Chapter

# Hypovitaminosis D in Postmenopause

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## Abstract

Hypovitaminosis D is a common health problem in postmenopausal women that predisposes to the development of various conditions, such as difficult-to-manage osteoporosis, cardiovascular diseases, metabolic syndrome, autoimmune diseases and cancer. In the last two decades, the extensive role of vitamin D has been characterized, where besides controlling bone mineral metabolism, it also precisely regulates the immune system and metabolism. Early detection of hypovitaminosis D can help provide timely care to improve the health of postmenopausal women. This chapter aims to discuss the most relevant aspects of vitamin D in postmenopausal women and the probable consequences that it has on the development of pathological processes characteristic of this stage.

**Keywords:** postmenopause, hypovitaminosis D, vitamin D sufficiency, vitamin D insufficiency, vitamin D deficiency, post-menopausal osteoporosis, vitamin D immunomodulation

## 1. Introduction

The reproductive system in women experiences a senescence process called menopausal transition. It leads to an imbalance in estrogenic hormonal regulation that is evident around the fifth to sixth decade of life [1–3]. Ovarian insufficiency during menopausal transition, triggers a series of adaptive physiological responses to estrogen reduction, producing clinical signs and symptoms related to central nervous system disorders, cardio-metabolic changes, musculoskeletal disorders, urogenital and skin atrophy, and sexual dysfunction [4]. After this period, menopause occurs. It is the last menstruation and represents the end of a woman's reproductive life. Nowadays, a demographic aging phenomenon is occurring worldwide, and it has been accompanied by a gender transition [5]. Indeed, the life expectancy of women will reach 82 years in 2025, which implies that one-third of women will have postmenopause [6].

Hypovitaminosis D is a public health problem considered a pandemic. In Mexico, we have a prevalence of hypovitaminosis of 89.79% in postmenopausal women. Hypovitaminosis D status in this population has been associated with musculoskeletal problems and a wide range of acute and chronic diseases, including heart disease,

autoimmune diseases, metabolic syndrome, and obesity [7, 8]. Furthermore, it can cause secondary hyperparathyroidism in most patients, increasing bone loss and the risk of developing osteomalacia, and predisposing to fragility-fractures in the elderly [9, 10]. It is thought that vitamin D deficiency, defined as serum concentrations of 25-hydroxy-vitamin D (25OHD) <30 nmol/L or <20 ng/mL, should be corrected. However, we have observed that also vitamin D insufficiency, defined as serum levels <50 nmol/L or <29 ng/mL, must also be corrected. Most international guidelines define vitamin D sufficiency as serum levels of 25OHD >50 nmol/L or >29 ng/mL to achieve optimal bone health in older adults. However, we have found that sufficiency levels should even be considered between 40-50 ng/mL of 25 OHD. In selected populations, randomized controlled trials (RCTs) with vitamin D and calcium supplementation, have shown a decrease in the incidence of hip fractures and non-vertebral fractures by ~15%, with the greatest effect in people 80 years or older [11, 12].

## 2. Vitamin D as a hormone

Formally, vitamin D is defined as a non-essential nutrient. However, It should be considered a hormone because of its biotransformation and transport, and the multiple functions it has in various enzymatic, metabolic, physiological, and even pathophysiological processes [13]. This concept makes the skin and liver the primary glands for the synthesis of vitamin D. As a result, cholecalciferol should be considered a prohormone, transformed into its active form by those organs that express the CYP27B1 enzyme, (mainly the kidney and the immune system), changing Cholecalciferol to Calcitriol. Considering the above, and adding the mechanism of action of vitamin D, this system would be quite reminiscent of the axis of thyroid hormones. Therefore, the concept of "Hormone D" should be considered a serious proposal [14, 15].

### 2.1 Rich sources of vitamin D

As vitamin D is considered a non-essential nutrient instead of a hormone, it is thought to mostly be acquired through diet. However, it is mainly obtained through an endogenous synthesis that begins in the skin after sunlight exposure. Nonetheless, it is important to address the main nutritional sources that provide vitamin D, since they provide the remaining 10% of daily requirements. The addition of vitamin D in dairy products was effective in the 1930s in the attempt to eradicate Rickets. Adolf Windaus, the Nobel Prize in Chemistry in 1928, had already described this process, in the studies on the constitution of sterols and their connection with vitamins [16, 17]. As we mentioned above, the major source of vitamin D is the production in the skin, which synthesizes 90% of the total vitamin D that we require daily. The rest is obtained through the diet. Plant-based products mainly provide ergocalciferol or vitamin D2, while animal-based products provide vitamin D3. Although current diets are theoretically considered sufficient in vitamin D, many countries have a high prevalence of malnutrition, like Mexico and other Latin American countries; so, this assumption cannot be generalized. As we have already mentioned, the diet only provides a small proportion of the daily needs of vitamin D. If we depended only on the diet completely to accomplish the daily vitamin D requirements, we would face serious problems since the amount of vitamin D in food is very low. For instance, the amount of vitamin D in international units (IU) in egg yolk is 44 IU, if the total

| Food and portion | IU of Vitamin D | Amount per day to obtain 4000 IU |
|---|---|---|
| Cod liver oil, 1 tablespoon | 1360 IU | 4 spoons |
| Cooked trout, 3 ounces | 645 IU | 18 ounces |
| Cooked salmon, 3 ounces | 570 IU | 21 ounces |
| Mushrooms, white, raw, sliced, exposed to UV light, ½ cups | 366 IU | 5 ½ cups |
| Milk, 2% milkfat, fortified with vitamin D,1 cup | 120 IU | 33 cups |
| Sardines (Atlantic), canned in oil, drained, 2 sardines | 46 IU | 172 sardines |
| 1 egg yolk | 44 IU | 90 eggs |
| Tuna, canned in water, 3 ounces | 40 IU | 300 ounces |
| Cheddar cheese, 1.5 ounces | 12 IU | 500 ounces |

*Adaptation from: [18].*

**Table 1.**
*Food requirements to meet the daily amount of vitamin D.*

needs depended on the diet, it would require 90 eggs per day to get almost 4000 IU of vitamin D from the diet, something unreasonable. **Table 1** shows some examples of these relationships [19–22].

