# Bone mass and vitamin D in patients with systemic sclerosis from two Spanish regions

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## Abstract

### Objective

*To study the bone mass in patients with scleroderma (SSc) from two different Spanish regions and to evaluate the prevalence of vitamin D deficiency and insufficiency in this population and its possible relation to bone mineral density (BMD).*

### Methods

*Disease, bone mineral density related variables and vitamin D were collected from all patients. Statistical analysis was carried out using the SPSS 17 statistics software for Windows. A $p<0.05$ was considered significant.*

### Results

*A Z-score <-1 was found in 21.9% of the control population and 43% of SSc patients. The prevalence of osteopenia/osteoporosis was 50% in the control population and 77% in SSc ($p<0.0001$). We did not find differences between the prevalence of low BMD in the south (79%) and in the north of Spain (76.3%); but patients from the north had lower levels of vitamin D (27.4±16.2 ng/dL vs. 20.7±11.0 ng/dl; $p<0.031$). Low levels of vitamin D (<30ng/ml) were found in 69 patients out of 90, ten of them with insufficiency (<10ng/ml). Eighty-four point six percent of the patients with low levels of vitamin D (<30ng/ml) had LBMD compared whith 66.7% of those with normal levels ($p=0.073$).*

### Conclusions

*The prevalence of osteoporosis/osteopenia in Spanish patient with SSc is very high. Although there are a high prevelence of vitamin D deficiency, we could not demonstrate a relationship of vitamin D deficiency with low mineral density.*

**Key words**

systemic scleroderma, limited scleroderma, diffuse scleroderma, osteoporosis, vitamin D

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## Introduction

Systemic sclerosis (SSc) is a disease of unknown etiology characterised by vascular injury, autoimmune phenomena and fibrosis. In recent decades, researchers have focused on some manifestations of the disease that do not increase mortality, but are associated with significant morbidity. One of these complications is osteoporosis (OP). There are few studies about bone mineral density in patients with SSc, and there is conflicting evidence as to whether or not an association between SSc and decreased bone mineral density (BMD) exists. Some researchers have postulated that prevalence of osteoporosis is higher in SSc (1, 2); however, there is no robust evidence in the literature proving lower bone mass or alterations in bone mineral metabolism in SSc patients. The clinical heterogeneity and small sample size of the different studies conducted have contributed to the difficulty in obtaining valid estimates of the risk for the development of OP in patients with SSc.

Bone density is influenced by a number of factors, incluiding peak bone mass and the ongoing balance between new bone formation and bone resorption throughout life. Peak bone mass and bone metabolism are not only affected by genetic factors, but also by physiological environmental and modifiable lifestyle factors. Postmenopausal status and advanced age account for approximately 80% of the cases of osteoporosis (3). In addition to the osteoporosis risk factors in the general population, there are other specific risk factors in patients with SSc. Besides subcutaneous calcinosis, assumed to have been drawn, to some degree, from the body calcium stores (*i.e.* from the skeleton), it has been hypothesised that patients with SSc may be osteopenic as a result of chronic inflammation, chronic ischaemia, immobilisation, occult malabsorption or malnutrition, glucocorticosteroid or immunosuppressive therapy, and early menopause (4). Additionally, the potential role of other factors – such as a deficit of vitamin D – is unclear. Among the general population, the association of vitamin D deficiency with osteoporosis is well known. Vitamin D exerts important effects on calcium metabolism and bone homeostasis. The prevalence of deficient vitamin D levels is high, even in Mediterranean countries (5). Low vitamin D levels have also been reported in patients with SSc (6, 7). In Granada (Spain), a sunny Andalucian city (37°11" north latitude) with 3016 hours of sunlight per year, we found that 39.1% of postmenopausal women with SSc had levels of vitamin D <15 ng/ml (8).

