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Review

Association between hypovitaminosis D and systemic sclerosis: True or fake?

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ABSTRACT

Background: Vitamin D insufficiency/deficiency is considered a major factor triggering and enhancing several autoimmune disorders; hypovitaminosis D has been reported to be common in Systemic Sclerosis (SSc). Previous studies assessing vitamin D insufficiency/deficiency in SSc have been reviewed, and the relation with pathogenesis and clinical features has been examined.
Content: Eligibility criteria were: reporting measurement of Vitamin D serum levels in all participants and evaluating adult onset-SSc individuals as patients group. Results: The association between clinical features and low hormone levels is controversial. Manifold data have shown vitamin D insufficiency/deficiency to have a potential role in the pathogenesis of disease, providing inconclusive findings.
Summary: Promoting the onset of SSc depends on the interaction between genetics, environment and infections. It remains a sound question whether Vitamin D insufficiency/deficiency is an environment-linked immunological heckler, making infectious agents taking root.

Contents

1. Introduction

Vitamin D is a steroid hormone mainly known as regulator of calcium/phosphate homeostasis. The active form of the hormone, calcitriol, is produced beginning from a precursor located on the skin, upon UVB rays exposure; the whole Vitamin D amount also depends on dietary intake and intestinal absorption.

Strong evidences have shown vitamin D biology to have broad areas of significance in immunological processes and inflammation [1,2,3].

Thus, the role of the hormone in autoimmune disorders has been greatly examined [4,5].

Abbreviations: SS, Systemic Sclerosis; BMD, Bone Mineral Density; ANA, anti-nuclear antibodies; ACA, anti-centromere antibodies; CRP, C-Reactive Protein; ESR, Erythrocyte Sedimentation Rate; PTH, parathyroid hormone; BMI, Body Mass Index; VDR, vitamin D receptor; APC, antigen presenting cells; RXR, retinoid acid receptor; VDREs, VDR responsive elements; DM, Diabetes Mellitus; SLE, Systemic Erythematosus Lupus; RA, Rheumatoid Arthritis; EBV, Epstein Barr Virus; HCMV, Human Cytomegalovirus; HP, *Helicobacter pylori*; mRSS, modified Rodnan skin score; NVC, Nailfold videocapillaroscopy; EDAS, European Disease Activity Score; DLCO, diffusion lung capacity for carbon monoxide; PAP, pulmonary artery pressure; SIBO, small intestinal bacterial overgrowth.

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Of some importance to report that not all immune disorders are linked to Vitamin D deficiency [6,7].

Systemic Sclerosis (SSc) is a connective tissue disorder characterized by skin fibrosis, internal organ involvement and fibroproliferative vasculopathy. Skin fibrosis is the hallmark of the disease and lung and gastrointestinal tract represent the most affected organs involved [8].

Both malabsorption and skin thickening might cause vitamin D deficiency [9]; thereby, it is an intriguing question, still unanswered, whether hypovitaminosis D has a role in the pathogenesis of SSc or it is a consequence of clinical features.

Manifold data [9–13] have been provided about the association between low Vitamin D serum levels and clinical features of disease, but few evidences were found to be concordant. Since understanding the pathogenesis implies advances in therapeutic strategies, it is a need to draw conclusions about the role, true or fake, of the hormone, in promoting the onset of SSc.

In this paper, previous studies assessing hypovitaminosis D in systemic sclerosis have been reviewed and the relation with pathogenesis and clinical features has been examined.

2. Methods

We searched the PubMed and the Cochrane Library electronic databases for articles with no limits for language, year, type and status of publication, using the keywords “systemic sclerosis” and “vitamin D”. Data was collected by two independent reviewers. Quality of each study was assessed by two reviewers working independently. Eligibility criteria were: reporting measurement of Vitamin D serum levels in all participants and evaluating of adult onset SSc individuals as patients group. Exclusion criteria were: evaluation of autoimmune diseases other than SSc, lack of vitamin D measurement, prospective and interventional studies evaluating vitamin D supplementation related to SSc development risk or to disease course modifying. No restrictions for gender and ethnic/geographical variables of participants were imposed. The reference lists of the relevant articles were scanned for additional studies. Two reviews and four letters were included. In all the studies reviewed deficiency and insufficiency of vitamin D were defined as serum hormone levels below 30 and 10 ng/ml, respectively. In this review, both deficiency and insufficiency were generally indicated as hypovitaminosis. In all the studies included in this review, differences in means and standard deviations were used to compare vitamin D levels among participants; the association between hypovitaminosis D and clinical features was evaluated via appropriate statistical analysis.

