Review

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Role of Vitamin D3 in Patients With Primary Sjögren's Syndrome: Links to Disease Severity and Immune Function

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Primary Sjögren's syndrome (pSS) is a chronic autoimmune disorder characterized by exocrine gland dysfunction. Vitamin D3 (VD3), known for its immunomodulatory properties, has been implicated in modulating severity and immune responses in pSS, although the precise mechanisms are yet to be thoroughly investigated. This narrative review consolidates current research regarding the role of VD3 in pSS, with emphasis on its relationship with disease activity and immune function. Studies consistently reveal that VD3 levels are lower in pSS patients, with a negative correlation between VD3 levels and the severity of glandular damage, particularly in the salivary and lacrimal glands. Additionally, VD3 levels have been significantly associated with immune function markers, including T cell subset distribution and immunoglobulin levels. Despite the evidence, further investigation is needed to elucidate the causal relationships and mechanistic pathways involved. Overall, the existing data underscore the potential role of VD3 in the immunopathogenesis of pSS and suggest it may serve as a potential biomarker and adjunctive therapeutic target in future disease management approaches.

Keywords: primary Sjögren's syndrome; vitamin D3 levels; degree of lesion; immune function; disease activity biomarker; T/B lymphocytes

Introduction

Primary Sjögren's syndrome (pSS) is a chronic autoimmune disease characterized primarily by dysfunction of exocrine glands, resulting in persistent symptoms such as dry mouth, excessive thirst, swallowing difficulties, increased risk of dental caries, and dry eyes. Beyond the exocrine glands, pSS can affect various non-exocrine organs, including joints, skin, lungs, and nervous system, resulting in diverse clinical manifestations [1].

pSS can occur independently (primary) or in association with other autoimmune diseases (secondary). Its epidemiology shows considerable geographical variation, yet pSS is generally considered a relatively common autoimmune disease. The global prevalence of pSS ranges from 0.01% to 2.7%, with a substantially higher incidence in females than males, at a ratio of approximately 9:1 [2,3]. However, the prevalence rates vary significantly across regions, with higher incidence observed in areas such as Northern Europe [4], the Middle East [5], South Asia [6], Sub-Saharan Africa [7], and the United States [8]. Although the condition most commonly occurs in middle-aged to older individuals, it can also affect younger individuals [9]. The exact etiology of pSS remains unclear; however, its pathogenesis has been reported to involve a combination of genetic predisposition, environmental factors, hormonal impacts, and immune system dysregulation [10].

Vitamin D3 (VD3), also known as cholecalciferol, is crucial not only for maintaining bone health but also plays a vital role in regulating the immune system [11]. As a fat-soluble vitamin, VD3 can be synthesized endogenously through exposure of the skin to ultraviolet B (UVB) radiation or obtained from dietary sources and supplements. In immune modulation, VD3 binds to the vitamin D receptor (VDR), a nuclear receptor that regulates gene expression and consequently influences the function of various immune cells (ICs) [12]. VD3 helps inhibit hyperactive immune responses by reducing aberrant T cell activation and autoantibody production seen in autoimmune diseases, thus alleviating autoimmune attacks. It also promotes the differentiation of regulatory T cells (Tregs), which are crucial for maintaining immune tolerance and dampening excessive immune responses [13–17]. Furthermore, it downregulates pro-inflammatory cytokines while upregulating anti-inflammatory factors, such as interleukin (IL)-10, thereby modulating inflammatory responses [18]. While VD3 exhibits immunosuppressive effects in the context of autoimmunity, it also enhances innate immune responses, including macrophage function, to combat infections [19]. Given its pivotal role in immune modulation, serum VD3 levels have been closely associated with the risk and disease

activity (DA) of various autoimmune disorders. Studies have suggested that low levels of VD3 are associated with a higher risk of developing autoimmune diseases, particularly Sjögren's Syndrome [20–24]. This association may be due to the disruption of immune balance by VD3 deficiency, elevating susceptibility to immune-mediated damage of exocrine glands and other tissues [25]. However, the precise molecular mechanisms through which VD3 modulates autoimmune conditions remain to be fully elucidated, and further research is required to investigate its potential as a preventive or therapeutic agent in autoimmune diseases.

In summary, pSS is a complex autoimmune disease with diverse clinical manifestations and underlying etiologies. VD3, a key regulator of immune function, plays a crucial role in maintaining immune balance and suppressing autoimmune responses. The association between VD3 deficiency and autoimmune diseases suggests the potential of VD3 supplementation as an adjunctive therapeutic strategy in managing conditions like pSS.

Role of VD3 in Immune Regulation

Underlying Mechanisms and Immunomodulatory Role of VD3 Within the Immune System

VD3, the biologically active form of the vitamin D family, plays a crucial role in regulating the human immune system. It contributes to multiple aspects of immune responses through intricate mechanisms, ranging from modulating the differentiation and function of ICs to directly participating in anti-inflammatory processes and regulating autoimmune conditions, thus exerting broad immunological impacts throughout immune activity [26]. The synthesis of VD3 begins in the skin, where 7-dehydrocholesterol is converted into cholecalciferol upon exposure to UVB radiation. This precursor is then hydroxylated in the liver to form 25-hydroxyvitamin D3, which is subsequently converted into its active form, 1,25-dihydroxyvitamin D3, in the kidneys. This active metabolite binds to the VDR, which is extensively expressed not only in classical target tissues but also across numerous ICs, including T cells, B cells, macrophages, dendritic cells (DCs), and neutrophils [27].

Moreover, in antigen-presenting cells (APCs), such as DCs, VD3 inhibits maturation and reduces antigen presentation by downregulating co-stimulatory signals, thereby suppressing T cell activation. This immunomodulatory effect plays a critical role in controlling excessive immune responses and maintaining immune tolerance. Furthermore, VD3 promotes the proliferation and function of Tregs, which are crucial for maintaining self-tolerance and suppressing autoreactive T cell activation [28]. Thus, VD3 helps to restrict inappropriate immune attacks, especially those observed in autoimmune diseases. Additionally, VD3 also impacts T cell differentiation by inhibiting the development of Th1 and Th17 cells and alleviating their production of pro-inflammatory cytokines, including IL-6, IL-12, interferon (IFN)-γ, and IFN-α. Concurrently, VD3 enhances the production of anti-inflammatory cytokines, such as IL-10, thereby contributing to immune homeostasis and reducing the occurrence and progression of inflammatory and autoimmune responses.

Moreover, VD3 plays a vital role in regulating humoral immune responses by influencing B cell maturation and modulating antibody production, thereby preventing tissue damage associated with the accumulation of aberrant immune complexes. It also directly participates in anti-inflammatory processes by stimulating programmed cell death (apoptosis) of inflammatory cells, reducing their replenishment, and downregulating the activity of the nuclear factor-kappa B (NF-κB), a key transcription factor in inflammatory signaling, leading to decreased production of pro-inflammatory mediators and the overall inhibition of systemic inflammation [26,28]. These characteristics underscore the therapeutic potential of VD3 in managing chronic inflammatory diseases. Furthermore, VD3 enhances innate immunity by promoting the phagocytic and bactericidal capabilities of immune cells such as macrophages, thereby improving their ability to clear pathogens. This function is particularly crucial in susceptible sites such as the respiratory and gastrointestinal tracts, substantially contributing to the host's defense against infectious diseases. The immunomodulatory role of VD3 is particularly pivotal in the context of autoimmune diseases. Studies have reported a close association between VD3 deficiency and elevated disease activity in various autoimmune diseases, including multiple sclerosis, rheumatoid arthritis, and type 1 diabetes [29,30]. Through its combined immunomodulatory and anti-inflammatory mechanisms, VD3 may help reduce or delay the development of autoimmune conditions, highlighting its potential as a preventive therapeutic agent.