The relevance of sun exposure comes from the impossibility of achieving sufficient vitamin D requirements solely through diet. However, the question would be, how much sun exposure is required to synthesize optimal vitamin D levels per day. That is known as the minimum erythema dose (MED), defined as the dose of ultraviolet B radiation (UV-B) radiation necessary to produce perceptible erythema after 24 hours of irradiation in an exposed subject. Exposure equivalent to 1/4 of the MED on the face, hands and arms produces approximately 1000 IU of vitamin D, while exposure equivalent to 1/6 produces 200 to 600 IU [23]. We have observed that at least 4000 IU daily of vitamin D are needed to reach sufficient serum levels of 25(OH) between 30-50 ng/mL. However, as we can analyze, we need a rich diet in vitamin D and high sun exposure, difficult to achieve because of several social issues. Moreover, high exposure to the sun's rays could also predispose to developing melanoma. Therefore, the daily use of vitamin D supplements could be the best source to get the daily requirements.

## 2.2 Vitamin D synthesis

Being endogenous synthesis the most important way to obtain vitamin D, we are going to explain the process briefly. After exposure to UV-B rays with a wavelength of 290 to 320 nm in the skin (basal layer of the epidermis), pre-vitamin D3 is synthesized from 7-dehydrocholesterol or pro-vitamin D, which is thermally unstable; therefore, it is spontaneously isomerized into vitamin D3. On the other hand, vitamin D2 and D3 obtained from the diet, are absorbed in the small intestine with the help of bile acids and later transported to the liver. The blood transport of vitamin D2 and vitamin D3 is done through the vitamin D-binding protein (DBP). Once in the liver, the 25 (OH) or vitamin D3 is bio-transformed through enzymes from the P450 complex that includes the CYP2R1, CYP3A4, and CYP2J3 [24, 25].

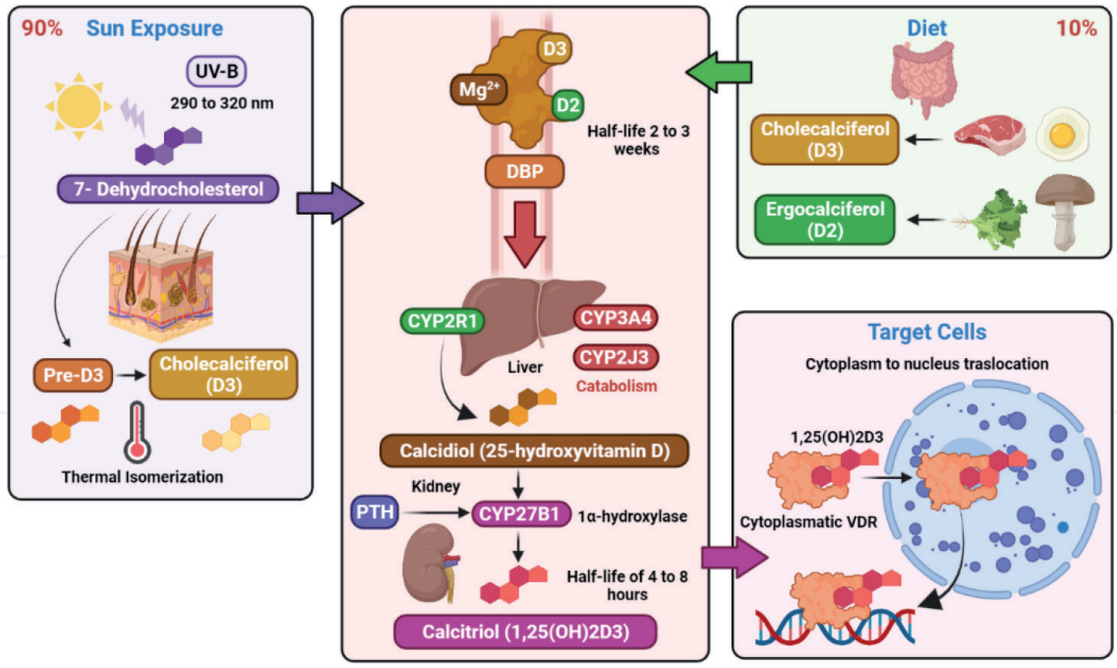



**Figure 1.**
*Vitamin D synthesis pathway.*

The main circulating form of vitamin D is vitamin D3, which has a half-life of approximately 2-3 weeks in the blood. This inactive form is transported from the liver to the kidney by DBP. Then, it is transformed into the active form in the proximal tube, the 1-alfa,25-dihidroxicolecalciferol (1,25 (OH) 2 D3) or calcitriol that has a half-life of 4 to 8 hours. This biotransformation is carried out by 1α-hydroxylase, also known as CYP27B1. This is expressed in renal tubular cells after stimulation by the parathormone (PTH). CYP27B1 synthesis is inhibited by high levels of calcium (Ca), phosphorous (P), fibroblast growth factor 23 (FGF23), and 1,25 (OH) 2 D3 itself by the action of 24-hydroxylase that produces 24,25 (OH) 2 vitamin D3 [26–28]. The 1,25 (OH) 2 D3 finally interacts with the vitamin D receptor (VDR) to exert its physiological function. Magnesium ($Mg^{2+}$) plays an essential role in some of the previously identified steps, such as the binding of vitamin D2, D3, and 1,25 (OH) 2 D3 to DBP, as well as the renal and hepatic hydroxylation for producing 25 (OH) D and the 1,25 (OH) 2 D. Thus, a magnesium deficiency could be relevant for the synthesis and transportation of vitamin D (**Figure 1**) [29].

