Review Article

Vitamin D Deficiency in Systemic Autoimmune Diseases: Clinical and Immunomodulatory Impact in Systemic Lupus Erythematosus and Rheumatoid Arthritis

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Abstract

Vitamin D is a secosteroid hormone with well-established roles in calcium homeostasis and bone metabolism, as well as increasingly recognized immunomodulatory functions. Its synthesis begins in the skin following ultraviolet B exposure and requires sequential hepatic and renal hydroxylation to generate the active metabolite, 1,25-dihydroxyvitamin D. In systemic autoimmune diseases, this metabolic pathway is frequently disrupted, resulting in a high prevalence of vitamin D deficiency. Conditions such as systemic lupus erythematosus and rheumatoid arthritis consistently exhibit lower serum vitamin D levels compared with the general population, a finding influenced by chronic

inflammation, photosensitivity, reduced sun exposure, glucocorticoid use, and genetic variability affecting vitamin D receptor function.At the immunological level, vitamin D exerts regulatory effects on both innate and adaptive immunity through its receptor, which is widely expressed in immune cells. It promotes immune tolerance by inducing a tolerogenic dendritic cell phenotype, enhancing regulatory T-cell differentiation, suppressing pro-inflammatory Th1 and Th17 responses, and modulating B-cell activation and autoantibody production. These mechanisms are particularly relevant in systemic lupus erythematosus, where vitamin D deficiency has been associated with increased disease activity, higher flare rates, fatigue, musculoskeletal involvement, renal disease, and cardiovascular risk, as well as elevated anti-double-stranded DNA antibody levels. Similarly, in rheumatoid arthritis, low vitamin D levels correlate with higher disease activity scores, pain severity, functional impairment, and increased risk of osteoporosis and fractures.Vitamin D supplementation has demonstrated immunomodulatory effects, including reductions in pro-inflammatory cytokines and potential improvements in disease activity and bone health. However, clinical trial outcomes remain inconsistent due to heterogeneous study designs, variable dosing regimens, and lack of baseline deficiency stratification. These limitations highlight the need for personalized supplementation strategies and further research to clarify the role of vitamin D as an adjunctive therapy in systemic autoimmune diseases.

Key words

Immune tolerance, cytokine regulation, vitamin D receptor polymorphisms, chronic inflammation, supplementation strategies, bone metabolism.

Introduction

Vitamin D deficiency represents a major global public health problem, affecting diverse populations across different age groups and geographic regions, and has been increasingly associated with a wide range of chronic conditions, including autoimmune diseases [1, 2]. In the context of systemic autoimmune disorders, this deficiency acquires particular clinical relevance. Among patients with systemic lupus erythematosus, a consistently high prevalence of vitamin D deficiency and insufficiency has been reported, with several studies demonstrating significant associations between low vitamin D levels, increased disease activity, and cumulative organ damage over time [3, 4].

Beyond its classical role in calcium homeostasis and bone metabolism, vitamin D functions as a pleiotropic secosteroid hormone with broad immunomodulatory effects. It exerts regulatory actions on both innate and adaptive immune responses, influencing immune tolerance and inflammatory balance [2, 5]. At the cellular level, vitamin D modulates the activity of myeloid dendritic cells and T lymphocytes, key components in the initiation and perpetuation of autoimmune responses. Through these mechanisms, vitamin D can alter antigen presentation, cytokine production, and T-cell differentiation, processes that are critically involved in the pathogenesis of systemic lupus erythematosus and other autoimmune diseases [6].

The rationale for focusing on systemic autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis lies in their shared features of chronic inflammation, immune dysregulation, and loss of self-tolerance. In these conditions, the immunomodulatory properties of vitamin D may have pathophysiological and therapeutic implications [1, 5]. Accumulating evidence indicates that vitamin D deficiency is associated with increased disease activity, greater clinical severity, and worse outcomes in both diseases, reinforcing the

hypothesis that vitamin D may play a modulatory role in autoimmune disease expression [7, 8].