In summary, VD3 plays a crucial role in maintaining immune system homeostasis and responsiveness by regulating the development, activity, and function of ICs, as well as contributing to anti-inflammatory and anti-microbial processes. These immunological properties provide valuable insights into the underlying mechanisms of immune regulation and open novel avenues for therapeutic interventions, particularly in the management of autoimmune diseases and the prevention and control of infectious diseases. Fig. 1 illustrates the mechanisms and immunological effects of VD3 within the immune system.

Effects of VD3 on the ICs

VD3 has garnered increasing attention in recent years due to its direct, cell-specific immunoregulatory functions. Apart from systemic effects, VD3 precisely regulates the differentiation, activation, and functional outcomes of various immune cell types involved in both innate and adaptive immunity [27,28]. Its interaction with immune cells begins with binding to the VDR, triggering transcriptional pro-

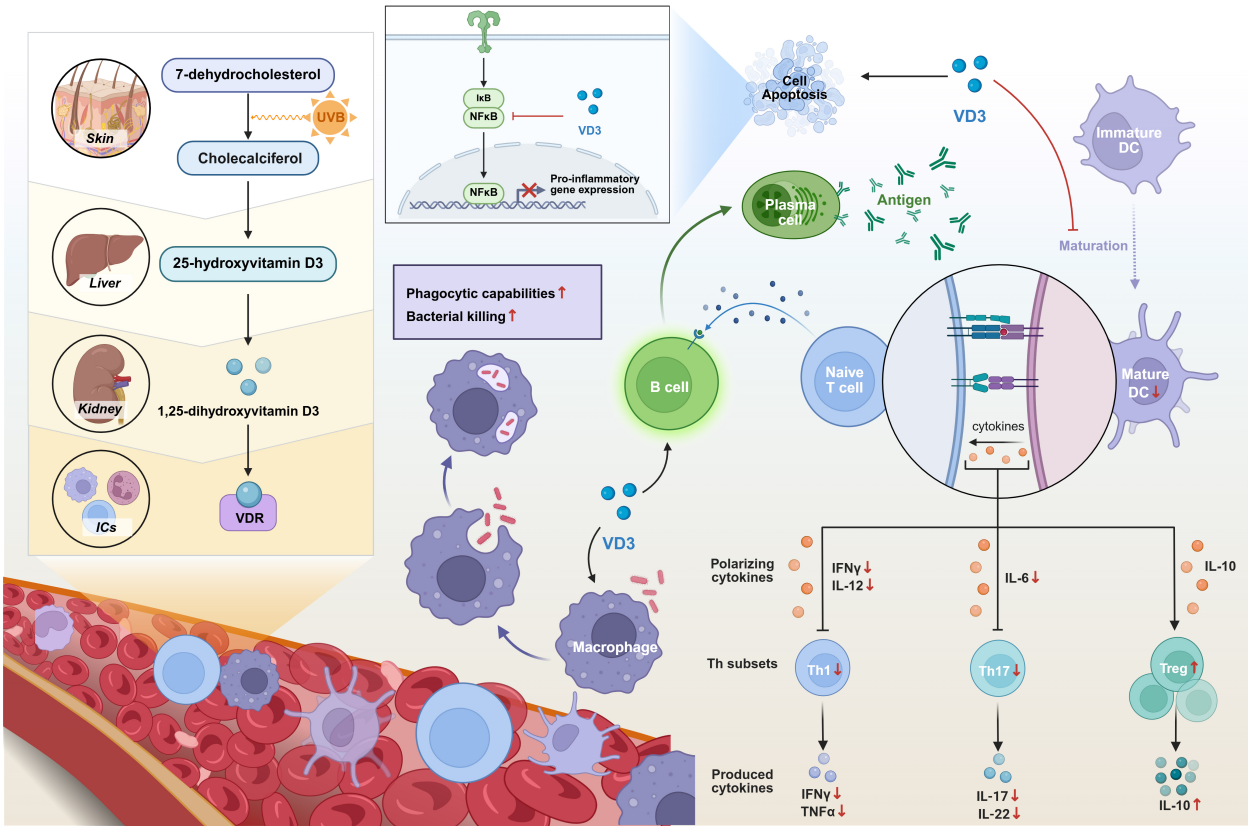

Fig. 1. Mechanisms and immunological impacts of Vitamin D3 (VD3) within the immune system. This figure illustrates the metabolic activation of VD3 from skin to liver and kidney, leading to the production of active 1,25-dihydroxyvitamin D3, which binds to vitamin D receptors (VDRs) in immune cells. VD3 modulates innate immunity by enhancing phagocytic capacity and downregulating pro-inflammatory genes via nuclear factor-kappa B (NF-κB) inhibition. It also shapes adaptive immunity by suppressing Th1 and Th17 responses ($\downarrow$ interferon (IFN)-γ, $\downarrow$ interleukin (IL)-12, $\downarrow$ IL-6, $\downarrow$ IL-17, $\downarrow$ IL-22) and promoting regulatory T cells ($\uparrow$ regulatory T cell (Treg), $\uparrow$ IL-10), while inhibiting dendritic cell maturation and B cell activity. The figure was created with BioRender.com. ICs, immune cells; VDR, vitamin D receptor; DC, dendritic cell.

grams that modulate cytokine profiles, cell surface marker presentation, and effector functions. Although the VDR-mediated signaling process is shared across various cell types, the downstream effects of VD3 are tailored to the distinct roles of each cell subset.

In APCs, particularly DCs, VD3 promotes a tolerogenic state by reducing maturation, antigen presentation, and the expression of co-stimulatory molecules. These changes reduce naïve T cell activation and redirect their differentiation away from pro-inflammatory subsets. Notably, VD3 facilitates the development of Treg cells, which are essential for maintaining immune tolerance and controlling autoimmune responses [31]. In the context of effector T cells, VD3 suppresses the differentiation of Th1 and Th17 cells, key contributors to the pathogenesis of many autoimmune and inflammatory disorders, by downregulating pro-inflammatory cytokines such as IFN-γ and IL-6, while upregulating anti-inflammatory cytokine IL-10. This regulation of cytokines promotes a balanced immune environment and helps mitigate excessive inflammation and immunopathology [32]. In terms of B cell modulation, VD3 influences their maturation and differentiation into plasma cells, as well as regulating immunoglobulin secretion. It reduces the survival of autoreactive B cells and inhibits the formation of pathogenic immune complexes, thereby offering protection against autoantibody-mediated tissue damage [33].

Beyond its effects on lymphocyte modulation, VD3 enhances the anti-microbial activity of innate ICs such as macrophages and neutrophils by stimulating chemotaxis, phagocytosis, and intracellular pathogen killing [34]. VD3 also promotes the resolution of inflammation by triggering apoptosis in activated ICs and suppressing the recruitment of new inflammatory infiltrates through the downregulation of pro-inflammatory mediators.

Importantly, VD3 is gaining recognition in tumor immunology due to its ability to induce cell cycle arrest, inhibit tumor cell proliferation, and promote apoptosis in malignant cells [35]. Furthermore, it also enhances immune surveillance by increasing the ability of cytotoxic T lym-

phocytes and natural killer (NK) cells to recognize and eliminate transformed cells [36]. These anti-tumor effects underscore the potential of VD3 as an adjunct in cancer immunotherapy. Emerging evidence also suggests that VD3 may influence the composition of gut microbiota, which may indirectly modulate systemic immune responses [37]. Although this area remains under active investigation, it highlights the increasing understanding of VD3's expanded immunomodulatory capabilities.

