Autoimmunity Reviews 16 (2017) 587–593

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Vitamin D and Sjögren syndrome

Mario Garcia-Carrasco [a,b], Erick Alejandro Jiménez-Herrera [a], Jose Luis Gálvez-Romero [c], Luis Vázquez de Lara [d], Claudia Mendoza-Pinto [a,b], Ivet Etchegaray-Morales [a], Pamela Munguía-Realpozo [e], Alejandro Ruíz-Argüelles [f,g], Rosas Jose [h], Mauricio Vera-Recabarren [i], Ricard Cervera [j,*]

[a] Systemic Autoimmune Diseases Research Unit, General Regional Hospital No. 36, Instituto Mexicano del Seguro Social, Puebla, Mexico
[b] Department of Rheumatology and Immunology, Medicine School, Benemérita Universidad Autónoma de Puebla, Puebla, Mexico
[c] Department of Inmuno-allergology, Puebla Regional Hospital, Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, ISSSTE, Puebla, Mexico
[d] Department of Experimental Medicine, Medicine School, Benemérita Universidad Autónoma de Puebla, Puebla, Mexico
[e] Department of Rheumatology, Centro Medico Nacional La Raza, Instituto Mexicano del Seguro Social, Puebla, Mexico
[f] Laboratorios Clinicos de Puebla, Puebla, Mexico
[g] Universidad de las Américas Puebla, Puebla, Mexico
[h] Department of Rheumatology, Marina Baixa Hospital, Villajoyosa, Alicante, Spain
[i] Department of Dermatology, Indisa Clinic, Santiago de Chile, Chile
[j] Department of Autoimmune Diseases, Hospital Clinic, Barcelona, Catalonia, Spain

ARTICLE INFO

Article history:
Received 23 February 2017
Accepted 28 February 2017
Available online 12 April 2017

Keywords:
Sjögren syndrome
Vitamin D
Immunomodulation
Environment

ABSTRACT

The immunomodulatory effects of vitamin D have been extensively studied in the context of autoimmunity. Multiple studies have demonstrated a high prevalence of vitamin D deficiency in autoimmune diseases. Recently, a possible protective role of vitamin D in autoimmunity has been described; however, this function remains controversial. Few studies have investigated the role of vitamin D in patients with Sjögren syndrome (SS). In this review, we compiled the main features of SS pathogenesis, the vitamin D immunomodulatory effects and the possible interaction between both. Data suggests that vitamin D may play a role in the SS pathogenesis. In addition, vitamin D low levels have been found in SS patients, which are associated with extra-glandular manifestations, such as lymphoma or neuropathy, suggesting a possible benefit effect of vitamin D in SS.

Contents

Abbreviations: APC, Antigen-presenting cell; BAFF, B-cell activating factor; DBP, Vitamin D-binding protein; EBV, Epstein-Barr virus; RA, Rheumatoid arthritis; SLE, Systemic lupus erythematosus; SS, Sjögren syndrome; Treg, T regulatory cell; VDR, Vitamin D receptor; VDRE, Vitamin D response element.

* Corresponding author at: Villarroel, 170, 08036 Barcelona, Spain.
E-mail address: rcervera@clinic.ub.es (R. Cervera).

http://dx.doi.org/10.1016/j.autrev.2017.04.004
1568-9972/

1. Vitamin D metabolism

Vitamin D is a true steroid hormone that shares common structures with glucocorticoids; both are synthetized from cholesterol [1]. Vitamin D may be considered a component of the "vitamin D endocrine system", which includes specific enzymes, active and inactive metabolites, the vitamin D receptor (VDR), the vitamin D-binding protein and regulatory hormones for the synthesis and catabolism of vitamin D [2]. The main source of vitamin D is its synthesis in the skin by UV-B radiation, with variations that depend on the latitude and season [3].

