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ABSTRACT

The prevalence of autoimmune diseases (ADs) has increased over the past few decades. Vitamin D deficiency is a common factor in many of these diseases, whose etiology remains poorly understood. The objective of this study was to review published data on the role of vitamin D in ADs. Vitamin D insufficiency has been described as an important factor in the development of some ADs, generally attributed to the key role of this vitamin in the immune system. Most studies show that adequate supplementation can prevent and improve the development of some of these diseases, although the optimal vitamin D dose remains controversial. We highlight the importance of measuring serum vitamin D levels of the population and developing strategies to improve and maintain levels with no health risks.

Keywords: Vitamin D; autoimmunity; Autoimmune Diseases; Supplementation.

INTRODUCTION

The role of vitamin D in bone metabolism is well documented [1], but fewer data are available on its impact on other organs or systems. The vitamin D receptor (VDR) and activation enzyme, 1-α-hydroxylase, are expressed by various cell types in kidney, pancreas, prostate, intestine, and platelets and by immune cells, indicating an active role for vitamin D in these cell populations [2,3].

Epidemiological studies have evidenced a progressive increase in the incidence of autoimmune diseases (ADs) over the past few decades, especially in western countries [4]. ADs are characterized by a loss of immune tolerance, resulting in the destruction of healthy tissues. The greatest increase has been reported for endocrine, rheumatic, and gastrointestinal ADs, attributed to changes in dietary habits, stress loads, and environmental exposure to pollution, among other factors [5,6].

ADs have recently been related to insufficient levels of vitamin D, which plays an important role in the immune system [7–9]. However, no consensus has been reached on vitamin D levels required to maintain a good health status or on optimal doses for the treatment or prevention of these diseases [10,11].

The objective of this study was to examine the role of vitamin D in the development of ADs.

Vitamin D

Vitamin D is a fat-soluble substance of steroidal nature that is essential for the human organism. Its origin can be endogenous, produced from skin-derived 7-dehydrocholesterol that is converted to vitamin D3 or cholecalciferol by ultraviolet sunlight, or exogenous, from the intake of vegetables (vitamin D2 or ergocalciferol) or

foods of animal origin (cholecalciferol) and their subsequent absorption *via* the intestine [12,13].

The active form of vitamin D or calcitriol is synthesized within the organism after transformation of its precursor cholecalciferol, which is biologically inert and requires two hydroxylations for its activation, as depicted in Fig. 1. The first hydroxylation takes place in the liver, where cholecalciferol is transformed into calcidiol or 25-hydroxycholecalciferol by mitochondrial enzyme 25-hydroxylase (CYP2R1). The second hydroxylation is in the kidney, where enzyme 1α-hydroxylase (CYP27B1) metabolizes calcidiol into calcitriol or 1-α,25- dihydroxycholecalciferol, which can bind to its nuclear receptor in different cell populations and modify various functions of these cells. Other hydroxylases are present in the kidney, including 24-hydroxylase (CYP24A1), which transforms calcidiol into other less active metabolites (e.g., 24, 25-dihydroxycholecalciferol and 1,24,25-trihydroxycholecalciferol) in order to regulate calcitriol concentrations. The different metabolites produced in these enzymatic stages are transported in the bloodstream towards the liver or kidney by binding to the vitamin D-transporting protein [14].

Concentrations of calcitriol are largely determined by the balance among 1α-hydroxylase, 24-hydroxylase, and another two proteins that have an important role in regulating this balance, fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH). FGF23 shifts the balance towards 24-hydroxylase, induced by high calcitriol concentrations and low serum phosphate levels, thereby inactivating vitamin D signaling. By contrast, PTH shifts the balance towards 1α-hydroxylase and the activation of vitamin D signaling, induced by low serum calcium levels and high calcitriol concentrations [15].

The kidney is the main organ responsible for producing the active vitamin D form, calcitriol, which modulates numerous cell functions *via* its specific nuclear receptor in

most body cells, including immune and inflammatory cells [15,16]. The following factors are known to affect serum vitamin D levels [2,10,17]: dermal synthesis from ultraviolet radiation in sunlight, which is influenced by the season of the year, geographic latitude, clothing, application of sunscreen lotions, skin pigmentation, and structural changes of skin with age; liver, kidney, and/or intestine diseases, which can alter calcitriol synthesis or the intestinal absorption of exogenous sources; medications that can alter vitamin D catabolism, including anticonvulsants, glucocorticoids, immunosuppressants, and antiretrovirals; and obesity, which can lead to vitamin D sequestration by adipose tissue.

