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Dualities of the vitamin D in systemic sclerosis: a systematic literature review

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Abstract

Background: Systemic sclerosis (SSc) is a chronic disease characterized by autoimmunity, vasculopathy, and visceral and cutaneous fibrosis. Vitamin D has several functions in the immunological system, and different studies have suggested a potential role in triggering autoimmune diseases. Patients with SSc may present with low serum levels of vitamin D, but the association between hypovitaminosis D and disease onset or any clinical manifestation is still obscure. Our goal was to verify the causal relationship between hypovitaminosis D and SSc onset or any particular clinical manifestation in the literature.

Methods: A systematic literature review was performed through February 24th, 2021 on Pubmed, Lilacs/BIREME, and Cochrane databases. The eligible studies were read in full text, and, in the absence of exclusion criteria, were included in this review after consensus between two reviewers.

Results: Forty articles met the eligibility criteria and the main results of each study are described. In most studies, SSc patients showed a higher prevalence of vitamin D deficiency and insufficiency compared to controls. Additionally, in some reports serum levels of vitamin D were inversely correlated with the severity of SSc. Oral supplementation did not seem to affect serum levels of vitamin D. Four of the included studies were with experimental models.

Conclusion: In conclusion, vitamin D deficiency seems to have a role in susceptibility to SSc, as well as in the clinical manifestations of the disease.

Keywords: Vitamin D, Systemic sclerosis, 25-hydroxyvitamin D, Deficiency

Introduction

Systemic sclerosis (SSc) is a multisystemic autoimmune disease with a complex pathophysiology. SSc is characterized by the presence of autoantibodies and arises from the interrelation between vascular dysfunction, adaptive and innate immunity dysregulation, and excess activation of fibroblasts and similar cells, resulting in the development of progressive tissue fibrosis [1–3]. With a multifactorial etiology, several environmental and genetic factors seem to trigger the onset of SSc and its outcomes [1]. SSc affects predominantly young adults and has an important impact on quality of life and mortality rates [4]. Treatment is multidisciplinary, with a focus on symptoms management and predominant visceral injuries. A better understanding of the pathophysiology behind the disease could help advance research on this area and allow for the development of new therapeutic options [4].

Vitamin D is a steroid hormone known for its function on the regulation of calcium homeostasis and bone metabolism. The active metabolite of vitamin D (calcitriol) is formed by the activation of a precursor on skin exposed to ultraviolet B (UVB) radiation [5]. Serum

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vitamin D levels may vary according to factors such as food intake (although to a lesser extent), bowel absorption, exposure to sunlight, and renal and hepatic metabolisms [5–7]. Vitamin D receptors (VDR) are present in antigen-presenting cells, natural killer cells, and activated B- and T-cell lymphocytes [5], which reinforces the evidence of its multiple immunomodulatory actions on adaptive and innate immune responses [8]. Vitamin D has a predominantly immunosuppressive effect, inhibiting proinflammatory cytokines production (IL6 and IL-17), stimulating anti-inflammatory cytokines production (IL4 and IL-10), and polarizing the Th1 response (IL-1, TNF-α, IFN-γ) into a Th2 response (autoantibodies, TGF-β) [5, 6]. Additionally, vitamin D inhibits the Th17 response and stimulates regulatory T cells. The immunomodulatory and tolerant effects of vitamin D on the adaptive and innate immune systems seem to play a protective role in the development of autoimmunity [6].

Hypovitaminosis D has been reported in several autoimmune diseases. Serum vitamin D levels are significantly lower in patients with SSc compared to healthy individuals [6]. Some studies have reported vitamin D insufficiency (< 30 ng/ml) in over 80% of patients with SSc [9, 10], usually in association with worse quality of life and lower bone mass [10–14]. The role of hypovitaminosis D in SSc pathophysiology and its possible therapeutic impact have been the subject of various studies in different scenarios. Therefore, this systematic review aims to verify the causal relationship between hypovitaminosis D and SSc onset or any particular clinical manifestation of the disease.

Methods

A comprehensive search in PubMed, Lilacs/BIREME, and Cochrane Library databases was performed through Fabruary 24th, 2021. The keywords used were “systemic sclerosis” and “vitamin D”. No restrictions for language, year or type of publication were added (Supplemental file 1).

