25-hydroxyvitamin D3 Levels and Their Clinical Associations in a Polish Cohort of Systemic Sclerosis Patients: A Cross-Sectional Study

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Abstract: Vitamin D exhibits immunomodulatory effects in autoimmune diseases. We aimed to evaluate the associations of vitamin D levels with clinical and laboratory features of systemic sclerosis (SSc) in a Polish cohort. The study was prospective in design. SSc patients who met ACR-EULAR 2013 criteria underwent comprehensive clinical and laboratory investigations using the European Scleroderma Trials and Research group (EUSTAR) methodology. We assessed patients’ sera for 25(OH)D3 using a radioimmunoassay, and the cutoff value for vitamin D deficiency was set at 20 ng/mL. Statistical analyses were performed using the Mann–Whitney U test, the Fisher’s exact, and the Spearman’s rho, where appropriate, with a significance threshold set at 0.05. We recruited 68 SSc patients (85% female). The mean 25(OH)D3 level was 21.6 ± 10 ng/mL, and 50% of subjects (n = 34) presented vitamin D deficiency (mean 13.7 ± 3.9 ng/mL). Vitamin D-deficient SSc patients exhibited higher prevalence of arterial hypertension (p = 0.002), proteinuria (p = 0.002), and lung fibrosis (p = 0.032), as well as higher CRP (p = 0.035). The modified Rodnan skin score correlated negatively with 25(OH)D3 in diffuse cutaneous SSc (dcSSc). We found no correlation with the disease duration, age, joints, and the heart. Vitamin D deficiency was common in the studied population of Polish SSc patients and was associated with arterial hypertension, proteinuria, lung involvement, and increased CRP.

Keywords: vitamin D; scleroderma; systemic; calcifediol

1. Introduction

Besides its well-known influence on the skeleton [1] and odontogenesis [2], vitamin D also plays numerous other roles in the human body. It impacts neuronal [3] and liver regeneration [4], as well as the growth of muscle mass [5]. In addition, it has immunomodulatory activity and an indirect anti-inflammatory effect [6] related to several health conditions. Vitamin D supplementation not only correlates with pathology, but may also affect etiopathogenesis; in infancy, vitamin D may reduce the risk of type 1 diabetes [7], and it reduces insulin resistance in adulthood [8]. Moreover, vitamin D is related to antiproliferative effects and may influence angiogenesis and apoptosis, which is vital in carcinogenesis [9]. Vitamin D also positively affects the female [10] and male [11] reproductive systems. Its deficiency can result in high blood pressure [12] and has been linked to several other diseases.
Systemic sclerosis (SSc) is a rare autoimmune connective tissue disorder of unknown etiology. Systemic vasculopathy, progressive fibrosis of almost all organs, and complex immunologic abnormalities seem to play a crucial role in SSc [13]. The evidence for vitamin D deficiency in SSc has been growing in recent years, although the literature on these effects in Polish patients with SSc is scarce. Thus, this study aimed to critically evaluate the relationship between vitamin D status and levels with a broad clinical and laboratory spectrum of SSc features.

2. Materials and Methods

The study was cross-sectional and prospective in design. It was performed between June 2012 and October 2018 within the population of outpatients and inpatients of the Department of Rheumatology and Internal Medicine in Poznan, Poland. The population studied consisted of 68 patients with SSc, classified using the criteria of the American College of Rheumatology and the European League Against Rheumatism (ACR-EULAR) 2013 criteria [14]. There were no exclusion criteria.

History taking and physical examination of all patients were carried out by the same physician (P.˙Z.), who has experience in the care of SSc patients. Clinical data were collected using MEDS (Minimal Essential Data Set) in line with the EUSTAR (EULAR Scleroderma Trials and Research group) methodology [15], also by the same practitioner. The following features were assessed: gender, age, time of disease since the onset of Raynaud’s phenomenon, time of disease since the onset of other symptoms characteristic of SSc, duration of the disease since the diagnosis, skin involvement using the modified Rodnan skin score (mRSS), Raynaud’s phenomenon, digital ulcerations, synovitis, joint contractures, muscle weakness, esophageal symptoms (heartburn and dysphagia), intestinal manifestations (diarrhea, constipation, and bloating), arterial hypertension, scleroderma renal crisis (ever), dyspnea, palpitations, and telangiectasias.