In conclusion, VD3 exerts cell-specific immunoregulatory effects by coordinating the activity of various immune cell types. Through its influence on APCs, T and B lymphocytes, and phagocytes, VD3 helps maintain immune equilibrium, prevent autoimmunity, increase anti-microbial defense, and potentially suppress tumorigenesis. These complex cellular interactions underscore the crucial role of VD3 in immune regulation and its potential in clinical interventions. Fig. 1 illustrates the cell-specific immunological effects of VD3 within the immune system.

Evaluation of VD3 Levels in Patients With pSS

Measurement of Serum VD3 Levels in Patients With pSS

In recent years, as understanding of the disease mechanisms has advanced, the role of VD3 in pSS has gained increasing attention, becoming a prominent research focus. Numerous studies have shown that serum VD3 levels are considerably lower in pSS patients compared to healthy individuals [38,39]. Beyond its crucial role in regulating calcium and phosphate metabolism, VD3 also directly participates in modulating immune responses, making it a key factor in the immunopathology of pSS.

VD3 interacts with the VDR expressed on ICs, influencing their proliferation, differentiation, and functional activity. These immunomodulatory effects include inhibiting the activation of autoreactive T cells, promoting the proliferation of Tregs, and regulating B cell differentiation and antibody production. Therefore, a deficiency or insufficiency of VD3 can theoretically lead to disruption of immune imbalance, potentially inducing autoimmune responses, an effect closely related to the pathogenesis of pSS. In pSS patients, low serum VD3 levels have been linked to DA, severity of salivary gland damage, and abnormal distribution of peripheral immune cell subsets ($r = –0.444$, $p < 0.001$), indicating a potential role of VD3 in regulating disease progression and immune dysregulation [40]. Furthermore, it has been reported that VD3 levels are substantially lower in patients with active pSS and are positively correlated with the pSS disease activity index (pSSDAI) scores ($r = –0.781$, $p < 0.001$) [38]. These observations suggest that serum VD3 not only serves as a biomarker of disease activity but also as a dynamic indicator of immune system fluctuations in pSS.

Additionally, correlation analysis between VD3 levels and specific symptoms in pSS patients reveals that lower serum VD3 levels are significantly associated with more severe symptoms of dry mouth and dry eyes, increased fatigue, and diminished quality of life, further highlighting the potential role of VD3 in alleviating clinical symptoms and improving overall well-being in pSS patients [41]. Similarly, a study explored the therapeutic potential of VD3 supplementation in pSS patients, aiming to restore serum VD3 levels, rebalance immune function, alleviate clinical symptoms, and possibly delay disease progression [42]. While existing research provides compelling evidence linking VD3 to pSS, further high-quality clinical trials and mechanistic research are needed to elucidate causal associations, investigate underlying pathways, and determine the exact effects and optimal dosage of VD3 supplementation in managing pSS.

Current Status of Serum VD3 Levels in Patients With pSS

pSS primarily affects the lacrimal and salivary glands, resulting in the hallmark symptoms of dry mouth and dry eyes, often accompanied by widespread systemic manifestations. In recent years, increasing research has consistently reported significantly reduced serum VD3 levels in pSS patients ($r = –0.38$, $p < 0.01$), a finding that not only enhances our understanding of the disease pathogenesis but also opens new avenues for clinical management [38,43]. VD3 is crucial for maintaining skeletal health and plays a vital role in immune regulation. Through its influence on the function of ICs, such as inhibiting autoimmune responses and regulating the activity of T and B cells, VD3 indirectly participates in the development and progression of various autoimmune diseases, including pSS [44].

In the context of pSS, low VD3 levels have been associated with increased DA, worsening of exocrine gland damage, and imbalance in specific IC subsets. These associations suggest that VD3 may directly or indirectly mediate the immunopathological mechanisms underlying pSS. Several studies have shown that serum VD3 levels in pSS patients are considerably lower compared to healthy controls, with this reduction closely correlating with key clinical manifestations, including the severity of dry mouth and eyes, increased fatigue, and reduced quality of life [45–47]. Furthermore, other studies have revealed associations between VD3 levels and both the diversity and concentration of autoantibodies in pSS patients, reinforcing the complex immunoregulatory role of VD3 in disease progression [45,48]. Some research suggests that reduced VD3 may promote the overactivation of B cells and elevated autoantibody production, a hallmark of pSS pathology [49].

Furthermore, VD3 deficiency has been associated with a higher risk of respiratory infections in pSS patients, possibly due to VD's role in maintaining the integrity of the mucosal barrier and supporting immune defense mech-

anisms in the upper respiratory tract [39]. Research also demonstrates that appropriate supplementation of VD3 can alleviate some symptoms, enhance overall quality of life, and potentially help manage DA in pSS patients [50]. The current evidence regarding serum VD3 levels in pSS patients reveals a close association between VD3 and the disease's underlying pathophysiology, suggesting its potential application as a biomarker for evaluating DA and prognosis, and also as a promising therapeutic target in the clinical management of pSS [51].

Relationship Between VD3 Levels and Disease Severity

Overview of the Relationship Between VD3 Levels and Disease Severity

pSS is a prevalent autoimmune disorder characterized by dysfunction of the exocrine glands, particularly the lacrimal and salivary glands, resulting in persistent symptoms such as dry mouth and dry eyes, often accompanied by systemic involvement [52]. VD3, which is typically synthesized in the skin upon exposure to ultraviolet radiation or acquired through dietary sources, undergoes hepatic and renal hydroxylation to produce its biologically active form, 1,25-dihydroxyVD3. This active form binds to VDRs expressed on ICs, thereby regulating their proliferation, differentiation, and function to modulate immune responses [53].

In patients with pSS, studies have consistently found substantially lower serum VD3 levels compared to healthy controls, prompting exploration into the underlying connection between VD3 deficiency and disease severity [54]. Several studies have reported a significant inverse correlation between VD3 levels and DA in pSS patients ($r = -0.44$, $p < 0.001$), suggesting that lower VD3 levels are associated with higher DA, more severe salivary gland inflammation, pronounced exocrine dysfunction, increased fatigue, and decreased quality of life [55–57]. These observations suggest a potential immunomodulatory role of VD3 in reducing disease progression by regulating immune balance and suppressing excessive autoimmune responses.

Furthermore, low VD3 levels in pSS patients have been correlated with IC subsets, including B cell hyperactivity, increased autoantibody production, and imbalanced proportions of T cell subsets, specifically decreased Tregs function and increased proportions of pro-inflammatory Th1 and Th17 cells, all of which are key contributors to the immunopathogenesis of pSS [58]. Through its impacts on immune cell differentiation and function, VD3 may help regulate autoimmune responses and reduce tissue damage.

Additionally, VD3 status has been associated with systemic inflammatory markers in pSS patients, with VD3 deficiency accompanying elevated levels of inflammatory cytokines such as IL-6 and TNF-α, suggesting that VD3 may exert protective anti-inflammatory effects in pSS [59]. Therefore, monitoring and managing VD3 deficiency could serve as a valuable adjunctive therapeutic strategy in treating pSS, potentially alleviating symptoms, reducing inflammation, and enhancing patient outcomes.

Mechanistic Studies of the Relationship Between VD3 Levels and Disease Severity

The decrease in VD3 levels not only reflects the underlying disease state in pSS but may also directly participate in its pathophysiology by influencing disease progression and clinical manifestations through complex immune regulatory mechanisms [58]. While VD3 is traditionally known for its role in supporting bone health, it also serves as a potent immunomodulator. Upon binding to the VDR on ICs, VD3 influences gene expression, thereby regulating various aspects of immune system activity [60,61]. This immunomodulatory function helps alleviate autoimmune responses and reduce inflammation in pSS [62].

