Low vitamin D status in systemic sclerosis and the impact on disease phenotype

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Abstract

Objective: Vitamin D has pleiotropic effects including immunomodulatory, cardioprotective, and antifibrotic properties and is thus able to modulate the three main links in scleroderma pathogenesis. The aim of the study was to evaluate the level of vitamin D in patients with systemic sclerosis and to analyze the associations between the concentration of vitamin D and the features of systemic sclerosis.

Material and Methods: Fifty-one consecutive patients were evaluated for visceral involvement, immunological profile, activity, severity scores, and quality of life. The vitamin D status was evaluated by measuring the 25-hydroxy-hydroxyvitamin D serum levels.

Results: The mean vitamin D level was 17.06±9.13 ng/dL. Only 9.8% of the patients had optimal vitamin D levels; 66.66% of them had insufficient 25(OH)D levels, while 23.52% had deficient levels. No correlation was found between vitamin D concentration and age, sex, autoantibody profile, extent of skin involvement, or vitamin D supplementation. Vitamin D levels were correlated with the diffusing capacity of the lung for carbon monoxide (p=0.019, r=0.353), diastolic dysfunction (p=0.033, r=−0.318), digital contractures (p=0.036, r=−0.298), and muscle weakness (p=0.015, r=−0.377) and had a trend for negative correlation with pulmonary hypertension (p=0.053, r=−0.29).

Conclusion: Low levels of vitamin D are very common in systemic sclerosis. Poor vitamin status seems to be related with a more aggressive disease with multivisceral and severe organ involvement, especially pulmonary and cardiac involvement.

Keywords: Systemic scleroderma, vitamin D, visceral involvement

Introduction

Systemic sclerosis (SSc) is an autoimmune disease in which vascular damage and immune activation leads to the excessive accumulation of extracellular matrix in the skin and internal organs (1).

In SSc patients, vitamin D deficiency was identified to be frequent and associated with disease activity or phenotype characteristics such as pulmonary hypertension, lung involvement, and extensive cutaneous forms (2-8). Vitamin D has pleiotropic effects that go beyond its traditional role in calcium homeostasis, which is related to vitamin D receptor (VDR) ubiquitous distribution (9). In the last few years, a large number of studies have suggested that vitamin D deficiency is a risk factor for a wide spectrum of acute and chronic illnesses including autoimmune diseases (9-10).

It has been documented that VDRs are present on the surface of antigen-presenting cells, natural killer cells, and B and T lymphocytes (11, 12), explaining multiple immunomodulatory effects on both innate and adaptive immune responses. In particular, vitamin D inhibits T helper-1 (Th1) lymphocytes and the production of Th1 cytokines such as interleukin (IL)-2, interferon gamma, and tumor necrosis factor alpha (13). Moreover, vitamin D reduces the level of other proinflammatory cytokines such as IL-6 and IL-17 and up-regulates anti-inflammatory mediators such as IL-4 and IL-10; further, it interferes with the differentiation and survival of dendritic cells (14).

VDR is present in many cells throughout the body including cardiomyocytes, vascular smooth muscle, and endothelium (15). Recent evidence has shown that 25-hydroxyvitamin(Oh)D deficiency is associated with vascular endothelial dysfunction in middle-aged and older adults and with a higher risk of developing incident cardiovascular disease (15). The mechanism of how vitamin D may protect individuals from cardiovascular disease has not yet been fully elucidated. Several mechanisms have been proposed including negatively regulating renin to lower the blood pressure (15), improving vascular compliance (15), decreased production of endothelium-derived contracting factors (16), increased vascular endothelial growth factor (VEGF) expression (17), decreased parathyroid hormone levels (15), and improved glycemic control (15).
Several studies have also proved the antifibrotic properties of vitamin D. The addition of 1,25-hydroxyvitamin D₃ to mesenchymal multipotent cells promotes the decreased expression of transforming growth factor beta-1 (TGF-β1) and plasminogen activator inhibitor (SERPINE1), which are two well-known profibrotic factors, and of collagen I, III, and other collagen isoforms and the increased expression of several antifibrotic factors such as bone morphogenetic protein-7, a TGF-β1 antagonist; matrix metalloproteinase-8, a collagen breakdown inducer; and follistatin, an inhibitor of the profibrotic factor myostatin (18).