From a clinical perspective, the relevance of vitamin D deficiency is particularly evident in systemic lupus erythematosus, where low serum levels have been correlated with higher disease activity scores and an increased risk of organ involvement, including renal manifestations [3, 4, 8]. These associations have prompted interest in vitamin D supplementation as a potential adjunctive strategy to modulate disease activity. Although some studies suggest that supplementation may contribute to reductions in disease activity, the overall evidence remains heterogeneous, with inconsistent results across clinical trials and observational studies [7, 8].

Similarly, in rheumatoid arthritis, vitamin D deficiency has been shown to be inversely related to disease activity, with lower levels associated with increased pain, inflammation, and functional impairment. In this context, vitamin D supplementation has been proposed as a supportive intervention that may help attenuate inflammatory symptoms and improve patient-reported outcomes, although its exact clinical impact continues to be investigated [1, 5].

This article aims to review the clinical and immunomodulatory effects of vitamin D deficiency in systemic lupus erythematosus and rheumatoid arthritis, focusing on its association with disease activity and potential therapeutic implications.

Methodology

This review on vitamin D deficiency in systemic autoimmune diseases, with a focus on systemic lupus erythematosus and rheumatoid arthritis, was conducted through a structured analysis of the current scientific literature. The objective was to evaluate its clinical relevance, immunomodulatory mechanisms, and association with disease activity, organ involvement, and therapeutic implications in autoimmune conditions. The methodological approach emphasized epidemiological data, immunological pathways, clinical outcomes, and the effects of vitamin D supplementation.

A systematic literature search was performed using the PubMed, Scopus, and Web of Science databases, applying predefined inclusion and exclusion criteria. Articles published between 2021 and 2026 in English or Spanish were included if they addressed vitamin D deficiency, immune modulation, disease activity, or clinical outcomes in systemic lupus erythematosus or rheumatoid arthritis. Studies lacking peer review, presenting incomplete data, or containing duplicated content were excluded. The search strategy incorporated the following keywords: Immune tolerance, cytokine regulation, vitamin D receptor polymorphisms, chronic inflammation, supplementation strategies, bone metabolism

A total of 34 relevant publications were identified, including original research articles, systematic reviews, meta-analyses, and international clinical guidelines. These sources were critically analyzed to extract data related to vitamin D metabolism, immune regulation, associations with disease severity, and the clinical impact of supplementation strategies. Artificial intelligence tools were used to assist in thematic organization and synthesis of the evidence, improving coherence and efficiency without altering the original content of the analyzed studies.The final analysis followed a qualitative and comparative approach, organizing findings to identify consistent associations, conflicting evidence, and existing knowledge gaps. This methodology allowed for an integrated, evidence-based overview of the role of vitamin D in systemic autoimmune diseases, highlighting its potential clinical significance and areas requiring further investigation.

Vitamin D metabolism and immune regulation

Vitamin D synthesis begins primarily in the skin following exposure to ultraviolet B radiation, where 7-dehydrocholesterol is converted into cholecalciferol, also known as vitamin D3. In addition to cutaneous production, vitamin D can be obtained through dietary sources, contributing to overall vitamin D status, particularly in individuals with limited sun exposure [10]. Once synthesized or ingested, vitamin D requires metabolic activation through two sequential hydroxylation steps. The first hydroxylation occurs in the liver, where vitamin D is converted into 25-hydroxyvitamin D, the main circulating form used to assess vitamin D status. The second hydroxylation takes place in the kidneys, leading to the formation of the biologically active metabolite 1,25-dihydroxyvitamin D, which exerts endocrine, paracrine, and autocrine effects throughout the body [11].

In the setting of chronic inflammatory diseases, vitamin D bioavailability and activation can be significantly altered. Systemic inflammatory states, such as those observed in systemic lupus erythematosus, are frequently associated with vitamin D deficiency, which has been linked to higher disease activity [12]. Persistent inflammation, immune-mediated metabolic alterations, and changes in enzymatic activity involved in vitamin D hydroxylation may impair both the activation and functional availability of vitamin D, further contributing to deficiency in these patients [1].

