

# *The importance of vitamin D levels in autoimmune diseases*

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## ABSTRACT

In addition to its role in calcium homeostasis, it is believed that the active form of vitamin D has immunomodulatory effects on cells of the immune system, particularly T lymphocytes, as well as on the production and action of several cytokines. The interaction of vitamin D with the immune system has been the target of a growing number of publications in recent years. Current studies have linked the deficiency of vitamin D with different autoimmune diseases, including insulin-dependent diabetes mellitus (IDDM), multiple sclerosis (MS), inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA). This article reviews the physiology and immunomodulatory role of vitamin D, emphasizing its involvement in rheumatic diseases such as SLE and RA.

**Keywords:** vitamin D, immune system, autoimmune diseases, systemic lupus erythematosus, rheumatoid arthritis.

## INTRODUCTION

Vitamin D and its prohormones have been the focus of a growing number of studies in past years, demonstrating their function not only in calcium metabolism and bone formation, but also their interaction with the immune system, which is not surprising, since vitamin D receptors are expressed in different tissues, such as brain, heart, skin, bowel, gonads, prostate, breasts, and immune cells, as well as bones, kidneys, and parathyroid glands.<sup>1</sup>

Current studies have related vitamin D deficiency with several autoimmune disorders, including insulin-dependent diabetes mellitus (IDDM), multiple sclerosis (MS), inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA).<sup>1-4</sup> In view of those associations, it has been suggested that vitamin D is an extrinsic factor capable of affecting the prevalence of autoimmune diseases.<sup>5</sup>

Vitamin D seems to interact with the immune system through its actions on the regulation and differentiation of cells like lymphocytes, macrophages, and natural killer

cells (NK), besides interfering in the in vivo and in vitro production of cytokines. Among the immunomodulatory effects demonstrated we should mention: a reduction in the production of interleukin-2 (IL-2), gamma interferon (INF $\gamma$ ), and tumor necrosis factor (TNF); inhibition of the expression of IL-6; and inhibition of the secretion and production of auto-antibodies by B lymphocytes.<sup>6,7</sup>

## VITAMIN D PHYSIOLOGY

Vitamin D, or cholecalciferol, is a steroidal hormone whose main function is the regulation of calcium homeostasis, and bone formation and reabsorption through the interaction with the parathyroid glands, kidneys, and bowel.<sup>8</sup>

The main source of vitamin D comes from the endogenous production in the skin after exposure to ultraviolet B light.<sup>8-10</sup> The diet is an alternative, but less effective, source of vitamin D, which is responsible for only 20% of the body needs, but it assumes a major role in the elderly, institutionalized people, and those living in temperate climates.

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Upon exposure to ultraviolet radiation, the cutaneous precursor of vitamin D, 7-dehydrocholesterol, undergoes photochemical cleavage, giving rise to previtamin-D3. Within 48 hours, this heat-susceptible molecule undergoes temperature-dependent molecular rearrangement, resulting in the formation of vitamin-D3 (cholecalciferol). Previtamin-D3 can also undergo isomerization, originating biologically inactive compounds (lumisterol and tachysterol), and this mechanism is important to prevent overproduction of vitamin D after prolonged exposure to sunlight. The degree of skin pigmentation is another limiting step in the production of vitamin D, since ultraviolet rays have limited penetration in dark skin.<sup>9</sup>

In the blood, vitamin D is bound, mainly, to a vitamin D-binding protein, although a small fraction is bound to albumin.<sup>9</sup> In a cytochrome P450-like enzyme-mediated reaction, vitamin D is hydroxylated in the liver and converted in 25-hydroxyvitamin D [25(OH)D], the most abundant circulating form, which is biologically inactive.<sup>8,9</sup> Hepatic hydroxylation is poorly regulated and, therefore, blood levels of 25(OH)D reflect the amount of vitamin D entering the circulation, which is proportional to the amount of vitamin D ingested and produced in the skin.<sup>9,10</sup>

The additional hydroxylation in the cells of the convoluted proximal tubule of the kidneys, originating 1.25-dihydroxyvitamin D [ $1.25(\text{OH})_2\text{D}_3$ ], the biologically active form,<sup>8,9</sup> is the final step in the production of the hormone.