After excluding duplicate studies, two reviewers independently reviewed all the articles found in different databases. Initially, titles and summaries were analyzed according to the eligibility criteria and all studies on the association between serum vitamin D levels and the clinical and pathophysiological aspects of SSc or on the role of vitamin D in the pathophysiology of SSc were selected. The selected articles were read in full and, in the absence of exclusion criteria, were included in this review after consensus between two reviewers. If no consensus were reached, a third reviewer would decide on study inclusion. The question that guided studies selection was: “What is the role of vitamin D in the pathophysiology and in the clinical manifestations of SSc?”, so all observation or intervention studies assessing vitamin D levels and its correlation with clinical and/or pathophysiological manifestations were eligible for inclusion in this review. We included all clinical and experimental studies published after peer-review, that would address the question guiding paper selection. Articles describing vitamin D levels on SSc patients without evaluation of clinical and/or pathophysiological manifestations were excluded, as well as other review articles and research on SSc therapy or treatment. Preprint studies were not included. In addition, the reference sections of the relevant articles were scanned for additional references that could have been missing from the databases.

Most of the studies included in this review defined vitamin D deficiency as a serum level < 10 ng/ml and insufficiency as a serum level of 10–30 ng/ml.

Results

Overall, 391 publications were identified in the different databases: 162 in PubMed, 211 in Lilacs/BIREME, and 10 in Cochrane Library. Of these, 118 were excluded after summary analysis, 205 were duplicate studies, two were not available online, and one was an erratum. Additionally, 17 publications were excluded after full text review for not meeting the eligibility criteria, and 12 were excluded due to being review articles. Eight additional articles were included after reference review. At the end of the selection process, 40 articles were included in this systematic review. Four included studies were experimental models on the effect of vitamin D or a vitamin D analogue. These data are shown in the flowchart on Fig. 1.

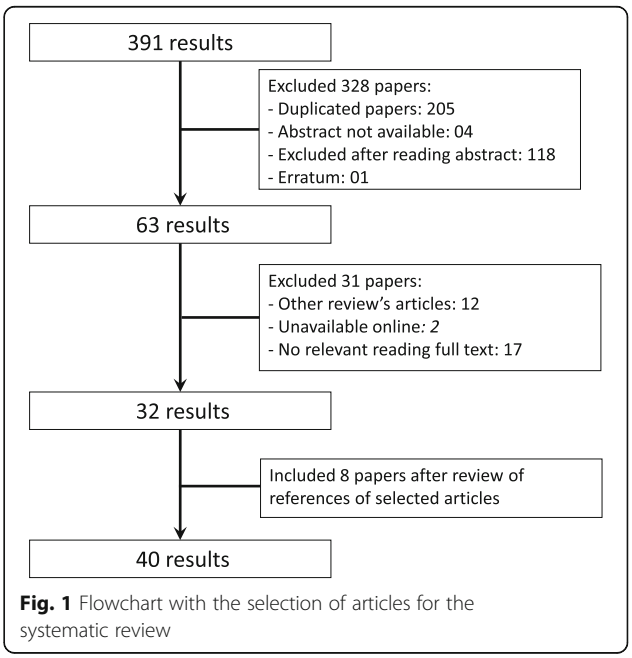

Fig. 1 Flowchart with the selection of articles for the systematic review

Characteristics of the selected articles, number of subjects, serum levels of vitamin D, proportion of patients with vitamin D < 10 and < 30 ng/mL and the main results of each study are presented in Table 1. Most studies showed vitamin D deficiency and insufficiency in SSc patients, regardless of season or oral vitamin D supplementation. Some studies identified association of vitamin D levels with clinical and pathophysiological manifestations, such as an inverse correlation of vitamin D levels with disease severity. Other reports did not identified an association between SSc manifestations and vitamin D.

The methodology and the main results of the experimental studies included in this review are summarized in Table 2.

Discussion

In the last two decades, several authors have reported lower levels of vitamin D in patients with SSc compared to healthy individuals [11–14, 16, 21, 25, 38, 48]. Despite the well-known seasonal variations in serum vitamin D levels, with peak values in summer [41], SSc patients present consistently lower levels throughout all seasons [38, 41]. Initially, we intended to estimate the mean serum vitamin D level among SSc patients across studies, but the great population heterogeneity could lead this estimation to substantial misinterpretation and inaccuracy. Seasonal variation, age, gender, comorbidities, life habits and drug treatment were some of the factors that could falsely impact this measure.

The evidence behind the association between hypovitaminosis D and SSc onset is scarce [15, 29–31, 34, 38]. So far, no published study has properly demonstrated this cause-effect relationship. Future research needs to add more on biologic plausibility, temporality, intensity, consistency and dose-response effect of hypovitaminosis D and SSc onset. An inception cohort study would be a suitable design. However, it may not be feasible due to the very low incidence of SSc in the general population. Longitudinal case-control studies would be the alternative; nonetheless vitamin D levels may not be generally available for comparison between groups.

Recently, An et al. (2017) have performed a meta-analysis to investigate the association between vitamin D and SSc, which included six case-control studies with a total of 554 SSc patients and 321 healthy controls. Meta-analysis results showed that SSc patients suffered from decreased vitamin D levels compared with healthy controls and in diffused SSc patients the vitamin D levels were significantly lower than those in limited SSc. Vitamin D level was not associated with Rodnan score, systolic pulmonary pressure, gastrointestinal ulcer, or pulmonary involvement, so the authors suggested that lower vitamin D levels in SSc patients may not be a factor accelerating disease severity [49].