Vitamin D levels can have major health repercussions, and it is essential to determine optimal serum calcidiol levels for disease prevention. The physiological level is considered to be around 30 ng/mL, with higher concentrations being optimal, whereas levels < 20 ng/mL have been associated with a greater risk of various disorders [18–20]. Intermediate metabolites and enzymes play a crucial role in the vitamin D activation pathway [21–23]. It is therefore essential to establish the optimal type and amount of metabolite to administer to individuals with vitamin D deficiency, which will depend on the characteristics of each individual.

Autoimmunity

ADs are characterized by the loss of immune tolerance, i.e., a failure of the organism to recognize its own cells and/or molecules, leading to the destruction of healthy tissues through the autoreactivity of its immune cells. The etiology of ADs is poorly understood but has been related to genetic, hormonal, and environmental factors. Females are more susceptible to ADs than males, attributed to hormonal factors, but the male sex is associated with more severe clinical manifestations of these diseases.

More than 100 ADs have been identified and predominantly associated with environmental stressors [24], including infectious diseases and low exposure to sunlight [5,7,25,26].

In recent years, inadequate levels of vitamin D have been related to the loss of immune tolerance, given its important role in both the adaptive immune response and the innate immune response [25,27,28].

Vitamin D and Autoimmunity

Various studies have demonstrated the beneficial effect of vitamin D against the development of some ADs [4]. All immune system cells express the VDR and are therefore susceptible to calcitriol-mediated modulation [29]. In addition, some immune cells can synthetize calcitriol by expressing 1α-hydroxylase, including dendritic cells (DCs), macrophages, and B and T cells [25]. Calcitriol can affect the maturation and migration of different DC subtypes and their production of cytokines and chemokines, giving them an immunoregulatory and tolerogenic role. The interaction of calcitriol with its receptor, VDR, halts DC differentiation and maturation of DCs and enhances their tolerogenic status, reducing the production of proinflammatory cytokines (IL-6, IL-12, IL-23) and tumor necrosis factor α (TNF-α), increasing the production of anti-inflammatory cytokines (IL-8, IL-10), and diminishing the expression of major histocompatibility complex class I and II and surface costimulatory molecules (CD40, CD80, CD83, CD86) [30].

Calcitriol inhibits the differentiation of B cells into plasma cells and their production of antibodies. It can also act on T cells when these express VDR after their activation. Specifically, Th1 and Th17 subpopulations are reduced and Th2 differentiation is promoted in $CD4^+$ T cells, producing IL-4. Calcitriol also stimulates the activity of

regulatory cells that suppress the immune response. These effects on immune cells may explain the beneficial effect of vitamin D observed against certain autoimmune diseases [31].

Type I Diabetes mellitus

Type I Diabetes Mellitus is a metabolic AD characterized by the selective destruction of pancreatic β cells. Calcitriol supplementation has been reported to reduce serum levels of antibodies and delay the progression of β cell destruction but only when the supplement is administered in early stages of the disease, explaining why some authors observed no beneficial effects. Supplementation with vitamin D or its analogues is therefore considered more of a preventive than curative measure against this disease [25]. On the other hand, a systematic review and meta-analysis by Sahebi *et al*. [32] reported improvements in glycemic control indices (fasting blood glucose, Homeostatic Model Assessment Insulin Resistance, and HbA1C) in diabetic patients, after vitamin D supplementation, supporting its administration as adjuvant therapy against this disease.

Sjögren syndrome

Sjögren syndrome is an AD that generally affects exocrine glands, with additional glandular manifestations in around half of patients. Some authors observed reduced vitamin D levels in patients with Sjögren syndrome *versus* controls [33–35], but others found no significant difference [36]. Nevertheless, Zardi *et al.* [34] recommended vitamin D supplementation as a prophylactic measure, despite the lack of consensus on its effects in these patients.