3. Results

A total of 115 articles were obtained from the databases. 86 articles were discarded because after reviewing the abstract they were found not including SSc patients groups or vitamin D serum levels determination; 2 were not available online and 1 was a duplicate due to an errata corrige. 26 articles remained and 9 were excluded after reviewing full text, because they did not meet the inclusion criteria as described above. A final total of 17 articles were selected based on the eligibility criteria. An additional 5 studies that met the inclusion criteria were obtained by checking the references of the relevant articles.

All were cross-sectional, small sample size studies, except that performed by Arnson et al. Two studies included Osteoarthritis and Rheumatoid Arthritis affected individuals as control group. Two independent reviewers assessed the main risk of bias for all the studies included, which mainly was due to lack of demographic and clinic information and drug interferences, consequently resulting in mendacious values of vitamin D.

All findings reported are summarized in Table 1.

4. Discussion

Among clinical features and laboratory measurement, Bone Mineral Density (BMD) and skin fibrosis were more frequently investigated in association with low vitamin D levels.

Auto-antibodies profile, including anti-topoisomerase antibody I (Scl 70), anti-nuclear antibodies (ANA) and anti-centromere antibodies (ACA), has been reported to be associated with low hormone levels by Vacca et al., but following reports in the same findings failed [9–11]; [13–17]. Lately, Carmel et al. reported no correlation between anti-vitamin D antibodies and some clinical features [18]. Acute-phase reactant including C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) were extensively investigated in some studies reviewed [11–14]. Serum calcium, phosphate and bone turnover metabolism were mostly measured in those papers having BMD or parathyroid hormone (PTH) determination in their study protocol [19–21].

To note that Braun-Moscovici [22] firstly found an association between hypovitaminosis D and PTH levels whereas in 2011 [23] reported opposite evidences.

Controversial findings about the association between Body Mass Index (BMI) and hypovitaminosis D was reported [11,16,17,24,25].

Not surprisingly, the association with pulmonary and gastrointestinal tests have been greatly sought, but inconsistent data have been provided [9,11,13,14,16];[24–26].

Findings of an association between vitamin D deficiency/insufficiency and clinical features of disease are greatly controversial, albeit intriguing. Since SSc is a relatively rare disease, small sample size, in all the studies considered, consequently makes the results quite inconclusive. Although Arnson et al. enrolled the most large patients group, demographic and clinical data was incomplete [10]. Other limitations due to mixed participants (Italian and French) were presented by Vacca et al. [14].

Many efforts have been made to understand the role of low hormone levels in the pathogenesis of the disease, as well as its relation with skin fibrosis and clinical features. Skin fibrosis is the mainly investigated aspect in this field; a sound reason why investigating lies in the pathogenesis of disease.

Corrado et al. [9] and Arnson et al. [10] found an inverse relation between skin fibrosis and low vitamin D serum levels; however, the former failed when seeking an association of Hypovitaminosis D with the extent of skin fibrosis [10]. Immune system dysfunction and extracellular matrix deposition are the main pathogenetic steps underlying the hallmarks of disease. Few studies have looked into this question, concluding both matrix deposition and immune dysfunction might be vitamin D-related [25,27–29].

Vitamin D is considered as a natural modulator and regulator of native and type 1 adaptative immune system [6,31], controlling neutrophils activity and inflammatory response [2]. It has an antifibrotic effect on fibroblasts, consequently inhibitingsynthesis and deposition of extracellular matrix [5]. Vitamin D receptor (VDR) signalling is partly responsible for immunoregulating effects on both innate and adaptative immune responses, due to the expression of VDR on the surface of antigen presenting cell (APC), natural killer cells, as well as activated B and T lymphocytes [32,33].

Immunomodulating effects of Vitamin D can be summarized by these few sentences: production of auto- antibodies; inhibition of Th1 cytokine (IL1,TNFα, IFNγ); reduction of proinflammatory cytokines (IL6 and IL17); up- regulation of anti-inflammatory cytokines (IL4–10) [34]. Concisely, vitamin D acts skewing T cells to Th2 polarization [5, 28]; a Th2 cytokine-mediated mechanism could be the native promoting factor responsible for TGFβ activity and profibrotic effects [9,10,28].

4.1. VDR, autoimmunity and infections

Some authors [27] suggested profibrotic direct effect on fibroblast to be VDR dependent; impaired VDR might lead to hyperactive TGFβ signalling and abnormal fibroblast activation [27]. It might have been

Table 1
Studies investigated the potential association 437 between hypovitaminosis D and serum 438 markers and/or clinical characteristics.