## 2.3 Mechanism of action

After obtaining the bio-active form of vitamin D, the interaction with the vitamin D receptor (VDRs) is essential to carry out all its functions. VDRs were initially described in the cytoplasm and the nucleus. Still, they were also found in some fundamental organelles, such as mitochondria [30]. This location reinforced the notion of non-genomic effects on vitamin D. Firstly, 1,25 (OH) 2 D3 interacts with the VDR located in the cytoplasm to form a complex VD/VDR. Then, VD/VDR complex is translocated to the cell nucleus to produce the modulation of multiple target genes, especially those that mediate the bone-mineral metabolism [31]. However, the 1,25 (OH) 2 D3 also regulates genes associated with malignant cell potency, hormone secretion, cytokines, and transcription factors that modulate immune cells. It is important to emphasize that estrogens increase VDRs in certain

cells, such as osteoblasts, osteoclasts, and immune cells [9]. Therefore, there is a close relationship between estrogen regulation and vitamin D responsiveness, which could have important consequences in conditions of estrogen deficiency, such as postmenopause.

The VDR gene has many copies in each subject, with several polymorphisms. The main polymorphism modifications occur in promoter and exon regions that have been studied using restriction enzymes, such as BsmI, ApaI, TaqI, and FokI [32]. People could be homozygous and heterozygous for any polymorphism. Indeed, each person has a combination of them due to their co-dominance property, similar to what happens with the Major Histocompatibility Complex (MHC). Hence, haplotype is the name given to the combination of the different polymorphisms in each person. Each different haplotype determines the responsiveness of the cells to vitamin D and can predispose them to develop some diseases, such as cancer or autoimmune diseases [33–37]. The recessive VDR-Bmsl GA/GG polymorphism and the heterozygous recessive VDR-Fokl Ff/FF polymorphism predispose to developing breast cancer. The homozygous dominant VDR-Bmsl BB polymorphism, the homozygous dominant VDR-Fokl FF polymorphism, and the homozygous dominant VDR-CDX2 GG polymorphism predispose to developing ovarian cancer [38]. Also, the fF/bB+ff/BB+FF/bb haplotype is more frequent in women with gestational hypertension and vitamin D deficiency [39]. Regarding the non-genomic effect, it is an action that takes place shortly, such as the mobilization of calcium contained in intracellular vesicles, or the activation of enzymes that metabolize phosphatidylinositol acid.

Moreover, recent studies have shown non-classical extraosseous effects of vitamin D, which are mainly related to immunomodulation and could play an important role in different autoimmune and autoinflammatory diseases, such as Type 1 Diabetes Mellitus, Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA), Inflammatory Bowel Disease (IBD), Psoriasis, among others [40, 41].

## 3. Postmenopause and hypovitaminosis D

As vitamin D is fat-soluble and requires bile salts to be absorbed in the duodenum, malabsorption syndromes could have significant consequences in this process. Therefore, the absorption of vitamin D is significantly affected by short bowel syndrome, celiac disease, cystic fibrosis, pancreatic insufficiency, and cholestatic liver diseases. Likewise, it is affected by the low intake of vitamin D in the elderly population and the amount of vitamin D in the different types of diets [42, 43].

As a result of current human behavior (long stays in hospital, the use of sunscreen, religious reasons), there is a significant deficiency of vitamin D. The type of skin also decreases the synthesis of vitamin D since melanin is a natural blocker of ultraviolet rays, slowing down the production of vitamin D. Also, age decreases vitamin D synthesis in the skin, whereby hypovitaminosis is very marked in postmenopausal women [44–46].

Chronic liver diseases such as cirrhosis and liver failure may have a defective hydroxylation that leads to a lack of vitamin D activation.

Likewise, renal biotransformation can be affected by hyperparathyroidism, renal failure, 1-α hydroxylase deficiency, and in elderly patients whose hydroxylation is decreased due to an idiopathic cause. Some drugs can induce hepatic p450 enzymes, which leads to increased vitamin D degradation, including phenobarbital, carbamazepine, tamoxifen, rifampin, spironolactone, dexamethasone, nifedipine, and clotrimazole, which activate the Pregnane X receptor (PXR) [47].

Obese people have a higher risk of vitamin D deficiency due to the decrease in its availability; since vitamin D is a fat-soluble vitamin, it might be sequestered in body fat. Moreover, adipose tissue has VDR receptors, so it could act as a sponge that also sequesters 80% of serum vitamin D, especially when the waist perimeter exceeds 85 cm [48, 49]

Moreover, the production of vitamin D could be affected by some polymorphisms, mutations, or epigenetic changes in genes associated with endogenous production, such as the gene of the CYP27B1 enzyme.