1.1. Synthesis of vitamin D, active metabolites and excretion

Pro-vitamin D (7-dehydro-cholesterol), produced from cholesterol metabolism, is the precursor of vitamin D (cholecalciferol). After exposure to UV-B radiation, pro-vitamin D generates pre-vitamin D, which is unstable and, after reorganization of its three double bonds, yields inactive vitamin D [2,3]. Next, vitamin D is transported by the blood stream by the vitamin D-binding protein (DBP) to the liver, where it is hydroxylated by 25-hydroxylase, forming 25-hydroxyvitamin D (25(OH)D) [4]. This molecule binds to the DBP and is carried to the kidney, filtered by the glomeruli and captured by the transmembrane proteins, cubilin and megalin, which function as DBP receptors in the proximal tubule and internalize 25(OH)D in the tubular epithelial cells. 25(OH)D is hydroxylated in carbon 1 of the A ring by 1α-hydroxylase, which finally generates 1,25 dihydroxy-vitamin D (1,25(OH)2D), the functional and active form of vitamin D [5]. 25(OH)D and 1,25(OH)2D are finally hydroxylated in carbon 24 by 24-hydroxylase in the kidney, yielding 24,25(OH)2D, an inactive molecule of easy excretion. All cells expressing the VDR also have 24-hydroxylase [3,6].

1.2. Vitamin D receptor

The biological actions of 1,25(OH)2D are mediated by the VDR, a member of the two protein domain-steroid receptor family. The N-terminal region is highly conserved and comprises the DNA-binding domain, while the ligand domain is located in the C-terminal region. The binding of 1,25(OH)2D to the receptor induces a conformational change that facilitates the interaction with RXR and co-regulatory complexes. The activated VDR receptor binds to specific sites in the DNA called vitamin D response elements (VDRE), affecting the transcription of the corresponding gene [7,8].

1.3. Regulation of vitamin D metabolism

The synthesis of 1,25(OH)2D is regulated by the parathyroid hormone (PTH), through the fluctuation of calcium serum levels. Hypocalcemia stimulates the production of PTH, which stimulates the synthesis of 1,25(OH)2D; in turn, this component lowers PTH levels by negative feedback [3,9].

2. Role of vitamin D as an immune system regulator

The vitamin D system coordinates growth, metabolic processes, differentiation, death, reproduction and regulation of the immune system cells as a consequence exposure to sunlight. This concept has been accepted since the discovery of the VDR in T lymphocytes [3].

2.1. Innate immunity

The vast majority of the immunoregulatory functions of vitamin D are carried out by its active form, 1,25(OH)2D [10], which stimulates the production of cathelicidin in some monocytes, lung, intestinal and epithelial cells, keratinocytes and placental trophoblasts. In addition, it is reported that VDR activation triggers the expression of the antimicrobial peptide, defensin beta 4, requiring the convergence of the IL-1β and VDR pathways [9,11]. In addition, 1,25(OH)2D increases the production of reactive oxygen species and the activation of antibacterial autophagy during the antimicrobial response in vitro [9].

2.2. Adaptive immunity

1,25(OH)2D plays a suppressor role in adaptive immunity, mainly on the synthesis pathways of cytokines in lymphocytes [10]. It diminishes the response mediated by Th1 lymphocytes, specifically in the synthesis of the pro-inflammatory cytokines IL-2 and IFNγ [12]. In contrast, 1,25(OH)2D favors the production of cytokines in Th2 lymphocytes. In regulatory T cells (Treg),1,25(OH)2D induces the expression of FoxP3, a transcription factor involved in the development and function of Treg lymphocytes; they are known to be vitamin D response elements in the promoter region of the FoxP3 gene [13]. In dendritic cells, 1,25(OH)2D inhibits differentiation, suppression of the pro-inflammatory cytokine IL-12 and increases in the anti-inflammatory cytokine IL-10 [14].

One of the most important cells suppressed by 1,25(OH)2D is the Th17 lymphocyte, which have been closely related to the pathogenesis of a number of autoimmune diseases [15]. There is evidence of the expression of genes associated with inflammation in Th17 lymphocytes, which are important in the defense mechanisms against mucocutaneous candidiasis and *Staphylococcus aureus* infections. In fact, inhibition of the effector pathways of IL-12, IL-17A and IL-17RA has therapeutic effects in psoriasis and rheumatoid arthritis (RA) [15]. It has been observed that CD4+ cells from VDR knocked-out mice showed more development towards Th17 in several in vitro conditions; in addition, T CD4+ cells presented overproduction of IL-17 [15,16]. This negative regulation of 1,25(OH)2D on Th17 has been reported in several studies, for example, Wen H et al. found that peripheral mononuclear cells in patients with RA had reduced IL-17, IL-6 and TNFα levels when cultured in the presence of 1,25(OH)2 D, which indicates a specific immunosuppressive effect on cytokine production for the development of Th17 [17].

