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Original article

Low vitamin D serum levels in diffuse systemic sclerosis: a correlation with worst quality of life and severe capillaroscopic findings

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ABSTRACT

Objective: The aim of this study was to analyze the correlation of vitamin D levels with clinical parameters, bone mineral density (BMD), quality of life (QoL) and nailfold capillaroscopy (NC) in patients with diffuse systemic sclerosis (SSc).

Methods: Thirty-eight female patients with diffuse SSc were analyzed regarding 25-hydroxyvitamin D (25OHD) serum levels. At inclusion, organ involvement, autoantibodies, modified Rodnan skin score (mRSS), Medsger Disease Severity Index (MDSI), body mass index (BMI), BMD, NC, Short-Form-36 Questionnaire (SF-36), and Health Assessment Questionnaire (HAQ), were performed through a standardized interview, physical examination and electronic chart review.

Results: Mean 25OHD serum level was 20.66 ± 8.20 ng/mL. Eleven percent of the patients had 25OHD levels $\leq$10 ng/mL, 50% $\leq$20 ng/mL and 87% $\leq$30 ng/mL. Vitamin D serum levels were positively correlated with BMI ($r = 0.338$, $p = 0.038$), BMD-total femur ($r = 0.340$, $p = 0.037$), BMD-femoral neck ($r = 0.384$, $p = 0.017$), SF-36-Vitality ($r = 0.385$, $p = 0.017$), SF-36-Social Function ($r = 0.320$, $p = 0.050$), SF-36-Emotional Role ($r = 0.321$, $p = 0.049$) and SF-36-Mental Health ($r = 0.531$, $p = 0.0006$) and were negatively correlated with HAQ-Reach ($r = -0.328$, $p = 0.044$) and HAQ-Grip Strength ($r = -0.331$, $p = 0.042$). A negative correlation with NC-diffuse devascularization ($p = 0.029$) and NC-avascular area ($p = 0.033$) was also observed.

Conclusion: The present study provides novel evidence demonstrating that low levels of 25OHD have a negative impact in diffuse SSc QoL and further studies are needed to define whether vitamin D supplementation can improve health related QoL in these patients. The additional observation of a correlation with severe NC alterations suggests a possible role of 25OHD in the underlying SSc vascular involvement.

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Baixos níveis séricos de vitamina D na esclerose sistêmica difusa: correlação com pior qualidade de vida e alterações capilaroscópicas graves

Palavras-chave:
Esclerose sistêmica
Vitamina D
Qualidade de vida
Capilaroscopia periungueal

RESUMO

Objetivo: O objetivo deste estudo foi analisar a correlação entre os níveis de vitamina D e parâmetros clínicos, densidade mineral óssea (DMO), qualidade de vida (QV) e capilaroscopia periungueal (CPU) em pacientes com esclerose sistêmica difusa (ES).
Métodos: Mensuraram-se os níveis séricos de 25-hidroxivitamina D (25OHD) de 38 pacientes do sexo feminino com ES difusa. No momento da inclusão, analisaram-se o envolvimento de órgãos, autoanticorpos, escore cutâneo de Rodnan modificado (ERM), Medsger Disease Severity Index (MDSI), índice de massa corporal (IMC), DMO, CPU, Short-Form-36 Questionnaire (SF-36) e Health Assessment Questionnaire (HAQ) por meio de uma entrevista padronizada, exame físico e avaliação de prontuário eletrônico.
Resultados: A média do nível sérico de 25OHD foi de 20,66 ± 8,20 ng/mL. Dos pacientes, 11% tinham níveis de 25OHD ≤ 10 ng/mL, 50% ≤ 20 ng/mL e 87% ≤ 30 ng/mL. Os níveis séricos de vitamina D estiveram positivamente correlacionados com o IMC (r = 0,338, p = 0,038), DMO-fêmur total (r = 0,340, p = 0,037), DMO-colo femoral (r = 0,384, p = 0,017), SF-36-Vitalidade (r = 0,385, p = 0,017), SF-36-Aspecto social (r = 0,320, p = 0,050), SF-36-Aspecto emocional (r = 0,321, p = 0,049) e SF-36-Saúde mental (r = 0,531, p = 0,0006) e se correlacionaram negativamente com o HAQ-Alcance (r = −0,328, p = 0,044) e HAQ-força de preensão (r = −0,331, p = 0,042). Também foi observada uma correlação negativa com a CPU-desvascularização difusa (p = 0,029) e CPU-área avascular (p = 0,033).
Conclusão: O presente estudo fornece evidências novas de que níveis baixos de 25OHD têm um impacto negativo sobre a qualidade de vida de pacientes com ES difusa e que são necessários mais estudos para definir se a suplementação de vitamina D pode melhorar a qualidade de vida relacionada com a saúde desses pacientes. A observação adicional de uma correlação com alterações graves na CPU sugere um possível papel da 25OHD no envolvimento vascular subjacente da ES.