Extra-renal hydroxylation of vitamin D, originating a vitamin with autocrine and paracrine effects that inhibits cellular proliferation, promotes cellular differentiation, and immune regulation, is currently accepted. Regulation of renal 1- $\alpha$ -hydroxylase depends on the ingestion of calcium and phosphate, circulating levels of  $1.25(\text{OH})_2\text{D}_3$  metabolites, and parathyroid hormone (PTH). On the other hand, the extra-renal regulation of hydroxylase is determined by local factors, such as the production of cytokines and growing factors, and by the levels of 25(OH)D, making it the most sensitive pathway to vitamin D deficiency.<sup>10</sup>

The increase in the intestinal absorption of calcium by participating in the stimulation of the active transportation of this ion in enterocytes, is main function of vitamin D.<sup>9,11</sup> It also participates in calcium mobilization from the bones, in the presence of PTH, and it increases the renal reabsorption of calcium from the distal tubule.<sup>12</sup> Prolonged vitamin D deficiency causes rickets and osteomalacia, and, in adults, when associated with osteoporosis, it increases the risk of fractures.<sup>13</sup>

Other actions of vitamin D in the positive regulation of bone formation include: inhibits the synthesis of type 1 collagen;

induces the synthesis of osteocalcin; and promotes the *in vitro* differentiation of monocytes-macrophages precursors into osteoclasts. It also stimulates the production of RANK ligand (RANK-L), which facilitates maturation of osteoclast precursors into osteoclasts, which, in turn, mobilize calcium storage in the bones to maintain calcium homeostasis.<sup>8,9</sup> Vitamin D exerts its biological actions through the binding of nuclear receptors, vitamin D receptors (VDR), which, similar to steroid, thyroid hormone, and retinoid receptors, regulate the transcription of DNA into RNA.<sup>9,11</sup> Those receptors are expressed by a variety of cells, including the epithelium of the small bowel and renal tubules, osteoblasts, osteoclasts, hematopoietic cells, lymphocytes, epidermal cells, pancreatic cells, myocytes, and neurons.<sup>11</sup>

More recently, noncalcemic actions of vitamin D mediated by VDR, such as cellular proliferation and differentiation, besides immunomodulation, have been recognized. Vitamin D receptor is widely expressed in the majority of immune cells, including monocytes, macrophages, dendritic cells, NK cells, and T and B lymphocytes.<sup>14</sup> However, its concentration is higher in immature immune cells in the thymus and immature CD8 lymphocytes, regardless of their activation status.<sup>8,12</sup> Table 1 shows a summary of the main effects of vitamin D in the immune system.

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## DETERMINATION OF THE SERUM LEVELS OF VITAMIN D

Although  $1.25\text{OH}_2\text{D}_3$  is the active form of this vitamin, it should not be used to evaluate serum levels, since it has a half-life of only four hours and its concentration is 1,000 times lower than that of 25(OH)D. Besides, vitamin D deficiency is associated with a compensatory increase of PTH secretion, which stimulated the kidneys to produce more  $1.25\text{OH}_2\text{D}_3$ . Thus, when 25(OH)D levels fall due to vitamin D deficiency, the concentrations of  $1.25\text{OH}_2\text{D}_3$  remain within normal limits and, in some cases, they might even be elevated.<sup>9,15</sup>

To determine whether adequate levels of vitamin D are present, one should measure the concentration of 25(OH)D, the predominant circulating form, with a half-life of approximately two weeks.<sup>9</sup>

A consensus on the ideal serum level of vitamin D does not exist. The majority of the specialists agree that the levels of vitamin D should remain with a concentration range that does not induce an increase in PTH levels.<sup>10,15</sup> Normal levels vary according to the commercial assay used, from 25-37.5 nmol/L (10-15 ng/mL) to 137.5-162.5 nmol/L (55-65 mg/mL).<sup>13</sup> Recent reviews have suggested that 50 to 80 nmol/L

