Clinica Chimica Acta 458 (2016) 115–119

Contents lists available at ScienceDirect

Clinica Chimica Acta

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

Review

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

Giulia Bivona [a,1], Luisa Agnello [a,1], Alessia Pivetti [a], Salvatore Milano [b], Concetta Scazzone [a], Bruna Lo Sasso [a], Marcello Ciaccio [a,b,*]

[a] Sezione Biochimica Clinica e Medicina Molecolare Clinica, Dipartimento di Biopatologia e Biotecnologie Mediche, Università degli Studi di Palermo, Italy
[b] UOC Medicina di Laboratorio - CoreLab, AOUP "P. Giaccone", Palermo, Italy

ARTICLE INFO

Article history:
Received 24 February 2016
Received in revised form 21 April 2016
Accepted 21 April 2016
Available online 3 May 2016

Keywords:
Vitamin D
Systemic Sclerosis
Hypovitaminosis D
Autoimmunity

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

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.

* Corresponding author at: Dipartimento di Biopatologia e Biotecnologie Mediche, , Università degli Studi di Palermo, Via del Vespro, 129, 90127 Palermo, Italy.
E-mail address: marcello.ciaccio@unipa.it (M. Ciaccio).

[1] These authors contributed equally to the study.

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].

http://dx.doi.org/10.1016/j.cca.2016.04.026
0009-8981/

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