Significance & innovations

1) Low vitamin D serum levels had a negative impact on physical and emotional domains of quality of life in diffuse SSc patients.
2) Low vitamin D serum levels were correlated with severe capillaroscopic findings.
3) Lower vitamin D levels were more frequently observed in patients with anti-Scl 70 positive.

Introduction

In the last two decades, the survival of patients with systemic sclerosis (SSc) has significantly improved.[1,2] Nevertheless, SSc can still cause increased disability and reduced quality of life. Several factors can be involved with these conditions, as disease subtype,[3] gender,[4] lung involvement,[3] pruritus,[5] fatigue,[6] anxiety and depression.[7,8] Hand, tendon and joint involvement are other factors which can cause significant functional disability, leading to consequent disuse and worsening of bone loss in patients with SSc,[9,10] contributing to a significant impairment in the quality of life of these patients.[10]

Low levels of 25-hydroxyvitamin D (25OHD) may also contribute to the chronic inflammation, immunological dysregulation and skeletal myopathy with a consequent reduction in quality of life in autoimmune diseases.[11,12] Studies evaluating vitamin D levels in SSc patients revealed a high frequency of this condition and a possible association with inflammation and pulmonary hypertension.[13–18] There are, however, no data regarding low vitamin D impact in quality of life in these patients.

The aim of this study was therefore, to analyze the correlation of vitamin D with quality of life, clinical parameters and nailfold capillaroscopy (NC) in patients with diffuse SSc.

Methods

Patients

This is a cross-sectional study analyzing 38 diffuse SSc patients who attended the Scleroderma Outpatient Clinic of the University of São Paulo from May 2012 to May 2013. All patients were classified as SSc according to the recent EULAR/ACR criteria.[19] Inclusion criteria were female gender; age between 18 and 50 years; diffuse SSc according to LeRoy et al. criteria[20]; capacity to understand the study and sign

the informed consent. Exclusion criteria included: diagnosis of another connective tissue disease (CTD), organ failure (renal, pulmonary or cardiac), gastric surgery, intestinal malabsorption, pregnancy, breast-feeding, severe infection and severe chronic comorbidities.

Clinical data

Clinical and demographic data were obtained through a direct interview and a review of the electronic register database. Esophageal involvement was considered when patient referred clinical complaint of dysphagia and barium esophagram revealed esophageal hypomotility. Interstitial lung disease was considered when patient presented the characteristic "ground-glass" aspect at the chest high resolution computed tomography. Modified Rodnan skin score (mRSS) was used to determine the extension of the skin involvement, classifying 17 anatomical sites from 0 (no skin involvement) to 3 (severe skin involvement), with maximal score of 51.[21]

Medsger Disease Severity Index (MDSI) was used to determine the SSc severity, defining severity as the total effect of disease on organ function. Scales were developed from 0 (no documented involvement) to 4 (endstage disease) for each organ system: general (weight loss in kg), peripheral vascular (digital vascular ischemia), skin (mRSS), joint/tendon, muscle (weakness), gastrointestinal tract, lung, heart, and kidney.[22] We considered a severe disease when the MDSI was superior to 3, according to previous studies.[16]

Quality of life

Health Assessment Questionnaire (HAQ) disability index (DI), validated to the Brazilian-Portuguese language[23] was applied. It contains 8 domains of activity (dressing, raising, eating, walking, personal hygiene, reach, grip strength, and usual daily activities) each of which has at least two questions, for a total of 20 items. For each item, patients report the amount of difficulty experienced performing the activity. A mean score is calculated for each domain, ranging from 0 (without any difficulty) to 3 (unable to do). A composite HAQ score is calculated by dividing the summed domain scores by the number of domains answered. The composite score is reported, falling between 0 (no impairment in function) and 3 (maximal impairment of function) on an ordinal scale.[24]

The Short Form Questionnaire (SF-36), validated to the Brazilian-Portuguese language,[25] was also applied. The SF-36 consists of 36 items organized into eight health domains measuring physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional aspects, and general mental health.[26] Among these domains, physical functioning, physical role, and bodily pain evaluate only physical dimensions; social functioning, emotional role, and general mental health assess mental aspects; general health perception and vitality evaluate both physical and mental dimensions. In SF-36 domains, scores are rated so that higher values correspond to better conditions and lower scores to worse conditions (range 0–100). The eight domains, weighted according to normative data, are also combined into a physical summary score (PSS) and a mental summary score (MSS), which are scored from 0 to 100, with higher values reflecting better health-related quality of life (HRQOL).[27]

Nailfold capillaroscopy (NC)