A specialist cardiac (echocardiography) and pulmonary examination (pulmonary function tests and high-resolution computed tomography) was carried out. The results were interpreted by certified specialist physicians: a cardiologist (T.M.K.) and a pulmonologist (T.P.), both with considerable experience in SSc diagnostics. A number of characteristics were sought: heart conduction blocks; palpitations, systolic, and diastolic dysfunction; ejection fraction; pulmonary arterial hypertension using Doppler ultrasonography; total lung capacity; pulmonary restriction using pulmonary function tests; and the presence of SSc-related interstitial lung disease (ILD) using HRCT.

Sera of patients were secured and assessed for the levels of 25(OH)D3. A radio immuno assay method (RIA) was used to measure serum concentration of 25(OH)D3 in patients with SSc using 25-OH Vitamin D3 RIA CT kit by DiaSource (Nivelles, Belgium). In line with recommendations from M. Hollick and the assay manufacturer, vitamin D deficiency was defined as 25-hydroxyvitamin D3 levels <20 ng/mL [16]. In addition, we determined the erythrocyte sedimentation rate (ESR), C-reactive protein concentration, serum creatinine concentration, the estimated glomerular filtration rate (chronic kidney disease epidemiology collaboration equation; eGFR CKD), as well as the presence or absence of proteinuria.

This study obtained the consent of the Bioethics Committee at the Poznan University of Medical Sciences (No. 624/12). All patients participating in the study gave their informed consent in writing according to the local law regulations.

Statistical analyses were conducted in Statistica 13.3 (TIBCO, Palo Alto, CA, USA). Data are presented as means ± standard deviation (SD) or percentage, unless stated otherwise. The Mann–Whitney U test was used to compare continuous or ordinal variables, whereas logical (Boolean) variables were compared using the Fisher’s exact test. The Spearman’s rank-sum coefficient was calculated to investigate possible correlations. The significance threshold was set at 0.05. Two-sided p-values are presented throughout.
3. Results

3.1. Study Population Characteristics

Sixty-eight patients meeting ACR-EULAR 2013 classification criteria were included in the study, two-thirds of whom presented with limited cutaneous SSc, and a third with diffuse cutaneous SSc. Most patients were female and were included at least five years after the SSc diagnosis of SSc. The patients were recruited from both outpatient and inpatient settings. A detailed clinical and laboratory characteristic of the population studied is presented in Table 1.

Table 1. Characteristics of the studied population of patients with SSc.

| Variable                                      | Mean (or %) | SD    |
|-----------------------------------------------|-------------|-------|
| Gender, female, %                             | 85%         |       |
| Limited cutaneous systemic sclerosis          | 66%         |       |
| Diffuse cutaneous systemic sclerosis          | 29%         |       |
| Polymyositis-scleroderma overlap syndrome     | 4%          |       |
| Age, years                                    | 53.8±13.5   |       |
| Disease duration since Raynaud, years         | 12.1±9.7    |       |
| Disease duration since diagnosis, years       | 7.0±8.8     |       |
| ESR, mm/h                                     | 18.4±15.5   |       |
| CRP, mg/L                                     | 3.1±4.8     |       |
| Serum creatinine, umol/L                      | 83.7±26.6   |       |
| eGFR CKD-EPI, mL/min/1.73 m²                  | 91.9±13.6   |       |
| 25(OH)D3, ng/mL                               | 21.6±10.0   |       |
| Vitamin D deficiency [25(OH)D3 < 20 ng/mL], % | 50%         |       |
| mRSS score 1                                  | 13.0±8.0    |       |
| Raynaud’s present, %                          | 99%         |       |
| Joint contractures, %                         | 78%         |       |
| Lung fibrosis (HRCT), %                       | 78%         |       |
| Esophageal symptoms (dysphagia, reflux), %    | 66%         |       |
| Dyspnea (≥NYHA 2), %                          | 62%         |       |
| Digital ulcers, %                             | 60%         |       |
| Joint synovitis, %                            | 49%         |       |
| Muscle weakness, %                            | 48%         |       |
| Telangiectasia, %                             | 47%         |       |
| Palpitations, %                               | 46%         |       |
| Arterial hypertension, %                      | 42%         |       |
| Intestinal symptoms (diarrhea, bloating, constipation), % | 31%     |       |
| Gastric symptoms (early satiety, vomiting), % | 29%     |       |
| Muscle atrophy, %                             | 26%         |       |
| Restrictive defect (VC < 80%) (n = 45), %     | 24%         |       |
| Systolic dysfunction (contractility), %       | 16%         |       |
| Conduction blocks, %                          | 16%         |       |
| Diastolic dysfunction, %                      | 16%         |       |
| CK-elevation, %                               | 14%         |       |
| Pulmonary hypertension (echocardiography),%   | 13%         |       |
| Tendon friction rubs, %                       | 7%          |       |
| Renal crisis, %                               | 2%          |       |
| FVC (%predicted) (n = 39), %                  | 89.4±20.4   |       |
| LVEF, %                                       | 61.9±6.1    |       |