1,25(OH)₂D₃ can also inhibit the profibrotic phenotype of lung fibroblasts and epithelial cells (19) and can block, at least partially, myofibroblastic transformation from interstitial fibroblasts induced by TGF-β1 (20).

Taking into consideration its immunomodulatory, cardioprotective, and antifibrotic properties, vitamin D could influence the three main pathogenic links of SSc.

Based on the data presented, we evaluated a group of scleroderma patients for the pathological significance of vitamin D deficiency.

### Material and Methods

#### Patients

Fifty-one patients were included in this cross-sectional study. The patients were selected according to The European League Against Rheumatism 2013 criteria for SSc. They were evaluated for disease pattern; Rodnan score; musculo-articular, gastrointestinal, cardiovascular, pulmonary, and renal involvement; inflammatory markers; autoantibodies (anti-nuclear, anticentromere, antiscleroderma-70); and cholesterol and triglyceride levels; nailfold capillaroscopy was also performed. Several questionnaires were completed: European Dis-

### Table 1. Demographic and clinical data of systemic sclerosis patients

<table>
<thead>
<tr>
<th>Population</th>
<th>n=51</th>
<th>Diffuse subset n=27</th>
<th>Limited subset n=24</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean(SD)</td>
<td>55.65±12.45</td>
<td>53.07±13.75</td>
<td>58.54±10.33</td>
<td>0.11</td>
</tr>
<tr>
<td>Disease duration (years), mean(SD)</td>
<td>11.7 (6.9)</td>
<td>11.17 (6.54)</td>
<td>12.29 (7.3)</td>
<td>0.57</td>
</tr>
<tr>
<td>Rodnan score, mean(SD)</td>
<td>9.59 (5.01)</td>
<td>13.11 (5.98)</td>
<td>5.63 (2.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Digital ulcers (%)</td>
<td>41.2%</td>
<td>29.63%</td>
<td>54.16%</td>
<td>0.07</td>
</tr>
<tr>
<td>Digital contractures (%)</td>
<td>45.1%</td>
<td>62.96%</td>
<td>25%</td>
<td>0.006</td>
</tr>
<tr>
<td>Acroosteolysis (%)</td>
<td>21.56%</td>
<td>33.33%</td>
<td>8.33%</td>
<td>0.02</td>
</tr>
<tr>
<td>Muscle atrophy (%)</td>
<td>23.5%</td>
<td>37.04%</td>
<td>8.33%</td>
<td>0.01</td>
</tr>
<tr>
<td>Gastrointestinal involvement (%)</td>
<td>84.3%</td>
<td>77.77%</td>
<td>91.66%</td>
<td>0.18</td>
</tr>
<tr>
<td>sPAP mmHg, mean(SD)</td>
<td>33.4 (13.94)</td>
<td>34.12 (12.65)</td>
<td>32.42 (15.84)</td>
<td>0.69</td>
</tr>
<tr>
<td>Pulmonary fibrosis (%)</td>
<td>1.96%</td>
<td>7.4%</td>
<td>0%</td>
<td>0.18</td>
</tr>
<tr>
<td>Renal crisis (%)</td>
<td>41.17%</td>
<td>59.25%</td>
<td>20.83%</td>
<td>0.002</td>
</tr>
<tr>
<td>Elevated ESR/CRP (%)</td>
<td>45.1%</td>
<td>62.96%</td>
<td>45.83%</td>
<td>0.22</td>
</tr>
<tr>
<td>Autoantibodies (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCL70+</td>
<td>60.78%</td>
<td>85.18%</td>
<td>33.33%</td>
<td>0.000</td>
</tr>
<tr>
<td>ACA+</td>
<td>17.64%</td>
<td>7.4%</td>
<td>41.66%</td>
<td>0.05</td>
</tr>
<tr>
<td>SCL70+ ACA+</td>
<td>11.78%</td>
<td>7.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCL70-ACA-</td>
<td>9.8%</td>
<td>12.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nailfold capillaroscopy (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>7.9%</td>
<td>9.52%</td>
<td>6.25%</td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>34.2%</td>
<td>38.09%</td>
<td>31.25%</td>
<td></td>
</tr>
<tr>
<td>Late</td>
<td>52.6%</td>
<td>52.38%</td>
<td>47.62%</td>
<td></td>
</tr>
<tr>
<td>Osteoporosis (%)</td>
<td>39.28%</td>
<td>26.67%</td>
<td>53.84%</td>
<td>0.13</td>
</tr>
<tr>
<td>Activity score (%)</td>
<td>3.43±2.14</td>
<td>4.06 (2.41)</td>
<td>2.73 (1.55)</td>
<td>0.02</td>
</tr>
<tr>
<td>Severity score (%)</td>
<td>6.84±3.15</td>
<td>8 (3.23)</td>
<td>5.54 (2.53)</td>
<td>0.004</td>
</tr>
<tr>
<td>HAQ, mean(SD)</td>
<td>0.83±0.67</td>
<td>0.94 (0.66)</td>
<td>0.7 (0.66)</td>
<td>0.023</td>
</tr>
<tr>
<td>25(OH)D level (ng/mL)</td>
<td>17.06±9.13</td>
<td>15.92±9.1</td>
<td>22.05±10.8</td>
<td>0.35</td>
</tr>
</tbody>
</table>