3. Vitamin D and autoimmunity

Vitamin D and its active form have been proposed as crucial factors related to autoimmune diseases and epidemiological studies have identified vitamin D deficiency as a risk factor for autoimmune diseases [18]. See Fig. 1.

Serum levels of 25(OH)D are the best markers of serum vitamin D levels. Vitamin D deficiency is defined as serum 25(OH)D < 10 ng/mL, and is commonly associated with muscle weakness, bone pain and fractures. However, vitamin D insufficiency, defined as serum 25(OH)D of 10–30 ng/mL, is mainly asymptomatic [15,19]. Low vitamin D levels have been associated with major immune system-mediated rheumatic diseases such as systemic lupus erythematosus (SLE) and RA [1,20]. The possible association between low levels of vitamin D and autoimmune diseases has been reinforced by clinical improvement after vitamin D supplementation in animal models [21]. It is speculated that

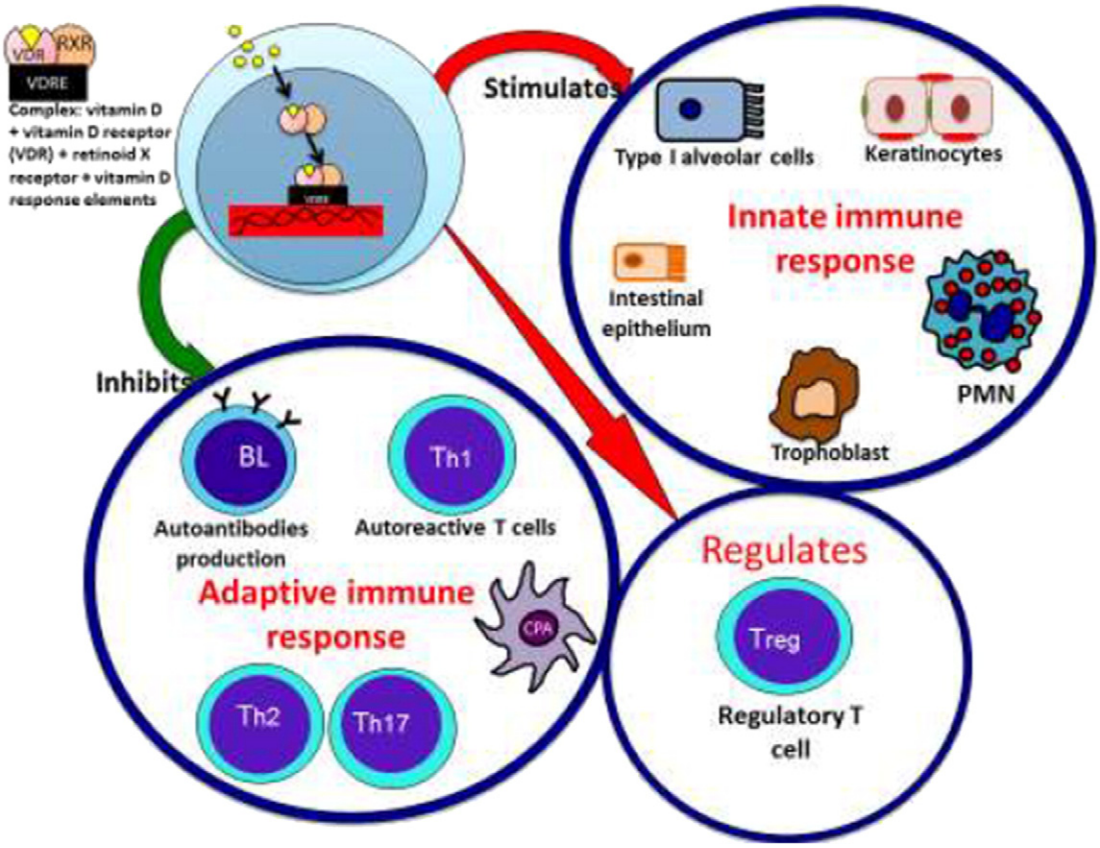

Fig. 1. Vitamin D and immune regulation. Once vitamin D binds to its receptor inside the nucleus, it also binds to the co-receptor R × R (retinoid × receptor): this complex binds to response elements for vitamin D (VDRE) and activates different groups of genes. The essential immunomodulation function of vitamin D is to stimulate the cells of the innate immune system, to inhibit the auto reactivity of the adaptive immune response and to regulate the intensity of the immune response via activation of regulatory T cells. As a consequence, vitamin D helps protect against microbial infections through the innate immune system, and against autoimmune diseases by means of the modulation of the adaptive immune response.