The immunological effects of vitamin D are mediated through the vitamin D receptor, which is widely expressed across cells of both the innate and adaptive immune systems. This receptor is present in T and B lymphocytes, macrophages, and dendritic cells, enabling vitamin D to exert broad regulatory effects on immune function and immune homeostasis [13]. Through this extensive receptor distribution, vitamin D is positioned to influence immune responses at multiple levels. Its biological actions are mediated through genomic mechanisms, whereby binding of vitamin D to the vitamin D receptor regulates the transcription of target genes, as well as through non-genomic pathways that allow for rapid modulation of immune cell activity independent of gene transcription [14].

At the cellular level, vitamin D plays a central role in shaping immune tolerance and limiting excessive immune activation. It promotes a tolerogenic phenotype in dendritic cells, reducing their maturation and antigen-presenting capacity, which in turn diminishes T-cell activation and downstream inflammatory responses [15]. In parallel, vitamin D influences T-helper cell differentiation by favoring the expansion of regulatory T cells while suppressing pro-inflammatory Th1 and Th17 subsets. This shift in T-cell balance contributes to the maintenance of immune tolerance and the attenuation of autoimmune processes [16].

Vitamin D also modulates humoral immunity by affecting B-cell function. It has been shown to reduce B-cell activation and limit the production of autoantibodies, which play a central pathogenic role in autoimmune diseases such as systemic lupus erythematosus [17]. Additionally, vitamin D exerts a significant impact on cytokine networks, promoting the expression of anti-inflammatory cytokines such as interleukin-10 while downregulating pro-inflammatory cytokines. Through these effects, vitamin D contributes to the regulation of inflammatory pathways and the overall modulation of immune-mediated tissue damage [18].

Prevalence and determinants of vitamin D deficiency in autoimmune diseases

Vitamin D deficiency is highly prevalent among patients with systemic autoimmune disorders, with consistent evidence demonstrating lower serum vitamin D levels compared to the general population. Conditions such as systemic lupus erythematosus, rheumatoid arthritis, and primary antiphospholipid syndrome show particularly high rates of deficiency and insufficiency. In patients with primary antiphospholipid syndrome, pooled prevalence estimates indicate

vitamin D deficiency in 32.2% of cases and insufficiency in 61.5%, with significantly lower serum concentrations when compared with control populations [19]. Similarly, in systemic lupus erythematosus, vitamin D insufficiency has been reported in up to 70.6% of patients, while frank deficiency has been observed in 4.2%, with both states showing clear associations with increased disease activity and cumulative organ damage [3].

Several disease-related factors contribute to the high burden of vitamin D deficiency observed in systemic autoimmune conditions. Chronic inflammation plays a central role, as low vitamin D levels have been associated with elevated inflammatory markers, including C-reactive protein and interleukin-6, particularly in patients with systemic lupus erythematosus [4]. This relationship suggests a bidirectional interaction in which inflammation may reduce vitamin D availability, while vitamin D deficiency may further amplify inflammatory pathways. In addition, clinical features intrinsic to autoimmune diseases, such as photosensitivity, significantly influence vitamin D status. In systemic lupus erythematosus, photosensitivity often leads to deliberate avoidance of sunlight, thereby limiting cutaneous vitamin D synthesis and contributing to persistently low serum levels [1].

Pharmacological factors also play a relevant role in modulating vitamin D status in autoimmune populations. Glucocorticoids, which are frequently used in the management of systemic autoimmune diseases, have been shown to be inversely correlated with vitamin D levels. In patients with systemic lupus erythematosus, higher cumulative doses of glucocorticoids are associated with lower serum vitamin D concentrations, potentially reflecting the effects of these agents on bone metabolism and vitamin D activation pathways [4]. Taken together, chronic inflammation, photosensitivity, reduced sun exposure, and glucocorticoid therapy represent interconnected contributors to vitamin D deficiency in systemic autoimmune disorders. Notably, elevated inflammatory markers such as C-reactive protein have been shown to correlate inversely with vitamin D status, supporting the hypothesis that deficiency may exacerbate ongoing inflammatory processes [20].