1The median modified Rodnan skin score was 11 (1st–3rd quartile: 7.5–16.0). SD = standard deviation, eGFR CKD-EPI—estimated glomerular filtration rate CKD-EPI equation, CRP—C-reactive protein, ESR—erythrocyte sedimentation rate, FVC—forced vital capacity, LVEF—left-ventricular ejection fraction, mRSS—modified Rodnan skin score, NYHA—New York Heart Association (NYHA) Functional Classification of heart failure.

3.2. Vitamin D and Clinical Associations in the Studied Population

We assessed several clinical and laboratory features using the EUSTAR methodology and found that patients with vitamin D deficiency presented a significantly higher prevalence of arterial hypertension (62.5% vs. 21.9%, p = 0.0021). No other associations were found, as presented in Table 2.
Table 2. Associations between clinical characteristics of SSc and vitamin D deficiency. Two-sided \( p \) values from the Fisher’s exact test are presented.

| Variable                              | \( p \) |
|---------------------------------------|--------|
| Gender, female                        | 0.73   |
| Raynaud’s present                     | 1.0    |
| Joint contractures                    | 0.56   |
| Lung fibrosis (HRCT)                  | 0.21   |
| Esophageal symptoms (dysphagia, reflux)| 0.07   |
| Dyspnea (≥NYHA 2)                     | 0.21   |
| Digital ulcers                        | 0.77   |
| Joint synovitis                       | 1.0    |
| Muscle weakness                       | 0.62   |
| Telangiectasia                        | 0.80   |
| Palpitations                          | 0.62   |
| Arterial hypertension                 | 0.002  |
| Intestinal symptoms (diarrhea, bloating, constipation) | 1.0    |
| Gastric symptoms (early satiety, vomiting) | 1.0    |
| Muscle atrophy                        | 0.26   |
| Restrictive defect (VC < 80%) (\( n = 45 \)) | 0.50   |
| Proteinuria                           | 0.18   |
| Conduction blocks                     | 0.30   |
| Diastolic dysfunction                 | 0.73   |
| Systolic dysfunction (contractility)  | 0.08   |
| Pulmonary hypertension (echocardiography) | 0.71   |
| CK-elevation                          | 0.73   |
| Tendon friction rubs                  | 1.0    |
| Renal crisis                          | 1.0    |

NYHA—New York Heart Association (NYHA) Functional Classification of heart failure, VC—vital capacity, CK—creatinine kinase.

In our study group, SSc patients with vitamin D deficiency showed higher CRP levels than those without the deficiency (4.2 mg/L vs. 2.0, \( p = 0.035 \); Table 3).