SD: standard deviation; sPAP: systolic pulmonary arterial pressure; DLCO: diffusing capacity for carbon monoxide; SCL 70: antiscleroderma-70 autoantibodies; ACA: anticentromere antibodies; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HAQ: health assessment questionnaire
and those with vitamin D deficiency

The table reports the comparison of clinical data between patients with vitamin D insufficiency and deficiency. Table 2.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Vitamin D insufficiency (n=34)</th>
<th>Vitamin D deficiency (12)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activity score, mean(SD)</td>
<td>3.09 (2.07)</td>
<td>3.43 (2.21)</td>
<td>0.64</td>
</tr>
<tr>
<td>Severity score, mean(SD)</td>
<td>6.79 (3.26)</td>
<td>7 (2.48)</td>
<td>0.84</td>
</tr>
<tr>
<td>Rodnan score, mean(SD)</td>
<td>11.50 (6.77)</td>
<td>8.76 (5.24)</td>
<td>0.15</td>
</tr>
<tr>
<td>Ulcers (%)</td>
<td>44.11%</td>
<td>33.33%</td>
<td>0.52</td>
</tr>
<tr>
<td>Pulmonary fibrosis (%)</td>
<td>67.49%</td>
<td>38.49%</td>
<td>0.09</td>
</tr>
<tr>
<td>Renal crisis (%)</td>
<td>2.94%</td>
<td>8.33%</td>
<td>0.001</td>
</tr>
<tr>
<td>sPAP (mmHg), mean(SD)</td>
<td>36.55 (19.98)</td>
<td>33.34 (11.95)</td>
<td>0.53</td>
</tr>
<tr>
<td>Diastolic dysfunction (%)</td>
<td>30%</td>
<td>45.45%</td>
<td>0.36</td>
</tr>
<tr>
<td>Systolic dysfunction (%)</td>
<td>5.88%</td>
<td>25%</td>
<td>0.03</td>
</tr>
<tr>
<td>Muscle weakness (%)</td>
<td>55.88%</td>
<td>91.66%</td>
<td>0.025</td>
</tr>
<tr>
<td>Muscle atrophy (%)</td>
<td>8.33%</td>
<td>55.88%</td>
<td>0.002</td>
</tr>
<tr>
<td>Gastrointestinal involvement (%)</td>
<td>55.88%</td>
<td>16.66%</td>
<td>0.05</td>
</tr>
<tr>
<td>HAQ, mean(SD)</td>
<td>3.5 (3.2)</td>
<td>4.9 (2.4)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

SD: standard deviation; sPAP: systolic pulmonary arterial pressure; HAQ: health assessment questionnaire

The mean vitamin D level was 17.06±9.13 ng/dL. Most patients have insufficient 25(OH)D levels, and only 9.82% have optimal levels.

The mean 25(OH)D level was 17.06±9.13 ng/dL (Figure 1). Only 5 patients had optimal vitamin D levels (9.8%), 66.66% of the patients had insufficient 25(OH)D levels, while 23.52% had deficient levels.