Furthermore, VD3 exerts significant impacts on B cells, regulating their maturation and differentiation, inhibiting the activation of autoreactive B cells, and reducing the production of autoantibodies, including anti–Sjögren's-syndrome-related antigen A antibody(anti-SSA) and anti–Sjögren's-syndrome-related antigen B antibody (anti-SSB) antibodies, which are key biomarkers in pSS associated with DA [58]. These mechanisms not only aid in explaining why pSS patients with low VD3 levels often exhibit elevated autoimmune activity and more severe clinical symptoms but also support the potential of VD3 as a therapeutic target.

Additionally, VD3 regulates the immune microenvironment within salivary and lacrimal glands by inhibiting local immune cell infiltration and inflammatory responses, thereby alleviating glandular damage and dysfunction, which directly correlates with improvement in hallmark symptoms of pSS [63]. Studies have demonstrated that pSS patients with lower serum VD3 levels tend to have more severe glandular inflammation and histopathological damage, further highlighting the protective role of VD3 in maintaining glandular function [64]. Furthermore, VD3 has been found to inhibit the NF-κB signaling pathway, leading to reduced production of pro-inflammatory cytokines and enhanced tissue repair process, which may play a crucial role in limiting tissue damage and contributing to disease stability in pSS patients [63].

Correlation Between VD3 Levels and Immune Function

Overview of the Association Between VD3 Levels and Immune Function

VD3 plays a crucial role in the human body, not only facilitating calcium absorption and promoting skeletal health, but also actively contributing to immune system regulation. This immunomodulatory function is particu-

larly prominent in patients with pSS. pSS is characterized by dysfunction of the exocrine glands, leading to hallmark symptoms such as dry mouth and eyes, and may involve systemic manifestations affecting multiple organ systems [65]. VD3 exerts its effect by binding to VDRs expressed on ICs, including T cells, B cells, and anti-inflammatory macrophages. Through this interaction, VD3 impacts intracellular signaling pathways, regulates cytokine production, and modulates IC activity. These mechanisms are critical for maintaining immune homeostasis and self-tolerance, and for preventing the disrupted immune responses characteristic of autoimmune diseases such as pSS.

In patients with pSS, VD3 levels are generally low, a finding closely associated with DA, severity of symptoms, and pathological damage to exocrine glands. This suggests that VD3 serves not only as a biomarker reflecting disease status but also as a key contributor to the disease pathogenesis [59]. The deficiency of VD3 in pSS patients may disrupt the balance of T cell subsets by promoting the differentiation of pro-inflammatory Th1 and Th17 cells while concurrently suppressing the development of Treg cells, which are crucial for immune tolerance. This imbalance exacerbates autoimmune responses, resulting in chronic inflammation and progressive damage to the exocrine glands and other affected tissues.

Furthermore, VD3 also influences B-cell maturation and autoantibody production. In pSS patients, reduced serum VD3 levels have been associated with decreased levels of autoantibodies such as anti-SSA and anti-SSB ($p < 0.001$), further substantiating the potential role of VD3 in modulating humoral immune responses [54]. These observations suggest that sufficient VD3 levels may help control autoantibody production and contribute to delaying the progression of the disease.

Mechanistic Studies on the Relationship Between VD3 Levels and Immune Function

pSS, a prototypical autoimmune disease, is characterized by aberrant activation of the immune system (IS), leading to dysfunction of the exocrine gland and involvement of multiple systems. In recent years, growing research interest has focused on the intricate relationship between VD3 and immune function in pSS, offering novel insights into the modulation of immune balance and the potential to alleviate disease progression through VD3 regulation. Although traditionally known for its role in maintaining bone health, VD3, a fat-soluble vitamin, possesses potent immunomodulatory potential. It exerts its effects by binding to VDRs expressed on ICs, thereby influencing cell proliferation, differentiation, and functional activity, making it a key molecule in the immunopathological processes of pSS.

In patients with pSS, VD3 levels are frequently lower than those of healthy controls, and this decline is significantly correlated with DA, greater exocrine gland damage, and abnormal B cell activation [66]. This evidence suggests that VD3 reduction not only reflects the current disease status but may also contribute critically to disease progression. VD3 mitigates systemic inflammation by inhibiting the NF-κB pathway, resulting in reduced production of pro-inflammatory cytokines such as IL-6 and TNF-α. Simultaneously, VD3 intervenes in T cell differentiation by suppressing pro-inflammatory Th1 and Th17 cells while enhancing the quantity and function of immunosuppressive Treg cells, thereby improving immune tolerance and alleviating autoimmune responses [67].

Regarding B cells, the regulatory role of VD3 is equally significant. In pSS, overactivated B cells produce large quantities of autoantibodies, such as anti-SSA and anti-SSB, which serve as diagnostic markers and also contribute significantly to tissue damage. Studies have revealed that VD3 can modulate B cell maturation, differentiation, and antibody production, potentially alleviating the levels of pathogenic autoantibodies and limiting damage to affected organs [68]. Furthermore, VD3 modulates the immune microenvironment by regulating communication, migration, and homing of ICs, thereby regulating inflammatory responses and promoting tissue repair. Therefore, VD3 serves not only as a potential marker of immune imbalance in pSS but also as an active modulator of immune responses across various stages of the disease, from initial immune activation to the effector phase. These findings underscore VD3's potential as a novel strategic target for both the prevention and management of pSS.

Supplementation of VD3 may potentially restore physiological levels, correct immune dysregulation, alleviate clinical symptoms, and potentially attenuate disease progression. However, further clinical studies are needed to determine optimal dosage, timing of treatment, and the impact of individual variability to fully harness the therapeutic potential of VD3 in pSS, optimize treatment regimens, and improve patient quality of life.

VD3 Levels and Their Relationship With the Thyroid and Parathyroid Glands

Overview of the Relationship Between VD3 Levels and the Thyroid and Parathyroid Glands

In recent years, research on the association between pSS and VD3 levels has gradually expanded to include investigations into its potential effects on thyroid and parathyroid function, underscoring the intricate role of this endocrine-immune axis in autoimmune regulation. While pSS is primarily characterized by immune-mediated damage to exocrine glands, its widespread immune dysregulation also involves other components of the endocrine system, particularly the thyroid and parathyroid glands, which are closely linked to VD3 metabolism and function. The decreased VD3 levels in pSS patients not only reflect prevalent nutritional and metabolic abnormalities but also indicate exacerbated immune dysfunction [69]. Research has

proved a strong correlation between VD3 deficiency and high DA in pSS, suggesting that VD3 may play a crucial role in modulating immune balance, potentially impacting thyroid and parathyroid function, through direct or indirect mechanisms [56].

Although the thyroid and parathyroid glands have distinct physiological functions, they are closely linked through their role in calcium-phosphate metabolism and systemic hormonal regulation, collectively maintaining overall homeostasis. Regarding thyroid function, while conclusive evidence demonstrating a causal relationship between VD3 levels and thyroid dysfunction in pSS patients remains limited, VD3 may indirectly affect thyroid function. VD3 is involved in regulating the secretion and function of multiple hormones, including thyroid-stimulating hormone (TSH), and may thereby affect thyroid hormone synthesis and release [70]. Importantly, thyrotoxicosis has been observed in some pSS patients, accompanied by mild hypertension, suggesting shared autoimmune mechanisms or disruptions in endocrine feedback regulation [71].

