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Vitamin D: Structure and Physiological Importance

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ABSTRACT

Vitamin D is a steroid hormone. Our body can synthesize vitamin D upon exposure to sunlight unlike all other vitamins, or obtain it from fortified foods or dietary supplements.

Interesting aspects have been clarified lately about this vitamin metabolism in the living cell and its different physiological roles concerning mineral and bone homeostasis, cardiovascular function, renal diseases, cancer and immune system modulation.

This review summarizes the impact of vitamin D and vitamin D metabolites (25-hydroxy vitamin D [25(OH)D] and 1,25-dihydroxy vitamin D [1,25(OH)2D]) in the human body.

KEY WORDS: Vitamin D, 25(OH)D, 1,25(OH)2D, Mineral metabolism, Bone metabolism, Diabetes, Cardiovascular diseases, Cancer, Immune system.

1. INTRODUCTION

Early in the 20th century, vitamin D was first described as a vitamin. Now, it is recognized as a fat-soluble vitamin, which acts as a hormone. Unlike a vitamin, which is an essential organic compound that cannot be synthesized by the body and must be ingested, vitamin D can be synthesized under ultraviolet radiation-B (UV-B: 290–320 nm) exposure (Ross, 2011; Sintzel, 2018). They are responsible for increasing intestinal absorption of calcium, magnesium, and phosphate, and many other biological functions after converting to active forms (Schmid and Walther, 2013; Omotosho, 2019).

Man can keep vitamin D levels in his body up by exposure to sunlight carefully on sunny days. Nevertheless, it may be better to consider vitamin D as an essential micronutrient at least during winter. Summer exposure to sunlight and supplementation in winter should keep vitamin D status on an optimal level in the body (Carlberg, 2014).

These requirements vary with age because of the decline in vitamin D biosynthesis with increasing age (Menezesa, 2014). The Food and Nutrition Board (FNB) of the Institute of Medicine (IOM) recommended dietary allowance (RDA) of vitamin D about 600 IU (15 μg) for children and adults up to age 70 and 800 IU (20 μg) for adults >70 years. This RDA is more than the previous recommended adequate intakes (AI) from 1997 of 200 IU (5 μg) daily for children and adults up to age 50 and 400- 600 IU (10-15 μg) for adults >70 (Ross, 2011; Phillips, 2011).

Vitamin D toxicity most often occurs from taking supplements. The low amounts of the vitamin found in food are unlikely to reach a toxic level, and a high amount of sun exposure does not lead to toxicity because excess heat on the skin prevents D3 from forming. It is advised to not take daily vitamin D supplements containing more than 4000 IU unless monitored under medical supervision (Norman, 2003; Holick, 2007).

Vitamin D toxicity has many symptoms such as hypercalcemia, hyperphosphatemia, hypercalciuria, renal calculus, ectopic calcification of soft tissues (kidney and lung), nausea, vomiting, loss of appetite, growth retardation, constipation, polyuria and dehydration (Buyuker, 2019).

Chemical Structure of Vitamin D: All the molecules collectively called vitamin D represents a group of fat-soluble secosteroids (steroids with a broken ring) produced by the photoconversion upon UV-B irradiation, so it is called "the sunshine vitamin" (Schmid and Walther, 2013; Omotosho, 2019).

Although vitamin D can occur in the diet, endogenous production is quantitatively much more important in most individuals. Therefore, vitamin D should be regarded as a substrate that is necessary for the synthesis of a family of hormones (Reid, 2004).

Several forms of vitamin D exist. They can be classified as the following (Figure.1) (Phillips, 2012).

Vitamin D2 (ergocalciferol): It is produced in plants, fungi and invertebrates by UV-B exposure (290-315 NM) of ergosterol (pro-vitamin D2) (Phillips, 2011; Holick, 2007; Japelt and Jakobsen, 2013).

Vitamin D3 (cholecalciferol): It is photolyzed by UVB-exposure of 7-dehydrocholesterol (pro-vitamin D3) in the skin of vertebrates including humans (Holick, 2007; Japelt and Jakobsen, 2013). The best sources of D3 are fatty fish (like salmon, mackerel, tuna and sardine), fish liver, red meat and liver of some animals (cow, beef, lamb and pork), Dairy products (milk, cheese and butter) and egg yolk (Schmid and Walther, 2013; Omotosho, 2019; Buyuker, 2019).