Clinical differences between patients with normal and suboptimal vitamin D levels

Patients with low vitamin D levels had higher systolic pulmonary arterial pressure than those with normal 25(OH)D levels (25.25 (3.77) mmHg vs. 34.2 (14.33) mmHg, respectively; p=0.008) and poor quality of life evaluated using HAQ (p=0.023). None of the patients with normal vitamin D levels developed cardiac involvement.

Clinical differences between patients with vitamin D insufficiency and deficiency

Patients with vitamin D deficiency developed more frequent systolic dysfunction (p=0.003), scleroderma renal crisis (p=0.001), muscle weakness (p=0.025), and muscle atrophy (p=0.002) and have poor quality of life (p=0.03) (Table 2).

Clinical differences between patients with or without vitamin D supplementation

Thirteen patients (25.49%) received vitamin D supplementation. The mean 25(OH)D level was higher for patients with supplements, but the difference between groups failed to reach statistical significance (p=0.488). Patients with vitamin D supplementation developed less frequent digital ulcers compared with those without (30.76% vs 44.73%, respectively; p=0.04).

Vitamin D concentrations and clinical parameters

No correlation was found between vitamin D concentration and age, sex, autoantibody profile, SSc subset, skin involvement evaluated by the modified Rodnan skin score, articular involvement (synovitis or acroosteolysis), presence or previous history of ischemic digital ulcers, activity and severity scores, and inflammatory syndrome.

The mean vitamin D level correlated with pulmonary fibrosis (p=0.011, r=−0.355) and diffusing capacity for carbon monoxide (DLCO) (p=0.019, r=−0.353) (Figure 2). The vitamin D status had a negative correlation with diastolic dysfunction (p=0.033, r=−0.318) and a trend for negative correlation with pulmonary hyp
pertension ($p=0.053$, $r=-0.29$). Digital contrac-
tures and muscle weakness were also correlat-
ed with the 25(OH)D level ($p=0.036$, $r=-0.298$
and $p=0.015$, $r=-0.377$, respectively).

**Discussions**

Similar to previous reports (3-9), our study also
showed a low vitamin D status in SSc (90.2%),
with a mean 25(OH)D level of 17.06±9.3 ng/
mL. Vitamin D deficiency in SSc may be linked
to multiple risk factors: skin thickening and
hyperpigmentation, insufficient sun exposure
due to disability, or insufficient intake and mal-
absorption. In our study, patients with a nor-
mal vitamin D status had higher Rodnan scores
than those with a suboptimal vitamin D status
($p=0.23$); further, patients with vitamin D insuf-
ficiency had higher Rodnan scores than those
with vitamin D deficiency ($p=0.15$). No cor-
relation was found between vitamin D serum
levels ($p=0.183$) and Rodnan scores ($p=0.124$).
Additionally, no difference was found when com-
paring 25(OH)D levels between diffuse and
limited subsets; patients with Rodnan
scores of $>10$ did not have significantly lower
25(OH)D levels than those with Rodnan scores
of $<10$ (9.61±1.72 ng/mL vs. 8.11±1.81 ng/mL,
respectively; $p=0.18$). All these results suggest
that cutaneous involvement is not the main
cause for a poor vitamin D status in SSc.

Patients with vitamin D deficiency in the stud-
ied group had more severe disease than those
with vitamin D insufficiency. Our results sug-
gest that the vitamin D status could influence
disease phenotype, especially lung and heart
involvement.

A weak correlation between 25(OH)D level and
systolic pulmonary arterial pressure was not-
ticed ($p=0.05$, $r=-0.29$) in the study group. Sev-
eral studies reported that vitamin D deficiency
is common among patients with pulmonary
hypertension (23, 24). The mechanism through
which vitamin D deficiency could induce pul-
monary hypertension is not fully understood;
it could be activation of the renin–angiotensin
system (25), reduced expression of prostacyclin
by vascular smooth muscle cells (25), or sec-
ondary hyperparathyroidism. The parathyroid
hormone is known to increase mesenchymal
stem cell proliferation and stimulates VEGF
expression in human umbilical vein endothelial
cells (26).

