0.05) and femoral neck bone mineral density (r = 0.07, P 0.05) there is a significant correlation between each of these markers and age. However, Ofelia study revealed that few healthy postmenopausal women had severe deficiency of vitamin D, suggesting that vitamin D status may not be a crucial factor in bone health [39].

Deficiency in vitamin D can induce a reduction in calcium absorption in the small intestine which can lead to an increase in serum PTH resulting in stimulation of osteoblast and promote the maturation of preosteoclasts. Osteoclasts break down the bone's mineralized collagen matrix causing bone loss and a decrease in bone mineral density.

Another possible reason for the link between low BMD and low serum 25-(OH)D is sedentary behavior. Bone loss would develop as a result of inactivity and a lack of exposure to sunshine. Frail elderly persons are more likely to suffer from vitamin D deficiency and physical inactivity. On the other side, immobility has been shown to hasten bone resorption, resulting in the bone mass loss [34].

Bone mineral density and vitamin D receptor gene polymorphism

Genetic variations are known to have a significant impact on BMD. According to studies of mother-daughter and twins pairings, up to 70 percent of the variation in BMD in men and women can be attributed to heredity [9].

In healthy Australian female and male twins, three-quarters of the genetic influence on bone mineral density (BMD) may be attributed to normal allelic variants in the vitamin D receptor (VDR) gene, according to Morrison *et al* [40]. Researchers in Australia proved a similar link in a group of 311 healthy women. To identify the VDR genotype, BsmI restriction site presence (b) or absence (B) was required. There is one type of heterozygote (Bb) and two of homozygote (BB and bb). In homozygotes, the more frequent b allele was connected to increased bone mineral density, whereas the less common B allele was linked to lower bone mineral density. While 311 women had lumbar spine and hip BMD differences of 8 and 4 percent, twins had BMD differences of 13 and 9 percent, respectively. b allele, in general, is connected to a higher BMD [41].

VDR polymorphisms (BsmI, TaqI, ApaI) and Chinese bone mineral density were studied by Zhao *et al*. [42] in 1997. In this group of young women, the 'BB' or ‘AA’genotype was associated with greater BMD at several locations, whereas the 'bb' or 'aa' genotype was associated with decreased BMD at the femoral neck and trochanter in the postmenoposal women. The BsmI, ApaI, and TaqI allele frequencies were studied by restriction fragment length polymorphisms (RFLPs) in about 144 healthy Chinese premenopausal (aged 30 to 40 years) women. The peak bone mass was linked to the VDR genotypes. These two haplotypes (BbAaTt, BbAATt) had the lowest peak bone mass, as determined by the VDR genotyping study. The increase in bone density after vitamin D supplementation in vitamin D-deficient older persons may be influenced by VDR genetic characteristics, despite the fact that several recent studies have identified no significant differences in VDR polymorphisms for BMD baseline levels [43]. Another study documented that the Bb and BB VDR polymorphisms were corresponding to a 3% increase in femoral neck bone mineral density following vitamin D treatment, whereas the bb genotype showed no change. An increase in 25(OH)D-induced bone mineral density was found to be considerably greater ($P = 0.03$) in the BB (BMD: 4.4 percent, $P = 0.04$) and Bb genotypes (BMD: 4.2 percent, $P = 0.007$) than in the bb genotype (BMD: –0.3 percent, $P = 0.61$), suggesting that VDR gene variants may play functional roles in bone mass. The VDR gene variation may explain why some people respond better to supplementation of vitamin D than others [44].

Vitamin D treatment and BMD changes

Bone mineral density (BMD) can be improved by supplementing with vitamin D, especially in persons who are vitamin D deficient. Osteoid mineralization, decreased parathyroid activity and reduced bone turnover might all contribute to an increase in bone density.

Vitamin D3 (cholecalciferol) and calcium supplementation in women and men 65 and older was studied in a three-year placebo-controlled, double-blind experiment published in 1997: 223 women and 176 men got either calcium (500 mg) with (cholecalciferol 700 IU) daily or placebo. Bone mineral density increases in the femoral neck, spine, and overall body were: +0.50 ± 4.80 and , –0.70 ± 5.03 percent (P = 0.02), +2.12 ± 4.06 % and +1.22 ± 4.25 percent (P = 0.04), +0.06 ± 1.83% and –1.09 ± 1.71% (P = 0.001) for the calcium + vitamin D and placebo groups, respectively. placebo and Calcium + vitamin D groups showed a considerable difference in all skeletal regions in the first year but only for total bone mineral density in the second and third years of treatment [45].