The aim of this study was: (i) to examine whether bone mass is lower in patients with SSc, as compared with healthy people; (ii) to study the prevalence of low mineral bone density in patients with SSc in two different regions in Spain; (iii) to investigate the relation of clinical variables with bone mineral density (BMD); (iv) to evaluate the prevalence of vitamin D deficiency and insufficiency among this population, and its possible relation with bone mineral density (BMD); and finally, (v) to identify clinical features associated with vitamin D levels in patients with SSc.

## Patients and methods

We analysed the clinical history of patients with SSc consecutively attended between September 2009 and March 2010 in three University Hospitals (Hospital Clínico San Cecilio of Granada and Hospital Universitario Virgen del Rocío of Seville, in the south of Spain, and Hospital Vall d'Hebron of Barcelona, in the north of Spain) on an outpatient basis, if they had a bone density test done in the past year. If the patient had no density test done we did it. We used the LeRoy and Medsger criteria for the classification of SSc (9).

Age, sex, age at onset, time of disease, subtype of SSc, clinical manifestations (Raynaud, calcinosis, digital ulcers, telangiectasia, osteomuscular, digestive, lung, kidney and cardiac involvement; interstitial lung disease, pulmonary hypertension, pericarditis, Sicca syndrome), creatinine levels, autoantibody profile (antinuclear [ANA], anticentromere [ACA], anti-Scl70 [ATA], anticardiolipin), type of treatment (specially administration of glucocorticosteroid, calcium and vitamin D supplements), 25-OH vitamin D levels (measured

**Table I.** Clinical and demographic characteristic of patients with SSc and controls.

| Variable | Control n=100 | SSc n=100 | *p*-value |
|---|---|---|---|
| Age (years, mean± SD) | 56.05 ± 11.1 | 56.49 ± 13.3 | ns |
| Female sex (%) | 100 | 100 | ns |
| Menopause (%) | 76 | 76 | ns |
| Body height (cm) | | 155.5 ± 6 | ns |
| Body weight (kg) | | 66.3 ± 12.8 | ns |
| Raynaud (%) | | 98 | ns |
| Calcinosis (%) | | 21 | ns |
| Digital ulcers (%) | | 44 | ns |
| Telangiectasia (%) | | 74 | ns |
| Osteomuscular involvement (%) | | 36 | ns |
| Digestive involvement (%) | | 81 | ns |
| Lung involvement (%) | | 53 | ns |
| Interstitial lung disease (%) | | 27 | ns |
| VFC (mean± SD) | | 94.7 ± 23.2 | ns |
| Pulmonary hipertension* (%) | | 32 | ns |
| Heart involvement (%) | | 36 | ns |
| Pericarditis (%) | | 7 | ns |
| Kidney involvement (%) | | 4 | ns |
| S. Sicca (%) | | 45 | ns |
| DLCO (%,mean± SD) | | 73.7 ± 21.8 | ns |
| PAPs (mm Hg, mean± SD) | | 34.6 ± 12.6 | ns |
| Creatinine (mg/dL, mean± SD) | | 0.8 ± 0.2 | ns |
| Anticardiolipin/ANA/ACA/ATA | | 6/93/53/12 | ns |
| Glucocorticosteroids therapy (%) | | 17 | ns |
| Calcium and vitamin D supplements (%) | | 58 | ns |
| Levels of vitamin D (ng/ml, mean± SD) | | 24.6 ± 14.6 | ns |
| LS T-score (mean± SD) | -0.7 ± 1.4 | -1.4 ± 1.4 | 0.000 |
| FN T-score (mean± SD) | -0.9 ± 1.1 | -1.3 ± 1.4 | 0.022 |
| LS Z-score (mean± SD) | 0.3 ± 1.2 | -0.3 ± 1.5 | 0.001 |
| FN Z-score (mean± SD) | 0.2 ± 1.1 | -0.3 ± 1.2 | 0.001 |

VFC: forced vital capacity; DLCO: Lung diffusion capacity for CO; LS: lumbar spine; PAPs: pulmonary artery systolic pressure; FN: femoral neck.
*Pulmonary hypertension was defined as a systolic pulmonary arterial pressure (PAPs) ≥40 mm Hg when resting, measured by echocardiography.