### 3.1 Postmenopausal osteoporosis and hypovitaminosis D

Osteoporosis is a condition most favored by the state of hypovitaminosis D in postmenopause. According to the National Institutes of Health Consensus Development Panel on Osteoporosis, it is defined as "a skeletal disorder characterized by compromised bone strength leading to an increased risk of fracture." According to the criteria of the World Health Organization (WHO), osteoporosis is defined as a bone mineral density that is 2.5 or more standard deviations (SD) below average [50, 51]. In February 2010, the United States Preventive Services Task Force conducted a systematic review of trials published and concluded that vitamin D reduced falls by 17% (95% CI, 11%-23%) over 6 to 36-month follow-up [52]. In the last decade, commercial assays for 25(OH)D have become widely available, allowing researchers to easily measure vitamin D stores in people. Subsequently, many research studies indicated that higher levels of 25(OH)D were associated with higher calcium absorption efficiency, lower risk of secondary hyperparathyroidism, higher bone mineral density, and lower risk of fractures. Physiopathological situations can be associated with the natural effect of aging and secondary hypoestrogenism (**Figure 2**).

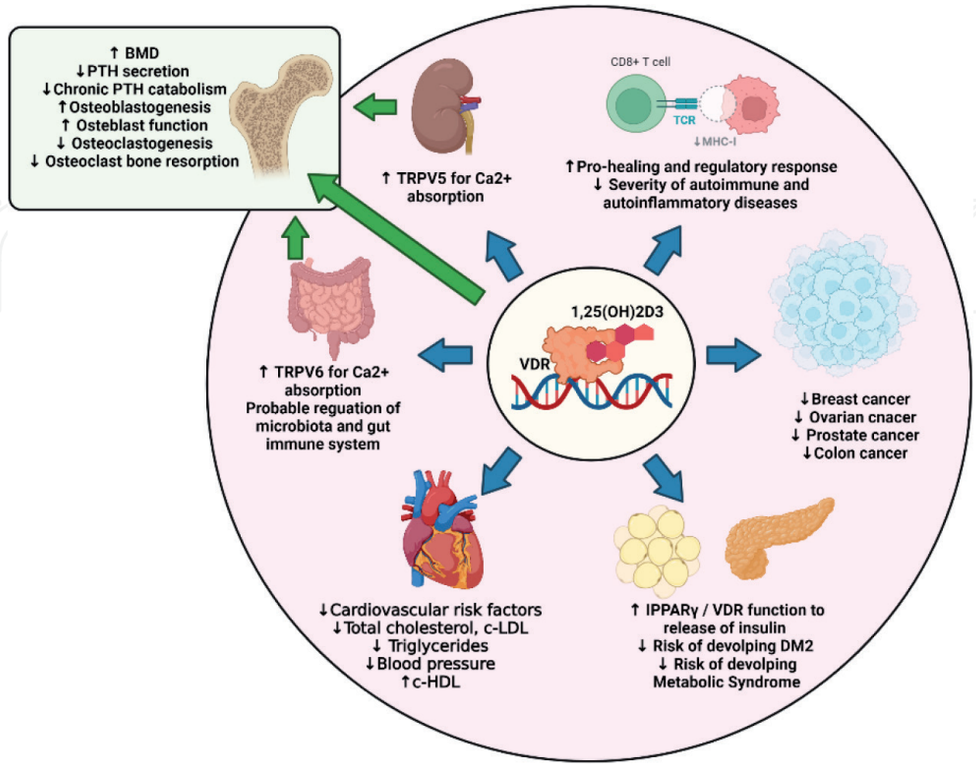



**Figure 2.**
*Effects of vitamin D on different organs and tissues.*

In 2005, six experts reviewed the literature and published a paper indicating that the optimal vitamin D level for bone health was 30 ng/mL or greater (75 nmol/L). However, others stated that a 25(OH)D level of 20 ng/mL or greater (50 nmol/L) was adequate. Laboratories across the country adopted 30 ng/mL as the new threshold showing regular stores of vitamin D.

The Institute of Medicine will improve a vitamin D intake of 400 IU/d for people between the ages of 0 and 1 year, 600 IU/day for people between 1 and 70 years (including pregnant and lactating women), and 800 IU/day for those older than 70 years [50]. However, we have already mentioned that most of the beneficial effects of vitamin D, both in bone-mineral metabolism and in the immune system, are reached when serum levels get between 30-50 ng/ml.

### 3.2 Vitamin D supplementation remit hyperparathyroidism

Intermittent pulses of parathyroid hormone (PTH) have shown to be osteo-anabolic. However, chronic exposure to high levels of PTH, like hyperparathyroidism, is catabolic for bone. Vitamin D therapy can reduce PTH levels and improve bone mineral density (BMD). Therefore, the serum level of 25(OH)D that minimizes PTH is relevant for bone health, particularly among individuals with normal renal function. Some authors concluded that the risk of secondary hyperparathyroidism was significantly reduced when serum 25(OH)D levels exceeded approximately 20-30 ng/ml [50].

Our experience has demonstrated that most of our post-menopausal patients with hypovitaminosis D also suffer from hyperparathyroidism and all respond to vitamin D supplementation. Indeed, we have had patients with levels above 30 ng/ml with hyperparathyroidism that also remit after vitamin D supplementation. Interestingly, the remission of hyperparathyroidism avoids the catabolism of bone and improves BMD in patients with severe osteoporosis [53]. Thereby, this is why we have questioned the current cut-off levels of "vitamin D sufficiency". Therefore, vitamin D sufficiency should be considered only when vitamin D serum levels are between 40-50 ng/ml, especially in postmenopausal women.

Currently, it exists a controversy regarding the dose of complementary administration of vitamin D. The Osteoporosis Clinical Practice Guidelines in Mexico recommend the administration of 1000 mg of calcium and 800 IU of vitamin D per day in women with postmenopausal osteoporosis. However, we have observed that supplementation with 4000 IU daily achieves an improvement in serum levels of vitamin D (41.7 ng/dL) with no adverse effects.