Numerous studies have proved this result. Women who took vitamin D supplementation of 800 IU during the winter season had greater bone mineral density in their lower backs than those who didn't take the supplement. Later, in a double-blind research of postmenopausal women, vitamin D (700 IU daily and 100 IU daily) were tested in the same group. The group that got the higher dosage of vitamin D had less femoral neck bone loss (–1.0 percent vs. –2.5 percent, P = 0.01) than the group that received the lower amount. Femoral neck BMD increased by 1.9% after one year and 2.2% after two years of supplementation with vitamin D3 (P = 0.01). The trochanter BMD did not alter significantly in the Amsterdam vitamin D research. We may conclude from this that cortical bone is more susceptible to damage. Calcium (1200 mg/day), vitamin D3 (800 IU/day) were shown to increase BMD of the whole hip by more than 6 percent in French nursing home patients. There were 12 senior persons in California who had a blood 25(OH)D level of 35 nmol/L and were administered 50,000 IU of vitamin D2 and 1000 mg of calcium carbonate every day for five weeks. Significant gains were found in both the lumbar spine (4.1 percent) and the femoral neck (4.9 percent). Calcium (750 mg/day), 25-(OH)D (15g/day), or a placebo were given to 316 old women and 122 elderly men in a recent study in Indiana. 25-(OH)D had an impact on bone loss that was in the midway of that of calcium and a sugar pill. At the start of this trial, the median blood 25 hydroxy vitamin D level was 59 nmol per liter which is a good starting point. According to this study, vitamin D therapy has a limited effect if vitamin D levels are already enough [9].

An active supplement (400 IU vitamin D with 1000 mg calcium) and a placebo were administered to 18,176 women as part of the Women's Health Initiative (WHI). Between the ages of 50 and 79, they were all in attendance. Calcium and vitamin D increased hip bone density by 1.06 percent after five years of therapy compared to the placebo group (P 0.01). There was no statistically significant difference between the calcium and vitamin D groups in terms of whole-body and spine BMD [46]. Papadimitropoulos *et al.* examined the impact of vitamin D on BMD and fracture in postmenopausal individuals. Bone mineral density was more affected by hydroxylated vitamin D than ordinary vitamin D according to the researchers. Hydroxylated vitamin D had a total body percentage change of 2.06 (0.72, 3.40) while control had a change of 0.40 (0.72, 3.40), whereas the difference between the two was 0.40 (0.25, 1.06) for the regular vitamin D. The forearm and lumbar spine were more responsive to higher dosages of hydroxylated vitamin D than were the lower levels [47]. Xia et al. investigated the effects of calcitriol (1,25-dihydroxy vitamin D) on bone mass in elderly Chinese women with osteoporosis or osteopenia. After a year of therapy, L2–4 BMD was much higher than it was at the beginning.

The L2–4 BMD changed by 2.8 percent (P 0.01) and the femur neck BMD changed by 2.0 percent (P 0.05). The response to vitamin D treatment will be determined by the severity and degree of vitamin D deficiency and the resulting changes in mineral and bone metabolism. More than 400 IU per day of vitamin D increases blood 1,25-dihydroxy vitamin D and reduces PTH release without creating any severe side effects." So taking vitamin D supplements can help prevent bone loss, especially in persons who are vitamin D deficient [48].

VITAMIN D AND MUSCLE FUNCTION AND FALLS

Vitamin D and Muscle function

Muscle metabolism can be influenced in a number of ways by vitamin D. Muscle weakness may be relieved by vitamin D supplementation after long-term vitamin D deficiency has been observed in the recent decade.

An association was found between blood 25-(OH)D concentrations (<30 nmol/L) and leg extension power in 12% of women and 18% of men, in an elderly people (65–95 years old) [49]. In a cross-sectional study of 349 senior persons (>70 years), blood 25-OHD concentrations were considerably reduced in those with lower handgrip strength and falls. Among 63 community-dwelling seniors (82.5 ± 5.4) years old, a low blood 25(OH) D concentration (less than 40 nmol/L) was connected to a poorer handgrip strength and walking distance. On the other hand, cross-sectional studies cannot establish a causal link. Vitamin D deficiency (less than 20 nmol/L) was found in 10 older women (average age: 76) who were given 0.5 μg α-calcidiol per day for six months. The improvement in both walking distance and knee extension strength in comparison to a vitamin D-deficient control group that didn't receive treatment was striking. Many comparable researches have been done, but additional randomized controlled studies are necessary to give trustworthy data.