**Table 1**  
Actions of vitamin D in the immune system<sup>13</sup>

Target cell population	Actions mediated by 1.25(OH) <sub>2</sub> D <sub>3</sub>
<b>APCs (monocytes, macrophages, dendritic cells)</b>	<p>Inhibits the expression of class II MHC molecules</p> <p>Inhibits the expression of co-stimulating molecules (CD40, CD80, and CD86) and other maturation-inducing proteins (CD1a, CD83)</p> <p>Increases chemotaxis and phagocytosis of monocytes and cytotoxicity against tumor cells and bacteria</p> <p>Inhibits the maturation of dendritic cells</p> <p>Induces tolerogenic dendritic cells capable of inducing Treg cells</p> <p>Inhibits the release of IL-12 p70</p> <p>Inhibits proinflammatory cytokines (IL-1 and TNF) by monocytes and macrophages</p>
<b>T lymphocytes</b>	<p>Inhibits T cell proliferation, secretion of cytokines, and progression of the cellular cycle from G1a to G1b</p> <p>Increases the production of IL-4, IL-5, IL-10</p> <p>Inhibits IL-12, INF-<math>\gamma</math>, and IL-2</p> <p>Inhibits activation of antigen-specific T lymphocytes</p> <p>Inhibits the expression of FasL by activated T lymphocytes</p>
<b>B cells</b>	<p>Expresses VDR</p> <p>Suppresses IgE secretion</p>
<b>NK cells</b>	Inhibits INF- $\gamma$

APC, antigen-presenting cell; MHC, major histocompatibility complex; IL, interleukin; TNF, tumor necrosis factor; FasL: Fas ligand; INF- $\gamma$ , gamma interferon; VDR, vitamin D receptor; NK, natural killer.

should be the ideal concentration, while others recommend levels between 75 and 125 nmol/L.<sup>16</sup> Using the elevation of PTH levels as a biomarker that reflects low levels of vitamin D, deficiency should be defined as a serum concentration below 32 ng/mL (80 nmol/L).<sup>16</sup>

The ideal level of vitamin D necessary to guarantee the immune system will work properly has not been defined. It is most likely that this level should be different than that necessary to prevent vitamin D deficiency or maintain calcium homeostasis.<sup>5</sup>

## EFFECTS OF VITAMIN D ON THE IMMUNE SYSTEM

Based on the ectopic production of vitamin D in cells of the immune system and the presence of VDR in tissues that are not related with bone physiology, the immunoregulatory properties of vitamin D have been better characterized.<sup>17</sup> Epidemiological studies have shown that deficiency of this vitamin could be

associated with an increased risk of colon and prostate cancer, cardiovascular disease, and infections.<sup>13,15,17,18</sup>

Several mechanisms have been proposed to explain the role of vitamin D in the physiology of the immune system, as can be seen in Table 1.

Among the main functions of vitamin D in the immune system, we could mention: regulation of the differentiation and activation of CD4 lymphocytes;<sup>5,11,19</sup> increase in the number and function of regulatory T cells (Treg);<sup>11</sup> in vitro inhibition of the differentiation of monocytes in dendritic cells;<sup>8,11</sup> reduction in the production of cytokines, interferon- $\gamma$ , IL-2, and TNF- $\alpha$  by Th1 cells, and stimulation of the function of Th2 helper cells;<sup>5,8,11,17</sup> inhibition of the production of IL-17 by Th1 cells;<sup>20</sup> and in vivo and in vitro stimulation of NK T cells.<sup>21</sup>

## VITAMIN D AND AUTOIMMUNE DISEASES

As a rule, the effects of vitamin D in the immune system translate into an enhancement of innate immunity associated with a multifaceted regulation of acquired immunity.<sup>22</sup> A relationship between vitamin D deficiency and the prevalence of some autoimmune diseases like IDDM, MS, RA, SLE, and IBD has been demonstrated.<sup>5,13</sup>

It has been suggested that vitamin D and its analogues not only prevent the development of autoimmune diseases, but they could also be used in their treatment.<sup>11</sup> Vitamin D supplementation has been shown to be therapeutically effective in different experimental animal models, such as allergic encephalomyelitis, collagen-induced arthritis, type 1 diabetes mellitus, inflammatory bowel disease, autoimmune thyroiditis, and SLE.<sup>8</sup>

Low serum levels of vitamin D could also be related with factors other than nutritional, such as reduction in physical capacity, decreased exposure to sunlight, increased frequency of polymorphisms of VDR genes, and side effects of drugs.<sup>10,11</sup>

### Rheumatoid arthritis

Rheumatoid arthritis is an autoimmune disorder with a very complex physiology. It is believed that the first event is the activation of antigen-dependent T cells triggering an immune response essentially of the Th1 type. This activation has multiple effects, including activation and proliferation of endothelial and synovial cells, recruitment and activation of proinflammatory cells, secretion of cytokines and proteases by macrophages and fibroblast-like synovial cells, and production of auto-antibodies.<sup>23</sup>