On the other hand, some studies have shown an association between vitamin D deficiency and severity of SSc [9, 16, 41]. Hypovitaminosis D is common in SSc and patients with vitamin D deficiency have a greater frequency of pulmonary disease, lower diffusion and higher estimated pulmonary hypertension compared to patients with vitamin D insufficiency [8, 22, 37]. Additionally, these patients have higher inflammatory markers [9, 22] and Cruz-Domínguez et al. (2017) have demonstrated lower vitamin D levels in patients with and without calcinosis [24]. Park et al. (2017) demonstrated that vitamin D deficiency is an independent risk factor for digital ulcers in SSc, suggesting an involvement with the microangiopathic manifestations of the disease. However, the study could not demonstrate an association with macrovascular conditions in SSc patients, such as arterial stiffness and atherosclerosis [35], which suggests that vitamin D may act differently on micro- and macrovascular mechanisms in SSc. Caimmi et al. (2019) found in a retrospective cohort study that a decrease in 25-hydroxyvitamin D (25(OH)D) is associated with the risk of developing digital ulcers after 5 years [20]. In spite of this, no consensus has been reached, and further studies are needed to clarify the association between low vitamin D levels and the vascular involvement of the disease [18, 21, 43, 49].

Hypovitaminosis D diagnosis is based on serum 25(OH) D levels, and there is no consensus regarding the ideal values that should be adopted. Several experts agree to define vitamin D deficiency as serum levels below 10 ng/ml [9, 10, 16, 18, 22, 38]. However, this definition is not universal, with some authors suggesting deficiency levels to be lower than 20 ng/ml (50 nmol/l) [39, 41], taking in consideration the regulatory variations of PTH. In turn, vitamin D insufficiency is commonly defined as serum levels between 10 and 30 ng/ml, with levels > 30 ng/ml being considered sufficient [9, 22, 24, 27]. Higher levels of vitamin D do not seem to provide any additional benefits [50]. Nevertheless, the optimal concentration of vitamin D for proper immune system function is not yet well-defined. Studies have demonstrated that genetic polymorphisms in the vitamin D binding protein, in enzymes or even in the VDR could determine variations in 25(OH) D serum levels, further complicating the definition of adequate serum levels [51–53].

Vitamin D deficiency in patients with SSc seems to be multifactorial. In a retrospective cohort comprising 327 SSc patients and 141 controls, Arnson et al. (2011) substantiate an inverse relation between serum vitamin D levels and the extent of cutaneous involvement, they showed that patients with a Rodnan score higher than 10 had a significantly lower serum vitamin D level compared to other patients (17.7 ± 10.4 ng/ml versus 8 ±