In vivo wide field capillary microscopy (10 and 20 magnifications) was performed and graded by the same rheumatologist. All ten digits were examined using a bifocal stereomicroscope (Zeiss, Germany) and lighting with a tungstenium lamp shaded by a green lens in order to have a better visualization. Immersion oil was applied for increasing transparency of the skin and the whole nailfold region was examined, including the edges. The normal findings for Brazilian population were defined as previously described.[28] Abnormal findings were recorded on a standardized data sheet, as follow: number of loops in a linear 1 mm wide, enlargement of capillary loops (absolute number, independently of the size of the limbs), presence of bushy capillaries and the avascular areas (loss of two consecutive loops of nail bed). In this study, it was used the following scores: (1) *Diffuse devascularization* (mean): 0 = normal (≥7 loops/mm); 1 = mild (≥ 6 to <6.9 loops/mm); 2 = moderate (≥4 to <5.9 loops/mm); 3 = severe (<4 loops/mm); (2) *Avascular areas*: 0 = no avascular areas; 1 = 1 or 2 discontinuous avascular areas (>0.3 mm and <0.5 mm); 2 = more than two discontinuous avascular areas (>0.3 mm and <0.5 mm); 3 = extense avascular areas (>0.5 mm); (3) *Capillarectasia*: 0 = rare (<8 capillaries); 1 = mild (8–30 capillaries); 2 = moderate (31–40 capillaries); 3 = severe (>40 capillaries); (4) *Microhemorrhages*: 0 = rare (<3/finger); 1 = mild (≥3 and <6/finger); 2 = moderate (≥6 and <8/finger); 3 = severe (≥8/finger).[29] The SD pattern was defined as the presence of avascular areas or enlarged loops associated with at least one additional SD-parameter (nailfold microhemorrhages, reduced capillary density, enlarged loops and avascular areas).[30]

NC was also classified in "early", "active" and "late" patterns, according to Cutolo et al.[31] "Early pattern": presence of giant capillaries without loss of capillaries, "Active pattern": presence of combination of giant capillaries, loss of capillaries and microhemorrhages. "Late pattern" presence of neoangiogenesis and loss of capillaries.

Laboratory data

Blood was collected in the morning, with a 12-h fasting. Serum and plasma were aliquoted and kept at −80 °C on Bone Metabolism Laboratory of Rheumatology Division, Faculty of Medicine. Laboratory parameters of bone metabolism were measured in all patients: calcium, phosphate, alkaline phosphate, parathormone, 25OHD serum levels and urinary calcium. A radioimmunoassay technique (DiaSorin, Stillwater, MN, USA) with a lower detection limit of 5 ng/mL was used to measure 25-hydroxyvitamin D (25OHD). The intra- and inter-assay variation coefficients in our laboratory were 10.5% and 17.8%, respectively. According to current recommendations, 25OHD concentrations ≤30 ng/mL were defined as insufficiency,[32,33] whereas values ≤10 ng/mL were classified as deficiency.[34]

The profile of autoantibodies for each patient was also obtained: antinuclear antibodies (ANA), anti-DNA topoisomerase I (anti-Scl 70).

Bone mineral density

BMD was analyzed by dual-energy X-ray absorptiometry (DXA; Hologic; QDR 4500, Bedford, MA, USA) of the lumbar region (L1-L4), total and femoral neck. Osteoporosis was defined by a *T* score ≤ -2.5 SD. Body mass index (BMI) was calculated by measuring the weight and height of each patient during interview.

Ethical approval

All patients gave their written informed consent and the study was approved by the Ethics Committee of the University of São Paulo (Research protocol 0294/11).

Statistical analysis

The results are reported as mean ± standard deviation and percentage. The data were analyzed by *t*-test or Mann–Whitney test to access the differences between the groups. Prism program software was used to correlation of Pearson; p values ≤ 0.05 were considered to be significant.

Results

Thirty-eight female patients with diffuse SSc attending the Scleroderma outpatient clinic of our institution were eligible to participate in this study. The mean age was 40.18 ± 7.27 years, and the mean disease duration was 8.25 ± 4.96 years (Table 1). Sixteen patients (42%) were currently using monthly doses of intravenous cyclophosphamide, while 18 (47%) patients referred previous use, and four (11%) had never used it. Among the 18 patients who previously used cyclophosphamide, 15 (39%) were currently using azathioprine and three (8%) were using mycophenolate mofetil. Sixteen patients (42%) also referred previous use of methotrexate.

Among the clinical manifestations, interstitial lung disease (79%), esophageal hypomotility (63%), digital ulcers (63%) and joint involvement (55%) were the most frequent findings. Hand deformities were observed in 21 patients (55%) and subcutaneous calcinosis in 5 patients (13%). Other clinical manifestations of SSc were present in <5% of the patients. Mean mRSS was 6.55 ± 4.67, and mean MDSI was 6.40 ± 2.64 (Table 1).