**Table II.** Differences between patients from the north and the south of Spain.

| Variables | South of Spain | North of Spain | *p*-value |
|---|---|---|---|
| Systemic sclerosis forms (%) | | | |
| lSSc | 55 | 21 | <0.001 |
| dSSc | 8 | 10 | |
| ssSSc | 1 | 7 | |
| Creatinine (mg/dL)* | 0.8 ± 0.2 | 0.9 ± 0.2 | <0.005 |
| Lung involvement (%) | 18 | 35 | <0.0001 |
| FVC (%)* | 102.9 ± 20.4 | 82.5 ± 21.8 | <0.006 |
| DLCO (%)* | 81.3 ± 22.6 | 62.2 ± 14.6 | <0.001 |
| Heart involvement (%) | 12 | 24 | <0.0001 |
| Calcium and vitamin D supplements (%) | 34 | 22 | 0.863 |
| Vitamin D levels (ng/dL)* | 27.4 ± 16.2 | 20.7 ± 11 | <0.031 |
| Vitamin D levels low/normal (%) | 35/17 | 34/4 | <0.014 |

*Results are shown as mean (SD),
lSSc: limited SSc; dSSc: diffuse SSc; ssSSc: sine scleroderma SSc.

by RIA), T-score, and Z-score in lumbar spine (LS) and femoral neck (FN) (measured with Hologic QDR-4000) were gathered as bone mineral density indicators for all patients. Lung diffusion capacity for CO (DLCO) and forced vital capacity (FVC) were collected as pulmonary function test. Pulmonary artery systolic pressure (PAPs) was calculated by echocardiography. With respect to bone mass, a T-score >-1 was considered normal bone mineral density (NBMD), a T-score <-1SD was defined as low bone mineral density (LBMD) (osteopenia if T-score was between -1 SD and -2.5 SD and osteoporosis if T-score <-2.5 SD). A Z-score <-1 was considered as low bone density for the age (LZ). According to current recommendations, levels of less than 10 ng/ml (25 nmol/L) of 25-OH vitamin D were considered as vitamin D insufficiency; levels of 25VitD from 10–29 ng/ml (25–72 nmol/L) as vitamin D deficiency, and levels of 30 ng/ml (75 nmol/L) or above were considered adequate (10).

The control group consisted of 100 healthy women (medical personnel), with the same menopausal status and age (same menopausal status and same age±2 years).

The statistical analysis was carried out using the SPSS 17 statistics software for Windows. The chi-square test and student's *t*-test were used to compare qualitative and quantitative variables respectively. Simple lineal regression was used to examine the relationship between vitamin D levels and various variables. Multiple logistic regresssion analysis was used to examine the relationship between bone mineral density and clinical and laboratory data. The multivariate lineal regression model was used to examine the relationship between vitamin D deficiency and clinical and laboratory data. A $p<0.05$ was considered significant.

## Results

One hundred patients were included in the study. All of them were women with a mean age of 56.49±13.3 years; 76% were postmenopausal. The time course of the disease was 15.4±10.9 years. Patient clinical characteristics are shown in Table I. Seventy-four patients had limited scleroderma (lSSc), 18% had diffuse scleroderma (dSSc) and 8% were clasificated as patients with SSc sine scleroderma (ssSSc). The limited form of the disease prevails in the two regions analysed, although in the north there were more patients with the dSSc form of the disease (probably because in this hospital are treated seriously ill patients referred from other smaller hospitals all over Spain), which prob-

ably explains the differences found in other variables (Table II). The mean age of the control population was 56.1±11.1 years (76% postmenopausal).

Our patients had a mean Z-score of -0.3±1.5 SD LS and -0.3±1.2 in FN. In the control population the mean Z-score was 0.3±1.2 in LS and 0.2±1.1 in FN ($p$=0.001). In percentage terms, a Z-score <-1 was found in 21.9% of the control population and in 43% of SSc patients (30 patients in LS; 30 patients in FN, [$p$=0.001]).