Table 1 Characteristics and results of the selected studies

Study	Study design	25(OH) D (ng/ml) levels *		SSc patients with low vitamin D levels		Main results
		SSc patients (n)	Controls (n)	< 10 ng/ml n (%)	< 30 ng/ml n (%)	
Ahmadi et al., 2017 [15]	Cross-sectional	15 ± 4.7 (60)	27.2 ± 8.7 (30)	- -	- -	Serum Klotho and vitamin D lower in SSc patients ($p < 0.001$). Higher intact PTH in SSc patients ($p < 0.001$).
Arnson et al., 2011 [16]	Cross-sectional	13.5 ± 9 (327)	21.6 ± 9.7 (141)	- -	- -	Lower vitamin D levels in SSc patients ($p < 0.001$). Association with lower DLCO ($p < 0.02$). Inverse association with skin extent (mRSS> 10; $p = 0.02$) and RF expression ($p < 0.001$).
Atteritano et al., 2013 [14]	Cross-sectional	18.3 ± 4.1 (54)	39.6 ± 7.5 (54)	- -	- -	Lower vitamin D levels in SSc patients ($p < 0.001$). Association with PTH ($p = 0.001$), osteocalcin ($p < 0.05$), deoxypyridinoline ($p < 0.05$) and BMD on lumbar spine and femur ($p < 0.05$).
Atteritano et al., 2016 [17]	Cross-sectional	25.8 ± 12.8 (40)	35.1 ± 9.1 (40)	0 (0)	20 (50)	Lower vitamin D levels in SSc patients ($p = 0.0003$). Association with skin extent (mRSS> 10; $p = 0.02$) and PASP> 35 mmHg ($p = 0.02$). No association with subtype and autoantibodies.
Belloli et al., 2011 [18]	Cross-sectional	18.1 ± 15.2 (43)	17.3 ± 12 (99 - OA)	15 (34.8)	37 (86)	No significantly difference in insufficiency or deficiency between groups, regardless of disease duration, subtype and autoantibodies.
Braun-Moscovici et al., 2008 [19]	Cross-sectional	- (60)	- -	26[a] (46)	- -	High PTH associated with vitamin D deficiency ($p = 0.01$), calcinosis ($p = 0.009$), and acrosteolysis ($p = 0.015$). No significant correlation between supplementation and vitamin D levels.
Caimmi et al., 2019 [20]	Cohort	(65)	-	-	-	Lower vitamin D levels in patients with incident DU in relation to patients with no incident DU over 5 years (– 17.4 vs 13.0, $p = 0,018$).
Calzolari et al., 2009 [21]	Cross-sectional	23(3–92)[b] (18)(60)	39(14–138)[b] (60)	4 (6.7)	38 (63.4)	Lower vitamin D levels in SSc patients ($p < 0.001$). No association with disease subtype, cutaneous ulcers, skin extent, gastrointestinal and joint involvement.
Caramaschi et al., 2010 [22]	Cross-sectional	15.8 ± 9.1 (65)	- -	19 (29.2)	62 (95.4)	Association with lung disease ($p = 0.009$),longer disease duration ($p = 0.026$), lower DLCO ($p = 0.014$), and higher PASP ($p = 0.037$), ESR ($p = 0.001$) and CRP ($p = 0.004$).
Carmel et al., 2015 [23]	Cross-sectional	- (54)	- (41)	- -	39 (82.1)	Anti-25(OH) D IgM antibodies more frequent in SSc patients and in a higher level ($p = 0.002$). No correlation with severity, other autoantibodies and target organ damage.
Corrado et al., 2015 [12]	Cross-sectional	15.7 ± 10.2 (64)	22.9 ± 9.1 (35)	- -	- -	Lower vitamin D levels in patients, especially in diffuse cutaneous SSc ($p < 0.001$). Negative correlation with mRSS ($p < 0.05$). No association with any internal organ involvement.
Cruz-Domínguez et al., 2017 [24]	Cohort	- (109)	- -	- -	- -	Lower vitamin D levels in SSc patients with and without calcinosis (19.1 vs. 13.1; $p = 0.56$).
Di Liberto et al., 2019 [25]	Cross-sectional	22.1 ± 9.7 (45)	-	-	-	Low vitamin D levels in SSc patients. Similar percentage of regulatory T-cells (Tregs) in SSc patients and control group, with higher percentage in SSc patients taking cholecalciferol. Impaired Tregs capability to suppress T cell proliferation in SSc patients. Increase in IL-10 in vitro production of patients Tregs after treatment with (1,25(OH)2D3).
Gambichler et al., 2011 [26]	Cross-sectional	13.1(4–48)[b] (133)	- -	49 (35.8)	123 (89.8)	No association with disease subtype, BMI, lung fibrosis, renal involvement, GERD, digital ulcers, mRSS, autoantibodies and therapy.
Giuggioli et al., 2017 [27]	Cross-sectional	9.8 ± 4.1[d] (140)	- -	40/91[d] (44)	91/91[d] (100)	Lower vitamin D levels in not supplemented patients (9.8 ± 4.1 vs. 26 ± 8.1; $p < 0.0001$), but only 15/49 (31%) supplemented patients reached the normal range of vitamin D.
Groseanu et al., 2016 [8]	Cross-sectional	17.1 ± 9.1 (51)	- -	12 (23.5)	46 (90.2)	Positive correlation with DLCO ($p = 0.019$). Negative correlation of vitamin D with diastolic dysfunction, digital contractures and muscle weakness. No correlation with autoantibodies or skin extent. Higher vitamin D levels in patients with usual supplementation (25.5%), but the difference between groups failed to reach statistical significance ($p = 0.488$).
Gupta et al., 2018 [28]	Cross-sectional	19.5 ± 77.8[c] (38)	100 ± 31.3[c] (38)	13 (34.2)	23 (60.5)	Lower vitamin D levels in SSc patients ($p = 0.001$). Inverse correlationwith mRSS. No correlation with age, disease duration, autoantibodies, digital ulcers, or systemic involvement.
Hajialilo et al., 2017 [29]	Cross-sectional	14.9 ± 4.6 (60)	30.4 ± 7.9 (60)	- -	- -	Serum ET-1 higher in SSc patients ($p = 0.001$). Serum α-Klotho and vitamin D lower in SSc patients ($p = 0.001$). Association of vitamin D with gastrointestinal involvement on Medsger severity scale ($p = 0.003$).
Hax et al., 2020 [30]	Cross-sectional	23.9 ± 8.5 (50)	30.2 ± 6.2 (35)	2 (4%)	36 (72%)	Lower vitamin D levels in SSc patients compared to control group and lower vitamin D levels in SSc patients not taking vitamin D supplementation. No associations between vitamin D and cytokine levels or between vitamind D levels and disease duration.
Ibn-Yacoub et al., 2012 [13]	Cross-sectional	10.9 ± 2.7 (30)	57.4 ± 4.2 (30)	8 (26.7)	30 (100)	Lower vitamin D levels in SSc patients ($p = 0.001$). Association with number of painful ($p = 0.006$) and swollen joints ($p = 0.013$) and anti-Scl70 ($p = 0.027$). Association of vitamin D with BMD