### 3.3 Glucose, vitamin D and Type 2 Diabetes Mellitus (DM2)

In obese postmenopausal women, lipid peroxidation can promote the sequestration of vitamin D in adipose tissue, increasing the risk of developing DM2 [54]. There are several mechanisms that could explain the association between glucose alterations, diabetes mellitus, and vitamin D, such as the relationship between the VDR and 1-α-hydroxylase in beta cells of the pancreas, as well as the interaction between the peroxisome proliferator-activated receptor γ (PPARγ) and the VDR to release insulin [55].

### 3.4 Biochemical and clinical markers of cardiovascular risk related to hypovitaminosis D

Dyslipidemia and high blood pressure are important cardiovascular risk factors in postmenopausal women. A recently published meta-analysis including 81 studies,

suggests that vitamin D supplementation is useful in protecting against cardiovascular disease by improving risk factors, including high blood pressure, hyperparathyroidism, dyslipidemia, and chronic inflammation. There were observed beneficial effects on lipid levels and high-sensitivity C-reactive protein (hs-CRP) after vitamin D supplementation. A dose of 3000 IU/day of vitamin D, showed a significant reduction in total cholesterol, LDL cholesterol (cLDL), and triglycerides, with an increase in HDL cholesterol (cHDL). Subgroup analysis showed that the effect on triglycerides and cHDL was more significant in participants who received vitamin D supplementation for ≥6 months. hs-CRP concentrations were slightly lower with vitamin D doses ≥4000 IU/day compared with lower doses [56].

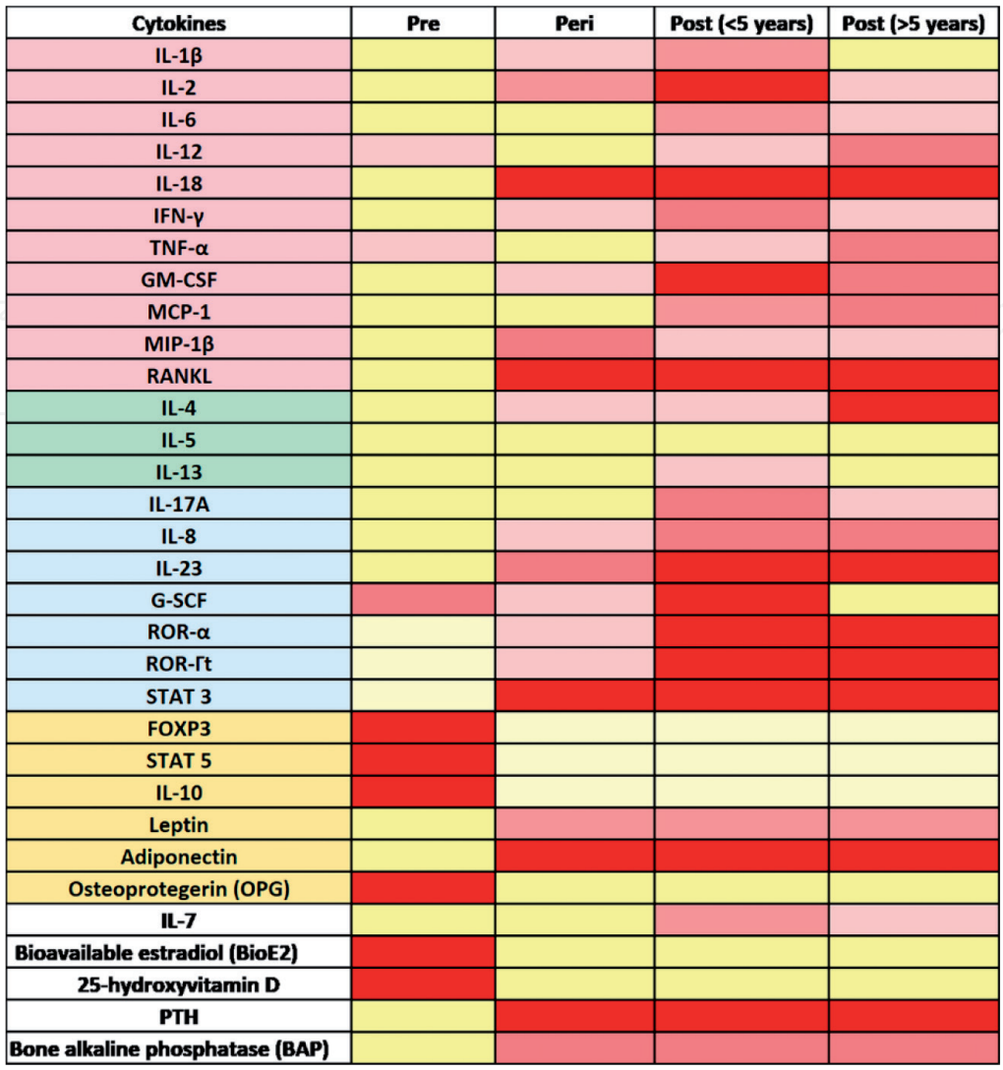
Arterial hypertension is the main cardiovascular risk factor that affects women. Cardiovascular aging is accelerated by the presence of risk factors that appear in postmenopause. The increased stiffness of the large arteries results in a larger pulse wave that increases arterial hypertension [57].

Some studies suggest that vitamin D deficiency can predispose to developing high blood pressure. Possible mechanisms in the association of vitamin D and blood pressure include an inverse relationship between vitamin D concentrations and the renin-angiotensin-aldosterone system (RAAS), as well as the prevention of secondary hyperparathyroidism [58]. Furthermore, high levels of PTH are related to vitamin D deficiency, which can be related to myocardial hypertrophy and elevated blood pressure.