this effect is due to a decrease in IL-12 and IL-17 and a concomitant increase in IL-10 [9,13,22] (see Fig. 2).

It is suggested that exposure to sunlight plays a protective role against these autoimmune diseases, partly due to an increase in the calcitriol available for the regulation of the T lymphocyte response. It is known that paracrine signaling of T lymphocytes inside tissues is the main pathway through which sunlight exerts its functions related to the autoimmune disease phenotype [23]. The mechanisms of vitamin D in the development of autoimmune diseases may be centered on the regulation of T lymphocytes, because these cells in an immunoreactive status are part of the onset of a number of autoimmune diseases [24].

Antigen-presenting cells (APC) are also involved in the development of autoimmune diseases [14]. There is evidence that these cells secrete calcitriol, producing a paracrine role for vitamin D in these immune cells [23]. Activation of the VDR in APC changes the phenotype towards a state of immune tolerance during the adaptive immune response. It is hypothesized that dendritic cells treated with VDR agonists promote the formation of regulatory T cells (lineage CD4 + CD25 + FoxP3), which can create immune tolerance and stop the development of autoimmune diseases [14]. For example, one of the main characteristic of immune dysregulation in SLE is an increase in dendritic cell maturation which induces an increase in Th1 and activation of B lymphocytes [25] Wahono et al. studied the behavior of the immune system in patients with SLE treated with 1, 10 or 100 nM of 1,25(OH)2D and found that the treatment inhibited dendritic cell maturation due to a decrease in the expression of CD40, CD86, HLA-DR and IL-12p70, which are co-stimulators of T cell activation. In addition, a reduction in Th17 cells and IL-17A levels in CD4 cells and an increase in Treg cells was observed. The dose of 100 nM rather than having an immunomodulatory effect was found to be toxic, activating other mechanisms to maintain homeostasis, with an increase in the percentage of Th17 cells and the production of IL-17A [26].

A possible role of some VDR polymorphisms in the development of autoimmune diseases has been postulated [27]. The VDR locus is located on chromosome 12q13.1, and four polymorphisms have been described: ApaI, FokI, BsmI and TaqI. FokI seems to have the closest association with autoimmune states, especially SLE, multiple sclerosis and type I diabetes mellitus. It has a second codon in the start site and the formation of two different sites, meaning it can synthetize two protein variants: one large version with three additional amino acids, named the f allele and a short version, the F allele [28]. In vitro studies have found that patients with the FF genotype showed more proliferation of monocytes and dendritic cells and produced more IL-12 when stimulated with phytohemaglutinin, when compared with their ff counterparts [29]. Patients with the ff phenotype had increased levels of serum 25(OH)D compared with patients with the FF phenotype [30].

4. Vitamin D and Sjögren syndrome

4.1. Vitamin D deficiency in Sjögren syndrome

The relationship between low levels of vitamin D and Sjögren syndrome (SS) is still controversial. The lack of exposure to UV rays as part of the treatment for the skin manifestations of the disease has been postulated as a risk factor for vitamin D deficiency [31].