Autoimmune thyroid diseases

A correlation has been observed between vitamin D deficiency and thyroid autoimmunity [37]. The thyroid hormone is involved in maintaining adequate vitamin D levels, and the immunomodulatory role of this vitamin would influence the development

of autoimmune thyroid disease [38]. However, contradictory reports have been published on the effects of vitamin D supplementation in these patients. Thus, some authors have associating it with significant reduction in levels of anti-thyroperoxidase antibodies, which might have a positive impact against these diseases, whereas others found no significant correlation [38].

Multiple sclerosis

Low vitamin D levels have been associated with a higher risk of the development and recurrence of this demyelinating AD of the central nervous system. Beneficial effects have been reported for Vitamin D supplementation when doses are between 500 and 2000 IU/day, including a reduction in optical neuritis and in the relapse rate, but high doses (5000–10,000 IU/day) have been associated with worse outcomes [39]. Vitamin D supplementation was found to exert a synergic beneficial effect in combination with interferon β [25,29].

Systemic Lupus Erythematosus

This chronic inflammatory disease is characterized by the involvement of multiple organs and systems and the presence of antinuclear antibodies. A higher prevalence of systemic lupus erythematosus has been reported among patients with vitamin D deficiency [40], but published data on cholecalciferol supplementation have been inconsistent. Thus, some studies found no beneficial effects, with no significant reduction in immune markers or disease activity [41], whereas others observed an improvement in these patients after supplementation, with a reduction in fatigue and significant changes in the serum levels of antibodies and proinflammatory cytokines [29,42,43]. The doses of vitamin D administered to these patients have ranged from 2,000 IU/day [44] to 50,000 IU/week [45], although the effects observed do not appear to vary as a function of the dose.

Autoimmune rheumatic diseases

Vitamin D deficiency is a common finding in patients with autoimmune rheumatic disease, which include more than 100 inflammatory, degenerative, and autoimmune diseases and are associated with articular damage, severe pain, disability, and even death [46,47]. One of the most widely studied autoimmune rheumatic diseases is rheumatoid arthritis (RA), characterized by persistent synovial inflammation that generates articular damage. Although De la Torre Lossa *et al.* [48] found no statistically significant correlation between vitamin D levels and RA activity, vitamin D deficiency is more frequent among patients with RA and may be a cause of its onset or progression [49]. Mateen *et al.* [50] observed low calcidiol and high inflammatory cytokine levels in these patients and suggest that calcidiol can no longer exert its immunomodulating function at reduced concentrations and that the resulting increase in cytokines is responsible for increasing disease severity. Although some clinical trials have demonstrated improved disease activity, results published to date appear insufficient to fully elucidate the immunomodulatory role of vitamin D.

Intestinal Bowel Disease

Vitamin D deficiency has also been associated with the onset of intestinal bowel diseases (e.g., Crohn's disease and ulcerous colitis), which are characterized by progressive chronic inflammation of the gastrointestinal tract, including [51].

Research on Crohn's disease has demonstrated that Vitamin D, through its receptor, inhibits the production of Th1 and Th17 T helper lymphocyte subpopulations and inflammatory cytokines in the gastrointestinal tract, reducing inflammation and maintaining gut microbiota, which have a key role in the function of the mucosal immune system [30]. Intestinal homeostasis has been associated with VDR expression, which limits IL-6 production by epithelial cells [25]. Vitamin D supplementation is considered

to be an effective and safe therapy in patients with Crohn's disease, at doses that should be considered on a case-by-case basis, taking account of the age of patents [52].

Psoriasis

Psoriasis is a chronic inflammatory AD characterized by the hyperproliferation of keratinocytes, which express VDR. Amon *et al.* [53] observed low serum vitamin D levels in patients with psoriasis (mean of 21.05 ng/mL), finding concentrations lower than 20 ng/mL in 44% of them. Topical treatment with the vitamin D analogue calcipotriol can modulate the expression of proinflammatory cytokines (e.g., TNF-α, IFN-γ, IL-2, and IL-8) and that of psoriasin and koebnerisin, proteins that amplify inflammatory reactions in psoriasis. By contrast, it produces an increase in IL-10, an anti-inflammatory cytokine that can inhibit proinflammatory cytokine synthesis by T lymphocytes and macrophages [29,54]. Likewise, a murine study found that the calcitriol analogue maxacalcitol reduced psoriasiform inflammation of their skin by inducing T-regulating cells and reducing IL-23 and IL-17 production, cytokines that play an important role in psoriasis, among other diseases [55].