## 4. Vitamin D and the immune system

Vitamin D plays an important role in the function of the immune system. The cessation of estrogens is typical in menopause and affects the function of the immune system, favoring a change in the basal immune response. After this event, the systemic immune response tends to be polarized towards a mixed type 1 and type 3 pro-inflammatory response, which is associated with the pathogenesis of multiple diseases. Type 1 and type 3 responses could be essential in the pathophysiology of various conditions in postmenopause. The mixed pro-inflammatory response that we previously mentioned generates an increase in other pro-inflammatory serum cytokines, such as TGF-β, adiponectin, adipsin, plasminogen activator inhibitor-1 (PAI), IL-6, IL-7, IL-12, IL-17 and IL-23, and decreases cytokines associated with a regulatory response or pro-healing type 2 response, such as IL-4 and IL-10 (**Figure 3**) [59–70].

Regarding the adaptive immune system cells, the number of CD4 T cells decreases with a predominance of T helper cells (Th) with Th1 and Th17 phenotypes. In addition, the number of CD8 T cells increases, causing a reversal of the CD4/CD8 cell ratio [71]. It is still to be discerned the importance of the type 3 response in the pathophysiology of classic postmenopausal disorders. Nevertheless, the involvement of this mixed pro-inflammatory response could explain many cases of treatment-resistant osteoporosis that have occurred in our clinic. The treatment of osteoporosis is often focused on inhibiting the action of the osteoclast and the RANKL pathway to enhance the synthesis of bone mineral matrix by osteoblasts. However, the osteoclastic and osteoblastic functions can also be regulated by other cytokines and cells from both type 1 and type 3 responses (**Figure 4**). Studies in murine models with monoclonal antibodies anti-IL-17 and anti-IL-23 have demonstrated to be capable of reducing the expression of pro-inflammatory cytokines type 1 and 3 and increasing the BMD, either



| Cytokines | Pre | Peri | Post (<5 years) | Post (>5 years) |
|---|---|---|---|---|
| IL-1β | | | | |
| IL-2 | | | | |
| IL-6 | | | | |
| IL-12 | | | | |
| IL-18 | | | | |
| IFN-γ | | | | |
| TNF-α | | | | |
| GM-CSF | | | | |
| MCP-1 | | | | |
| MIP-1β | | | | |
| RANKL | | | | |
| IL-4 | | | | |
| IL-5 | | | | |
| IL-13 | | | | |
| IL-17A | | | | |
| IL-8 | | | | |
| IL-23 | | | | |
| G-SCF | | | | |
| ROR-α | | | | |
| ROR-Γt | | | | |
| STAT 3 | | | | |
| FOXP3 | | | | |
| STAT 5 | | | | |
| IL-10 | | | | |
| Leptin | | | | |
| Adiponectin | | | | |
| Osteoprotegerin (OPG) | | | | |
| IL-7 | | | | |
| Bioavailable estradiol (BioE2) | | | | |
| 25-hydroxyvitamin D | | | | |
| PTH | | | | |
| Bone alkaline phosphatase (BAP) | | | | |

**Figure 3.**
*Heat map of cytokine impairment during perimenopause and post-menopause.*

of cancellous and cortical bone [72]. Anti-IL-23 treatment also inhibits osteoclastogenesis and promotes osteogenic differentiation of mesenchymal stem cells (MSCs).

Also, anti-IL-17 therapy has shown a greater improvement in BMD and a greater decrease in type 1 and type 3 cytokines, compared to monoclonal anti-RANKL and anti-TNFα [73]. Although hormone therapy has shown an effect in reducing IL-2, TNF-α, and even IL-17, it does not completely reverse the effects of immune dysregulation.

### 4.1 The non-classical role of vitamin D on the immune system and the consequences of hypovitaminosis in postmenopausal women

This impairment in the immune response has also been associated with a state of hypovitaminosis D and hyperparathyroidism in post-menopause [74–76]. Vitamin D is an essential hormone to maintain the homeostasis of bone mineral metabolism. However, vitamin D also plays a vital role in maintaining a proper immune response. The active form of calcitriol has autocrine and paracrine effects on both innate and adaptive immune cells.