Table 1 Characteristics and results of the selected studies *(Continued)*

Study	Study design	25(OH) D (ng/ml) levels *		SSc patients with low vitamin D levels		Main results
		SSc patients (n)	Controls (n)	< 10 ng/ml n (%)	< 30 ng/ml n (%)	
						on lumbar spine ($p = 0.002$) and femoral neck ($p = 0.032$).
Kamal et al., 2016 [31]	Cross-sectional	- (30)	- (60)	- -	- -	No association between VDR polymorphisms (ApaI and TaqI) and SSc susceptibility. Significant association between ApaI and diffuse cutaneous SSc.
Matsuoka et al., 1991 [32]	Cross-sectional	28 ± 3 (19)	29 ± 3 (19)	- -	- -	Hypovitaminosis D common in SSc patients and healthy controls. No correlation with skin extent.
Montabone et al., 2016 [33]	Cross-sectional	18.5(7.5–37)[b] (35)	- -	4 (11)	30 (85)	Association with a worse physical component on SF-36 and physical function ($p < 0.04$). No association with gastrointestinal, kidney and cardiopulmonary involvement.
Orbach et al., 2007 [34]	Cross-sectional	11 ± 5.8 (229)	- -	- -	- -	Lower vitamin D levels in different autoimmune diseases (SSc, SLE, PM, DM, APS, and RA).
Park et al., 2017 [35]	Cross-sectional	43.7(25–68)[b] (40)	57.5(40–81)[b] (80)	2 (5)	12 (30)	Association with digital ulcers ($p = 0.012$). No association with arterial stiffness, atherosclerosis, autoantibodies, mRSS, lung disease, PASP, ESR and CRP.
Rios Fernández et al., 2010 [36]	Cross-sectional	- (48)	- -	5 (9.5)	39 (81)	No significant vitamin D correlation with PASP or lung fibrosis. Hypovitaminosis D was common, despite 60.4% of patients were taking usual supplementation.
Rios Fernández et al., 2012 [37]	Cross-sectional	- (90)	- -	10 (11)	69 (76.7)	Association of vitamin D with calcinosis ($p < 0.034$), heart involvement ($p < 0.012$), DLCO ($p < 0.006$) and positive ANA ($p < 0.017$). Hypovitaminosis D was common, despite 58.9% of patients were taking usual supplementation. Vitamin D deficiency was not different between groups (52% vs. 66.7%).
Sampaio-Barros et al., 2016 [10]	Cross-sectional	20.7 ± 8.2 (38)	- -	4 (11)	33 (87)	Vitamin D positive correlation with anti-Scl70 ($p = 0.039$) and some SF-36 domains (vitality, social function, emotional role and mental health). Negative correlation with HAQ-reach and HAQ-grip strength. Positive correlation of vitamin D with BMI ($p = 0.038$) and femur BMD ($p = 0.037$).
Seriolo et al., 2011 [38]	Cross-sectional	21.7 ± 13.4 (53)	39.4 ± 15.4 (35)	13 (24)	47 (88)	Seasonal variation in patients and controls (highest values in summer, $p < 0.01$). Significantly lower levels in SSc patients in all seasons.
Shinjo et al., 2011 [39]	Cross-sectional	18.1 ± 6.4 (10)	25.1 ± 6.6 (10)	- -	- -	Lower vitamin D levels in juvenile SSc patients ($p = 0.04$). Positive correlation with femur BMD ($p = 0.02$).
Taylan et al., 2019 [40]	Cross-sectional	8.7(4.5–18)[b] (46)	16.5(9–21)[b] (30)			Lower serum vitamin D levels in SSc patients ($p = 0.02$). No correlation with mRSS.
Trombetta et al., 2017 [41]	Cross-sectional	18.7 ± 9 (154)	- -	- -	124 (80.5)	Association of vitamin D with pulmonary fibrotic changes ($p = 0.04$). Correlation with some domains of Medsger severity scale (peripheral vascular, renal and gastrointestinal involvement). Vitamin D levels not influenced by usual supplementation ($p = 0.81$).
Ursini et al., 2017 [42]	Cohort	15.4(8–25)[b] (124)	- -	- -	13 (89.5)	Inverse correlation with mRSS ($p = 0.03$) and subclinical liver fibrosis (evaluated using the aspartate aminotransferase-to-platelet ratio index; $p = 0.02$). No correlation with age and disease duration.
Vacca et al., 2009 [9]	Cross-sectional	19 ± 11 (156)	- -	44 (28)	131 (84)	Association of vitamin D with higher PASP ($p = 0.004$), lung fibrosis ($p = 0.04$), anticentromere ($p = 0.04$) and ESR ($p = 0.008$). No association with calcinosis, HAQ, or Medsger severity score. Negative correlation with EDAS ($p = 0.04$). Vitamin D levels not influenced by usual supplementation ($p = 0.1$).
Zhang et al., 2017 [43]	Cross-sectional	26.5 ± 6.3 (60)	36.3 ± 14.2 (60)	- -	45 (75)	Lower vitamin D levels in SSc patients ($p < 0.001$). More frequent lung involvement, but without significance ($p = 0.08$). No difference in joint involvement, autoantibodies, ESR and CRP.