The relationship between parathyroid function and VD3 is widely recognized. Research has indicated that parathyroid hormone (PTH) and VD3 play central roles in maintaining blood calcium homeostasis. In response to hypocalcemia, PTH increases calcium absorption, bone calcium resorption, and renal calcium reabsorption [72]. VD3 deficiency can disrupt this balance, resulting in elevated PTH levels as a compensatory mechanism, which can eventually predispose individuals to secondary hyperparathyroidism.

Mechanistic Studies of the Relationship Between VD3 Levels and the Thyroid and Parathyroid Glands

In patients with pSS, reduced VD3 levels are closely associated with increased DA, immune dysfunction, and exacerbated inflammation of the exocrine gland. These correlations highlight the potential critical role for VD3 in the immunopathology of pSS. When focusing its effects on the thyroid and parathyroid glands, the mechanisms through which VD3 acts appear to be more complex. The thyroid gland is the primary metabolic regulator, influencing crucial physiological processes such as energy expenditure, thermoregulation, and growth through the secretion of thyroid hormones. VD3 deficiency may disrupt this balance by indirectly affecting thyroid hormone synthesis and secretion, and may also increase the risk of autoimmune thyroid diseases, such as Graves' disease or Hashimoto's thyroiditis, through its effects on immune tolerance and altering hormone regulatory pathways [73]. These autoimmune conditions have been observed in some pSS patients, reflecting the broader systemic nature of autoimmune responses. The primary function of the parathyroid gland is to maintain calcium homeostasis through the secretion of PTH. VD3 and PTH work in a tightly regulated feedback loop within calcium-phosphate metabolism. VD3 deficiency reduces intestinal calcium absorption, stimulating a compensatory increase in PTH levels, which promotes calcium release from bone and enhances renal tubular calcium reabsorption to restore serum calcium levels ($p < 0.001$) [74].

In patients with pSS, low VD3 levels may indirectly affect calcium-phosphate metabolism, thereby influencing bone health and overall endocrine homeostasis through mechanisms mediated by PTH [51]. Studies have indicated an association between VD3 deficiency and the development of primary hyperparathyroidism, highlighting the foundational role of VD3 in regulating parathyroid function and in preventing both secondary and primary hyperparathyroidism [75–77].

Reduced VD3 levels in pSS affect endocrine function through multiple mechanisms, by modulating immune responses that may indirectly disrupt thyroid function, and by directly affecting calcium-phosphate balance through its regulatory effects on the parathyroid glands. These interconnected mechanisms enhance our understanding of the complex pathophysiology of pSS and open new perspectives for potential therapeutic strategies. VD3 supplementation, by maintaining immune balance and supporting endocrine function, potentially alleviates symptoms and slows disease progression. These insights underscore the clinical significance of monitoring and maintaining optimal VD3 levels in the management of pSS. Future research should further elucidate the precise molecular mechanisms underlying these interactions and validate the efficacy of VD3 supplementation in clinical settings. This will help open the way for more targeted and comprehensive treatment options for patients with pSS.

Limitations and Inconsistencies

Although increasing evidence supports the role of VD3 in immune regulation and its correlation with disease activity in pSS, several limitations and inconsistencies must be acknowledged. First, the majority of existing studies are observational and cross-sectional, limiting the ability to infer causal relationships between VD3 levels and immune dysfunction. Second, significant heterogeneity exists in the methodologies used to evaluate VD3 levels—some studies measure serum 25(OH)D3, while others assess its active form, $1,25(OH)_2D3$—leading to inconsistencies in reported concentrations and their clinical interpretations. Additionally, population-level factors such as ethnicity, geographic location, sunlight exposure, dietary habits, and underlying health conditions may influence VD3 metabolism and immune response, further contributing to variability across findings. The lack of unified thresholds for defining VD3 deficiency complicates cross-study comparisons and data analysis. Moreover, immunological assessment also differs considerably, with variations in T and B phenotyping, cytokine profiling methods, and criteria for assessing disease

activity which restricts the comparability of immunological observations. While some interventional studies suggest that VD3 supplementation may provide therapeutic advantages in pSS, these studies vary significantly in terms of dosage, treatment duration, and clinical outcomes, making it difficult to draw definitive conclusions or generalize the findings.

To address these limitations, there is a need for well-designed prospective cohort studies and randomized controlled trials to elucidate the therapeutic potential of VD3 in managing pSS. These studies should focus on VD3 in the context of pSS, and should adopt standardized methods for VD3 detection, establish uniform criteria for defining deficiency thresholds, and incorporate comprehensive immunological profiling. Stratifying patients based on clinical phenotype, disease stage, and baseline VD3 status will be critical in identifying subgroups most likely to benefit from supplementation. Furthermore, mechanistic studies are warranted to explore the molecular pathways through which VD3 modulates immune cell function in pSS. Such approaches will not only enhance our understanding of VD3's role as a biomarker but also support its development as a potential adjunctive agent. Ultimately, these efforts will contribute to more targeted and individualized approaches for managing pSS.

Conclusion

VD3 deficiency is commonly observed in patients with pSS and is closely associated with increased disease activity and immune system disturbances, including T and B cell dysregulation and elevated autoantibody production. Emerging evidence suggests that VD3 acts not only as a nutritional component but also as a key immunomodulatory agent, influencing both innate and adaptive immune responses. By suppressing pro-inflammatory cytokine production, inhibiting dendritic cell maturation, downregulating Th1 and Th17 responses, and enhancing the function of regulatory T cells, VD3 helps promote immune tolerance and reduce chronic inflammation in pSS.

Given these immunological impacts, VD3 holds potential as a biomarker reflecting disease severity and immune dysfunction, as well as a promising adjunctive therapeutic target. However, further mechanistic investigations and well-structured prospective clinical trials are needed to validate its role and to establish standardized strategies for VD3 assessment and supplementation in the clinical management of pSS.

Availability of Data and Materials

Not applicable.

Author Contributions

Conceptualization, LY; formal analysis, LY; writing—original draft preparation, LY; visualization, JM; supervision, JM; writing—critical review and editing, JM. Both authors have read and approved the final manuscript, and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. Fig. 1 was created using BioRender. The authors has no financial or personal relationship with BioRender, and the use of this tool does not imply any endorsement.

References

[1] Ghalwash D, El-Gawish A, Ammar A, Hamdy A, Ghanem R, Ghanem M, *et al*. Epidemiology of Sjogren's syndrome in a sample of the Egyptian population: a cross-sectional study. The Journal of International Medical Research. 2024; 52: 3000605241289292. https://doi.org/10.1177/03000605241289292.

[2] Alani H, Henty JR, Thompson NL, Jury E, Ciurtin C. Systematic review and meta-analysis of the epidemiology of polyautoimmunity in Sjögren's syndrome (secondary Sjögren's syndrome) focusing on autoimmune rheumatic diseases. Scandinavian Journal of Rheumatology. 2018; 47: 141–154. https://doi.org/10.1080/03009742.2017.1324909.

[3] Liampas A, Nteveros A, Parperis K, Akil M, Dardiotis E, Andreadou E, *et al*. Primary Sjögren's syndrome (pSS)-related cerebellar ataxia: a systematic review and meta-analysis. Acta Neurologica Belgica. 2022; 122: 457–463. https://doi.org/10.1007/s13760-021-01784-1.

[4] Haugen AJ, Peen E, Hultén B, Johannessen AC, Brun JG, Halse AK, *et al*. Estimation of the prevalence of primary Sjögren's syndrome in two age-different community-based populations using two sets of classification criteria: the Hordaland Health

Study. Scandinavian Journal of Rheumatology. 2008; 37: 30–34. https://doi.org/10.1080/03009740701678712.