				Low vitamin D serum levels (<30 ng/ml)
Serum markers	Acute phase reactants	CRP		+ Caramaschi et al. (2010)[a], Vacca et al. (2009), − Atteritano et al. (2013)
		ESR		+ Caramaschi et al. (2010)[a], Vacca et al. (2009), − Zhang et al. (2015) and Atteritano et al. (2013)
	Rheumatoid factor			+ Arnson et al. (2011) −
	C3			+ Zhang et al. (2015) −
	Autoantibodies (ANA, SCL70.)			+ Vacca et al. (2009), Ibn Yacoub et al. (2012), − Corrado et al. (2015)[b], Caramaschi et al. (2010)[a], Gambichler et al. (2011), Zhang et al. (2015), Arnson et al. (2011), Belloli et al. (2011) and Carmel et al. (2015)
Clinical characteristics	Skin fibrosis (mRSS)			+ Corrado et al. (2015)[b],Arnson et al. (2011), − Gambichler et al. (2011), Zhang et al. (2015), Calzolari et al. (2009), Kilic et al. (2013), Belloli et al. (2011) and Caramaschi et al. (2010)[a]
	Cutaneous subtype (limited/diffuse)			+ Vacca et al. (2009), Corrado et al. (2015)[b], − Kilic et al. (2013), Belloli et al. (2011), Calzolari et al. (2009), Caramaschi et al. (2010)[a], Arnson et al. (2011) and Gambichler et al. (2011)
	NVC			+ Caramaschi et al. (2010)[a] −
	Disease duration			+ Caramaschi et al. (2010)[a], − Vacca et al. (2009), Corrado et al. (2015)[b], Kilic et al. (2013), Belloli et al. (2011), Calzolari et al. (2009) and Atteritano et al. (2013)
	Disease activity (EDAS)			+ Vacca et al. (2009), − Caramaschi et al. (2010)[a] and Braun-Moscovici et al. (2011)
	Disease severity (Medsger's severity score)			+ Caramaschi et al. (2010)[a], −Vacca et al. (2009), Kilic et al. (2013), Belloli et al. (2011) and Calzolari et al. (2009)
	Internal organ involvement	Lung	DLCO	+ Caramaschi et al. (2010)[a], Arnson et al. (2011), Vacca et al. (2009), − Zhang et al. (2015) and Corrado et al. (2015)[b]
			PAP	+ Vacca et al. (2009), Caramaschi et al. (2010)[a], − Corrado et al. (2015)[b], Zhang et al. (2015) and Rios et al. (2010)
			Imaging techniques	+ Caramaschi et al. (2010)[a], Vacca et al. (2009), − Rios et al. (2010), Arnson et al. (2011), Zhang et al. (2015) and Corrado et al. (2015)[b]
		GI	SIBO	+ Corrado et al. (2015)[b], Calzolari et al. (2009) and Arnson et al. (2011) −
			Malabsorption	+ Corrado et al. (2015)[b] and Kilic et al. (2013) −
			Reflux	+ Corrado et al. (2015)[b], Calzolari et al. (2009) and Gambichler et al. (2011) −
	BMI			+ Zhang et al. (2015), − Gambichler et al. (2011), Kilic et al. (2013), Belloli et al. (2011), and Calzolari et al. (2009)
	Serum calcium and phosphate			+ Atterritano et al. (2013) and Vacca et al. (2009) −
	BMD/osteoporosis			+ Atterritano et al. (2013), Carbone et al. (1999), Kamen et al. (2006), Morgan et al. (2000), Caramaschi et al. (2010)[a], Braun-Moscovici et al. (2008), Ibn Yacoub et al. (2012), − Rios et al. (2010), and Corrado et al. (2015)[b]
	PTH			+ Atterritano et al. (2013), Hollis et al. (2005), − Braun-Moscovici et al. (2008), Vacca et al. (2009), and Braun-Moscovici et al. (2011)

+: Authors found an association between hypovitaminosis D and clinical or laboratory variables; −: Authors did not find an association between hypovitaminosis D and clinical or laboratory variables. CRP: C Reactive Protein; ESR: Erythrocyte Sedimentation Rate; mRSS: modified Rodnan Skin Score; NVC: Nailfold videocapillaroscopy; EDAS: European Disease Activity Score; DLCO: Diffusion Lung CO; PAP: Pulmonary Alveolar Proteinosis; GI: Gastro Intestinal; SIBO: Small Intestinal Bacterial Overgrowth; BMI: Body Mass Index; BMD: Bone Mineral Density; PTH: Parathyroid Hormone.

[a] These Authors compared clinical and laboratory variables between a group of SS patients with Vitamin D deficiency and a group of SS patients with Vitamin D insufficiency.