Abbreviations: *ANA* antinuclear antibodies, *APS* antiphospholipid syndrome, *BMD* bone mineral density, *BMI* body mass index, *CRP* C-reactive protein, *DLCO* diffusion capacity of carbon monoxide, *DM* dermatomyositis, *DU* digital ulcers, *EDAS* European Disease Activity Score, *ESR* erythrocyte sedimentation rate, *ET-1* Endotelina 1, *GERD* gastroesophageal reflux disease, *HAQ* Health Assessment Questionnaire, *mRSS* modified Rodnan skin score, *OA* osteoarthritis, *PASP* pulmonary arterial systolic pressure on Doppler echocardiography, *PM* polymyositis, *RA* rheumatoid arthritis, *RF* rheumatoid factor, *SF-36* Short-Form-36 Questionnaire, *SLE* systemic lupus erythematosus, *SSc* systemic sclerosis, *TGF-β* transforming growth factor β, *VDR* vitamin D receptor

* Data are presented as mean ± standard deviation, except when indicated otherwise

[a]These author presented only the proportion of patients with 25(0H) D < 12 ng/ml

[b]Median (25–75th percentile)

[c]Median ± IQR

[d]Vitamin D levels only in non-supplemented patients (91/140)

10.1 ng/ml; $p = 0.02$) [16], a result recently replicated in another study [17]. Since then, other authors also demonstrated an inverse correlation between serum vitamin D levels and the extent of cutaneous involvement [11, 12, 28, 42]. On the other hand, some studies did not evidence the same correlation between cutaneous involvement and vitamin D levels [8, 26, 32, 35, 40, 49]. These authors suggest that the epidermal synthesis could

Table 2 Characteristics and results of the selected experimental models of systemic sclerosis

Author	Year	Research Design	Main results
Slominski et al. [44]	2013	Culture of skin fibroblasts from patients and controls	Efficacy of vitamin D in inhibiting TGF-induced collagen synthesis and inhibiting cell proliferation in fibroblasts from patients and controls; vitamin D suppressed fibrogenesis in a bleomycin-induced sclerosis model.
Terao et al. [45]	2015	Experimental model	Effect of vitamin D analogue on periostin expression in fibroblasts and bleomycin-induced sclerosis model; maxacalcitol reduces the expression of periostin and TGF-β and suppresses the Th2 response.
Usategui et al. [46]	2014	Cutaneous fibrosis in animal model	Effect of the topical analogue of vitamin D (calcipotriol) on cytokines and the development of fibrosis in rats with bleomycin-induced sclerosis; calcipotriol overexpressed Th2 axis expression, with antifibrotic effect.
Zerr et al. [47]	2014	Culture of skin fibroblasts from patients and controls	Expression of VDR in experimental model and fibroblasts; effect of paricalcitol on bleomycin-induced fibrosis model and overexpression of TGF-β receptor (TBRICA); VDR characterization as a negative regulator of TGF-β / Smad pathway signaling.

Abbreviations: *TGF-β* transforming growth factor β, *VDR* Vitamin D receptor

remain virtually normal, and that the hepatic and renal hydroxylation mechanisms of vitamin D could also work normally in this disease. Gastrointestinal involvement in SSc seems to contribute to vitamin D malabsorption, although these data are still controversial [19, 22]. Furthermore, it is possible that some medications used by SSc patients, such as corticosteroids or anticonvulsants for neuropathic pain control, could interfere with vitamin absorption [16]. In spite of this, not all authors were able to evidence differences in vitamin D levels between patients on and off these medications [41]. In addition to the cutaneous and gastrointestinal involvement, reduced sun exposure due to physical incapacity, self-image disorders, depression, and social and psychological limitations could compound the deficit [9, 34]. As one might expect, serum vitamin D levels could simply reflect a better health in general due to better life habits, such as exercise, outdoor activities and a healthier diet. This hypothesis is corroborated by previous research showing an association between low levels of 25(OH) D and a worse quality of life and physical function in SSc patients [10, 33].