Osteoporosis (total femur, femoral neck and/or lumbar spine) was found in 37% of the diffuse SSc patients. Mean 25OHD serum levels were 20.66 ± 8.20 ng/mL. Four patients (11%) had levels of 25OHD ≤ 10 ng/mL, 19 patients (50%) had ≤20 ng/mL and 33 patients (87%) had ≤30 ng/mL (Table 1).

Further analysis of vitamin D levels in patients with and without esophageal involvement (20.40 ± 8.23 vs. 21.12 ± 8.43, $p = 0.80$), interstitial lung disease (19.76 ± 7.90 vs. 24.05 ± 8.93, $p = 0.19$), digital ulcers (20.63 ± 8.28 vs. 20.71 ± 8.36, $p = 0.98$), hand deformities (18.70 ± 8.33 vs. 23.09 ± 7.57, $p = 0.10$), joint involvement (19.40 ± 7.74 vs. 22.23 ± 8.71, $p = 0.30$), and calcinosis (17.40 ± 9.61 vs. 21.16 ± 8.02, $p = 0.35$) revealed no association of lower serum levels of this hormone and the different clinical manifestations. Nevertheless, anti-Scl 70 positive patients presented lower levels of vitamin D compared to anti-Scl 70 negative (17.94 ± 7.10 vs. 23.40 ± 8.49, $p = 0.039$).

Table 1 – Anthropometric, clinical, and laboratory parameters in diffuse SSc patients.

Variables	SSc $n = 38$
Age, years (mean ± SD)	40.18 ± 7.27
Disease duration, years (mean ± SD)	8.25 ± 4.96
Modified Rodnan skin score (mean ± SD)	6.55 ± 4.67
Interstitial lungdisease (%)	79
Esophageal hypomotility (%)	63
Digital ulcers (%)	63
Acroosteolysis (%)	61
Joint involvement (%)	55
Calcinosis (%)	13
Pulmonary hypertension (%)	3
Heart (%)	0
Kidney (%)	0
Intestine (%)	0
ANA (%)	100
Anti-Scl70 (%)	50
Medsger Disease Severity Index (mean ± SD)	6.40 ± 2.64
Osteoporosis (%)	37
25OH Vitamin D, ng/mL (mean ± SD)	20.66 ± 8.20
25OH Vitamin D ≤10 ng/mL (%)	11
25OH Vitamin D ≤20 ng/mL (%)	50
25OH Vitamin D ≤30 ng/mL (%)	87
PTH, pg/mL (mean ± SD)	49.87 ± 19.95
PTH ≥ 65 pg/mL (%)	21
Calcium, mg/dL (mean ± SD)	9.22 ± 0.61
24 h urinary calcium (mean ± SD)	107.85 ± 70.47

ANA, antinuclear antibody; SD, standard deviation.

The possible correlations of vitamin D with demographic, bone mineral density and nailfold capillaroscopy data was performed and revealed a positive correlation with weight ($r = 0.333$; $p = 0.041$), BMI ($r = 0.338$; $p = 0.038$), total femur BMD ($r = 0.340$; $p = 0.037$), femoral neck BMD ($r = 0.384$; $p = 0.017$) and fat mass ($r = 0.323$; $p = 0.048$). No correlation was observed between 25OHD with age, disease duration, mRSS and MDSI (Table 2).

All the patients presented the characteristic "SD pattern" and the mean NC score was 5.50 ± 2.29. The mean scores for capillaroscopic characteristics were: diffuse devascularization = 1.71 ± 0.73; avascular areas = 1.92 ± 0.88; capillary ectasia = 0.42 ± 0.76; and microhemorrhages = 0.45 ± 0.92. Eighteen (47%) patients presented "active pattern" and 20 (53%) "late pattern" in NC. There was negative correlation among 25OHD serum levels and diffuse devascularization ($r = -0.355$; $p = 0.029$) and avascular areas ($r = -0.347$; $p = 0.033$) (Table 2).

Mean SF-36 was 53.05 ± 8.71. The analysis of the 8 domains of SF-36 showed a positive correlation among 25OHD serum levels and SF-36-Vitality ($r = 0.385$; $p = 0.017$); SF-36-Social Function ($r = 0.320$; $p = 0.050$); SF-36-Mental Health ($r = 0.531$; $p = 0.0006$); and SF-Emotional Role ($r = 0.321$; $p = 0.049$) (Table 3).

Mean total HAQ was 0.68 ± 0.25. Analysis of the 8 domains revealed a negative correlation of 25OHD serum levels

Table 2 – Correlation of 25OHD with age, weight, height, body mass index (BMI), disease duration, bone mineral density (BMD), nailfold capillaroscopy (NC), Medsger Disease Severity Index (MDSI) and Modified Rodnan Skin Score (mRSS) in 38 diffuse SSc patients.