[b] These Authors investigated association between Vitamin D and clinical or laboratory variables in three groups: controls, limited cutaneous subtype of SS and diffused cutaneous subtype of SS.

underrated the role of VDR signalling in these patients on the side. VDR complex comprises retinoid acid receptor (RXR) and VDR responsive elements (VDREs); the complex vitamin D/VDR/VDRE is known to control the expression of over two hundreds genes [35]. Szdoray et al. [4] in 2008 reported no correlation between VDR polymorphism and the frequency of the development of Diabetes Mellitus (DM), Systemic Erythematosus Lupus (SLE), Rheumatoid Arthritis (RA), but following studies reported opposite data [6], thereby further investigations might be reasonable. Owing to its key role in innate response, VDR dysfunction makes prone to chronic autoimmune disorders infections- related [36]; it might be sound to evaluate the association between infectious agent seroprevalence and VDR polymorphisms. An argued list of viruses and bacteria that may be reasonable to seek in association with VDR polymorphisms and SSc clinical features is provided below.

About endothelial cell dysfunction, which is the first step toward vasculitis in SSc, it has been suggested the role of viruses and bacteria in inducing injury [37,38]. Self-reactive antibodies against endothelial cells might represent an example for molecular mimicry mechanism, which typically occurs in such an autoimmune disease and explains pathogenicity of antibodies direct against viruses and bacteria [39].

4.2. Impact of ethnic, geographical and cultural variables on vitamin D cutaneous absorption

All the papers reviewed were performed in both sunny environment and high latitude countries. It's of some importance to note that control groups in such studies reviewed, including north-European individuals as well as Mediterranean ones, often showed vitamin D deficiency [9,11].

Seriolo et al. reported seasonal variations in vitamin D serum levels, showing average values to be significantly lower in SSc patients compared to controls throughout the year [40]. Summer levels were, as expected, lower than other seasons.

Differences among ethnic groups appear to be of relevant impact when referred to the Afroamerican population. Dark-skinned individuals probably developed sun protection strategies due to migration from low to high sun environments [41].

Cultural differences in many countries might influence vitamin D skin absorption due to traditions and habits, as dress code. One paper suggested a risk of hypovitaminosis D in ethnic isolates but reported no differences among three ethnic groups in Israeli [41].

4.3. Outlooks

Two main vitamin D-based therapeutic approaches for autoimmune disorders are considered, which are supplementary intake and vitamin D analogues. About supplementary intake many data suggests vitamin D supplementation not to protect against deficiency [14,42,43] in SSc patients; however, it remains harmless and inexpensive to administer it.

Vitamin D analogues act as suppressor of cytokine signalling, including TGFβ. Major efforts have been done to minimize the effect on calcium metabolism and maximize the effect of immune modulation in these molecules. Albeit interesting, all the results provided in this field are rather far from an application on clinical practice [6,30–45].

4.4. Low vitamin D level, infections and Systemic Sclerosis

There is a triangular link between infections, autoimmunity and environment [6]. Low vitamin D serum levels are an increasingly described phenomenon worldwide, at least over the last 10–15 years [5,46]. Waterhouse et al. in 2009 subordinated low vitamin D levels in autoimmunity to VDR dysfunction and down regulation [36]; then, Pender et al. [47] suggested the hormone to represent a major environmental-linked factor promoting Epstein Barr virus (EBV)-induced autoimmune diseases. Generally, many infections are known to trigger autoimmune rheumatic disorders, including RA, SLE and Sjogren Syndrome. Joint involvement in SLE patients has been reported to correlate with the presence of high titers of EBV antibodies [48]. About Parvovirus B19, a possible role of infection in the evolution of SSc has been suggested, reporting B19 viremia or B19 presence in bone marrow, without viremia; the latter evidence gave the hint to hypothesize that bone marrow may represent a reservoir from which the virus spread to target tissues [49]. A case report of SSc following human Cytomegalovirus (HCMV) infection in 2002 has been described [50]; moreover, a cross-reaction of the UL70 protein of HCMV and Scl 70, which are characteristic of diffuse SSc, has been suggested [51]. Helicobacter Pylori (HP) has been detected in very high percentage of SSc patients [52,53]. Bilgin et al. [37] in 2015 reported higher prevalence of HP, CMV, EBV, and parvovirus B19 in 30 patients with SSc compared with healthy controls. Unfortunately, no data is available about the association between Vitamin D deficiency/insufficiency and increased seroprevalence of viruses and bacteria.

5. Conclusions

Although many efforts have been done, the relation between low vitamin D and SSc remains unclear. Environment, autoimmunity and infections are a cross-linked triad greatly unknown. To arrange the hormone in its right place throughout this triad, further investigations might evaluate the association of VDR genotype and past/current infections markers with SSc clinical features.

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