Vitamin D4 (22-dihydroergocalciferol): Vitamin D4 is produced in yeast, mushrooms and lichens (*Cladina* spp.) by UV-B exposure of 22,23-dihydro ergosterol (Phillips, 2012; Williams, 2011).

Vitamin D5 (sitocalciferol): It is produced from 7-dehydrositosterol in some plants like *Arabidopsis thaliana* under UV-B irradiation (Silvestro, 2018).

Vitamin D6 ((22*E*)-(24*R*)-Ethyl-22,23-didehydrocaIciol): It is converted from 7-dehydrostigmasterol) upon UV-B exposure (JCBN, 1982).

Vitamin D7: It is photolyzed from 7-dehydrocampesterol in some plants like in *Helianthus annuus* (sunflower) seed oil (Phillips, 2012).

The two major forms of vitamin D supplements are vitamin D2 and vitamin D3 (Holick, 2007). Both of them are produced commercially and found in dietary supplements or fortified foods as mentioned above (Ross, 2011).

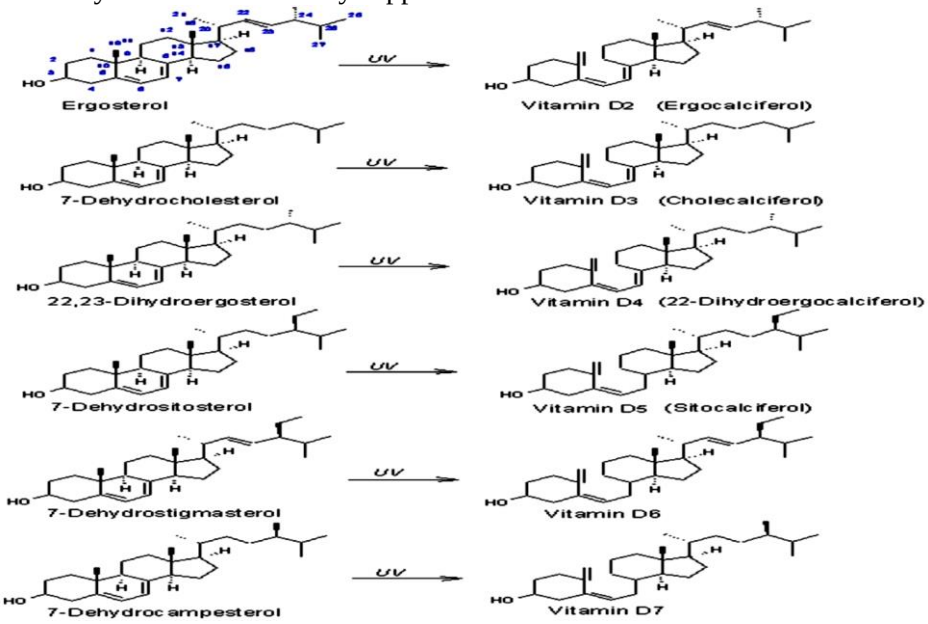

Figure.1. Structures of vitamin D types their sterol precursors (Phillips, 2012)

Vitamin D Metabolism in Human: During exposure UV-B, 7-dehydrocholesterol in the skin converts to provitamin D3, which instantly converts to vitamin D3 in a temperature-dependent process (Holick, 2007).

Vitamin D3 from the skin diffuses into the blood vessels, where it is transported to the liver by vitamin D binding protein (DBP). As for vitamin D from the diet (mainly vitamin D2 and vitamin D3), it is absorbed in the small intestine and combines with chylomicrons, enters the lymphatic system reaching the venous circulation and binds to DPB which carries it to the liver. Vitamin D (hereafter "D" stands for D2 or D3) is biologically inactive and the activation involves two hydroxylations processes (Holick, 2007; Japelt and Jakobsen, 2013). First, vitamin D is turned to calcidiol (25-hydroxyvitamin D [25(OH)D]) by vitamin D-25-hydroxylase. 25(OH)D is biologically inactive and must be converted in the kidneys by 25-hydroxyvitamin D-1α- hydroxylase (1-OHase) to the biologically active hormone calcitriol, (Figure 2) (1,25-dihydroxy vitamin D [1,25$(OH)_2$D]) (Ross, 2011; Sintzel, 2018; Holick, 2007; Nair and Mas, 2012; Chang and Lee, 2019).

It's worth noting that the half-life of 25(OH)D in the body is 15 days while the half-life of 1,25$(OH)_2$D is 15 h (Chang and Lee, 2019; Marcinowska, 2018).