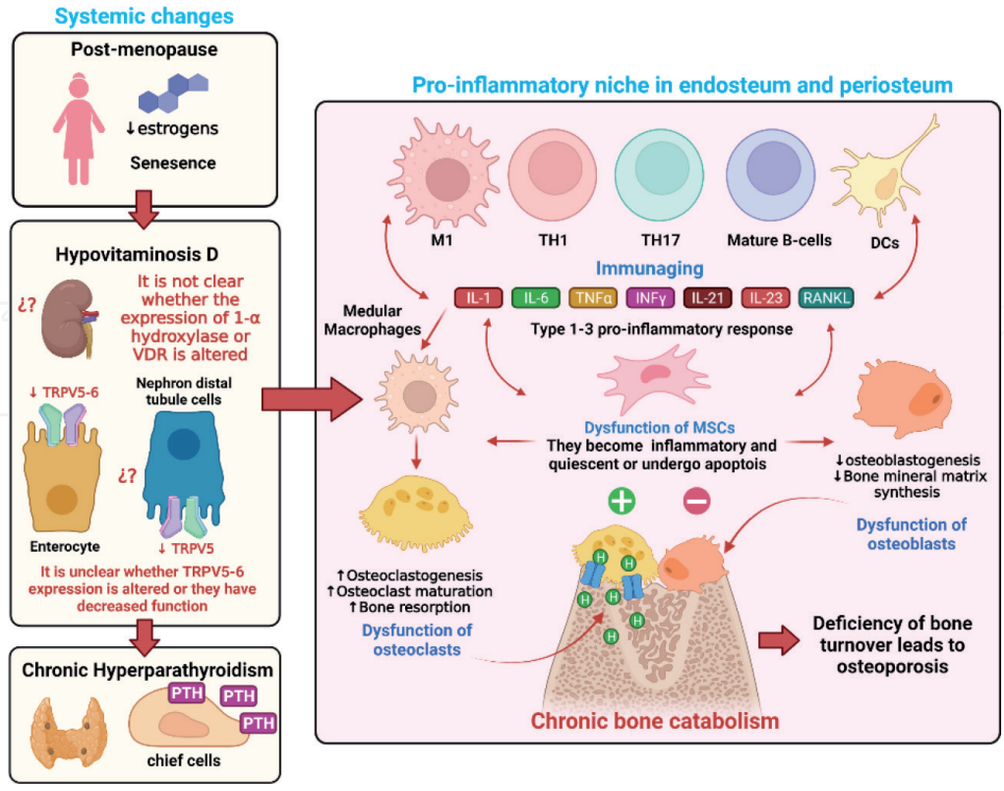



**Figure 4.**
*The effect of the mixed pro-inflammatory response type 1 and type 3 in bone homeostasis.*

Antigen-presenting cells (APCs), such as macrophages, dendritic cells, and B cells, express the enzyme 1-α-hydroxylase, also known as CYP27B1, an enzyme previously thought to be expressed only by renal tubular cells. This enzyme converts 25 (OH) to 1,25 (OH)2 D3 or calcitriol, the active form of vitamin D [77]. Contrary, T cells express a very low amount of this enzyme, thus requiring APCs to bio-transform 25 (OH) into 1,25 (OH)2 D3, illustrating the important role of APCs in regulating the bioavailability of calcitriol for T cells. Interestingly, CYP27B1 expression on APCs is increased after contact with their major histocompatibility complexes (MHCs) with T cell receptors (TCRs). This means that APCs can always use vitamin D, but in the case of T cells, vitamin D metabolism and utilization, only efficiently occur after antigen presentation (**Figure 5**) [78].

To understand better the function of vitamin D in the immune system, it is essential to remember the interaction between APCs and T cells, which comprises three signals wonderfully explained by Janeway [79]. The first signal corresponds to the initial contact of T-cells with APCs through the TCR and the MHC, besides the interaction of CD4 or CD8 co-receptors. The second signal comprises stimulation through the interaction of CD80 or CD86 with CD28, enhancing the state of lymphocyte activation. These interactions occur a dozen times within a close contact zone between the APC and the lymphocyte, called the immunological synapse. It is well known that these two signals trigger many downfall pathways either in the APCs and T cells. Regarding APCs, these pathways trigger the transcription of many cytokines, constituting the third signal, which helps to polarize the stimulated T-cells towards the distinct Th phenotypes. Moreover, these signals are necessary to enhance the transcription of the CYP27B1 enzyme, which stimulates the production of calcitriol in APCs, being released to lymphocytes with the rest of the cytokines as part of the third signal [80]. In this context, the stimulation of 1,25 (OH)2 D3

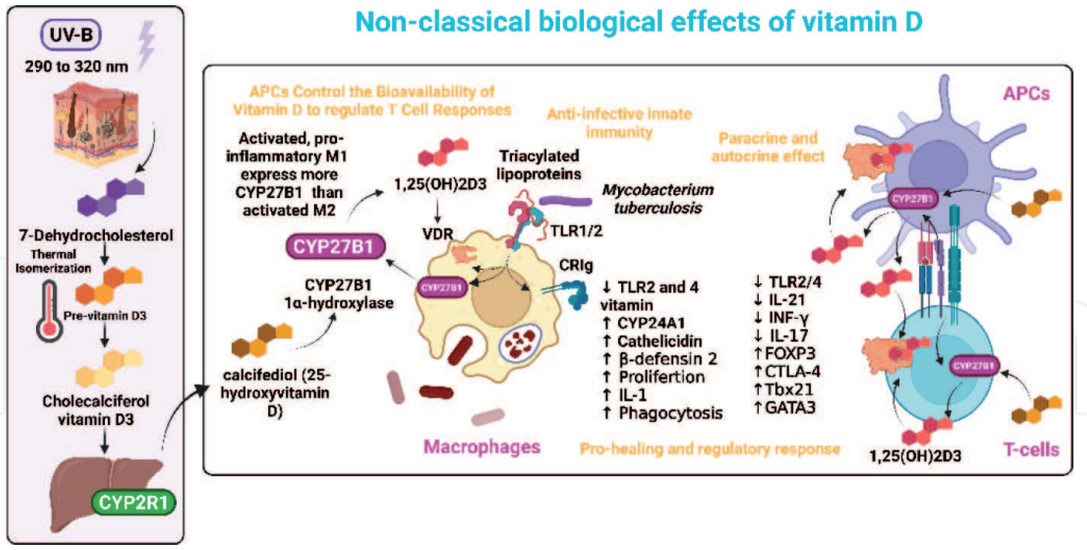



**Figure 5.**
*The role of vitamin D in both innate and adaptative immune systems.*

Decreases the production, of type I and type 3 proinflammatory cytokines, such as IL-21, IFN-γ, and IL-17, and stimulates the production of transcription factors and regulatory cytokines (such as FOXP-3, IL-10, and CTLA-4), as well as transcription factors that polarize the response towards a pro-healing type 2 response (such as GATA-3). Likewise, the autocrine stimulation of vitamin D on APCs produces a decrease in Toll-like receptors 2 and 4 and decreases their proliferation. Furthermore, calcitriol increases the production of CYP24A, cathelicidin, β-defensin 2, and IL-1. Together, these phenomena enhance the antimicrobial activity and phagocytosis of APCs without triggering an exaggerated inflammatory response, showing the undoubted capacity of immunomodulation that vitamin D possesses (**Figure 5**) [77–81].