The SSc population had a mean T-score of -1.4±1.4 SD in LS and -1.3±1.4 SD in FN. The control population had a mean T-score of -0.7±1.4 ($p$<0.0001) in LS and -0.9±1.1 ($p$=0.022) in FN. The prevalence of osteopenia/osteoporosis was different in the two populations, globally ($p$<0.0001) and in FN ($p$=0.005) and LS ($p$<0.0001) (Fig. 1, Table A).

When we analysed the two Spanish populations, we did not find any differences in the prevalence of LBMD between the south (79%) and the north of Spain (76.3%), but patients from the north had lower levels of vitamin D (27.4±16.2 ng/dL *vs*. 20.7±11.0 ng/dl; $p$<0.031).

There were significant differences in the demographic and clinical characteristics of patients with NBMD and LBMD (Table III). The patients with LBMD were older, with a longer course of disease; most of them were postmenopausal and took calcium and vitamin D supplements. Patients taking glucocorticosteroids did not show a major rate of osteoporosis/osteopenia than those not taking supplementation.

When we analysed bone mass in terms of Z-score, in order to adjust for age, LZ was more prevalent in patients with dSSc or ssSSc, with digital ulcers, Scl70 (+) and worse FVC and DLCO (Table IV). In the multivariate study, we only found a positive correlation for age ($p$<0.009) and DLCO with LZ ($p$<0.004).

In 90 patients we could obtain 25-OH vitamin D levels. Low levels of vitamin D (<30ng/ml) were found in 69 patients, ten of which had insufficiency (<10ng/ml), despite the fact that 58.9% of our patients were receiving "conventional"

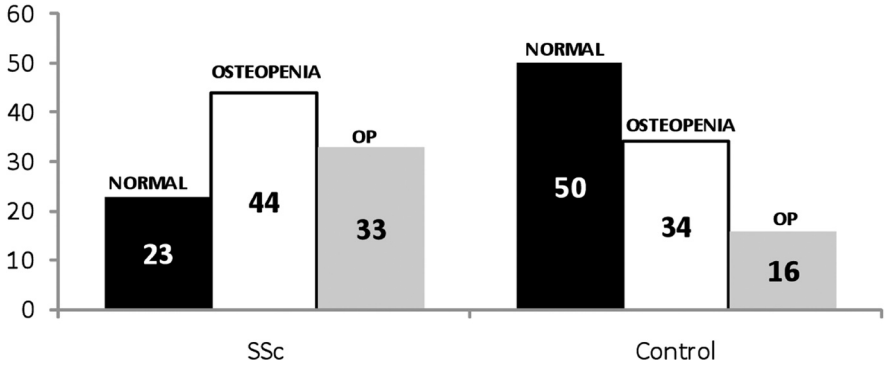


**Fig 1.** Percentage of osteoporosis and osteopenia, in lumbar spine and femoral neck, in patients with SSs *vs*. controls. OP: osteoporosis. SSc patients had a higher frequency of osteoporosis and osteopenia; $p$=0.000

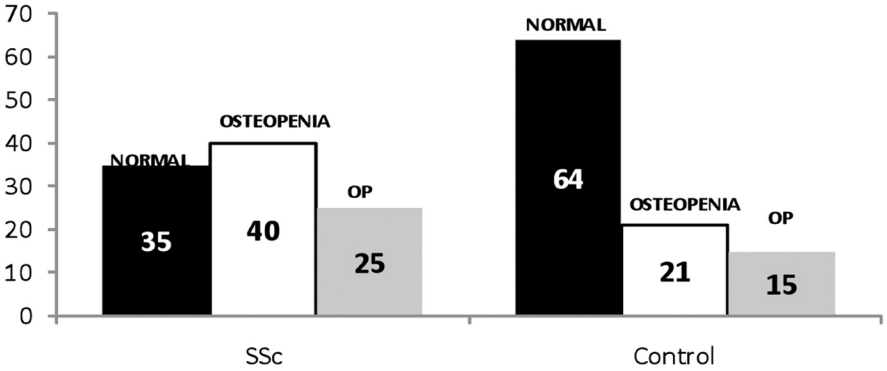


**Fig 1a.** Percentage of osteoporosis and osteopenia, in lumbar spine (LS), in patients with SSs *vs*. controls. OP: osteoporosis. SSc patients had a higher frequency of osteoporosis and osteopenia in LS than controls; $p$=0.000.