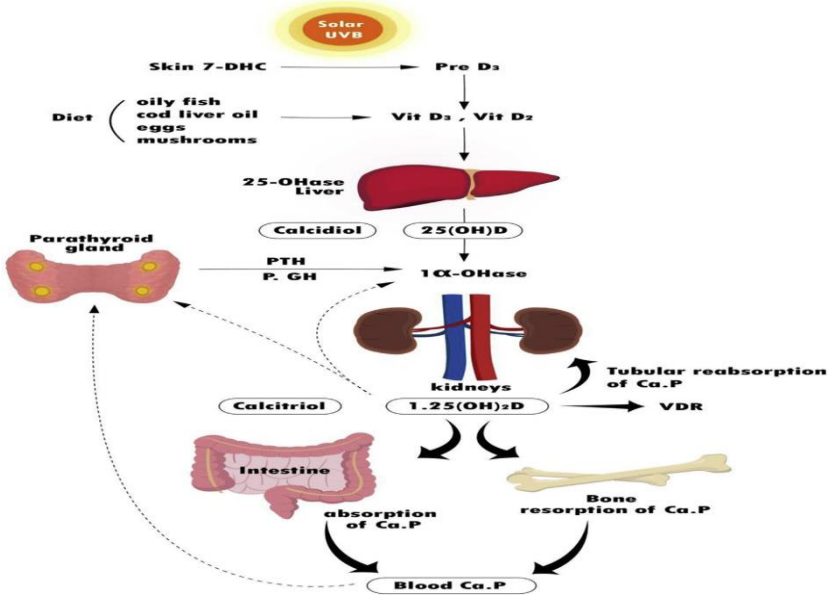

Figure.2. Vitamin D metabolism in the human body (Chang and Lee, 2019)

Vitamin D Deficiency: Although scientists didn't agree on the optimal level of serum 25(OH)D, most experts defined vitamin D deficiency as a 25(OH)D level less than 20 ng/ml (50 nmol/l) (Holick, 2007; Ferder, 2013). Vitamin D deficiency is common all over the world. It affects <20% of the population in Northern Europe, between 30–60% in Western, Southern and Eastern Europe and up to 80% in Middle East countries (Lips, 2019).

Consequences of vitamin D deficiency include mineralization disorder and lower bone mineral density. This leads to rickets in young children, osteomalacia in adults and increasing sway and frequent falls in the elderly increasing the risk of fracture (Perez-Lopeza, 2011; Gani and How, 2015). As to the non-skeletal consequences of vitamin D deficiency, they involve the increased risk of common cancers, cardiovascular disorders (coronary heart disease, hypertension, heart failure and stroke), autoimmune diseases and infectious diseases (Holick, 2007; Holick and Chen, 2008).

The Physiological Importance of Vitamin D:

Vitamin D and the metabolism of minerals and bone: Without vitamin D, 60% of dietary phosphorus and less than 15% of calcium are absorbed. The interaction of $1,25(OH)_2D$ with the vitamin D receptor increases the efficiency of intestinal calcium and phosphorus absorption to 40% and 80%, respectively (Holick, 2007).

In general, plasma calcium concentrations are maintained at a constant value, which is supersaturating concerning bone mineral. If the plasma becomes less than saturated with calcium and phosphate, mineralization fails which in its turn causes rickets amongst children and osteomalacia amongst adults (DeLuca, 2004).

Calcium and bone homeostasis are highly connected, as calcium is a main component of the bone and gives the skeleton its strength. On the other hand, the bone is the biggest store of calcium in the body. Accordingly, the bone structural integrity depends on adequate calcium supply from the serum and thus indirectly from intestinal absorption and renal reabsorption of calcium. Moreover, calcium can be taken from the bone to preserve normal serum calcium levels (Christakos, 2016).

Vitamin D induces the proteins involved in active intestinal calcium and phosphate absorption. Besides, even when an individual is under a no-calcium diet, blood calcium concentrations retain in the normal range. In this case, vitamin D stimulates osteoblasts to produce receptor activator nuclear factor-κB ligand (RANKL), which mediates differentiation, induces osteoclastogenesis and activates osteoclasts for bone resorption (DeLuca, 2004; Khammissa, 2018; Chacar, 2020; Charoenngam and Holick, 2020). Hence, vitamin D contributes to allowing individuals mobilizing calcium from the bone when it is absent from the diet. It is noteworthy that vitamin D, parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23) are required together for this mobilization event (Christakos, 2016; Chacar, 2020). Besides, the distal renal tubule is responsible for the reabsorption of the final 1% of the filtered load of calcium. Again, both PTH and vitamin D are required (Figure.3) (DeLuca, 2004; Chacar, 2020).