[5] Friedman JA, Miller EB, Green L, Huszar M, Schattner A. A community-based cohort of 201 consecutive patients with primary Sjögren's syndrome in Israel: Ashkenazi patients compared with those of Sephardic descent. Clinical and Experimental Rheumatology. 2006; 24: 274–280.

[6] Brito-Zerón P, Acar-Denizli N, Zeher M, Rasmussen A, Seror R, Theander E, *et al*. Influence of geolocation and ethnicity on the phenotypic expression of primary Sjögren's syndrome at diagnosis in 8310 patients: a cross-sectional study from the Big Data Sjögren Project Consortium. Annals of the Rheumatic Diseases. 2017; 76: 1042–1050. https://doi.org/10.1136/annrheumdis-2016-209952.

[7] Norval M, Coussens AK, Wilkinson RJ, Bornman L, Lucas RM, Wright CY. Vitamin D Status and Its Consequences for Health in South Africa. International Journal of Environmental Research and Public Health. 2016; 13: 1019. https://doi.org/10.3390/ijerph13101019.

[8] Maciel G, Crowson C, Matteson E, Cornec D. Prevalence of primary Sjögren's syndrome in a population-based cohort in the United States. Annals of the Rheumatic Diseases. 2017; 76: 591. https://doi.org/10.1136/annrheumdis-2017-eular.1179.

[9] Trotta MC, Herman H, Balta C, Rosu M, Ciceu A, Mladin B, *et al*. Oral Administration of Vitamin D3 Prevents Corneal Damage in a Knock-Out Mouse Model of Sjögren's Syndrome. Biomedicines. 2023; 11: 616. https://doi.org/10.3390/biomedicines11020616.

[10] Barkhordari S, Azouji R, Yazdanjou F, Neshati A, Abareghi A, Shirvani M, *et al*. Estimating the prevalence of Sjögren's syndrome in the world using systematic review and meta-analysis. Journal of Renal Injury Prevention. 2025; 14: e38323. https://doi.org/10.34172/jrip.2025.38323.

[11] Seror R, Chiche L, Beydon M, Desjeux G, Zhuo J, Vannier-Moreau V, *et al*. Estimated prevalence, incidence and healthcare costs of Sjögren's syndrome in France: a national claims-based study. RMD Open. 2024; 10: e003591. https://doi.org/10.1136/rmdopen-2023-003591.

[12] Thurtle E, Grosjean A, Steenackers M, Strege K, Barcelos G, Goswami P. Epidemiology of Sjögren's: A Systematic Literature Review. Rheumatology and Therapy. 2024; 11: 1–17. https://doi.org/10.1007/s40744-023-00611-8.

[13] Martens PJ, Gysemans C, Verstuyf A, Mathieu AC. Vitamin D's Effect on Immune Function. Nutrients. 2020; 12: 1248. https://doi.org/10.3390/nu12051248.

[14] Costenbader KH, Cook NR, Lee IM, Hahn J, Walter J, Bubes V, *et al*. Vitamin D and Marine n-3 Fatty Acids for Autoimmune Disease Prevention: Outcomes Two Years After Completion of a Double-Blind, Placebo-Controlled Trial. Arthritis & Rheumatology (Hoboken, N.J.). 2024; 76: 973–983. https://doi.org/10.1002/art.42811.

[15] Cutolo M, Smith V, Paolino S, Gotelli E. Involvement of the secosteroid vitamin D in autoimmune rheumatic diseases and COVID-19. Nature Reviews. Rheumatology. 2023; 19: 265–287. https://doi.org/10.1038/s41584-023-00944-2.

[16] Wimalawansa SJ. Infections and Autoimmunity—The Immune System and Vitamin D: A Systematic Review. Nutrients. 2023; 15: 3842. https://doi.org/10.3390/nu15173842.

[17] Sîrbe C, Rednic S, Grama A, Pop TL. An Update on the Effects of Vitamin D on the Immune System and Autoimmune Diseases. International Journal of Molecular Sciences. 2022; 23: 9784. https://doi.org/10.3390/ijms23179784.

[18] Ghaseminejad-Raeini A, Ghaderi A, Sharafi A, Nematollahi-Sani B, Moossavi M, Derakhshani A, *et al*. Immunomodulatory actions of vitamin D in various immune-related disorders: a comprehensive review. Frontiers in Immunology. 2023; 14: 950465. https://doi.org/10.3389/fimmu.2023.950465.

[19] Dupuis ML, Pagano MT, Pierdominici M, Ortona E. The role of vitamin D in autoimmune diseases: could sex make the difference? Biology of Sex Differences. 2021; 12: 12. https://doi.org/10.1186/s13293-021-00358-3.

[20] Hahn J, Cook NR, Alexander EK, Friedman S, Walter J, Bubes V, *et al*. Vitamin D and marine omega 3 fatty acid supplementation and incident autoimmune disease: VITAL randomized controlled trial. BMJ (Clinical Research Ed.). 2022; 376: e066452. https://doi.org/10.1136/bmj-2021-066452.

[21] Günay NE, Buğday İ, Akalın T. Relationships of the Vitamin D and Platelet Indices in Sjögren's Syndrome. Korean Journal of Clinical Laboratory Science. 2018; 50: 484–491. https://doi.org/10.15324/kjcls.2018.50.4.484.

[22] Brusilovsky M, Rochman M, Shoda T, Kotliar M, Caldwell JM, Mack LE, *et al*. Vitamin D receptor and STAT6 interactome governs oesophageal epithelial barrier responses to IL-13 signalling. Gut. 2023; 72: 834–845. https://doi.org/10.1136/gutjnl-2022-327276.

[23] Chiewchalermsri C, Sangkanjanavanich S, Pradubpongsa P, Mitthamsiri W, Jaisupa N, Jindarat S, *et al*. Randomized, Double-Blind, Placebo-Controlled Trial of Vitamin D Supplementation in the Build-up Phase of House Dust Mite-Specific Immunotherapy. Allergy, Asthma & Immunology Research. 2023; 15: 336–347. https://doi.org/10.4168/aair.2023.15.3.336.

[24] Bychinin MV, Klypa TV, Mandel IA, Yusubalieva GM, Baklaushev VP, Kolyshkina NA, *et al*. Effect of vitamin D3 supplementation on cellular immunity and inflammatory markers in COVID-19 patients admitted to the ICU. Scientific Reports. 2022; 12: 18604. https://doi.org/10.1038/s41598-022-22045-y.

[25] Huang FC, Huang SC. Active vitamin D3 attenuates the severity of Salmonella colitis in mice by orchestrating innate immunity. Immunity, Inflammation and Disease. 2021; 9: 481–491. https://doi.org/10.1002/iid3.408.

[26] Pop TL, Sîrbe C, Benţa G, Mititelu A, Grama A. The Role of Vitamin D and Vitamin D Binding Protein in Chronic Liver Diseases. International Journal of Molecular Sciences. 2022; 23: 10705. https://doi.org/10.3390/ijms231810705.

[27] Lasoń W, Jantas D, Leśkiewicz M, Regulska M, Basta-Kaim A. The Vitamin D Receptor as a Potential Target for the Treatment of Age-Related Neurodegenerative Diseases Such as Alzheimer's and Parkinson's Diseases: A Narrative Review. Cells. 2023; 12: 660. https://doi.org/10.3390/cells12040660.

[28] Yang C, Du X, Hao R, Wang Q, Deng Y, Sun R. Effect of vitamin D3 on immunity and antioxidant capacity of pearl oyster Pinctada fucata martensii after transplantation: Insights from LC-MS-based metabolomics analysis. Fish & Shellfish Immunology. 2019; 94: 271–279. https://doi.org/10.1016/j.fsi.2019.09.017.