Vitamin D deficiency is relatively frequent in patients with primary SS, thus suggesting a possible role in the pathogenesis of the disease [32]. Ragamolopan et al. analyzed admission records and hospital deaths in England from 1999 to 2011 in order to investigate correlations between serum vitamin D levels and autoimmune diseases in patients

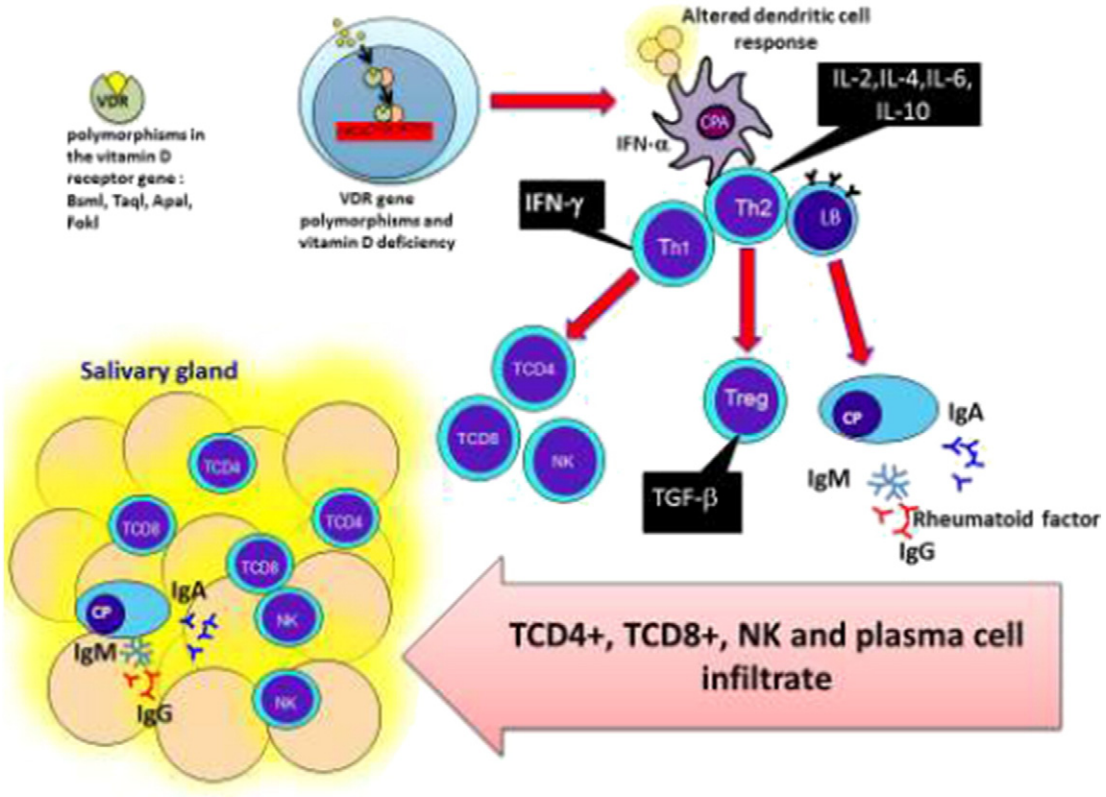

Fig. 2. Role of vitamin D in Sjögren syndrome. Polymorphisms in the vitamin D receptor gene (Bsml, Taql, Apal, y Fokl) and vitamin D deficiency may contribute to the development of Sjögren syndrome. Faced with this association, it is possible that the antigen presenting cell (dendritic cell) directly damages the gland tissue via the release of IFN-α; on the other hand, there is also release of cytokines that promote an autoimmune response. Autoreactive B cells (Th2 response and related to IL-2, 4, 6 and 10) differentiate to plasma cells, which synthesize rheumatoid factor (IgM, IgG and IgA). There is also a cell mediated immune response (via IFN-γ) with activation of TCD4+, TCD8+ y NK autoreactive cells; in addition, the activation of regulatory T cells is related to the production of TGF-β. The final result is infiltration of the salivary gland by T cells, NK, plasma cells and, probably, fibrotic tissue.

admitted for vitamin D deficiency or a related disease (osteomalacia and rickets). Of the 8.6 million patients in the reference cohort, 13, 260 had vitamin D deficiency (71% women) and showed a significantly-increased risk for a number of autoimmune diseases. Specifically, there was a significantly increased risk for SS in patients with vitamin D deficiency, osteomalacia and rickets. The authors suggested that vitamin D deficiency was related to the development of autoimmune diseases due to defective immune regulation or that there was an inverse causality, that is to say, either a subclinical autoimmune disease or clinically-overt disease not registered in the hospital admission, which caused a reduction in vitamin D levels as a result of the chronic inflammatory state or the lack of sun exposure [18]. In contrast, some studies have been unable to demonstrate that SS is associated with low levels of vitamin D [21,33].