This information suggests that vitamin D plays an essential role in every immune response, works as a handbrake to prevent excess production of proinflammatory cytokines, and helps to produce regulatory cytokines, optimizing the clearance process of pathogens or damaged products and promoting tissue repair and homeostasis. The immunomodulatory effect of vitamin D on type 1 and 3 responses helps to explain why high-dose vitamin D supplementation improves the severity of signs and symptoms in cohorts of patients with SLE and RA. Likewise, it aids in explaining why vitamin D has a protective effect on patients at risk of developing breast and ovarian cancer. In addition, it is possible to understand the relevance of hypovitaminosis D in cohorts of postmenopausal patients by knowing the role of vitamin D in the immune system.

This can have consequences on the bone and also on the immunological system, explaining why numerous women with post-menopausal osteoporosis do not show significant improvement in BMD with antiresorptive therapies or even with the monoclonal therapies based on RANKL neutralization until they receive supplementation with high doses of vitamin D. Moreover, improvement of hard-to-treat osteoporosis with vitamin D supplementation could be due to immunomodulation of osteoclastic function and other immune cells associated with bone marrow, endosteum and periosteum [82–87]. Future studies will be necessary to continue learning more about the relevance of immuno-endocrine effect of vitamin D. However, it is time to break with the dogma and start treating the hypovitaminosis D in our patients to achieve a proper performance of their immune systems.

## 5. Conclusion

Vitamin D or "Hormone D", has multiple functions on various tissues and organs, especially in the immune system. This important regulation over the immune system could explain why a deficiency of this hormone can predispose to the development of some pathological conditions in postmenopause women, such as osteoporosis, cancer, metabolic, and cardiovascular diseases. It is necessary to continue carrying out more studies to know the physiological scope of vitamin D, as well as to finish understanding the therapeutic benefits of reaching optimal levels of vitamin D.

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## Conflict of interest

The authors declare no conflict of interest.

## Note

All the images were created with BioRender.com.

## Abbreviations

| | |
|---|---|
| APCs | Antigen-Presenting Cells |
| BAP | Bone Alkaline Phosphatase |
| BioE2 | Bioavailable Estradiol |
| BMD | Bone Mineral Density |
| $Ca^{2+}$ | Calcium |
| CD | Cluster of Differentiation |
| cHDL | HDL cholesterol |
| cLDL | LDL cholesterol |
| CRIg | Complement Receptor of Immunoglobulin superfamily |
| CYP | Cytochrome P450 |
| CTLA | 4-Cytotoxic T-Lymphocyte Antigen 4 |
| DBP | Vitamin D Binding Protein |
| Dc | Dendritic cells |
| DM2 | Type 2 Diabetes Mellitus |
| D2 | Ergocalciferol |
| D3 | Cholecalciferol |
| FGF23 | Fibroblast Growth Factor 23 |
| FOXP3 | Forkhead Box P3 |
| GATA3 | GATA-binding protein 3 to DNA sequence [A/T]GATA[A/G] |
| G-CSF | Granulocyte Colony-Stimulating Factor |

| | |
|---|---|
| GM-CSF | Granulocyte-macrophage colony-stimulating factor |
| hs-CRP | High-sensitivity C-reactive protein |
| IBD | Inflammatory Bowel Disease |
| IL | Interleukin |
| INF-γ | interferon gamma |
| IU | International Units |
| MCP-1 | Monocyte Chemoattractant Protein-1 |
| MED | Minimum Erythema Dose |
| $Mg^{2+}$ | Magnesium |
| MHC | Major Histocompatibility Complex |
| MHCs | Major Histocompatibility Complexes |
| MIP | 1alpha-Macrophage Inflammatory Protein-1beta |
| MSCs | Mesenchymal Stem Cells |
| OH | Hydroxyl group |
| OPG | Osteoprotegerin |
| P | Phosphorous |
| PAI | Plasminogen Activator Inhibitor-1 |
| PPARγ | Proliferator-Activated Receptor γ |
| PTH | Parathormone |
| PXR | Pregnane X Receptor |
| RAAS | Renin-Angiotensin-Aldosterone System |
| RA | Rheumatoid Arthritis |
| RANKL | Receptor Activator for Nuclear Factor κ B Ligand |
| RCTs | Randomized Controlled Trials |
| ROR α | Retinoid-related orphan receptor alpha |
| ROR γ | Retinoid-related orphan receptor gamma |
| SD | Standard Deviation |
| SLE | Systemic Lupus Erythematosus |
| STAT | Signal Transducer and Activator of Transcription |
| TBX21 | T-Box Transcription Factor 21 |
| TCR | T cell receptor |
| TCRs | T cell receptors |
| TGF-β | Transforming growth factor β |
| Th | T Helper cells |
| TLR | Toll-like Receptor |
| TLRs | Toll-like Receptors |
| TNF-α | Tumor Necrosis Factor α |
| TRPV5 | Transient receptor potential cation channel subfamily V member 5 |
| TRPV6 | Transient receptor potential cation channel subfamily V member 6 |
| UV-B | Ultraviolet-B |
| VD | Vitamin D |
| VDR | Vitamin D receptor |
| WHO | World Health Organization |
| 1,25 (OH)2 D3 | 1-alfa,25-dihidroxicolecalciferol |
| 25OHD | 25-hydroxy-vitamin D |

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