There was no correlation between blood 1,25(OH)2D concentration and knee extension strength in a group of healthy, vitamin D-replete senior adults, and no meaningful change was seen after treatment with the calcidiol supplement. It's not uncommon for people to have a stable vitamin D level, yet their muscular strength declines with time. Supplementing with vitamin D pills may benefit persons with low levels of vitamin D who are otherwise healthy but have muscular weakness due to a variety of other diseases [50]**.**

Vitamin D and the risk of falling

Falls play a role in osteoporotic fracture pathogenesis in addition to decreased BMD. The danger of a fracture increases with any factor that increases one's propensity to fall.

More than 30% of people over 65 fall each year because of muscular weakness which may be caused by a lack of vitamin D. Studying the elderly, researchers found a correlation between 25(OH)D levels in the blood and the risk of falling [51].

Vitamin D supplementation appears to have a stronger impact in reducing the chance of falling. When used appropriately, it has a higher rate of effectiveness than any alternative treatment. In a study of 148 elderly women with 25(OH)D levels below 50 nmol/L, supplementing with calcium and vitamin D for eight weeks reduced body sway by 9% (P 0.05) and decreased the number of

falls. There were 489 women in the STOP/IT research (Sites Testing Osteoporosis Prevention and Intervention Treatments) who received calcitriol, estrogen, combined calcitriol and estrogen or a placebo for three years. There were fewer fractures as a consequence of falls in the group taking calcitriol as compared to the group using estrogen (OR: 0.78 and 0.94, respectively) [45].

Vitamin D supplementation appears to be dosage-dependent, with an optimal daily intake of 800 IU being documented. Vitamin D (400 IU/day) was shown to be unsuccessful in reducing the fractures frequency in two randomized controlled studies while a high-dose therapy study revealed no indication of reduced falls among frail outpatients. It was shown that elderly women who took calcium plus 800 IU of vitamin D daily had 47% reduced falls and fractures than those who took calcium alone in a 12-month randomized controlled study. Compared to those who got calcium alone, elderly people who received 800 IU of vitamin D per day fell half as often and had improved overall musculoskeletal health according to another study [46]. Vitamin D insufficiency is merely one of several factors that might cause an aged person to trip and shatter their bones.

Due to the fact that vitamin D supplementation is of little effect in the vitamin D-rich population, vitamin D deficiency is more common risk factor for fall and fracture**.** In spite of the fact that further randomized controlled trials are required, vitamin D deficiency is an important and common risk factor that may be managed to minimize falls and related fractures.

VITAMIN D AND FRACTURES

Vitamin D for the prevention of fractures

In spite that past randomized controlled experiments (RCTs) have yielded contradictory findings, resulting in uncertainty about the optimum dosage and supplementation regimes, as well as the overall efficiency of vitamin D and calcium supplements for fracture prevention [52].

Fracture risk increases with osteoporosis because of decreased bone density and microstructure fragmentation [53]. Every two women and every five males over the age of 50 will have an osteoporotic fracture. There is a 30% likelihood of mortality one year following a hip fracture [54], which is the most deadly form of osteoporotic fracture. People who are 60 years old and beyond are more likely to have a hip fracture than those who are younger [55].

The absorption of calcium, the production of osteoid tissue in bone mineralization and the function of muscles are all made possible by vitamin D. Secondary hyperparathyroidism, bone thinning and muscle wasting are all symptoms of low vitamin D levels [56].

Observational studies have linked lower blood levels of 25-hydroxyvitamin D (25[OH]D) to an increased risk of falls and fractures. In a mendelian randomization trial, vitamin D had no positive effects on fracture, however the study had a weak instrument bias and was tested in groups with a low overall risk of fracture [57]. Supplementation with 800 international units of vitamin D and 1200 milligrams of Calcium per day has been suggested for the prevention of fractures in senior residents of institutions and those with low levels of vitamin D [58].