As mentioned before, vitamin D deficiency is associated with an exacerbation of Th1 immune response. Thus, in the last few years, the possible role of vitamin D in the pathogenesis, activity, and treatment of RA has been raised based on the results and observations of clinical and laboratorial studies.<sup>5</sup>

The rationale for relating vitamin D deficiency and RA is based on two facts: evidence indicate that patients with RA have vitamin D deficiency and the presence of  $1.25(\text{OH})_2\text{D}_3$  and VDR in macrophages, chondrocytes, and synovial cells in the joints of those patients.<sup>14,24</sup>

The relationship between polymorphisms of the VDR gene and the onset of RA activity has been demonstrated in a study in which patients with BB or Bb genotypes for VDR had higher indices in the HAQ, erythrocyte sedimentation rate (ESR), cumulative dose of corticosteroids, and number of disease-modifying antirheumatic drugs (DMARDs) when compared to patients with the BB genotype.<sup>25</sup>

In collagen-induced arthritis models, dietarian supplementation or oral administration of vitamin D prevented the development or delayed the progression of arthritis.<sup>1,26</sup> Similarly, a study with 29,386 women showed that the risk of developing RA was inversely related to higher ingestion of vitamin D.<sup>27</sup> However, in another large prospective study that evaluated 186,389 women from 1980 to 2002, an association between the increased ingestion of vitamin D and the risk of developing RA or SLE was not observed.<sup>28</sup> Corroborating this result, a study with 79 blood donors evaluated the serum levels of vitamin D; differences between the basal levels of vitamin D of patients who later developed RA and the control group were not observed.<sup>29</sup> Those findings demonstrate that this is still a very controversial subject, lacking a consensus among the authors on the real relationship between vitamin D and RA.

In an open study with 19 patients with RA treated with traditional DMARDs, oral supplementation with high doses of alfacalcidol for three months reduced the severity of the symptoms in 89% of the patients, 45% of which achieved complete remission and 44% had satisfactory results. Higher incidence of side effects, such as hypercalcemia, was not observed.<sup>30</sup>

There also seem to be an inverse relationship between disease activity and the concentration of vitamin D metabolites in patients with inflammatory arthritis.<sup>31</sup> In basal, pre-treatment conditions, a proportional inverse relationship among the levels of  $25(\text{OH})$  vitamin D and the number of painful joints, DAS28, and HAQ is observed. For each increase in 10 ng/mL in vitamin D serum levels, the DAS28 reduced by 0.3 points and the levels of CRP by 25%.<sup>31</sup>

## Systemic lupus erythematosus

Several authors have demonstrated a higher prevalence of vitamin D deficiency in SLE patients when compared to individuals with other rheumatologic diseases and healthy individuals.<sup>3,32,34</sup> In a transversal study, Muller *et al.*<sup>33</sup> observed that the levels of vitamin D were significantly lower in SLE patients (mean 13 ng/mL) when compared to patients with RA (24 ng/mL), osteoarthritis (32 ng/mL), and healthy controls (27 ng/mL). Huisman *et al.*<sup>34</sup> observed that 50% of SLE patients had vitamin D deficiency (cut off <50 nmol/L or 20 ng/mL). However, when those individuals were compared to those with fibromyalgia, differences in PTH,  $25(\text{OH})\text{D}$ , and  $1.25(\text{OH})_2\text{D}_3$  levels were not observed.

Patients with systemic lupus erythematosus have multiple risk factors for  $25(\text{OH})\text{D}$  deficiency. Photosensitivity, characteristic of the disease, and the recommendation to apply sunscreen are responsible for lower sun exposure, decreasing the production of vitamin D in the skin. Chronic treatment with corticosteroids and hydroxichloroquine seems to affect vitamin D metabolism, although evidence are not so clear yet. Besides, severe renal involvement, which can be seen in patients with lupus nephritis, can affect the hydroxylation step of  $25(\text{OH})\text{D}$ .<sup>13</sup>

The higher incidence and severity of SLE in individuals of African descent has been well documented. It is believed that this is a consequence of not only genetic factors, but it is speculated that lower serum concentrations of  $25(\text{OH})\text{D}$ , due to the lower cutaneous conversion rate secondary to skin color, would be another important factor.<sup>19</sup>

It has been observed that critical levels of vitamin D (<10 ng/mL) are more common in patients with renal involvement and photosensitive skin lesions.<sup>3</sup> The association between low serum levels of vitamin D and disease activity scores, according to the SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) and ECLAM (European Consensus Lupus Activity Measurement) has been documented.<sup>19,35</sup> Thudi *et al.*<sup>35</sup> demonstrated that functional assessment using combined scores (modified HAQ, global VAS by the patient, and fatigue scale) was worse in patients with probable or confirmed diagnosis of lupus and vitamin D deficiency. However, this study did not demonstrate an association between vitamin D deficiency and the levels of auto-antibodies, including anti-DNA.