25OHD	Mean ± SD	Pearson *r*	*p*-Value
Age, years	40.18 ± 7.27	0.289	0.079
Weight, kg	63.78 ± 14.20	0.333	0.041
Height, m	1.58 ± 0.06	0.149	0.373
BMI, kg/m²	25.49 ± 4.96	0.338	0.038
Disease duration, years	8.25 ± 4.96	−0.280	0.088
L1–L4 BMD, g/cm²	0.917 ± 0.163	0.239	0.149
Total femur BMD, g/cm²	0.795 ± 0.167	0.340	0.037
Femoral neck BMD, g/cm²	0.710 ± 0.130	0.384	0.017
Distal radius BMD, g/cm²	0.516 ± 0.071	0.272	0.099
Fat mass, g	23.05 ± 8.17	0.323	0.048
Lean mass, g	38.38 ± 7.11	0.264	0.109
NC			
Diffuse devascularization	1.71 ± 0.73	−0.355	**0.029**
Avascular area	1.92 ± 0.88	−0.347	**0.033**
Capillar ectasia	0.42 ± 0.76	0.114	0.498
Microhemorrhages	0.45 ± 0.92	0.164	0.325
MDSI	6.40 ± 2.64	−0.277	0.092
mRSS	6.55 ± 4.67	0.028	0.866

Table 3 – Correlation of 25OHD with Short Form Questionnaire (SF-36) and Health Assessment Questionnaire (HAQ) in 38 diffuse SSc patients.

25OHD	Mean ± SD	Pearson r	*p*-Value
SF-36			
Physical functioning	51.58 ± 27.46	0.270	0.101
Physical role	42.76 ± 42.28	0.074	0.659
Bodily pain	51.80 ± 27.30	0.245	0.139
General health	49.40 ± 25.30	0.309	0.059
Vitality	48.95 ± 22.73	0.385	0.017
Social function	70.39 ± 26.22	0.320	0.050
Emotional role	48.24 ± 45.65	0.321	0.049
Mental health	61.26 ± 16.35	0.531	0.0006
HAQ			
Dressing	0.82 ± 0.77	−0.231	0.164
Raising	0.54 ± 0.61	−0.293	0.075
Eating	0.58 ± 0.67	−0.042	0.803
Walking	0.32 ± 0.47	−0.154	0.356
Hygiene	0.43 ± 0.53	−0.206	0.214
Reach	1.01 ± 0.80	−0.328	0.044
Grip strength	0.88 ± 0.74	−0.331	0.042
Activities	0.87 ± 0.73	−0.197	0.235

with HAQ-Reach ($r = -0.328$; $p = 0.044$) and HAQ-Grip Strength ($r = -0.331$; $p = 0.042$) (Table 3).

Discussion

This is the first study identifying that vitamin D is significantly correlated with QoL and severe capillaroscopic findings in diffuse SSc. The decision to focus the analysis on diffuse SSc and female gender was important to select a more homogeneous group of patients in a heterogeneous disease as SSc. Considering that limited and diffuse SSc subtypes can present distinct profiles of organ involvement,[20,35] they could affect QoL in a distinct way; in fact, diffuse SSc patients present higher global and local disability, and lower QoL than limited SSc patients.[36] The inclusion of only female gender may be relevant since a possible association of gender with disease clinical expression and anxiety in patients with SSc was reported.[4] In fact, a recent cross-sectional study observed that psychiatric symptoms, particularly anxiety and depression, are more associated with increased disability and altered health-related QoL in SSc patients, than with disease-specific organ manifestations.[8] Moreover, hand deformity, a complication which is known to have a deleterious effect in disability and reduced health-related QoL in SSc,[36] is reported to have a positive association with anti-Scl70 antibody.[37]

We confirmed previous studies showing a high frequency of low levels of 25OHD and higher risk for autoimmune

diseases,[11,12] including diffuse SSc.[13–18] Although there was no association with SSc- specific organ manifestations, there was a statistical association with SSc-specific autoantibody, the anti-Scl70 (a known biomarker of diffuse SSc), which presented lower levels of 25OHD.

Despite recent studies have clearly evidenced a high prevalence of 25OHD deficiency in SSc, its role has not been completely understood in SSc disease pathogenesis. Although it could be advisable to regularly check 25OHD status in these patients, there is no consensus that 25OHD supplementation might be sufficient to modulate immunological homeostasis, and reduce disease activity or severity.[13,14] Several studies about lower serum 25OHD concentrations are linked with various clinical aspects in SSc patients. In our study, the presence of osteoporosis/osteopenia was frequent in our patients and the positive correlation between 25OHD and total femur and femoral neck BMD was also found in the literature, but there is no clear demonstration about the relationship of 25OHD deficiency with low bone mineral density.[15,17,38]

As vitamin D supplementation was not a routine practice for the Outpatient Scleroderma Clinic before this study, no scleroderma patient was previously supplemented with vitamin D.