Table 3. Associations between clinical parameters in SSc and vitamin D deficiency. Two-sided \( p \) values from the Mann–Whitney U test are presented.

| 25(OH)D3 Deficiency | 25(OH)D3 > 20 ng/mL |
|---------------------|---------------------|
| Mean                | Mean                |
| Age, years          | 56.1                | 51.6                |
| SD                  | 12.5                | 14.3                |
| Disease duration since Raynaud onset, y | 11.3 | 12.9 |
| ESR, mm/h           | 6.0                 | 7.6                 |
| CRP, mg/L           | 17.8                | 19.0                |
| Serum creatinine, µmol/L | 4.2 | 6.0 |
| eGFR CKD-EPI, mL/min/1.73 m² | 86.2 | 14.3 |
| mRSS \(^1\)         | 90.5                | 93.3                |
| LVEF                | 14.3                | 11.8                |
| FVC (%predicted) (\( n = 39 \)) | 61.4 | 62.3 |

\(^1\) The median modified Rodnan skin score in patients with vitamin D deficiency was 11.5 (1st–3rd quartile: 7.5–21.5) vs. 11.0 (7.5–15.5) in participants without deficiency. CRP—C-reactive protein, ESR—erythrocyte sedimentation rate, FVC—forced vital capacity, LVEF—left-ventricular ejection fraction, mRSS—modified Rodnan skin score, eGFR CKD-EPI—estimated glomerular filtration rate according to CKD-EPI equation.

No difference was observed between the groups in terms of kidney function, measured by eGFR, although patients with proteinuria presented significantly lower mean vitamin D levels (13.7 vs. 23.0 ng/mL, \( p = 0.0021 \)).

We also found that mean serum 25-hydroxyvitamin D3 concentration was lower in patients with SSc-related ILD than in the rest of the SSc patients (19.5 ng/dL vs. 27.2 ng/dL, \( p = 0.032 \)). An exploration of the data using the Mann–Whitney U test and the Spearman’s rank-sum correlation did not allow for the identification of other clinical or laboratory factors associated with 25-hydroxyvitamin D3 serum concentrations in this group of patients with SSc, as shown in Tables 4 and 5.
Table 4. Comparison of serum 25-hydroxyvitamin D3 levels depending on the presence or absence of clinical characteristics of SSc. The Mann–Whitney U test was used. Two-sided \( p \)-values are presented.

| Characteristic                                | Characteristic Present | CharacteristicAbsent |
|----------------------------------------------|------------------------|----------------------|
| 25(OH)D3, ng/mL                              | Mean | SD | Mean | SD | \( p \) |
| Gender, female                               | 22.3 | 10.0 | 17.6 | 9.3 | 0.18 |
| Raynaud’s present                            | 21.6 | 9.7  | 5.6  |   | 1.0 |
| Joint contractures                           | 20.6 | 10.5 | 23.0 | 6.4 | 0.18 |
| Lung fibrosis (HRCT)                         | 19.5 | 8.4  | 27.2 | 12.8 | 0.032 |
| Esophageal symptoms (dysphagia, reflux)      | 22.1 | 8.4  | 19.3 | 12.0 | 0.084 |
| Dyspnea (≥NYHA 2)                            | 19.5 | 8.4  | 23.8 | 11.2 | 0.14 |
| Digital ulcers                               | 21.3 | 10.3 | 20.9 | 9.0  | 0.97 |
| Joint synovitis                              | 21.5 | 9.6  | 20.8 | 10.0 | 0.80 |
| Muscle weakness                              | 20.2 | 8.8  | 22.0 | 10.6 | 0.58 |
| Telangiectasia                               | 21.9 | 12.2 | 20.8 | 7.2  | 0.85 |
| Palpitations                                 | 21.5 | 8.2  | 20.9 | 11.0 | 0.50 |
| Arterial hypertension                        | 20.1 | 10.5 | 22.4 | 9.0  | 0.14 |
| Intestinal symptoms (diarrhea, bloating, constipation) | 20.8 | 9.0  | 21.3 | 10.2 | 0.99 |
| Gastric symptoms (early satiety, vomiting)   | 20.2 | 9.0  | 21.6 | 10.1 | 0.62 |
| Muscle atrophy                               | 18.6 | 9.7  | 22.0 | 9.7  | 0.18 |
| Restrictive defect (VC < 80%) (n = 45)       | 18.9 | 10.0 | 21.1 | 9.5  | 0.47 |
| Proteinuria                                  | 13.7 | 6.2  | 23.0 | 9.9  | 0.0021 |
| Conduction blocks                            | 16.2 | 9.4  | 21.9 | 9.5  | 0.071 |
| Diastolic dysfunction                        | 21.3 | 7.3  | 21.0 | 10.1 | 0.85 |
| Systolic dysfunction (contractility)         | 16.9 | 8.9  | 22.1 | 9.5  | 0.11 |
| Pulmonary hypertension (echocardiography)    | 18.3 | 12.0 | 21.8 | 9.3  | 0.25 |
| CK-elevation                                 | 19.8 | 8.1  | 21.8 | 10.2 | 0.70 |
| Tendon friction rubs                         | 15.5 | 9.5  | 22.1 | 10.0 | 0.15 |
| Renal crisis                                 | 17.9 | -    | 21.2 | 9.8  | 1.0  |