In patients with SS, some authors have linked vitamin D deficiency to the appearance of peripheral neuropathy, non-Hodgkin lymphoma and congenital heart block in siblings of mothers with positive anti-SSA and anti-SSB antibodies [34]. With respect to peripheral neuropathy, it is known that 1,25(OH)2D plays several roles in the nervous system: biosynthesis of neurotropic factors, production of enzymes for neurotransmitter synthesis, inhibition of inducible nitric oxide synthase (iNOS) synthesis and it increases the levels of glutathione and gamma-glutamyl-transpeptidase [4]. Agmon-Levin et al. found that patients with SS and sensorial or motor-sensory neuropathy had lower levels of vitamin D compared with patients without neuropathy [21]. In light of this evidence, it may be speculated that low levels of vitamin D in patients with SS might play a significant role in the development of this extraglandular manifestation, but well-designed studies are needed to test this hypothesis.

There is strong epidemiologic evidence of a higher incidence of lymphoma in patients with SS compared with the general population, and the pathogenesis is well documented [35]. Low serum 25(OH)D levels have been found in patients with lymphoma, and there is a correlation with the clinical manifestations, prognosis and therapy [36]. Agmon-Levin found lower levels of vitamin D in patients with SS and lymphoma compared with patients without lymphoma, with low vitamin D levels being independent of the presence of clinical and serological parameters associated with lymphoma [21].

Antinuclear antibodies, rheumatoid factor and especially Ro/SSA and La/SSB antibodies are the key serological findings in patients with SS. Positivity of Ro/SSA and La/SSB antibodies have been associated with glandular dysfunction, a higher prevalence of extra-glandular manifestations, hypergammaglobulinemia and other markers of B cell activation; Ro/SSA and La/SSB antibodies have also been associated with congenital cardiac block in neonates of mothers with SS [37]. Recently, a possible relationship between anti-Ro and anti-La positive congenital cardiac block and low vitamin D levels has been described. Ambrosi et al. found a seasonal influence for the development of anti-Ro and anti-La positive congenital cardiac block in children of Swedish cohort of 80 families. There was a significant increase in the proportion of neonates with congenital heart block in the summer: an explanation was that patients who had the critical pregnancy period (18–24 weeks of gestation) for the development of antibody associated-congenital cardiac block during the winter also had the lowest levels of vitamin D. During the winter, there is a marked decrease in sun exposure and low vitamin D levels (based on samples from 1068 Swedish women). They found that average vitamin D levels for each month inversely correlated with the proportion of congenital heart block pregnancies [38]. In light

of these results, low levels of vitamin D during weeks 18 to 24 could be involved in the pathogenesis of this disease in mothers positive for anti Ro/La, and this situation would be more prevalent in women with autoimmune diseases, such as SS.

4.2. Vitamin D as a possible environmental factor in the pathogenesis of Sjögren syndrome

4.2.1. Viral infection

Multiple viruses have been associated with the pathogenesis of SS, including cytomegalovirus, Epstein-Barr virus (EBV) and Human Herpes virus-6,7,8 [39]. EBV infection is controlled mainly by CD8+ T cells, which suppress proliferation through lysis of infected B lymphocytes. The importance of EBV infection resides in its putative participation in the process of autoimmunity. Recently, several steps in the generation of EBV-mediated autoimmunity have been defined in people with immune susceptibility: 1) deficiency of CD8+ T lymphocytes, 2) primary EBV infection, 3) a decrease in infection control due to low levels of CD8+ T lymphocytes, 4) an increase in the EVB load and anti-EVB antibodies, 5) EVB infection in target organs, 6) clonal expansion of self-reactive B lymphocytes in target organs, 7) infiltration of self-reactive T lymphocytes in target organs and 8) development of ectopic lymphoid follicles in target organs [40]. The initial step, deficiency of CD8+ T lymphocytes and an increase in the CD4+/CD8+ ratio has been observed in the immune profile in patients with SS. In addition, these abnormalities in the lymphoid lineage have been demonstrated in relatives of SS patients, including some without clinical evidence of disease [41]. These abnormalities are also associated with age, with a decrease in CD8+ cells as age increases [42,43], which is in agreement with the age-related increase in the prevalence in SS [44]. Accordingly, it has been proposed that the deficiency of CD8+ T lymphocytes would allow an accumulation of EBV-infected B lymphocytes in target organs. This aspect has been highlighted in several studies that associate the immunobiology of SS with EBV infection [45].