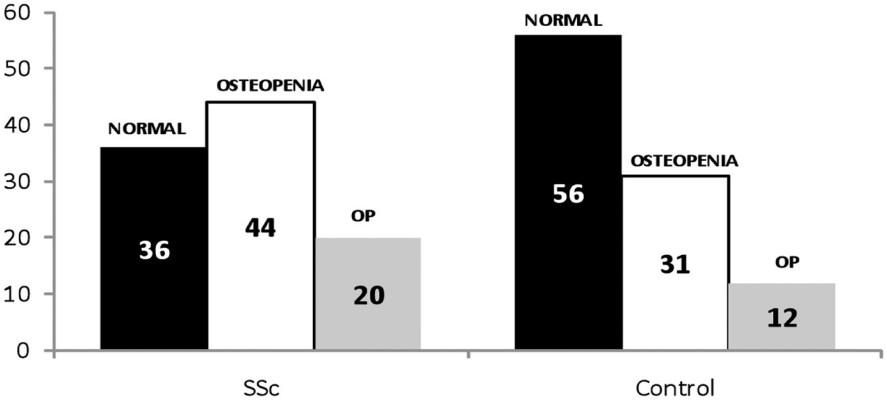


**Fig 1b.** Percentage of osteoporosis and osteopenia, in femoral neck (FN), in patients with SSs *vs*. controls. OP: osteoporosis. SSc patients had a higher frequency of osteoporosis and osteopenia in LS than controls; $p$=0.005.

**Table A.** Percentage of osteoporosis and osteopenia, in lumbar spine (LS) and femoral neck (FN) in patients with SSc *vs*. controls

| | SSc | | | Control | | | *p*-value |
|---|---|---|---|---|---|---|---|
| | Nomal (%) | Osteopenia (%) | Osteoporosis (%) | Normal (%) | Osteopenia (%) | Osteoporosis (%) | |
| LS and FN | 23 | 44 | 33 | 50 | 34 | 16 | 0.000 |
| LS | 35 | 40 | 25 | 64 | 21 | 15 | 0.000 |
| FN | 36 | 44 | 20 | 56 | 31 | 12 | 0.005 |

**Table III.** Differences in clinical characteristics between patients with low bone mineral density (LBMD) and normal bone mineral density (NBMD).

| Variables | LBMD | NLBMD | *p*-value |
|---|---|---|---|
| Age (years)* | 58.4 ± 13.2 | 49.7 ± 11.6 | <0.006 |
| Course of disease (years)* | 16.3 ± 11.6 | 11.4 ± 6.3 | <0.012 |
| Postmenopausal (%) | 63 | 13 | <0.048 |
| Creatinine mg/dL* | 0.9 ± 0.2 | 0.8 ± 0.1 | <0.007 |
| Calcium and vitamin D supplements (%) | 50 | 8 | <0.028 |
| SSc/control (frequency) | 22/50 | 78/50 | =0.000 |

*Results are shown as mean (SD).
LBMD low bone mineral density, NLBMD non low bone mineral density.