SD = standard deviation, VC—vital capacity, NYHA—New York Heart Association (NYHA) Functional Classification of heart failure.

Table 5. Correlations between the selected clinical parameters (continuous or ordinal) and serum 25-hydroxyvitamin D3 levels. The Spearman’s rank sum correlation coefficient (R) is presented, along with \( p \)-values.

| R     | \( p \) |
|-------|--------|
| Age   | -0.09  | 0.45 |
| Disease duration since Raynaud onset | 0.13 | 0.28 |
| Disease duration since diagnosis | 0.06 | 0.65 |
| ESR, mm/h | 0.14 | 0.26 |
| CRP, mg/L | -0.19 | 0.12 |
| Serum creatinine, umol/L | 0.04 | 0.76 |
| eGFR CKD-EPI | 0.02 | 0.87 |
| mRSS  | -0.16  | 0.21 |
| LVEF  | 0.07   | 0.59 |
| FVC (%predicted) (n = 39) | 0.11 | 0.49 |

CRP—C-reactive protein, ESR—erythrocyte sedimentation rate, LVEF—left-ventricular ejection fraction, mRSS—modified Rodnan skin score, eGFR CKD-EPI—estimated glomerular filtration rate CKD-EPI equation, FVC—forced vital capacity.

The essential analyses were repeated separately in limited cutaneous systemic sclerosis (lcSSc) and diffuse cutaneous systemic sclerosis (dcSSc) subgroups. The main findings included increased CRP in vitamin D-deficient patients with lcSSc (\( p = 0.039 \)), and a weakly negative correlation between CRP and 25-hydroxyvitamin D3 in this subgroup (\( \rho = -0.30, p = 0.039 \)). Additionally, lcSSc analysis of two-way tables revealed a positive association of vitamin D deficiency with arterial hypertension (\( p = 0.029 \)), and a possible relationship between vitamin D deficiency and esophageal symptoms of SSc (\( p = 0.055 \)).

In dcSSc, mRSS negatively correlated with 25-hydroxyvitamin D3 (\( \rho = -0.52, p = 0.020 \)). There was a clear link between vitamin D deficiency and lung fibrosis in dcSSc patients (\( p = 0.011 \)), with all the deficient patients presenting pulmonary fibrosis, compared with approximately half of those without the deficiency. Further research may focus on
muscle atrophy and arterial hypertension in dcSSc (both $p = 0.070$). Only one out of nine dcSSc patients without vitamin D deficiency suffered from muscle atrophy, compared with six out of eleven in the vitamin D-deficient subgroup.

4. Discussion

Vitamin D deficiency in SSc has been widely reported [17–21]. In the population studied, its prevalence reached 50%, and the association between vitamin D deficiency and a higher prevalence of arterial hypertension was one of the strongest findings in this study. It is surprising given the lack of similar data in the present literature, to the best of the authors’ knowledge. There is some evidence that vitamin D demonstrates a blood pressure lowering effect; nevertheless, it is inconsistent and requires more research [22].

Furthermore, we found a strong link between vitamin D deficiency and proteinuria. A similar effect was demonstrated in the past in other rheumatic diseases, such as systemic lupus erythematosus, but not in SSc. In fact, vitamin D supplementation was shown to reduce proteinuria in lupus [23]. There are very little data with regard to kidney abnormalities in SSc beyond the scleroderma renal crisis. Seiberlich et al. found albuminuria in 25% of SSc subjects, as well as an increased total protein excretion in 17% of the same population. Thus, they suggested that it should be more thoroughly investigated, as it was related to kidney involvement and systemic vasculopathy [24].