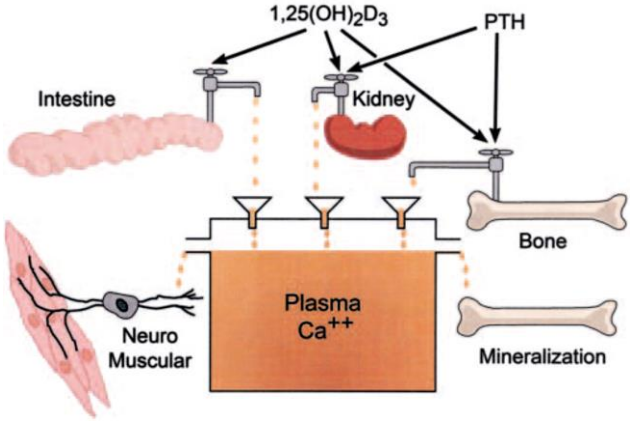

Figure.3. The role of vitamin D and PTH in increasing plasma calcium levels (DeLuca, 2004)

Vitamin D and chronic kidney disease: Chronic kidney disease (CKD) is an irreversible and progressive illness that courses with persistent abnormalities in kidney morphology and function.

Senescence is strongly correlated with the pathogenesis of CKD. Klotho, which is an anti-ageing gene, is implicated in many pathways of the senescence processes. The overexpression of Klotho causes a longer life span, whereas its suppression leads to ageing-like phenotypes with hyperphosphatemia (Chacar, 2020; Buchanan, 2020).

CKD represents a state of accelerated ageing combined with hyperphosphatemia induced by Klotho deficiency. In people with CKD, the expression of Klotho reduces and Klotho deficiency is strongly involved in chronic kidney disease mineral and bone disorders (CKD-MBD) (Chacar, 2020; Hu, 2011; Haussler, 2012; Hu, 2013).

CKD-MBD is reported since the early stages of CKD and it is associated with high mortality rates. Therapeutic strategies for CKD intent to delay the onset of mineral and bone disorders, therefore avoiding the progression of CKD (Chacar, 2020).

Concerning vitamin D, it has an important role in regulating mineral metabolism, alongside the Klotho/Fibroblast Growth Factor (FGF)-23-axis, PTH, and calcitonin. Vitamin D deficiency is common in people along with CKD even in the early stages of it. Nowadays, vitamin D supplements in patients with CKD have been widely used, to prevent or attenuate the development of CKD-MBD (Chacar, 2020).

Vitamin D and diabetes: Recent studies demonstrate that 25(OH)D levels are negatively related to the prevalence of diabetes mellitus type 2(T2DM), islet beta-cell function, insulin resistance, body fat, and Body mass index (BMI) levels (Vimaleswaran, 2013; Wang, 2017). On the contrary, 25(OH)D levels are positively correlated with insulin sensitivity (Wang, 2017; Al-Timimi and Ali, 2013; Nakashima, 2016).

$1,25(OH)_2D$ can be combined with vitamin D receptor (VDR) on the islet β cells, which raises insulin sensitivity, inhibits inflammatory factors and alleviates the chronic inflammation process of the pancreas to improve the function of islet β cells (Wang, 2017; Nakashima, 2016). Besides, it inhibits the activity of the renin-angiotensin system, which promotes insulin secretion. Vitamin D supplements can enhance islet β cell function and glucose tolerance (Wang, 2017; Martin and Campbell, 2011; Harinarayan, 2014).

Vitamin D and cancer: The majority of studies suggested a negative association between vitamin D status and tumour incidence risk including colon, breast, prostate, and ovarian cancer (Garland, 2006; Weinstein, 2015; Ekmekcioglu, 2017). Low levels of vitamin D binding protein (VDBP) appear to be correlated to different malignant tumours (Chandler, 2020). Epidemiologic studies demonstrated that levels of 25(OH)D <20 ng/ml are associated with a 30-50% increased risk of colon, prostate and breast cancer, along with higher mortality rates from these cancers (Wang, 2017; Feskanich, 2004; Robsahm, 2019). On the contrary, increased vitamin D intake (by 1100 IU) reduced the relative risk of cancer (Wang, 2017; Lappe, 2007). However, there are some inconsistencies about the protective impact of vitamin D supplements against developing cancer as Cheney and her colleagues revealed in their study (Cheney, 2018; Manson, 2019).