[29] Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, *et al*. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. The Journal of Clinical Endocrinology and Metabolism. 2011; 96: 1911–1930. https://doi.org/10.1210/jc.2011-0385.

[30] Charoenngam N, Holick MF. Immunologic Effects of Vitamin D on Human Health and Disease. Nutrients. 2020; 12: 2097. https://doi.org/10.3390/nu12072097.

[31] Aranow C. Vitamin D and the immune system. Journal of Investigative Medicine: the Official Publication of the American Federation for Clinical Research. 2011; 59: 881–886. https://doi.org/10.2310/JIM.0b013e31821b8755.

[32] Athanassiou L, Kostoglou-Athanassiou I, Koutsilieris M, Shoenfeld Y. Vitamin D and Autoimmune Rheumatic Diseases. Biomolecules. 2023; 13: 709. https://doi.org/10.3390/biom13040709.

[33] Radić M, Kolak E, Đogaš H, Gelemanović A, Bučan Nenadić D, Vučković M, *et al*. Vitamin D and Sjögren's Disease: Revealing the Connections-A Systematic Review and Meta-Analysis. Nutrients. 2023; 15: 497. https://doi.org/10.3390/nu15030497.

[34] Small AG, Harvey S, Kaur J, Putty T, Quach A, Munawara U, *et al*. Vitamin D upregulates the macrophage complement receptor immunoglobulin in innate immunity to microbial pathogens. Communications Biology. 2021; 4: 401. https://doi.org/10.1038/s42003-021-01943-3.

[35] Al-Jaberi FAH, Crone CG, Lindenstrøm T, Arildsen NS, Lindeløv ES, Aagaard L, *et al*. Reduced vitamin D-induced cathelicidin production and killing of *Mycobacterium tuberculosis* in macrophages from a patient with a non-functional vitamin D receptor: A case report. Frontiers in Immunology. 2022; 13: 1038960. https://doi.org/10.3389/fimmu.2022.1038960.

[36] Giampazolias E, Pereira da Costa M, Lam KC, Lim KHJ, Cardoso A, Piot C, *et al*. Vitamin D regulates microbiome-dependent cancer immunity. Science (New York, N.Y.). 2024; 384: 428–437. https://doi.org/10.1126/science.adh7954.

[37] Singh P, Rawat A, Alwakeel M, Sharif E, Al Khodor S. The potential role of vitamin D supplementation as a gut microbiota modifier in healthy individuals. Scientific Reports. 2020; 10: 21641. https://doi.org/10.1038/s41598-020-77806-4.

[38] Athanassiou P, Mavragani C, Athanassiou L, Kostoglou-Athanassiou I, Koutsilieris M. Vitamin D Deficiency in Primary Sjögren's Syndrome: Association with Clinical Manifestations and Immune Activation Markers. Mediterranean Journal of Rheumatology. 2022; 33: 106–108. https://doi.org/10.31138/mjr.33.1.106.

[39] Sandhya P, Mahasampath G, Mashru P, Bondu JD, Job V, Danda D. Vitamin D Levels and Associations in Indian Patients with Primary Sjögren's Syndrome. Journal of Clinical and Diagnostic Research: JCDR. 2017; 11: OC33–OC36. https://doi.org/10.7860/JCDR/2017/28493.10697.

[40] Lee SJ, Oh HJ, Choi BY, Jang YJ, Lee JY, Park JK, *et al*. Serum 25-Hydroxyvitamin D3 and BAFF Levels Are Associated with Disease Activity in Primary Sjogren's Syndrome. Journal of Immunology Research. 2016; 2016: 5781070. https://doi.org/10.1155/2016/5781070.

[41] Zilahi E, Chen JQ, Papp G, Szántó A, Zeher M. Lack of association of vitamin D receptor gene polymorphisms/haplotypes in Sjögren's syndrome. Clinical Rheumatology. 2015; 34: 247–253. https://doi.org/10.1007/s10067-014-2639-6.

[42] Zheng M, Zhu S, Li Y, Chen J, Lai W. Interferon alpha serum level association with low vitamin D levels in Chinese patients with primary Sjögren's syndrome. European Journal of Inflammation. 2021; 19: 1–6. https://doi.org/10.1177/20587392211014053.

[43] Dabravolski SA, Churov AV, Starodubtseva IA, Beloyartsev DF, Kovyanova TI, Sukhorukov VN, *et al*. Vitamin D in Primary Sjogren's Syndrome (pSS) and the Identification of Novel Single-Nucleotide Polymorphisms Involved in the Development of pSS-Associated Diseases. Diagnostics (Basel, Switzerland). 2024; 14: 2035. https://doi.org/10.3390/diagnostics14182035.

[44] de Souza MDM, Moraes Dantas RL, Leão Durães V, Defante MLR, Mendes TB. Vitamin D Supplementation and the Incidence of Fractures in the Elderly Healthy Population: A Meta-analysis of Randomized Controlled Trials. Journal of General Internal Medicine. 2024; 39: 2829–2836. https://doi.org/10.1007/s11606-024-08933-1.

[45] Agmon-Levin N, Kivity S, Tzioufas AG, López Hoyos M, Rozman B, Efes I, *et al*. Low levels of vitamin-D are associated with neuropathy and lymphoma among patients with Sjögren's syndrome. Journal of Autoimmunity. 2012; 39: 234–239. https://doi.org/10.1016/j.jaut.2012.05.018.

[46] Baldini C, Delle Sedie A, Luciano N, Pepe P, Ferro F, Talarico R, *et al*. Vitamin D in "early" primary Sjögren's syndrome: does it play a role in influencing disease phenotypes? Rheumatology International. 2014; 34: 1159–1164. https://doi.org/10.1007/s00296-013-2872-3.

[47] Zhao SS, Burgess S. Vitamin D is associated with reduced risk of Sjögren's syndrome: a Mendelian randomization study. Rheumatology (Oxford, England). 2024; 63: e32–e33. https://doi.org/10.1093/rheumatology/kead356.

[48] Lee JH, Kim SJ, Byun YS, Lee J, Park SH, Chung SH. The Association of Serum Vitamin D Level With the Severity of Dry Eye Parameters in Primary Sjögren Syndrome. Cornea. 2020; 39: 702–705. https://doi.org/10.1097/ICO.0000000000002234.

[49] Yamamoto EA, Nguyen JK, Liu J, Keller E, Campbell N, Zhang CJ, *et al*. Low Levels of Vitamin D Promote Memory B Cells in Lupus. Nutrients. 2020; 12: 291. https://doi.org/10.3390/nu12020291.

[50] Ao T, Kikuta J, Ishii M. The Effects of Vitamin D on Immune System and Inflammatory Diseases. Biomolecules. 2021; 11: 1624. https://doi.org/10.3390/biom11111624.

[51] Yilmaz Z, Karabulut G, Kitapcioglu G, Kabasakal Y. Vitamin D levels and the correlation with disease activity in primary Sjögren's syndrome. Annals of the Rheumatic Diseases. 2013; 72: A909. https://doi.org/10.1136/annrheumdis-2013-eular.2719.

[52] Sleem B, Ghazi V, El Hasbani G, Uthman I. Urinary Retention as an Initial Clinical Manifestation of Primary Sjögren's Syndrome. Cureus. 2024; 16: e72729. https://doi.org/10.7759/cureus.72729.

[53] Zmijewski MA. Vitamin D and Human Health. International Journal of Molecular Sciences. 2019; 20: 145. https://doi.org/10.3390/ijms20010145.