Importantly, the main causes of vitamin D deficiency, such as intestinal malabsorption, gastrectomy, kidney and liver failure, were exclusion criteria for this study. As in Brazil the seasons are not clearly demonstrated as they are in European and North American countries, the patients participating in this study had their clinical and laboratory evaluation consecutively, from May 2012 to May 2013, regardless of the season. Reduced sun exposure for psychological and social reasons was not evaluated in our study and may contribute to this deficiency in scleroderma patients.[14] Of note, one fourth of patients had high PTH levels, which may reflect secondary hyperparathyroidism associated with a silent malabsorption. In limited SSc, vitamin D deficiency was correlated with hyperparathyroidism and the latter was associated with acroosteolysis.[39]

Another important concern is the interaction among vitamin D and the drugs used in the long term treatment of SSc. Some of these drugs, like cyclophosphamide, calcium channel blockers (ex. nifedipine) and proton-pump inhibitors (ex. omeprazol), which are metabolized through cytochrome P450 3A4 (CYP3A4), could theoretically interfere with vitamin D metabolism.[40] However, there are no specific studies analyzing its effects on bone metabolism in SSc.

Interestingly, this is the first study to reveal the importance of vitamin D for several physical and emotional domains of quality of life in diffuse SSc. Vitamin D was correlated with vitality, social function, mental health and emotional role in SF-36. This finding is further supported by the recent observation in community-based elderly Canadians demonstrating the importance of this hormone in health quality of life.[41] The significant correlation of vitamin D in SSc patients with mental health observed here in is consistent with the hypothesis of a recent systematic review in more than 30,000 adults demonstrating that low vitamin D concentration is associated with depression[42] and also with anxiety in a large community sample.[41]

The novel correlation of low vitamin D with HAQ reach and grip strength domains may be related to the fact that vitamin D improves muscle strength, and its supplementation has a positive effect in mobility and physical function.[43] In fact, higher levels are associated with a better mobility and usual activities performance.[43] In this regard, future studies analyzing hand grip in diffuse SSc will be interesting, since vitamin D status was reported to predict hand-grip strength in young adult women.[44]

The well-established role of capillaroscopy for the early diagnosis of SSc, and its inclusion in the recent ACR/EULAR classification criteria, combined with its potential for monitoring disease progression and treatment response, makes NC an important assessment in clinical practice and research.[31,45] In the present study, as most patients presented late diffuse SSc, the “active” and the “late” capillaroscopic patterns were predominant. We confirmed the negative correlation of 25OHD serum levels and NC – diffuse devascularization and avascular areas,[14] although not associated with lung involvement. This finding raises the hypothesis that low levels of this hormone may contribute to endothelial dysfunction in SSc. In fact, low vitamin D status was associated with arterial dysfunction and vitamin D supplementation was reported to counteract this endothelial alteration in asymptomatic subjects and diabetes patients.[46,47] Current evidence indicates that vitamin D supplementation may have a small to moderate effect on quality of life when used on a short-term basis in diseased populations. However, the evidence for a beneficial effect of long-term vitamin D supplementation on health-related quality of life is lacking.[48–50]

The present study provides novel evidence demonstrating that low levels of 25OHD can contribute to a decreased QoL in patients with diffuse SSc through its association with the underlying vascular involvement (worst capillaroscopic findings) and the autoantibody production (anti-Scl70).

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Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Tyndall AJ, Bannert B, Vonk M, Airò P, Cozzi F, Carreira PE, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis. 2010;69(10):1809–15.