Many authors have explored the association between lower vitamin D levels and SSc phenotype. Sampaio-Barros et al. (2016) demonstrated an association between lower serum vitamin D levels, underlying vascular involvement and the production of anti-Scl70 autoantibodies [10]. In addition, lower levels of vitamin D were described in patients with diffuse cutaneous SSc when compared with limited cutaneous disease [12, 49]. On the other hand, Vacca et al. (2009) showed an association between lower serum vitamin D levels and the presence of anti-centromere autoantibodies [9]. Other authors, however, have failed to demonstrate any association between serum vitamin D levels and disease subtype or specific autoantibodies [18, 43]. Therefore, the role of vitamin D in the clinical and serological phenotypes of SSc is not yet well known. Further studies should seek to clarify the possible associations between hypovitaminosis D and disease subtype, also considering the prognostic impact of these findings.

Considering the pathogenesis of SSc, several studies have suggested that vitamin D is related to the regulation of cellular immunity mechanisms [6–8]. The synthesis of 1,25 dihydroxyvitamin D (1,25(OH)2D) and presence of VDR in activated immune cells have attracted the attention of several researchers. Vitamin D acts as a regulator of innate and adaptive immune responses, promoting monocyte differentiation into macrophages, modulating macrophage response and inhibiting production of chemokines and inflammatory cytokines [54]. Polymorphisms in the VDR gene also seem to be associated with vitamin D deficiency, as suggested by Kamal et al. (2016). The authors found no association between VDR polymorphisms (ApaI and TaqI) and susceptibility to SSc, but reported an association between the ApaI polymorphism and disease subtype [31]. In a recent study, an association between some VDR single nucleotide polymorphisms and SSc susceptibility was stablished [55].

Interestingly, Carmel et al. (2015) reported a higher frequency and an increased level of anti-25(OH) D IgM antibodies in SSc patients when compared to controls, similarly to what has been described in patients with systemic lupus erythematosus (SLE). However, the same study reported lower levels of anti-25(OH) D IgG antibodies in SSc patients than in controls [23]. The pathophysiological significance and clinical relevance of these autoantibodies in SSc remains controversial.

Vitamin D also seems to have an important role in modulating TGF-β activity, an essential factor in collagen production by fibroblasts. Zerr et al. (2015) analyzed VDR expression in fibroblasts of SSc patients and in a murine model of bleomycin-induced fibrosis. The authors characterized the VDR as a negative regulator of TGF-β signaling. Furthermore, they demonstrated that treatment with a vitamin D analogue (paricalcitol) was able to restore VDR signaling and reduce the pro-

fibrotic effects of TGF-β on fibroblasts [47]. Similar findings were described in a study on skin fibroblast cultures from SSc patients and controls, which demonstrated the inhibitory effects of vitamin D in collagen and hyaluronate production induced by TGF [44]. The research of Boelsma et al. (1995) supports these findings by demonstrating evidence of cutaneous fibrosis in humans, which was also correlated with lower serum levels of vitamin D [56]. However, this finding could also result from reduced vitamin D production due to cutaneous fibrosis [57]. When assessing the therapeutic use of topical vitamin D analogues on SSc patients with hypovitaminosis D, a reduction in cutaneous fibrosis was observed. These results may be due to the role of vitamin D in reducing pro-fibrotic signaling by TGF-β and in inducing a polarization of the local immune response by producing potentially pro-fibrotic Th2 cytokines [45, 46]. A study by Ahmadi et al. (2017) analyzed the serum levels of fibroblast growth factor 23 (FGF-23), which has an essential role in the kidney-bone axis, and its membrane co-receptor Klotho. Klotho is a protein predominantly expressed in the renal tubules and possibly involved in calcium and phosphate homeostasis, prevents hyperphosphatemia, fibrosis, arteriosclerosis and inflammation [15]. A deficiency in α-Klotho expression has been studied for its potential involvement in endothelial dysfunction, microangiopathy, calcinosis and fibrosis, which are common features of scleroderma. Serum levels of soluble Klotho tend to decrease with age, and a defect in its gene increases the risk for age-related diseases. Significantly lower serum levels of Klotho in SSc patients were identified [29]. It is believe that an increase in inflammatory markers could reduce the renal expression of this protein [15].

In two independent European cohorts, Vacca et al. (2011) assessed the frequency of vitamin D insufficiency and deficiency in SSc patients. These studies found no difference in serum levels between SSc patients under the standard dose of vitamin D supplementation (800 IU/day) or under placebo [58]. In a Spanish retrospective cohort, Rios-Fernández et al. (2010) also described a high prevalence of vitamin D deficiency in SSc patients and corroborated the finding that supplementation with the usual dose of vitamin D was insufficient (60.4% of patients with low vitamin D levels were taking supplements) [36]. Therefore, conventional vitamin D supplementation (800 IU/day) does not seem to correct deficiency in SSc patients. Higher doses could be needed, especially in patients with severe disease or high inflammatory activity.