Vitamin D and cardiovascular diseases (CVD): According to clinical studies, low serum levels of 25(OH)D (along with high cholesterol, smoking, obesity, high blood pressure and diabetes) are closely related to cardiovascular diseases. Besides, hypertension incidence may be correlated with low levels 25(OH)D (Ferder, 2013; Wang, 2017).

The role of vitamin D in the cardiovascular system is noteworthy considering the presence of its receptors not only in the heart but also in the entire cardiovascular system. Several cell types, such as vascular smooth muscle cells, endothelial cells and cardiomyocytes produce 1α-hydroxylase, which is responsible for converting 25(OH)D to calcitriol, the natural ligand of the VDR. Calcitriol inhibits vascular smooth muscle cell proliferation, regulates the renin-angiotensin-aldosterone system (RAAS) pathways and decreases coagulation (Wang, 2017; Danik and Manson, 2012).

Vitamin D has protective effects on atherosclerosis through numerous mechanisms. It protects against endothelial dysfunction, vascular smooth muscle cell proliferation and migration and immune system modification (Menezesa, 2014). Furthermore, *In vitro* studies revealed that vitamin D suppresses pro-inflammatory cytokines and increases anti-inflammatory cytokines (Wang, 2017).

Yet, some studies disagree with the mentioned above concerning the protective role of vitamin D on CVD. So, more investigations should be made in this context (Manson, 2019; Barbarawi, 2019; Purow and Sokol, 2020).

Vitamin D and neurological and neuropsychological diseases: Vitamin D is reversely correlated to neurological disorders, neuropsychological diseases, cognitive impairment and neurodegenerative disorders (Somma, 2017).

Multiple Sclerosis (MS): MS is a debilitating slow progressive disorder of the central nervous system, which is characterized by axonal injury and demyelination in the spinal cord and brain. MS is an autoimmune disease influenced by environmental risk factors like obesity, infections, cigarette smoking, and inadequate serum levels of vitamin D and/or its metabolites (Somma, 2017).

Clinical studies point to the positive influence of vitamin D in reducing MS development and disease activity namely the risk of relapse, grey matter volume loss and clinical course of MS (Sintzel, 2018; Lauer, 2020). Altogether with improving the efficacy of glucocorticoids in relapse therapy and up-regulating methylprednisolone induced apoptosis (Miclea, 2020).

Alzheimer's disease (AD): AD is the most common cause of cognitive decline in the elderly. It is a neurodegenerative disorder characterized by progressive and irreversible cognitive deficits, behavioural alterations, memory impairment and loss of spatial memory (Somma, 2017; Dursun, 2010).

Vitamin D has been implicated to be crucial in maintaining cognitive function in old age. The presence of VDR in the brain regions which are responsible for memory development and cognitive functions may suggest being involved in plaque clearance (Annweiler, 2010; Yang, 2019).

Evidence suggests that vitamin D might protect against cognitive dysfunction through interfering with Amyloid-β (Aβ) metabolism, neuroprotection, synaptic plasticity, immune modulation, neuronal calcium regulation, enhancing nerve conduction and increasing the expression of the neuroprotective cytokine IL-34 (Somma, 2017; Lauer, 2020; Yang, 2019; Jia, 2019).

Still, there are gaps in understanding and evaluating the association between serum vitamin D levels and the incidence of AD, so more studies should be conducted in this context (Yang, 2019).

Parkinson's disease (PD): PD is a progressive neurodegenerative disorder characterized by slow dopaminergic neuronal loss. PD has many symptoms like dyskinesia, rigidity, tremor, postural instability and gait disorders (Somma, 2017; Lauer, 2020). Vitamin D could play an essential protective role of PD through indirect inhibiting of nitric oxide synthesis, stimulating glutathione synthesis and acting as a neurotrophic factor, via the inducing nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF) and neurotrophin 3 (NT3) (Somma, 2017; Bhardwaj and Deshmukh, 2018).

Neuropsychiatric diseases:

Autism spectrum disorders (ASD): Vitamin D deficiency during pregnancy is associated with a higher ASD risk (Lauer, 2020; Chen, 2016; Vinkhuyzen, 2018). Besides, vitamin D levels in children with ASD is lower comparing to controls, indicating that vitamin D supplement may improve the development to them, especially the younger ones (Feng, 2017; Petruzzelli, 2020).