On the other hand, sun exposure increases CD8+ T lymphocyte counts and decreases the CD4+/CD8+ ratio [46], which has been associated with the immunomodulatory effects of vitamin D [40]. Currently, no specific mechanism for the immunologic effects of sun exposure has been described, but some studies have described effects of vitamin D that could explain how the sun exposure may exert this immune modification. It has been observed that vitamin D can increase the CD8+ T cell count and increase the CD4+/CD8+ ratio [47]. However, these findings remain unclear because in vitro, 1,25(OH)D inhibits T CD8+ lymphocyte proliferation, but not the T CD8+ VDR KO, which proliferates and, in fact, there is generation of pathogenic T CD8+ lymphocytes from rapidly-proliferating cells [48]. Therefore, changes in the CD4+/CD8+ ratio, together with an increase in CD8+ T cells caused by adequate levels of vitamin D, in theory, could participate as a protective factor for SS, because it would control the first step in the pathogenesis of the disease, specifically the reduced CD8+ count linked to the development of SS, as previously mentioned.

4.2.2. UV radiation

Currently, there is evidence that there is some degree of immunosuppression related to exposure to sunlight that can condition the development of neoplastic and autoimmune diseases. Kelly et al. found that suberythemal exposure to UV radiation from sunlight decreases the local immune response to locally-applied antigens [49]. The activation of enzymes associated with the plasma membrane induces the activation of several transcription factors, such as NF-kB, which may regulate the production of immunomodulatory cytokines; for example, dendritic cell radiated with UV show a cytokine profile that favors an environment for the development of Th2 lymphocytes [49]. Some authors have postulated that the immunosuppression caused by UV radiation can lead to organ-specific autoimmune disease, specifically with those associated with Th1 activity, which would benefit from UV exposure [50].

Some mechanisms have been suggested to explain how UV radiation could modify the immune response mediated by Th1 lymphocytes: (1) UV radiation can induce immunosuppression through the release of cytokines which can, in turn, increase the levels of soluble mediators that could lead to systemic immunosuppression, (2) the effects of the active form of vitamin D, induced by UV radiation and (3) the suppression of melatonin secretion, considering that melatonin receptor activation in helper T lymphocytes reinforces the characterization towards the Th1 lineage with liberation of IFN γ [51].

There is no conclusive evidence that the immunosuppressive effects of UV radiation are due directly to the immune properties of vitamin D. It has been shown that 1,25(OH)2D production by UV radiation does not correlate with local immune regulation. However, as the half-life of 1,25(OH)2D is two and a half weeks, it is possible that the immunoregulatory action of 1,25(OH)2D is mainly mediated by the vitamin D produced by intermittent UV radiation and not to radiation exposure per se [52]. In fact, the participation of vitamin D in protecting against the damage associated with UVB radiation exposure is necessary, as has been shown in VDR-depleted mastocytes and transferred to mice chronically exposed to UV radiation, where vitamin D was necessary for mastocyte activation in order to reduce inflammation and disease in the regions of exposed skin, and also for the production of IL-10 [53].

With respect to the immunobiology of SS, it is known that T lymphocytes are the first to infiltrate the exocrine glands in a process called "autoimmune epithelitis" which is mediated by overexpression of inflammatory cytokines in salivary gland epithelial cells [35,40,54]: this would locate SS in the group of autoimmune diseases mediated by T lymphocytes. On the other hand, there is currently no evidence on the possible interactions of UV radiation between the recently-described important subclasses of T-CD4+ cells, the pathogenic effector T cell and the FOXP3+ T effector regulatory cell+ [55], in the process of autoimmune epithelitis.

4.3. Sjögren syndrome immunobiology and its possible relationship with vitamin D

The most prominent cytokines in the physiopathology of SS are: IFNα, which is secreted by dendritic cells at the beginning of the activation of the immune system; IFNγ, which secreted by activated T cells

Table 1
Comparison of the immunomodulatory effects of vitamin D and the immunobiology of Sjögren syndrome.