Vitamin D supplementation

There is a need to establish the optimal serum levels of vitamin D levels. In 2011, guidelines published by Holick *et al.* [56] and supported by the US Endocrine Society defined vitamin D deficiency as a serum calcidiol concentration < 50 nmol/L (20 ng/mL), insufficiency as a serum concentration of 50 - 74.9 nmol/L (20-29.9 ng/mL), and sufficiency as a serum concentration of 75 - 250 nmol/L (30-100 ng/mL).

Hilger *et al.* [57] conducted a systematic review of serum vitamin D (calcidiol) levels of populations in all five continents. They reported a mean value was <50 nmol/L in 37.3 % of studies, observing the highest levels in North America and finding a greater

risk of lower values among newborns and institutionalized elderly people in various populations.

Serum vitamin D levels depend on multiple factors, including the characteristics and habits of the individual. There is also evidence in the published literature suggesting that, in comparison to native populations, migrants from tropical regions residing in high latitudes and who are not obtaining vitamin D through diet or supplementation may be at a greater risk of developing vitamin D deficiency and some associated diseases [58,59]. ~~For this reason~~ In this sense, the recommended vitamin D dose in supplements varies as a function of age, receipt of medication (e.g., anticonvulsants or glucocorticoids), and the presence of pregnancy or obesity or AD, among other diseases. ~~-~~In relation to the dose selection, ~~it~~ has been reported that the administration of 100 IU vitamin D increases serum calcidiol levels by around 1 ng/mL, although this is currently under discussion [19,60]. Moreover, regarding adequate vitamin D status, it may be useful to establish threshold doses of vitamin D supplementation at which optimal serum 25(OH)D levels and vitamin D sufficiency can be expected in different population subgroups such as obese, elderly, pregnant/lactating women, children, people with dark skin pigmentation, people spending most of the day indoors and away from sunlight, people with impaired vitamin D metabolism/hydroxylation (e.g., inadequate expression of the enzyme CYP27B1 to form functional 1,25(OH)2D), people with defective vitamin D receptor (VDR), people with chronic diseases, allergies and asthma, immuno-compromised individuals, and those living in the regions of high geographical latitude. Drincic *et al*. [61] indicate that "it has been shown for normal weight adults that total body utilization of vitamin D needed to sustain a serum level of 25(OH)D of 32 ng/ml (80 nmol/l) is on the order of 4,000 IU/day and for 40 ng/ml (100 nmol/l), 5,000 IU/day" and that "vitamin D replacement therapy

needs to be adjusted for body size if desired serum 25(OH)D concentrations are to be achieved".

When supplementation is required, calcidiol is consider to be the ideal form to reach adequate vitamin D levels in elderly adults with deficiencies or receiving higher glucocorticoid doses, given that it is 5-fold more effective than cholecalciferol. Nevertheless, cholecalciferol is the form of choice for supplementation and the most widely used in clinical trials. Analogues are also used, e.g., alfacalcidol, which may be more effective than cholecalciferol in the short term [62].

Recommendations by the US Endocrine Society to prevent and treat vitamin D deficiency/insufficiency vary by age: 400-1,000 IU (10-25 μg) vitamin D/day for children aged 0-1 years, 600-1,000 IU/day (15-25 μg/day) for older children; and 37.5-50 μg/day (1,500-2,000 IU/day) for adults [56]. Various authors have suggested that the regular intake of 2,000 - 4,000 IU vitamin D /day, can reduce the risk of the development and relapse of various diseases, including ADs and cancer [63]. In addition, it has been estimated that 2,990 IU/day are required to reach serum calcidiol concentrations of ≥ 50 nmol/L in 97.5 % of healthy individuals [64]. In a recent study, Pludowski *et al.* [19] recommended doses ranging between 400 and 2,000 IU/day to prevent/correct vitamin D deficiency depending on the age, body weight, ethnic origin, presence of certain diseases, and pharmaceutical consumption. They emphasized that the adverse effects of vitamin D self-administration (e.g., hypercalcemia and hypercalciuria) are rare and generally result from consuming extremely high doses for prolonged time periods. Nevertheless, vitamin D supplementation should be prescribed with caution in people with granulomatous diseases, sarcoidosis, metastatic bone disease, or William's syndrome, given the risk of hypercalcemia and/or hypercalciuria [20].