[54] Yamamoto EA, Jørgensen TN. Relationships Between Vitamin D, Gut Microbiome, and Systemic Autoimmunity. Frontiers in Immunology. 2020; 10: 3141. https://doi.org/10.3389/fimmu.2019.03141.

[55] Zardi EM, Basta F, Afeltra A. Levels of Vitamin D, Disease Activity and Subclinical Atherosclerosis in Post-menopausal Women with Sjögren's Syndrome: Does a Link Exist? In Vivo (Athens, Greece). 2016; 30: 721–725.

[56] Genç D, Sezer Kürkçü M, Günaydın B, Tarhan EF. 1,25-dihydroxyvitamin D3 regulates t helper and b lymphocyte responses substantially in drug-naive primary Sjögren's syndrome patients' mononuclear cells. Turkish Journal of Medical Sciences. 2021; 51: 2467–2476. https://doi.org/10.3906/sag-2103-240.

[57] Wang X, Bootsma H, de Koning J, Kroese FGM, Pringle S. Novel approaches for rescuing function of the salivary gland epithelium in primary Sjögren's syndrome. Clinical and Experimental Rheumatology. 2020; 38 Suppl 126: 261–270.

[58] Hong X, Meng S, Tang D, Wang T, Ding L, Yu H, *et al*. Single-Cell RNA Sequencing Reveals the Expansion of Cytotoxic CD4$^+$ T Lymphocytes and a Landscape of Immune Cells in Primary Sjögren's Syndrome. Frontiers in Immunology. 2021; 11: 594658. https://doi.org/10.3389/fimmu.2020.594658.

[59] Kuo CY, Huang YC, Lin KJ, Tsai TY. Vitamin D Deficiency Is Associated with Severity of Dry Eye Symptoms and Primary Sjögren's Syndrome: A Systematic Review and Meta-Analysis. Journal of Nutritional Science and Vitaminology. 2020; 66: 386–388. https://doi.org/10.3177/jnsv.66.386.

[60] Hysa E, Gotelli E, Campitiello R, Paolino S, Pizzorni C, Casabella A, *et al*. Vitamin D and Muscle Status in Inflammatory and Autoimmune Rheumatic Diseases: An Update. Nutrients. 2024; 16: 2329. https://doi.org/10.3390/nu16142329.

[61] Plantone D, Primiano G, Manco C, Locci S, Servidei S, De Stefano N. Vitamin D in Neurological Diseases. International Journal of Molecular Sciences. 2022; 24: 87. https://doi.org/10.3390/ijms24010087.

[62] Bischoff-Ferrari HA, Vellas B, Rizzoli R, Kressig RW, da Silva JAP, Blauth M, *et al*. Effect of Vitamin D Supplementation, Omega-3 Fatty Acid Supplementation, or a Strength-Training Exercise Program on Clinical Outcomes in Older Adults: The DO-HEALTH Randomized Clinical Trial. JAMA. 2020; 324: 1855–1868. https://doi.org/10.1001/jama.2020.16909.

[63] Tan Z, Wang L, Li X. Composition and regulation of the immune microenvironment of salivary gland in Sjögren's syndrome. Frontiers in Immunology. 2022; 13: 967304. https://doi.org/10.3389/fimmu.2022.967304.

[64] Cuny C, Vaerst B, Gabrielpillai J, Tahtali A, Balster S, Lissner R, *et al*. Polyvalent immunoglobulins with vitamin D3 and vitamin B12 in the treatment of Sjogren's syndrome in a vegetarian with stomatitis, glossodynia, xerostomia, and elevated antinuclear antibodies: Case report. International Journal of Clinical Pharmacology and Therapeutics. 2018; 56: 24–27. https://doi.org/10.5414/CP203143.

[65] Dumusc A, Bowman S. Sjögren syndrome (Sjögren disease). Medicine. 2024; 103: e007. https://doi.org/10.1016/j.mpmed.2024.09.007.

[66] Mehrani Y, Morovati S, Tieu S, Karimi N, Javadi H, Vanderkamp S, *et al*. Vitamin D Influences the Activity of Mast Cells in Allergic Manifestations and Potentiates Their Effector Functions against Pathogens. Cells. 2023; 12: 2271. https://doi.org/10.3390/cells12182271.

[67] Susanto A, Sunggoro A, Wati F. Correlation of serum 25(OH)-vitamin D levels with TNF-α and caspase levels in Sjögren's syndrome patients. Jurnal Ilmiah Kedokteran Wijaya Kusuma. 2025; 14: 4136. https://doi.org/10.30742/jikw.v14i1.4136.

[68] Kapsogeorgou E, Tzioufas A. Autoantibodies in Sjögren's Syndrome and Laboratory Markers. 2016. In Roccatello D, Emmi L (eds.) Connective Tissue Disease (pp.319–345). Springer: Cham. https://doi.org/10.1007/978-3-319-24535-5_21.

[69] Liu Y, He Z, Huang N, Zeng L, Wang Y, Li R, *et al*. Impact of thyroid autoimmunity and vitamin D on *in vitro* fertilization/intracytoplasmic sperm injection outcomes among women with normal thyroid function. Frontiers in Endocrinology. 2023; 14: 1098975. https://doi.org/10.3389/fendo.2023.1098975.

[70] Zhou L, Wang Y, Su J, An Y, Liu J, Wang G. Vitamin D Deficiency Is Associated with Impaired Sensitivity to Thyroid Hormones in Euthyroid Adults. Nutrients. 2023; 15: 3697. https://doi.org/10.3390/nu15173697.

[71] De Martinis M, Allegra A, Sirufo MM, Tonacci A, Pioggia G, Raggiunti M, *et al*. Vitamin D Deficiency, Osteoporosis and Effect on Autoimmune Diseases and Hematopoiesis: A Review. International Journal of Molecular Sciences. 2021; 22: 8855. https://doi.org/10.3390/ijms22168855.

[72] Babić Leko M, Jureško I, Rozić I, Pleić N, Gunjača I, Zemunik T. Vitamin D and the Thyroid: A Critical Review of the Current Evidence. International Journal of Molecular Sciences. 2023; 24: 3586. https://doi.org/10.3390/ijms24043586.

[73] Tang J, Shan S, Li F, Yun P. Effects of vitamin D supplementation on autoantibodies and thyroid function in patients with Hashimoto's thyroiditis: A systematic review and meta-analysis. Medicine. 2023; 102: e36759. https://doi.org/10.1097/MD.0000000000036759.

[74] Hemmati H. Interactions of vitamin D with parathyroid glands: an updated mini-review. Journal of Parathyroid Disease. 2023; 11: e11228. https://doi.org/10.34172/jpd.2023.11228.

[75] Rao SD, Miragaya J, Parikh N, Honasoge M, Springer K, Van Harn M, *et al*. Effect of vitamin D nutrition on disease indices in patients with primary hyperparathyroidism. The Journal of Steroid Biochemistry and Molecular Biology. 2020; 201: 105695. https://doi.org/10.1016/j.jsbmb.2020.105695.

[76] Yildiz S, Ekinci O, Ucler R. The relationship between 25 hydroxy Vitamin D3 and thyroid antibodies with thyroid benignmalign neoplasms. Nigerian Journal of Clinical Practice. 2019; 22: 1224–1228. https://doi.org/10.4103/njcp.njcp_440_18.

[77] Alrefaie Z, Awad H. Effect of vitamin D3 on thyroid function and de-iodinase 2 expression in diabetic rats. Archives of Physiology and Biochemistry. 2015; 121: 206–209. https://doi.org/10.3109/13813455.2015.1107101.