Skin involvement, measured using a widely employed mRSS score, was not correlated with vitamin D deficiency in all the investigated patients, similarly to other findings [21,25–27]. However, in the dcSSc subgroup alone, mRSS negatively correlated with vitamin D levels. Gupta et al. and Arnson also reported an inverse relationship between mRSS and serum vitamin D levels, even though they investigated smaller groups of patients ($n = 38$ and $n = 39$, respectively) [19,28].

SSc-related ILD (lung fibrosis) was significantly correlated with vitamin D deficiency, confirming the findings of Gupta, Zhang, and Vacca et al. [28–30]. Vitamin D has been shown to have antifibrotic effects through different molecular mechanisms including decreased serum levels of IL-13 and IL-17, directly through T regulatory lymphocytes, TGF-β/SMAD signaling, and the renin-angiotensin system [31]. In our study, the link between pulmonary fibrosis and vitamin D deficiency seemed particularly strong in patients with dcSSc.

The increased levels of CRP among vitamin D-deficient patients in our study were in line with the observations reported by Caramaschi et al. [20]. Yet, Park et al. and Zhang et al. found no association with CRP [26,29]. However, this could be explained by smaller sample sizes in these two studies. It lies in the nature of CRP that a plethora of transient factors might confound its level (at the low values). Consequently, we cannot draw definite conclusions with such small sample sizes and a relatively weak link, which was not confirmed with the Spearman’s correlation. Moreover, Hax et al. demonstrated increased levels of interleukin 6 that positively (albeit weakly) correlated with the modified Rodnan skin score ($r = 0.291, p = 0.041$) in their SSc group [32]. Interestingly, Caramaschi et al., as well as Vacca et al. [30], reported a link between increased ESR and vitamin D deficiency, which we could not corroborate.

The limitations of the study include the lack of information on the enrollment season. In fact, a seasonal influence variation in vitamin D levels has been reported [33,34], and there is a study that demonstrated the influence of seasons on the disease activity in Thai SSc patients [35]. However, there was no specific seasonal trend in the course of the recruitment in our research, and the recruitment process spread over six years, thus there is little risk of seasonal bias. This study was monocentric, but it had a moderate number of patients that were evaluated prospectively as compared with other published studies. Nevertheless, further work in larger groups is required to confirm the obtained results, link the serial 25(OH)D3 measurements with the disease evolution in cohort studies, and investigate its usefulness in interventional studies. One of the factors that has not been investigated specifically in this study involves medications. Typically, few medications
for SSc were taken and approximately one-third of the enrolled patients received low dose steroids. None of the patients received systematic vitamin D3 supplementation upon enrollment to the study, and the use of laxatives, which could affect vitamin D3 levels, was very rare. Importantly, the Polish population of SSc patients has not been previously explored regarding 25(OH)D3.

It should be added that vitamin D has not been assessed in a randomized trial in sufficiently large groups of SSc patients. There have been preliminary studies, one of which was small, but yielded encouraging results [36,37]. This year saw the end of the recruitment to a randomized study on the effects of 25-hydroxyvitamin D3 on the immune system in SSc (ClinicalTrials.gov NCT04822038). However, the results have not yet been published. A recent systematic review on vitamin D deficiency in SSc confirmed that SSc patients frequently present vitamin D deficiency and that its levels inversely correlate with the disease severity [18]. However, it also emphasized the lack of evidence for the beneficial impact of vitamin D in SSc and highlighted a need for future trials and fundamental research. While the practitioners treating patients with SSc await more data on this topic, it seems prudent to bear in mind the guidelines of vitamin D supplementation in the general population [38].

5. Conclusions

According to the results of this study, vitamin D deficiency was common in Polish SSc patients, and it was associated with arterial hypertension, proteinuria, lung involvement, and increased CRP. However, further research is warranted to confirm these results in larger, multi-centric groups of patients.

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