A recent review and guidance paper indicated the health benefits of vitamin D food fortification or supplementation, supported by reports of its effectiveness in different countries [65]. Given all of the above evidence on the role of serum vitamin D levels in maintaining good health status and reducing the risk of ADs, primary care programs appear warranted to periodically measure vitamin D levels in the general population and to promote activities that increase these levels, including outdoor exercise and a balanced diet.

CONCLUSION

Vitamin D insufficiency or deficiency is associated with the onset and progression of some ADs. Most studies on vitamin D supplementation have observed beneficial preventive or curative effects. The ideal supplementation dose of vitamin D for patients with ADs remains under debate; however, there is consensus on the need to promote healthy habits in the population to increase their levels of this vitamin as a preventive measure against ADs and other diseases. Therefore, considering the importance of vitamin D for the function of the immune system, it is reasonable to recommend maintenance of adequate vitamin D status for the general population. Vitamin D insufficiency or deficiency should be identified and addressed accordingly.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

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Figure. 1 Synthesis and metabolism of vitamin D

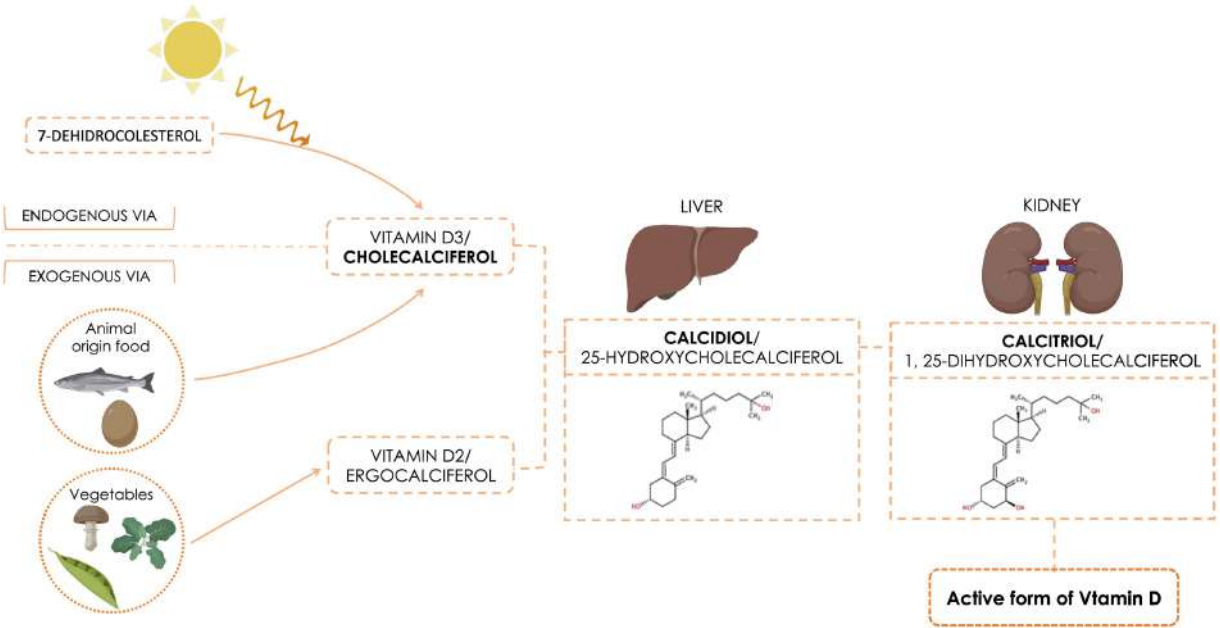
7-DEHIDROCOLESTEROL
ENDOGENOUS VIA
EXOGENOUS VIA
Animal origin food
Vegetables
VITAMIN D3/
CHOLECALCIFEROL
VITAMIN D2/
ERGOCALCIFEROL
LIVER
CALCIDIOL/
25-HYDROXYCHOLECALCIFEROL
KIDNEY
CALCITRIOL/
1, 25-DIHYDROXYCHOLECALCIFEROL
Active form of Vtamin D

Figure 1