Beyond environmental and disease-related factors, genetic determinants may further influence vitamin D metabolism and function in autoimmune diseases. Polymorphisms in the vitamin D receptor gene have been investigated in conditions such as systemic lupus erythematosus, suggesting a potential impact on vitamin D signaling and its immunomodulatory effects [1]. These genetic variations may contribute to interindividual differences in serum vitamin D levels, immune responses, and clinical manifestations. Moreover, such polymorphisms may partially explain the variability in response to vitamin D supplementation observed among patients with autoimmune diseases, highlighting the relevance of genetic background in modulating therapeutic efficacy [11].

Vitamin D deficiency in systemic lupus erythematosus

Vitamin D has relevant immunomodulatory effects capable of influencing both innate and adaptive immune responses, and its deficiency may therefore exacerbate immune dysregulation, contributing to the loss of immunological tolerance characteristic of systemic lupus erythematosus [1, 21]. Within this framework, vitamin D deficiency has also been linked to altered regulation of interferon signaling pathways, which are typically upregulated in systemic lupus erythematosus. Because interferon-related pathways participate in the differentiation of B cells into autoantibody-producing plasma cells, vitamin D has been proposed as a potential modulator of this process, particularly in settings where interferon activation sustains autoreactive immune responses [21, 22].

These pathophysiological links have clinical correlates that are repeatedly observed in systemic lupus erythematosus cohorts. Lower vitamin D levels have been associated with higher systemic lupus erythematosus disease activity index scores, supporting an association between deficiency and more active disease states [3, 8]. In parallel, vitamin D deficiency has been linked to a greater frequency of disease flares, increased fatigue, and a higher burden of musculoskeletal manifestations, which are common and clinically relevant symptoms in systemic lupus erythematosus and contribute substantially to functional impairment and reduced quality of life [7, 23]. Beyond symptomatic burden, lower vitamin D levels have also been associated with a higher likelihood of renal involvement, including lupus nephritis, as well as an increased prevalence of cardiovascular risk factors, reinforcing the relevance of vitamin D status in organ-specific complications and systemic risk profiles in this disease [3, 7].

At the serological level, vitamin D deficiency has been associated with higher concentrations of anti-double-stranded DNA antibodies, which are frequently used as markers of disease activity and immune activation in systemic lupus erythematosus. This association supports the concept that vitamin D status may relate not only to clinical activity but also to immunological profiles driven by autoantibody production. However, the relationship between vitamin D deficiency and complement levels appears less consistent, as some studies have reported no significant changes, suggesting that this component of lupus immunopathology may not be uniformly influenced by vitamin D status or may vary according to disease phenotype and study design [23, 24].

Vitamin D deficiency in rheumatoid arthritis

Vitamin D plays an important immunological role in rheumatoid arthritis by modulating immune mechanisms involved in synovial inflammation and osteoimmunology. It influences the activity of key immune cells, including T lymphocytes, B lymphocytes, and macrophages, which are central to the inflammatory processes occurring within the synovial tissue. Through these effects, vitamin D contributes to the reduction of pro-inflammatory cytokine production, potentially attenuating synovial inflammation and limiting immune-mediated bone remodeling characteristic of rheumatoid arthritis [1, 25].

At the level of adaptive immunity, vitamin D influences T-cell polarization by promoting the differentiation of regulatory T cells while inhibiting the expansion of Th17 cells, which are major sources of pro-inflammatory cytokines in rheumatoid arthritis. This shift toward a more regulatory immune profile may contribute to reduced inflammation and diminished autoimmune activity, supporting the immunomodulatory role of vitamin D in the pathophysiology of the disease [26].