Recent findings suggest vitamin D as an environmental and genetic factor influencing ASD. Besides, oxidative stress or neuroinflammation appears to play a role in ASD, and they could present a potential relation to vitamin D (Lauer, 2020).

Depression: Currently, there is a rising opinion that correlates vitamin D deficiency to the pathophysiology of depression (Holick, 2007; Lauer, 2020; Cuomo, 2017). Several pieces of evidence support this opinion, such as considering the distribution of VDR in various areas of the brain (limbic system, cerebellum, and cortex) which control behaviours and interfere with emotional processing and affective-related disorders (Boulkrane, 2020), the lower levels of vitamin D in depressed people compared to controls (Cuomo, 2017), and the vitamin D substantial role in the regulation of immuno-inflammatory pathways which are relevant to the pathophysiology of depression by inducing the stress response (Boulkrane, 2020).

Posttraumatic stress disorder (PTSD): PTSD is a serious psychiatric disorder characterized by intrusive memories, avoidance attitude as well as hyperarousal (Terock, 2020).

VDR and the 1α-hydroxylase are highly expressed in the brain regions which are related to the pathophysiology of PTSD including the prefrontal cortex, the hypothalamus as well as the cingulate cortex (Eyles, 2005). This can explain the inverse association between 25(OH)D and PTSD. Besides, the impact of vitamin D levels in expressing the genes involved in the regulation of different neurotransmitters implicated in the pathophysiology of PTSD (Terock, 2020).

Vitamin D and the immune system: The innate immune system represents the first line of defence against infection. It is responsible for responding rapidly, recognizing and eliminating invading pathogens to prevent exacerbation of infection. The innate immune system involves activation of Toll-like receptors in monocytes leading to the induction of antimicrobial peptides (including cathelicidins) and killing the bacteria eventually (Wei and Christakos, 2015).

Vitamin D metabolizing enzymes and VDR are scattered in many immune cells such as antigen-presenting-cells, T cells, B cells and monocytes (Prietl, 2013). It possesses a noticeable role in regulating immune function, inhibiting inflammatory reactions and autoimmune diseases (Wang, 2017).

Recent studies confirm the direct effects of calcitriol on B cell homoeostasis (inhibition of memory- and plasma-cell generation) and promoting apoptosis of immunoglobulin-producing B cells. This control on B cell activation and proliferation may be crucial in autoimmune diseases as B-cells have a crucial role in the pathophysiology of autoimmunity (Prietl, 2013; Adams and Hewison, 2008; Trombetta, 2018).

$1,25(OH)_2D$ has been reported to be a major regulator of human cathelicidin antimicrobial peptide (CAMP) not only in monocytes but also in lung and intestinal epithelial cells, keratinocytes, and trophoblasts of the placenta (Charoenngam and Holick, 2020; Wei and Christakos, 2015; Adams and Hewison, 2008; Martens, 2020).

Additionally, vitamin D provokes innate antimicrobial effector responses through reactive oxygen intermediates induction and antibacterial autophagy activation (Wei and Christakos, 2015; Aranow, 2011).

Even though 1,25(OH)D promotes the innate immune response, it suppresses adaptive immunity. $1,25(OH)_2D$ inhibits immune responses mediated by Type 1 T helper (Th1) cells which produces inflammatory cytokines (Interleukin-2 (IL-2) and interferon γ (IFNγ)) (Wang, 2017; Wei and Christakos, 2015; Trombetta, 2018).

Long-term follow-up for patients who used vitamin D supplements revealed that secosteroids have harmful effects, especially when accompanied by chronic diseases. High-dose vitamin D supplementation in infancy increased the risk of atopy, allergic rhinitis and asthma later in life. However, it should be noted that these results were not apparent until the patients turned 31 years of age (Hypponen, 2004).

2. CONCLUSION

Vitamin D is a group of secosteroids that can either be synthesized upon UV-B exposure or be provided as dietary supplements. Vitamin D metabolites are a piece of delicate homeostasis that permits the living cells to express genes when needed.

As indicated by hundreds of researches, vitamin D has a relatively considerable role in hypocalcemia, hypophosphatemia, mineralization, bone metabolism and chronic diseases (renal, cardiovascular, neurological and neuropsychological diseases), not to mention its impact on the immune system.

Despite that, further studies are needed to elucidate many gaps in the knowledge and clarify the role of the so-called ‘‘sunshine vitamin’’.

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