2. Sampaio-Barros PD, Bortoluzzo AB, Marangoni RG, Rocha LF, Del Rio AP, Samara AM, et al. Survival, causes of death, and prognostic factors in systemic sclerosis: analysis of 947 Brazilian patients. J Rheumatol. 2012;39(10):1971–8.
3. Schnitzer M, Hudson M, Baron M, Steele R, Canadian Scleroderma Research Group. Disability in systemic sclerosis – a longitudinal observational study. J Rheumatol. 2011;38(4):685–92.
4. Nguyen C, Bérezné A, Baubet T, Mestre-Stanislas C, Rannou F, Papelard A, et al. Association of gender with clinical expression, quality of life, disability, and depression and anxiety in patients with systemic sclerosis. PLoS ONE. 2011;6(3):e17551.
5. El-Baalbaki G, Razykov I, Hudson M, Bassel M, Baron M, Thombs BD, et al. Association of pruritus with quality of life and disability in systemic sclerosis. Arthritis Care Res (Hoboken). 2010;62(10):1489–95.
6. Sandqvist G, Scheja A, Hesselstrand R. Pain, fatigue and hand function closely correlated to work ability and employment status in systemic sclerosis. Rheumatology (Oxford). 2010;49(9):1739–46.
7. Del Rosso A, Mikhaylova S, Baccini M, Lupi I, Matucci Cerinic M, Maddali Bongi S. In systemic sclerosis, anxiety and depression assessed by hospital anxiety depression scale are independently associated with disability and psychological factors. BioMed Res Int. 2013;2013:507493.
8. Nguyen C, Ranque B, Baubet T, Bérezné A, Mestre-Stanislas C, Rannou F, et al. Clinical, functional and health-related quality of life correlates of clinically significant symptoms of anxiety and depression in patients with systemic sclerosis: a cross-sectional survey. PLOS ONE. 2014;9(2):e90484.
9. Mouthon L. Hand involvement in systemic sclerosis. Presse Med. 2013;42(12):1616–26.
10. Bassel M, Hudson M, Baron M, Taillefer SS, Mouthon L, Poiraudeau S, et al. Physical and occupational therapy referral and use among systemic sclerosis patients with impaired hand function: results from a Canadian national survey. Clin Exp Rheumatol. 2012;30(4):574–7.
11. Orbach H, Zandman-Goddard G, Amital H, Barak V, Szekanecz Z, Szucs G, et al. Novel biomarkers in autoimmune diseases: prolactin, ferritin, vitamin D, and TPA levels in autoimmune diseases. Ann N Y Acad Sci. 2007;1109:385–400.
12. Antico A, Tampoia M, Tozzoli R, Bizzaro N. Can supplementation with vitamin D reduce the risk or modify the course of autoimmune diseases? A systematic review of the literature. Autoimmun Rev. 2012;12(2):127–36.
13. Vacca A, Cormier C, Mathieu A, Kahan A, Allanore Y. Vitamin D levels and potential impact in systemic sclerosis. Clin Exp Rheumatol. 2011;29(6):1024–31.
14. Caramaschi P, Dalla Gassa A, Ruzzenente O, Volpe A, Ravagnani V, Tinazzi I, et al. Very low levels of vitamin D in systemic sclerosis patients. Clin Rheumatol. 2010;29(12):1419–25.
15. Arnson Y, Amital H, Agmon-Levin N, Alon D, Sánchez-Castañón M, López-Hoyos M, et al. Serum 25-OH vitamin D concentrations are linked with various clinical aspects in patients with systemic sclerosis: a retrospective cohort study and review of the literature. Autoimmun Rev. 2011;10:490–4.
16. Avouac J, Koumakis E, Toth E, Meunier M, Maury E, Kahan A, et al. Increased risk of osteoporosis and fracture in women with systemic sclerosis: a comparative study with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2012;64(12):1871–8.
17. Rios-Fernández R, Callejas-Rubio JL, Fernández-Roldán C, Simeón-Aznar CP, García-Hernández F, Castillo-García MJ, et al. Bone mass and vitamin D in patients with systemic sclerosis from two Spanish regions. Clin Exp Rheumatol. 2012;30(6):905–11.
18. Atteritano M, Sorbara S, Bagnato G, Miceli G, Sangari D, Morgante S, et al. Bone mineral density, bone turnover markers and fractures in patients with systemic sclerosis: a case control study. PLoS ONE. 2013;8(6):e66991.
19. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum. 2013;65(11):2737–47.
20. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA Jr, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol. 1988;15(2):202–5.
21. Furst DE, Clements PJ, Steen VD, Medsger TA Jr, Masi AT, D'Angelo WA, et al. The modified Rodnan skin score is an accurate reflection of skin biopsy thickness in systemic sclerosis. J Rheumatol. 1998;25(1):84–8.
22. Medsger TA Jr, Silman AJ, Steen VD, Black CM, Akesson A, Bacon PA, et al. A disease severity scale for systemic sclerosis: development and testing. J Rheumatol. 1999;26(10):2159–67.
23. Ferraz MB, Oliveira LM, Araujo PM, Atra E, Tugwell P. Cross cultural reliability of the physical ability dimension of the health assessment questionnaire. J Rheumatol. 1990;17(6):813–7.
24. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. J Rheumatol. 2003;30:167–78.
25. Ciconelli RM, Ferraz MB, Santos WS, Meinão I, Quaresma MR. Tradução para a língua portuguesa e validação do questionário genérico de qualidade de vida SF-36 (Brasil SF-36). Braz J Rheumatol. 1999;39(3):143–50.
26. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473–83.
27. Del Rosso A, Boldrini M, D'Agostino D, Placidi GP, Scarpato A, Pignone A, et al. Health-related quality of life in systemic sclerosis as measured by the short form 36: relationship with clinical and biologic markers. Arthritis Rheum. 2004;51(3):475–81.
28. Andrade LE, Gabriel A Jr, Assad RL, Ferrari AJL, Atra E. Panoramic nailfold capillaroscopy: a new reading method and normal range. Semin Arthritis Rheum. 1990;20(1):21–31.
29. Diógenes AHM, Bonfa E, Fuller R, Correia Caleiro MT. Capillaroscopy is a dynamic process in mixed connective tissue disease. Lupus. 2007;16(4):254–8.
30. Maricq HR. Widefield capillary microscopy technique and rating scale for abnormalities seen in scleroderma and related disorders. Arthritis Rheum. 1981;24(9):1159–65.
31. Cutolo M, Sulli A, Smith V. How to perform and interpret capillaroscopy. Best Pract Res Clin Rheum. 2013;27(2):237–48.
32. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. Osteoporos Int. 2005;16(7):713–6.
33. Hollis BW, Wagner CL. Normal serum vitamin D levels [letter]. N Engl J Med. 2005;352(5):515–6.
34. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357:266–81.
35. Steen VD, Medsger TA Jr. Severe organ involvement in systemic sclerosis with diffuse scleroderma. Arthritis Rheum. 2000;43(11):2437–44.
36. Maddali-Bongi S, Del Rosso A, Mikhaylova S, Francini B, Branchi A, Baccini M, et al. Impact of hand and face disabilities on global disability and quality of life in systemic sclerosis patients. Clin Exp Rheumatol. 2014;32 6 Suppl. 86:S15–20.
37. Foocharoen C, Suwannachat P, Netwijitpan S, Mahakkanukrauh A, Suwannaroj S, Nanagara R, the Scleroderma Research Group. Clinical differences between