RCTs and meta-analyses of vitamin D alone or in combination with calcium for the prevention of fractures among patients in the community or in institutions have showed no effect [59]. Fall risk factors, fall descent, impact and bone strength all have a role in the fracture rate, which is around 10% of all falls. Falls are a leading cause of fractures and mortality among the elderly, thus fall prevention is critical. Environmental dangers, training routes and hip guards, as well as prudent use of support devices and balance exercises, are some of the ways to prevent falls [60]

Vitamin D and calcium supplementation may impact calcium homeostasis, muscular strength, body sway, parathyroid hormone production, and bone resorption, hence reducing the risk of falling. Deficiency in vitamin D and calcium intake can lead to a rise in serum parathyroid hormone (PTH) levels, which can contribute to bone loss and turnover. PTH levels may be lowered and body sway improved by treatment with vitamin D and calcium. The risk of tripping and falling may be reduced by reducing body sway [60]. Vitamin D and PTH work together to keep calcium levels in the blood and bones balanced by adjusting absorption from the small intestine. Vitamin D deficiency can hinder the absorption of calcium from the diet. Bones may become weaker as a result of the loss of calcium in the bones. Vitamin D and calcium insufficiency can also induce hyperparathyroidism which results in accelerated bone turnover, bone loss and fractures. Bone mineral density (BMD) and fracture rates were lowered by treatment with vitamin D and calcium [60].

Vitamin D treatment and fracture reduction

Debate persists about whether vitamin D supplementation can prevent low-level trauma or osteoporosis fractures. 3270 older French women were given (800 IU vitamin D3) and (1200 mg calcium) daily for three years which decreased the hip fracture risk of by 43 percent and non-vertebral fracture by 32 percent [61]. 38 389 people over 65 who received vitamin D3 (700 IU) and calcium (500 mg) daily had a 58% decrease in non-vertebral fractures [62]. For postmenopausal women, a research found that vitamin D decreased the risk of vertebral fractures (RR 0.63, P 0.01) and suggested a tendency toward a lower risk of non-vertebral fractures (RR 0.77, 95% P= 0.09) [47]. There was a meta-analysis conducted in 2005 that attempted to reconcile the conflicting findings. The incidence of non-vertebral or hip fractures was shown to be unaffected by 400 IU of vitamin D3 per day in a meta-analysis of seven randomized clinical studies [63]. Although studies employing dosages of 700–800 IU of vitamin D3 daily have shown a 26% reduction in hip fractures and a 23% reduction in non-vertebral fractures when compared to calcium or placebo [42]. In contrast, a large-scale research undertaken by the Women's Health Initiative indicated that 400 IU of vitamin D3 and 1000 mg of calcium per day increased the incidence of kidney stones in more than 36,000 postmenopausal women. However, the study found no influence on the risk of hip fracture. As a result, it is possible that low vitamin D levels in the WHI trial are the cause [64]. Using data from nine studies, Jackson *et al*.[65] found that vitamin D3 supplementation reduced the incidence of falls and fractures among postmenopausal women. That vitamin D3 prevented falls had a pooled relative risk (RR) of 0.88 (95% confidence interval: 0.78–1.00). There was no significant difference in the pooled RR of vitamin D3 prophylaxis for nonvertebral fractures (0.96) (95% CI 0.84–1.09) and for vertebral fractures (1.22) (95 percent CI 0.64–2.31). Vitamin D3 had a combined relative risk (RR) of 0.92 (95 percent confidence interval [CI] of 0.75–1.12) for the prevention of falls, while the combined

relative risk (RR) for the prevention of non-vertebral fractures was 0.81 CI] (0.48–1.34) for postmenopausal women. For osteoporosis, vitamin D3 alone can reduce the chance of falling, recommended that vitamin D3 must be an important part of successful treatment. The mismatch between the meta-analysis and current study is most likely related to target populations differences and publication bias. The general population is unlikely to benefit from high-dose vitamin D, even if it is good for persons in institutions [66].

It's critical to consume adequate vitamin D since it aids with calcium absorption, bone health, muscular function, balance and falls risk. Clinical guidelines from the National Osteoporosis Foundation for osteoporosis prevention and therapy in 2008 recommend that those over 50 consume 800–1000 IU of vitamin D3 daily. Consumption of this dose of vitamin D will raise the average adult's serum 25(OH)D levels to 30 ng/mL or more [67].

Conclusion

Bone density, bone turnover, and fracture risk have all been found to be affected by vitamin D supplementation in the majority of clinical trials. Uncertainty persists on whether supplementing with vitamin D is beneficial simply for those who are vitamin D deficient or whether it should be done for the general older population. Some studies suggest that it works best with those who have been institutionalized. It's not clear if increasing vitamin D doses can boost the reaction or if there is a dose-response relationship. Taking calcium supplements is a major concern. In order for vitamin D to be effective, numerous meta-analyses suggest that it should be supplemented with calcium. On the other side, a meta-analysis of calcium supplementation studies indicated that it may increase the risk of heart disease. Another debate is whether vitamin D should be administered to everyone over the age of 65, or only those who are at risk. In addition, the optimal dosage may be affected by genetic polymorphisms, chronic diseases, and co-medication.

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