Clinically, lower vitamin D levels have been shown to correlate inversely with established disease activity indices, such as the disease activity score in 28 joints, suggesting that vitamin D deficiency may be associated with greater disease severity and increased pain burden [25, 27]. Beyond inflammatory activity, vitamin D deficiency has also been linked to impaired muscle strength and reduced physical performance, factors that negatively affect functional status and overall quality of life in patients with rheumatoid arthritis [28].

In addition to its immunological and functional implications, vitamin D plays a crucial role in bone health, which is of particular importance in rheumatoid arthritis. Deficiency has been associated with an increased risk of osteoporosis and fractures, especially among postmenopausal women, who already represent a vulnerable population within the rheumatoid arthritis spectrum [29]. From a structural perspective, vitamin D deficiency may contribute to

radiographic disease progression by promoting bone resorption and joint damage. Although vitamin D supplementation has shown potential benefits in reducing radiographic progression, findings across studies remain inconsistent, highlighting the need for further investigation into its role in modifying long-term structural outcomes in rheumatoid arthritis [5, 27].

Therapeutic implications of Vitamin D supplementation

Vitamin D supplementation has been shown to exert measurable effects on immune and inflammatory markers, as demonstrated in both observational studies and clinical trials. In individuals with vitamin D deficiency, supplementation has been associated with reductions in pro-inflammatory cytokines such as interleukin-6 and interleukin-17A, suggesting a direct immunomodulatory effect even in otherwise healthy subjects [30]. In the context of systemic lupus erythematosus, vitamin D has been observed to modulate immune responses more specifically by inhibiting the activation of myeloid dendritic cells and by maintaining the balance between regulatory T cells and Th17 cells, a regulatory axis that is critical for immune homeostasis and tolerance [6].

At the mechanistic level, vitamin D acts on immune cells through its receptor, thereby influencing cytokine production and immune cell activation patterns. Through these pathways, vitamin D has been shown to reduce the expression of pro-inflammatory cytokines while enhancing the production of anti-inflammatory mediators, contributing to a more balanced immune response [10].

With regard to clinical outcomes, vitamin D supplementation in systemic lupus erythematosus has been associated in some studies with reductions in disease activity, as reflected by lower scores on the systemic lupus erythematosus disease activity index. However, these findings are not uniform across the literature, as other studies have reported no significant differences in disease activity indices between patients receiving supplementation and those who did not. This variability underscores the heterogeneity of patient populations, supplementation protocols, and outcome measures used in existing studies. In addition to disease activity, vitamin D plays a well-established role in bone health, and deficiency has been linked to an increased risk of fractures in patients with systemic lupus erythematosus. Supplementation may improve bone mineral density and reduce fatigue and musculoskeletal symptoms, although results across studies remain mixed and inconsistent [7, 9].

From a practical perspective, several supplementation strategies have been evaluated in autoimmune populations. Daily, weekly, and biweekly dosing regimens have all been explored, with no significant differences in efficacy reported among these approaches, suggesting that regimen selection may reasonably be guided by patient preference and treatment adherence. Although vitamin D supplementation is generally considered safe, excessive intake carries a risk of hypervitaminosis D, which may lead to hypercalcemia and related complications. Consequently, regular monitoring of serum vitamin D and calcium levels is recommended to ensure therapeutic safety and to minimize the risk of toxicity during long-term supplementation [30].

Controversies and knowledge gaps

Clinical trials evaluating vitamin D supplementation in autoimmune diseases, particularly systemic lupus erythematosus, have yielded inconsistent results. While some studies report beneficial effects on disease activity and clinical parameters, others have failed to demonstrate a significant impact, leading to uncertainty regarding the true clinical value of supplementation in these conditions [7]. One factor contributing to these discrepancies is the design of large randomized controlled trials, which frequently include heterogeneous

populations and do not consistently restrict enrollment to individuals with documented vitamin D deficiency. This lack of stratification may dilute potential effects and complicate the interpretation of outcomes [31]. Additionally, methodological limitations have been highlighted in several trials, including the absence of baseline vitamin D measurements and the use of supplementation doses that may be insufficient to achieve meaningful biological effects, further contributing to variable and inconclusive findings [32].