**Table IV.** Differences in clinical characteristics between patients with low bone mineral density for age (LZ) and normal bone mineral density for age (NZ).

| Variables | LZ | NZ | *p*-value |
|---|---|---|---|
| Age (years)* | 52.8 ± 14.4 | 59 ± 12 | <0.022 |
| Subtype of SSc(%) | | | <0.008 |
| Limited | 24 | 50 | |
| Diffuse | 12 | 6 | |
| Sine SSc | 6 | 2 | |
| Ulcers (%) | 23 | 18 | <0.032 |
| Scl70+(%) | 9 | 2 | <0.008 |
| FVC (%)* | 85.1 ± 30 | 98 ± 18.8 | <0.022 |
| DLCO(%)* | 63.4 ± 20.3 | 77.8 ± 23.2 | <0.04 |

*Results are shown as mean (SD).
LZ low bone mineral density for age, NLMDA normal bone mineral density for age.

**Table V.** Variables associated with 25VitD levels.

| Variables | $R^2$ | β | *p*-value |
|---|---|---|---|
| Age | 0.003 | -0.057 | 0.596 |
| Calcinosis | 0.052 | 0.228 | <0.034 |
| Heart involvement | 0.072 | -0.268 | <0.012 |
| DLCO (%) | 0.073 | -0.269 | <0.017 |
| ANA (+) | 0.085 | -0.291 | <0.006 |
| Calcium and vitamin D supplements | 0.005 | 0.074 | 0.563 |

DLCO: Lung diffusion capacity for CO; ANA: antinuclear antibodies.

vitamin D supplementation (cholecalciferol 400-800 IU/day). The prevalence of vitamin D deficiency was analysed separately in patients on supplements and in patients without supplements and we did not find any diferences (52% *vs*. 66.7%).

A total of 84.6% of the patients with low levels of vitamin D (<30ng/ml) had LBMD, contrasting with 66.7% of those with normal levels ($p$=0.073). Significant lineal regression between vitamin D levels and clinical and biochemical variables is shown in Table V. Of interest was that, in addition to age, heart involvement, positive ANA and low DLCO were associated with low levels of vitamin D. Only PAPs ($p$<0.034) and cardiac involvement ($p$<0.003) were significant in the multivariate analysis, which was adjusted to vitamin D supplementation too.

## Discussion

To avoid the influence of age, we used the Z-score to evaluate BMD, and the results obtained showed that SSc patients had lower bone mass than healthy population. This lower bone mass is observed in both, cortical and trabecular bone. These results are difficult to compare with others in the literature, because most of them express BMD as g/cm$^2$. There is discrepancy in the literature about bone mineral density in patients with SSc. Some authors have found (1, 3, 11-14) lower bone mass in SSc patients than in controls, but others, like Da Silva (15) and Neumann (17), did not find any differences in bone mass of spine, proximal femur and total body, as compared with age-matched controls; Carbone *et al*. (16) showed a significant reduction of BMD in the total hip, but they did not find any significant differences in the lumbar spine. Although the design of most of these studies is case-control, most of them are not broad enough to detect any real BMD differences between subjects with SSc and controls. In addition, it is very difficult to compare studies, because of the different sample sizes, the wide age range (from 21 to 62 years), the different time course of the disease, and because some studies included only females, while others included females and males (4).

The prevalence of osteoporosis/osteopenia must be considered in terms of age, menopausal status and origin of the population. This explains the diversity that exists in literature. Serup *et al*. (3), in a SSc population of males and females with a mean age of 55.7 (20-69) years, found that 37% of their patients had osteopenia; in a population of 99 SSc females, La Montagna *et al*. (13) found that 35% had osteopenia (22% in lSSc and 13% in dSSc); in a female population of 30 patients, Neumann *et al*. (17) found that 3% had osteoporosis and 36.7% had osteopenia. In a female population of 61 patients aged between 25-51 years, Sampaio Barros *et al*. (11) found that 44.3% of patients had osteopenia and 23% had osteoporosis. Finally, in 129 patients (females and males aged 62.2±10.7 years) with SSc, Yuen *et al*. (18) found that 39.3% had osteoporosis. The prevalence of osteoporosis/osteopenia found in our patients was higher than that described in literature, probably because our population is mostly postmenopausal.