The association between vitamin D deficiency and disease activity was demonstrated in a Brazilian study with 36 patients: levels of  $25(\text{OH})\text{D}$  were lower (mean  $17.4 \pm 12.5$  ng/mL) in patients with high disease activity (SLEDAI  $\geq 12$ ) when compared to those with mild disease activity (SLEDAI  $\leq 3$ ) and the control group<sup>36</sup>. In a Spanish study with 92 SLE patients,

the authors observed low levels of vitamin D (< 30 ng/mL) in 75% of the patients and deficiency (< 10 ng/mL) in 45% of them. In this study, 45% of the patients with low levels and 35% of those with deficiency were on calcium and vitamin D supplementation at the time of the evaluation. This study also showed higher degree of fatigue in patients with vitamin D deficiency, although a relationship between disease duration, SLEDAI, or SLIC-ACR was not observed.<sup>13</sup>

Carvalho *et al.*<sup>37</sup> investigated the presence of anti-vitamin D antibodies in the serum of SLE patients to better explain vitamin D deficiency in autoimmune diseases. One-hundred and seventy-one SLE patients were investigated and 4% of them had vitamin D antibodies but the levels of 25(OH)D were similar in patients with or without those autoantibodies. Among the clinical and laboratorial associations investigated, the presence of anti-dsDNA was the only one that showed a strong relationship with anti-vitamin D antibodies ( $P = 0.0004$ ).

#### Undifferentiated connective tissue disease (UCTD)

A study by Zold *et al.*<sup>38</sup> demonstrated the presence of a seasonal variation in the levels of 25(OH)D in patients with UCTD and that those levels were lower in this population than in the control population. In this same study, 21.7% of patients with UCTD and vitamin D deficiency developed established connective tissue disease (especially RA, SLE, Sjögren's syndrome, and mixed connective tissue disease); their level of vitamin D was lower than that of patients who remained with undifferentiated disease.

#### Inflammatory bowel disease (IBD)

Inflammatory bowel disease (Ulcerative Colitis and Crohn's disease) is an immunomediated disorder whose pathophysiology involves Th1 cells, with the production of IL-2, TNF- $\alpha$ , and IFN- $\gamma$ .<sup>14</sup> Low serum levels of 25(OH)D have been described in IBD. In a study by Jahnsen *et al.*,<sup>39</sup> the authors observed vitamin D deficiency in 27% of the patients with Crohn's disease and in 15% of those with ulcerative colitis.

It seems that a combination of factors, such as low ingestion and malabsorption of vitamin D, and decreased exposure to the sun, are responsible for the higher frequency of vitamin D deficiency in IBD.<sup>8</sup>

In experimental IBD with IL-10 knockout rats, vitamin D deficiency accelerated the disease, with earlier development of diarrhea and cachexia and higher mortality rate.<sup>14</sup> On the other hand, treatment with 1.25(OH)<sub>2</sub>D<sub>3</sub> prevented the development

of symptoms, besides reducing the progression and activity of the disease.<sup>1,3</sup>

#### Multiple sclerosis

Multiple sclerosis is an autoimmune disease of the central nervous system characterized by inadequate recognition of auto-epitopes in myelinated nerve fibers by cells of the acquired immune system, generating an inflammatory immune response mediated by lymphocytes and macrophages, resulting in localized areas of inflammation and demyelination.<sup>14</sup>

Some studies have also demonstrated the association of vitamin deficiency and MS and its role not only in the reduction of relapse rates, as well as in the prevention of its development.<sup>40,41</sup> The risk of MS decreases considerably (up to 40%) in Caucasian individuals with a high ingestion of vitamin D. The same benefit was not observed in individuals of African descent and Hispanics.<sup>40</sup>

In a study with experimental models of MS, the administration of vitamin D prevented the onset of autoimmune allergic encephalitis and slowed down the progression of the disease.<sup>42</sup>