Important correlations were noticed between
the vitamin D status and cardiovascular in-
volvement. Patients in the group with optimal
vitamin D levels neither had systolic or diastol-
ic dysfunction nor rhythm and conduction
disturbances, while those with vitamin D de-
ficiency had the highest prevalence. Patients
with vitamin D supplementation developed
less digital ulcers ($p=0.04$). Primary myocardial
involvement in SSc is related to repeated focal
ischemic injury causing myocytes apoptosis, replacement with fibroblasts, and subsequent
irreversible myocardial fibrosis (27). In mouse
models, vitamin D deficiency is associated
with energetic metabolic changes, cardiac
inflammation, oxidative stress, fibrosis and
apoptosis, cardiac hypertrophy, left chamber
alterations, and systolic dysfunction. Further-
more, the restriction length influenced these
cardiac changes (28). Vitamin D deficiency has
been shown in observational and prospective
studies to be associated with cardiovascular
diseases including coronary artery disease, left
ventricular hypertrophy, and systolic heart fail-
ure (29). On the other hand, in large popula-
tion-based studies, 25(OH)D was not associat-
ed with better left ventricular systolic function
when adjusted for other risk factors and for the
season of vitamin D sampling (30).

Vitamin D also has some influence on mus-
culo-articular involvement. Although results
failed to reach statistical significance, patients
with vitamin D deficiency developed more
frequent synovitis than those with vitamin
D insufficiency (25% vs. 20.58%, respective-
ly; $p=0.4$). Patients with synovitis have lower
25(OH)D levels than those without synovitis
(15.93±7.69 ng/mL vs. 20.36±12.21 ng/mL,
respectively; $p=0.061$). These results may be
closely related to the anti-inflammatory and
immunomodulatory properties of vitamin D. In
the last few years, the possible role of vitamin
D in the pathogenesis, activity, and treatment
of inflammatory arthritis has been raised based
on the results and observations of clinical and
laboratory studies from laboratory models or
patients with rheumatoid arthritis. The ratio-
nale for the relationship between vitamin D
deficiency and rheumatoid arthritis is based on
two facts: evidence indicate that patients with
rheumatoid arthritis have vitamin D deficiency
and the presence of 1,25(OH)2D and VDR in
macrophages, chondrocytes, and synovial cells
in the joints of these patients (31). There seems
to be an inverse relationship between disease
activity and vitamin D metabolite concentra-
tion in patients with inflammatory arthritis (31).

A negative correlation was also identified be-
 tween the vitamin D status and muscle weak-
ness ($p=0.015$, $r=-0.37$); patients with muscle
weakness had lower 25(OH)D levels than those
without (15.32±9.14 ng/mL vs. 20.24±8.45
ng/mL, respectively; $p=0.06$). Patients with
vitamin D insufficiency developed significantly
less muscle weakness ($p=0.001$) and muscle
atrophy ($p=0.002$) compared to those with
vitamin D deficiency. Vitamin D deficiency-as-
 sociated myopathy has been known for more
than 30 years; age-related sarcopenia is asso-
ciated with VDR polymorphism. Vitamin D has
non-genetic and non-genetic effects in skeletal
muscle, impacting both calcium metabolism and
protein transcription (32).

Several in vitro analyses have suggested key
mechanistic pathways through which vitamin
D decreases fibrosis in different tissue types
(33). Recently, VDR expression was analyzed in
SSc skin, experimental fibrosis, and human fi-
broblasts (34). VDR expression decreases in the
fibroblasts of SSc patients and murine models
of SSc in a TGF-β-dependent manner. The au-
tors suggest that impaired VDR signaling with
reduced VDR expression and decreased levels
of its ligand may contribute to hyperactive
TGF-β signaling and aberrant fibroblast acti-
vation in SSc (34). In our group, the vitamin D
status was related to the clinical equivalent of
fibrosis as digital contractures and pulmonary
fibrosis.

The 25(OH)D level was negatively correlat-
ed with the presence of digital contractures
($p=0.036$, $r=-0.029$). Vitamin D serum lev-
els were significantly lower in patients with
digital contractures than in those without
(19.40±10.22 ng/mL vs. 14.20±6.75 ng/mL,
respectively; $p=0.042$). Although results failed
to reach statistical significance, patients with
vitamin D deficiency have more digital con-
tractures those with insufficient vitamin D level
(58.33% vs. 44.11%, respectively; $p=0.07$), as did
the patients with suboptimal levels compared
to those with a normal vitamin D status (20%
vs. 47.82%, respectively; $p=0.235$) and patients
not receiving supplementation compared to
those receiving supplementation (38.46% vs.
47.36%, respectively; $p=0.36$). There are no pre-
vious reports regarding this association.