In our study, the variables associated with LBMD statistically significant, were age, time course of the disease, menopausal status, and the presence of SSc. That the administration of calcium and vitamin D supplements was

found to be associated with LBMD is explained by the fact that patients with LBMD were more likely to receive treatment with these medications, because the study was conducted in terms of clinical practice.

More interest has the analysis of the factors associated with LZ in relation with the Z-score. Patients with LZ suffered more often from digital ulcers and lung involvement, and also had Scl-70 antibodies, as compared with patients with NZ. Sampaio-Barros *et al*. (11) found LBMD in infertile and postmenopausal SSc patients. Similarly, they found that the SSc subtype, race, previous use of glucocorticosteroids and cyclophosphamide were independent variables to develop LBMD; Frediani *et al*. (1) found that BMD was reduced in women with dSSc and in women with one or more internal organs affected; and Di Munno *et al*. (12) found a relation between the diffuse form and the time course of the disease, and LBMD. The presence of calcinosis was not found to have any effect on BMD (12). In summary, patients with more severe forms of the disease appear to be at higher risk of suffering low bone mass.

As regards vitamin D, the results obtained showed that low vitamin D levels are very common in Spanish SSc patients. This is consistent with the findings by other authors in other countries; Vacca *et al*. (7) found that 84% of patients had vitamin D values <30 ng/ml, and 28% had values <10 ng/ml, while among our patients 76.7% had values <30 ng/ml, and 11.1% had <10 ng/ml (vit D). Patients from the south of Spain had higher levels of vitamin D, probably because in the north of Spain there is much less incidence of UVB during winter months, which increases the risk of vitamin D deficiency (19).

When we analysed the relationship between vitamin D levels and BMD, we found that patients with vitamin D deficiency showed lower BMD, although the association was not statistically significant, probably due to the number of patients studied.

The role of vitamin D in autoimmune diseases remains unclear. Evidence from large prospective studies in patients with rheumatoid arthritis -an undifferentiated connective tissue disease, multiple sclerosis and type 1 diabetes suggest an important role of vitamin D as a modifiable environmmental factor in autoimmune diseases (20-24). Vitamin D affects the immune system at many levels and with different mechanisms; thus deficiency might influence the development of a more active disease (25). Several studies have addressed vitamin D deficiency in SLE, RA and Behçet's patients (20, 23). In SSc patients, vitamin D deficiency is probably multifactorial. Abnormal absorption of calcium and vitamin D, sedentary habits, poor sun exposure, decreased activation of vitamin D in the altered fibrotic skin (26), renal failure, and decreasing vitamin D hydroxylation are findings that can influence vitamin D levels in these patients. However, findings regarding a potential correlation between vitamin D deficiency and disease activity in SSc patients have been inconclusive, due to the small sample size and the cross-sectional nature of most studies. In our study, lower vitamin D levels were found in older patients and in those patients with a more aggressive disease. But, to demonstrate that higher levels of vitamin D have a beneficial role in the course of the disease, prospective cohort studies should be undertaken.

It is important to note that conventional vitamin D supplementation (400-800 U/d of colecalcifediol) was inefficient in getting adequate vitamin D levels in most cases

Our study has some limitations. The design was cross-sectional and was done in terms of clinical practice. Patients with bone densitometry scan may have more risk factors for osteoporosis. But, in our clinical practice, we usually perform a bone density test in all patients with SSc, and the fact that patients were included in a consecutive form could minimise the selection bias. On the other hand, we did not determine the biochemical markers of bone metabolism, so we cannot know whether the observed osteoporosis can be a problem of bone formation or resorption.

In conclusion, the prevalence of osteoporosis in Spanish patients with SSc is very high. It seems to be more frequent in patients with a more severe expression of the disease. Although there is a high prevalence of vitamin D deficiency, we could not demonstrate that a relationship exists between vitamin D deficiency and low mineral density, probably due to the limited sample size of the study. The role of vitamin D in the development of SSc manifestations, if any, remains unclear, and further investigations are necessary to clarify it.

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