Thai systemic sclerosis patients with positive versus negative anti-topoisomerase I. Int J Rheum Dis. 2016;19:312–20.
38. Corrado A, Colia R, Mele A, Di Bello V, Trotta A, Neve A, et al. Relationship between body mass composition, bone mineral density, skin fibrosis and 25(OH) vitamin D serum levels in systemic sclerosis. PLOS ONE. 2015;10(9):e0137912.
39. Braun-Moscovici Y, Furst DE, Markovits D, Rozin A, Clements PJ, Nahir AM, et al. Vitamin D, parathyroid hormone, and acroosteolysis in systemic sclerosis. J Rheumatol. 2008;35(11):2201–5.
40. Robien K, Oppeneer SJ, Kelly JA, Hamilton-Reeves JM. Drug-vitamin D interactions: a systematic review of the literature. Nutr Clin Pract. 2013;28(2):194–208.
41. Chao YS, Ekwaru JP, Ohinmaa A, Griener G, Veugelers PJ. Vitamin D and health-related quality of life in a community sample of older Canadians. Qual Life Res. 2014;23(9):2569–75.
42. Anglin RE, Samaan Z, Walter SD, McDonald SD. Vitamin D deficiency and depression in adults: systematic review and meta-analysis. Br J Psychiatry. 2013;202:100–7.
43. Bunout D, Barrera G, Leiva L, Gattas V, de la Maza MP, Avendaño M, et al. Effects of vitamin D supplementation and exercise training on physical performance in Chilean vitamin D deficient elderly subjects. Exp Gerontol. 2006;41(8):746–52.
44. von Hurst PR, Conlon C, Foskett A. Vitamin D status predicts hand-grip strength in young adult women living in Auckland, New Zealand. J Steroid Biochem Mol Biol. 2013;136:330–2.
45. Ingegnoli F, Gualtierotti R. A systematic overview on the use and relevance of capillaroscopy in systemic sclerosis. Expert Rev Clin Immunol. 2013;9(11):1091–7.
46. Tarcin O, Yavuz DG, Ozben B, Telli A, Ogunc AV, Yuksel M, et al. Effect of vitamin D deficiency and replacement on endothelial function in asymptomatic subjects. J Clin Endocrinol Metab. 2009;94(10):4023–30.
47. Shab-Bidar S, Neyestani TR, Djazayery A, Eshraghian MR, Houshiarrad A, Gharavi A, et al. Regular consumption of vitamin D-fortified yogurt drink (Doogh) improved endothelial biomarkers in subjects with type 2 diabetes: a randomized double-blind clinical trial. BMC Med. 2011;9:125.
48. Hoffmann MR, Senior PA, Mager DR. Vitamin D supplementation and health-related quality of life: a systematic review of the literature. J Acad Nutr Diet. 2015;115(3):406–18.
49. Lima GL, Paupitz J, Aikawa NE, Takayama L, Bonfa E, Pereira RM. Vitamin D supplementation in adolescents and young adults with juvenile systemic lupus erythematosus for improvement in disease activity and fatigue scores: a randomized, double-blind placebo-controlled trial. Arthritis Care Res. 2016;68(1):91–8.
50. Hussin AM, Ashor AW, Schoenmakers I, Hill T, Mathers JC, Siervo M. Effects of vitamin D supplementation on endothelial function: a systematic review and meta-analysis of randomised clinical trials. Eur J Nutr. 2016, http://dx.doi.org/10.1007/s00394-016-1159-3 [Epub ahead of print].