Uncertainty also persists regarding the optimal serum levels of 25-hydroxyvitamin D required for the management of autoimmune diseases. Although general health recommendations commonly suggest maintaining serum concentrations between 30 and 60 ng/mL, there is no clear consensus on disease-specific targets for autoimmune conditions such as systemic lupus erythematosus [11]. This challenge is further complicated by evidence from genetic studies indicating that systemic lupus erythematosus itself may negatively influence vitamin D levels, thereby affecting both baseline status and responsiveness to supplementation and making the definition of optimal therapeutic targets more complex [33].

The limitations of the current body of evidence extend beyond trial design and target definition. Many studies fail to account for interindividual variability in response to vitamin D supplementation, which may be influenced by genetic polymorphisms, baseline vitamin D status, and overall health conditions [11]. Moreover, the reliance on pharmaceutical trial frameworks rather than nutrient-specific research paradigms has been criticized, as it may not adequately capture the biological nuances of vitamin D as a hormone-like nutrient. The absence of personalized approaches in clinical trials limits the generalizability and clinical applicability of findings [32].

Future directions

Personalized approaches to vitamin D supplementation have been proposed as a strategy to address interindividual variability in vitamin D metabolism and response, with the potential to improve clinical outcomes in patients with autoimmune diseases. Such approaches recognize that uniform dosing strategies may be insufficient in the context of autoimmune conditions, where metabolic, genetic, and environmental factors can significantly influence vitamin D status and biological activity. Within this framework, precision nutrition emerges as a relevant concept, allowing vitamin D dosages to be tailored according to individual characteristics, including genetic predispositions, baseline vitamin D levels, and environmental influences that affect synthesis and metabolism [33].

Genetic factors play a particularly important role in shaping vitamin D metabolism and function in autoimmune diseases. Polymorphisms in the vitamin D receptor have been investigated in conditions such as systemic lupus erythematosus, suggesting that genetic variability may influence both vitamin D signaling pathways and disease activity. These variations may help explain differences in susceptibility to deficiency, immune responses, and clinical outcomes among patients. A better understanding of vitamin D receptor polymorphisms could therefore support the development of more targeted therapeutic strategies, enhancing the effectiveness of vitamin D supplementation in the management of autoimmune conditions [1].

The integration of vitamin D into comprehensive autoimmune disease management is supported by its documented immunomodulatory effects, including the reduction of inflammatory activity and the promotion of immune tolerance. These properties position vitamin D as a potentially valuable adjunctive intervention in diseases such as systemic lupus erythematosus and rheumatoid arthritis. Incorporating the assessment of vitamin D status into clinical management algorithms may allow clinicians to identify and correct

deficiency-related contributors to disease exacerbation, thereby supporting more holistic and individualized patient care [1, 34].

Conclusions

Vitamin D plays a central role in immune regulation through its effects on innate and adaptive immune cells, cytokine networks, and mechanisms of immune tolerance. In systemic autoimmune diseases, alterations in vitamin D metabolism and bioavailabilitydriven by chronic inflammation, disease-related factors, pharmacological therapies, and genetic determinantscontribute to high rates of deficiency and may amplify immune dysregulation and inflammatory activity.

In systemic lupus erythematosus and rheumatoid arthritis, vitamin D deficiency is consistently associated with higher disease activity, increased symptom burden, and greater risk of organ and structural complications, including renal involvement, cardiovascular risk, osteoporosis, and fractures. These associations extend from clinical manifestations to serological and immunological markers, supporting a link between vitamin D status and both disease expression and immune activation.

Although vitamin D supplementation demonstrates immunomodulatory effects and potential clinical benefits, evidence from clinical trials remains heterogeneous due to methodological limitations, lack of stratification by baseline deficiency, and interindividual variability. Future research should prioritize personalized supplementation strategies, incorporate genetic and disease-specific factors, and define optimal therapeutic targets to better integrate vitamin D assessment and management into comprehensive care for systemic autoimmune diseases.

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