#### Type I diabetes mellitus

Several effector mechanisms that lead to cell destruction, including the presence of CD8<sup>+</sup> lymphocytes and macrophages, which regulate the differentiation of Th1 cells through IL-12, are involved in the pathophysiology of type 1 diabetes mellitus (DM1).<sup>43</sup> In experimental models using non-obese diabetic mice (NOD mice), vitamin D deficiency accelerated the onset of DM1.<sup>44</sup> Using this same model, early supplementation of 1.25 (OH)<sub>2</sub>D<sub>3</sub>, before the progression of a mononuclear infiltrate within pancreatic cells, reduced autoimmune insulinitis and prevented the development of diabetes.<sup>45</sup>

Epidemiological studies have demonstrated that dietary supplementation of vitamin D in childhood can reduce the risk of developing DM1. A Finish study with a 30-year follow-up observed a significant reduction in the prevalence of DM1 in children who received daily vitamin D supplementation (RR = 0.12).<sup>46</sup>

#### Inflammatory cutaneous diseases

Dysfunction of cathelicidins, antimicrobial peptides (AMPs) present in the skin, is relevant in the pathogenesis of several cutaneous diseases, including atopic dermatitis, rosacea, and psoriasis.<sup>47,48</sup> A recent study demonstrated that vitamin

D3 is one of the main factors responsible for regulating the expression of cathelicidins, involving epigenetic alterations, such as histone acetylation.<sup>49</sup> Thus, treatments aimed at the metabolism and signaling of vitamin D3 could be beneficial in cutaneous inflammatory diseases.<sup>48,53</sup>

In psoriasis, blocking the expression of human peptides of cathelicidins (LL-37) can inhibit the activation of dendritic cells and cutaneous inflammation.<sup>53</sup> Paradoxically, vitamin D3 analogues were used for a long time in the treatment of psoriasis. Those compounds bind vitamin D receptors, activating them, therefore increasing the levels of cathelicidins in the keratinocytes and, presumably, worsening inflammation. However, the opposite occurs: improvement of cutaneous inflammation and reversion of the morphological changes in damaged skin.<sup>53</sup>

The use of vitamin D3 and its analogues in the treatment of psoriasis has been studied for several years, demonstrating the effects of calcitriol on the improvement of psoriatic lesions. However, due to hypercalcemia and hypercalciuria, long-term use of those agents is limited. Those findings led to the investigation of other vitamin D3 analogues that could have the antipsoriatic effects of vitamin D3 without the undesirable side effects in calcium homeostasis. Calcipotriene (also known as calcipotriol), one of those compounds, has an effect of differentiation and inhibition of the proliferation of keratinocytes *in vitro*, while the effects in calcium metabolism were 100 to 200 times smaller than those of calcitriol.<sup>54</sup> Currently, topical synthetic vitamin D analogues represent one of the safest and most effective alternatives for the treatment of mild to moderate psoriasis, comparable to high-potency topical corticosteroids.<sup>55,56</sup>

### Vitamin D supplementation in the prophylaxis and treatment of autoimmune diseases

Despite clinical and experimental evidence that vitamin D deficiency is an important factor responsible for increasing the prevalence of specific autoimmune diseases and the proven immunomodulatory effects of this compound,<sup>5</sup> as described above, little is known about the effects of vitamin D supplementation in the prevention and treatment of those disorders; however, it is believed that its supplementation is relevant for the control of graft rejection and in the prevention and treatment of autoimmune diseases.<sup>22</sup>

Most studies available have used experimental models of lupus,<sup>6</sup> MS,<sup>57,58</sup> IBD,<sup>59</sup> arthritis,<sup>60,61</sup> and type 1 DM,<sup>45,62</sup> and all have demonstrated the beneficial effects of vitamin D supplementation in modulating the components of the immune system responsible for the inflammation, such as the

expression of cytokines, growth factors, nitrous oxide, and metalloproteinases.

Only small and non-controlled studies have been carried out in humans; however, they also seem to indicate the beneficial effects of vitamin D supplementation in preventing the development of autoimmune diseases, as well as in reducing the severity of pre-existing disease.<sup>63-69</sup>

### FINAL CONSIDERATIONS

Evidence suggest that vitamin D deficiency can play an important role in regulating the immune system and, probably, in the prevention of immune-mediated diseases. However, further studies are necessary to determine the risks and benefits of vitamin D supplementation, when and in which patients the levels of 25(OH)D should be measured, which reference levels should be considered deficiency/insufficiency, clinical actions, and the real impact of this association in daily clinical practice.

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