Patients with a poor vitamin D status have
more severe lung involvement. This finding
confirms the results of other studies (2, 4, 8).
The frequency of pulmonary fibrosis was
87.5% in the diffuse subset and 25% in patients
with the limited form of SSc for patients with
vitamin D deficiency ($p=0.003$) and 56.2% for
the diffuse subset and 28.5% for the limited
subset in patients with vitamin D insufficiency
($p=0.04$). Correlations were identified between
25(OH)D levels and lung involvement ($p=0.011$,
$r=-0.035$) and DLCO ($p=0.019$, $r=0.037$). None
of the patients with a normal vitamin D status
had lung involvement. Multifactorial regression
analysis concluded that compared to patients
with an optimal vitamin D status, pulmonary
fibrosis developed more often in patients vitamin D insufficiency, irrespective of the disease subset; when comparing the subsets of SSc, lung involvement developed more frequently in patients with diffuse form and vitamin D deficiency. To date, very few drugs are available to stabilize or improve lung function in randomized clinical trials, and their beneficial effect is quite small (34). Considering our findings, we may consider adding vitamin D as an adjuvant for immunosuppression.

As previously mentioned, studies on cells of murine origin incubation of mesenchymal multipotent cells with vitamin D decrease the expression of TGF-β1 and concomitantly reduce the expression of collagen I and III; moreover vitamin D is able to oppose the action of TGF-β1 on fibroblast proliferation and myofibroblast transdifferentiation, as demonstrated by the reduced expression of α-smooth muscle actin (18). Vitamin D also acts on the transdifferentiation of lung epithelial cells into myofibroblasts (19). These murine studies show a direct link between vitamin D and fibrosis pathways and may furnish a plausible explanation of a more severe lung disease in SSc patients with hypovitaminosis D.

A study on 118 patients with interstitial lung disease, including 67 patients with connective tissue disorders, revealed significantly low vitamin D levels (35). In patients with connective tissue disorders, correlations between vitamin D level and forced vital capacity and DLCO were identified.

Although scleroderma renal crisis seems to be more frequent in patients with vitamin D deficiency in the group (p=0.001), the small number of patients raises doubts on the statistical significance of the results. Still, to our knowledge, this is the first study to report this association.

Taking into account the more severe musculo-articular, lung, and heart involvement in patients with suboptimal 25(OH)D levels, there is little doubt that the vitamin D status was related to the quality of life. Patients with a low vitamin D status had higher HAQs than those with normal 25(OH)D levels (p=0.03), as did the patients with vitamin D deficiency compared to those with vitamin D insufficiency (p=0.023). We observed that a standard dose of vitamin D supplement does not correct the deficiency. This could have practical repercussions as our results strongly suggest the need for a higher supplement dosage, but this remains to be validated together with potential effects on the clinical phenotype of vitamin D normalization.

Our study has some limitations. One is the lack of a control group of healthy subjects. The design was cross-sectional; therefore, the direction of associations could not be conclusively determined. Moreover, the data could be confounded by the fact that patients with severe organ involvement had worse health status, and thus had a diet lacking in vitamin D or had less ultraviolet exposure. Another point is that we did not assess the dietary intake of vitamin D.

The role of vitamin D in the pathogenesis of autoimmune disease is still unclear. Well-designed trials to determine whether vitamin D could be a modifiable factor able to interfere with SSc evolution are required.

In conclusion, low levels of vitamin D are very common in patients with SSc; other causes except the extent of skin involvement are thought to be involved. Poor vitamin status seems to be related with a more aggressive disease with multivisceral and severe organ involvement, especially pulmonary and cardiac involvement. Usual vitamin D supplementation does not correct vitamin D deficiency in scleroderma patients. Well-designed trials to determine whether vitamin D could be a modifiable factor able to interfere with SSc evolution are required.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of St Maria Clinica Hospital.

Informed Consent: Written informed consent was obtained from the patients.

Conflict of Interest: No conflict of interest was declared by the authors.

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