Vitamin D effects	Sjögren syndrome
Decrease in lymphocyte activation (Th1)	Increase in differentiation to Th1 (increase in IFNγ and TNFα)
Decrease in IL-12. Decrease in lymphocyte activation (Th1)	Increase in IL-12 by dendritic cells[b]
Decrease in IFN-γ	Increase in IFN-γ
Decrease in Th17 through decrease in IL-6 and IL-23[a]	Increase in Th17: IL-17
Tolerogenic dendritic cells: Th2, Treg, IL-10	Reactive dendritic cells: BAFF, IL-7, IL-22, IL.6, CXCL10, CXCL12, CXCL13
Increase in Treg CD25+ Foxp3+ cells	
Decrease in the proliferation of T lymphocytes through decrease in IL-2	Increase in T lymphocytes via IFNα
Decrease in proliferation and differentiation of B cells (inhibition of differentiation in plasma cells and memory B cells	Increase in the production and differentiation of B cells via BAFF and IFNγ
Decrease in synthesis of immunoglobulins	
Inhibition of NFkB (via p105/p50) B naive cells	Expression of the genes NF-kB TNFAIP3, TNIP1 (related to B-cell activation)

References: [1,3,54,58,59]
[a] Cell linked to autoimmunity.
[b] High levels related to an increase in Tfh cells (also IL-21).

and related to direct damage to the gland tissue; and, B-cell activating factor (BAFF), a cytokine secreted by epithelial and dendritic cells involved in the stimulation of autoreactive B lymphocytes [54]. The main aspects of the immunobiology of SS and the effects of vitamin D are shown in Table 1.

Muller et al. described abnormal vitamin D metabolism in SS: 35 women with primary SS were treated with nonsteroidal anti-inflammatory drugs without immunosuppressive treatment. The authors measured serum levels of 25(OH)D, $1,25(OH)_2D$, vitamin D binding protein, rheumatoid factor (IgA and IgM), antinuclear antibodies (IgG) and plasma concentrations of immunoglobulins. They found that serum levels of $1,25(OH)_2D$ and vitamin D binding protein were normal, in contrast with low levels of 25(OH)D. IgM and IgA rheumatoid factor levels were high (72 and 60%, respectively). High levels of rheumatoid factor correlated inversely with serum levels of 25(OH)D. There was no significant correlation between either 25(OH)D or $1,25(OH)_2D$ levels and the rest of the measured parameters. It is uncertain whether changes in vitamin D metabolism affect the immune mechanisms present in SS, since there was no correlation between serum levels and titers of the antibodies analyzed, except for a correlation between 25(OH)D and high levels of IgM rheumatoid factor. Low levels of 25(OH)D did not correlate with normal levels of vitamin D binding protein, suggesting that the polyclonal activation of B lymphocytes is responsible for vitamin D deficiency through the consummation of activated lymphocytes [56].

In contrast, a study by Szodoray et al. aimed to determine whether vitamin A, D and E levels correlated with a number of clinical and immunological parameters in primary SS. Fasting levels of these vitamins were measured, together with NK, NK-T, B and T (CD4+ and CD8+) lymphocyte levels and serum levels of soluble cytokines (IL-1, -2, -4, -6, -10, TNF-α, TGF-β and INF-γ); healthy subjects were used as controls. Vitamin A serum levels of patients with SS were similar to those of normal subjects, but the subset of patients with extraglandular manifestations showed decreased levels. Vitamin D levels were similar in both groups, with no significant differences between patients with extraglandular manifestations and healthy subjects. In patients with SS, vitamin E levels were significantly higher than in the control group [33].

Finally, some VDR polymorphisms have been associated with the development of SS. VDR gene polymorphisms correlated with dysregulation in the absorption and metabolism of vitamin D, even in the VDR activity in response to 1,25(OH)D3. Only one study has analyzed the possible relationship between any VDR gene polymorphisms, specifically BsmI, TaqI, ApaI and FokI, and primary SS. The study found that these polymorphisms do not seem to be a genetic marker for SS [57].

Conflict of interest

The authors declare no conflict of interest.

Acknowledgement

We would like to thank David Buss for his valuable guidance and advice during this project.

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