In a cross-sectional study with 140 SSc patients, 91 patients did not receive vitamin D supplementation, while 49 received 8000 to 12,500 IU of 25(OH) D weekly for a minimum period of 6 months. Non-supplemented patients had lower serum levels of vitamin D (9.8 ± 4.1 vs. 26 ± 8.1 ng/ml, $p < 0.0001$), although less than one-third of supplemented patients had reached normal levels by the end of the study [27]. In contrast, a retrospective cohort by Trombetta et al. (2017) was not able to demonstrate any changes on serum vitamin D levels in SSc patients supplemented with 1000 IU/day of cholecalciferol for 6 to 12 months [41]. The authors raised several hypotheses to justify these findings, with the strongest ones pointing to an interference in vitamin D activation caused by cutaneous fibrosis and to cholecalciferol malabsorption [27]. In spite of the variation in results for studies on vitamin D supplementation and the need for further research, most experts still recommend correcting vitamin D deficiency. The dose required to achieve and maintain adequate 25(OH) D levels depends on several factors. Some authors have suggested that a raise of 1 ng/ml of 25(OH) D in serum levels would require about 100 IU/day of vitamin D intake for approximately 3 months to reach a steady state once supplementation is initiated [59, 60]. In spite of this estimate, individual responses can vary, and the known risk factors for vitamin D deficiency should be considered for a personalized therapeutic approach.

Our study has some limitations. The major one is the lack of prospective cohort studies or randomized controlled trials assessing the role of vitamin D in the pathophysiology and in the clinical manifestations of SSc, so no definitive conclusions could be drawn regarding cause-effect relationship between hypovitaminosis D and SSc onset or any clinical manifestation. Besides, literature on Medline/EMBASE was not included in this systematic literature review due to access restrictions, however, considering the great number of overlaps between Medline/EMBASE and Medline/PubMed, it is not likely that any major study was left out of this review. Also, we have chosen to include as many peer-reviewed articles as possible, in this regard, a quality assessment of included articles was not performed and methodologically distinct studies were included. Our article selection strategy was based on the fact that systematic reviews evaluate areas where evidence may be too heterogeneous for comparison and a meta-analysis study is not possible [61, 62].

Conclusion

In conclusion, vitamin D deficiency is frequent in SSc patients and seems to be associated with some clinical and serological features of the disease. However, to date, there is no evidence that the usual supplementation interferes with vitamin D deficiency, and its clinical impact remains uncertain. Further randomized trials on the clinical effects of vitamin D supplementation are necessary to verify the effects of vitamin D on the clinical

characteristics of SSc, as well as to identify the potential role of vitamin D on immunomodulation and treatment of the disease. Thus, the optimal dosage of vitamin D supplementation and the need for monitoring of 25(OH) D serum levels in SSc patients are still open fields for research. Further studies are also needed to clarify the relationship between serum vitamin D levels and the pathophysiology of SSc. It remains unclear if vitamin D deficiency is an epiphenomenon or if it actually determines an increase in susceptibility and a worse prognosis for this complex disease.

Abbreviations

1,25(OH)2D: 1,25 dihydroxyvitamin D; 25(OH)D: 25-hydroxyvitamin D; ANA: Antinuclear antibodies; APS: Antiphospholipid syndrome; BMD: Bone mineral density; BMI: Body mass index; CRP: C-reactive protein; DLCO: Diffusion capacity of carbon monoxide; DM: Dermatomyositis; DU: Digital ulcers; EDAS: European Disease Activity Score; ESR: Erythrocyte sedimentation rate; ET-1: Endotelina 1; FGF-23: Fibroblast growth factor 23; GERD: Gastroesophageal reflux disease; HAQ: Health Assessment Questionnaire; mRSS: Modified Rodnan skin score; OA: Osteoarthritis; PASP: Pulmonary arterial systolic pressure on Doppler echocardiography; PM: Polymyositis; RA: Rheumatoid arthritis; RF: Rheumatoid factor; SF-36: Short-Form-36 Questionnaire; SLE: Systemic lupus erythematosus; SSc: Systemic sclerosis; TGF-β: Transforming growth factor β; Tregs: Regulatory T-cells; UVB: Ultraviolet B; VDR: Vitamin D receptor

Supplementary Information

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Additional file 1. search strategy and paper selection.

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Authors' contributions

LS, VH, TFM and RKMB acquired the data, conceived and designed the research, and drafted the manuscript. OM, RC and NAM made a critical revision of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

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Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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