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Are the clinical phenotypes of systemic sclerosis determinant for osteoporosis and fragility fractures?

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Abstract

Aim Systemic sclerosis (SSc) is associated with an increased risk of osteoporosis and fractures. The aim of this single-center cross-sectional study was to evaluate whether clinical phenotype and nailfold videocapillaroscopy (NVC) pattern could influence bone mineral density (BMD) values and fragility fractures in patients with SSc.

Methods A cohort of 84 consecutive outpatients (age 63.7 ± 13.7 years) diagnosed with SSc, 43 classified as diffuse cutaneus SSc (dSSc) and 41 as limited cutaneus SSc (lSSc), were enrolled in the study. All patients underwent BMD by Dual Energy X-ray Absorptiometry (DX, pulmonary function tests for diffusing capacity of carbon monoxide (DLCO), and NVC to be assigned to an "early," "active," or "late" pattern.

Results Patients with dSSc exhibited significantly lower BMD values compared to those with lSSc; moreover, the prevalence of osteoporosis and major osteoporotic fractures were higher in dSSc than in lcSSc (39,6% and 41,9% vs. 29,2% and 34,1%, respectively). Patients with a "late" or "active" NVC pattern had a more marked reduction in BMD with respect to those with a "early" pattern ($p < 0.05$). Moreover, patients with dSSc showed a greater reduction in DLCO values compared to those with lSSc in all three capillaroscopic patterns ($p < 0.05$). DLCO reduction and history of previous fracture were independent predictors of total hip BMD in dSSc patients.

Conclusion Patients with SSc, and particularly those with a "diffuse" phenotype, have a high prevalence of osteoporosis and major osteoporotic fractures. Furthermore, in both SSc phenotypes, the presence of an "active" or "late" capillaroscopic pattern was associated with reduced BMD and DLCO values.

Keywords Systemic sclerosis, Nailfold videocapillaroscopy, Osteoporosis, Fracture, Vitamin D, DLCO

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Introduction

Systemic sclerosis (SSc) is a rare inflammatory disease of the connective tissue, with a chronic and progressive course, autoimmune pathogenesis and multifactorial etiology. SSc predominantly affects women of childbearing age and, despite progress in therapy, remains one of the rheumatic diseases with the highest mortality rate [1, 2]. Systemic sclerosis is characterized by vascular lesions of a proliferative and obliterative nature of the small vessels and progressive fibrosis with involvement of the dermis, subcutaneous tissue and connective stroma [2, 3]. The marked heterogeneity of clinical manifestations of this rare disease creates difficulties for clinicians in accurately categorizing the condition, particularly concerning the involvement of internal organs [4, 5].

SSc can manifest in various phenotypes characterized by specific clinical manifestations and antibody patterns. The two phenotypes into which SSc patients are commonly divided are limited SSc, with skin involvement limited to the distal extremities, slow evolution and onset preceded by the onset of Raynaud's phenomenon, and diffuse SSc characterized by rapid evolution, the skin lesions much more widespread and visceral involvement [2–7]. Visceral involvement may primarily affect the gastrointestinal tract, lungs, heart, and kidneys. Musculoskeletal involvement (arthralgia, erosions, ankylosis) also occurs frequently with a prevalence of 24–97% and represents an important cause of disability [8]. Bone involvement has been reported in numerous studies and is a major cause of morbidity in patients with SSc. In fact, most studies, although not all, have documented that patients with systemic sclerosis have a higher prevalence of osteoporosis and an increased risk of fracture compared to healthy subjects [9–14]. Multiple factors such as chronic inflammation, immobilization, premature menopause, use of cyclophosphamide, proton-pump inhibitors and glucocorticoids, vitamin D deficiency (due to altered cutaneous metabolism and intestinal malabsorption) result in bone loss, thereby contributing to development of osteoporosis [15, 16]. Other studies conducted using High-Resolution peripheral Quantitative Computed Tomography (HR-pQCT) or Trabecular Bone Score (TBS) have also documented the presence of alterations in bone microstructure in patients with SSc [12, 17, 18].

Nailfold-vidoecapillaroscopy (NVC) is the gold standard for the evaluation of microangiopathy in SSc. The typical capillaroscopic alterations have been classified into three distinct groups: early or initial pattern, with few enlarged/giant capillaries, few capillary haemorrhages and no evident loss of capillaries; active pattern, characterized by megacapillaries and microhemorrhages; late or advanced pattern, with a total disorganization of the capillary architecture, with extensive avascular areas [19, 20]. More recently several studies have reported that progressive capillaroscopic changes as assessed by NVC are associated to the severity of the internal organs impairment, such as the lung, heart and digestive system [21–25]. There are relatively few studies to date on the relationship between capillaroscopic patterns and bone status in the different clinical phenotypes of SSc. Furthermore, guidelines on the management of bone involvement in these patients are lacking.

The aim of this cross-sectional study conducted at a single center was to evaluate the potential impact of clinical phenotype and nailfold videocapillaroscopy pattern on bone mineral density and the occurrence of major fragility fractures in patients with systemic sclerosis.

Methods

Patients

A cohort of 84 consecutive Caucasian outpatients (77 women and 7 men, age range 40–85 years; mean age 63.7 ± 13.7 years), affected by systemic sclerosis and referred to the Scleroderma Unit at the University Hospital of Siena (Italy) between January 2021 and June 2023 were enrolled in the study. Each patient underwent a structured medical interview (including detailed questions on smoking history, concomitant diseases, etc.); additionally, SSc-specific internal organ involvement including interstitial lung disease, gastrointestinal involvement, scleroderma renal crisis was investigated. Information about therapy was collected from patient interviews and medical records. All SSc patients met ACR/EULAR 2013 criteria for SSc [26]. In accordance with the Le Roy criteria 43 patients were classified as diffuse cutaneus SSc (dSSc) and 41 patients as limited cutaneus SSc (lSSc) [6, 7]. Eighty healthy controls, matched by age and sex, were recruited from a subgroup of individuals residing in the Siena area, Italy, who had been participating in a larger epidemiological study [27], and from a small group of healthy volunteers from the hospital staff. Height and weight were measured systematically in all patients and healthy controls using standardized methods. The body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters. This study adhered to the principles of Declaration of Helsinki, and was approved by the Institutional Review Board for Human Research of the Siena University Hospital (ID:10412). Written consent was obtained from all participants. Prior to statistical analysis, all collected data underwent anonymization procedures.

Nailfold videocapillaroscopy

The videocapillaroscopic examination of the nail bed was performed, according to the standard method, using a Videocap 3.0 video-capillaroscope from DS Medica (VideoCap 9.0 image processing software) with a 200x lens, by the same examiner. All patients were advised not to cut

cuticles at least seven days before the examination, not to apply or remove nail polish if already present, and not to smoke or consume coffee for at least twenty-four hours before the examination to avoid artifacts. Each subject was allowed to acclimate for at least 15 min at room temperature. Videocapillaroscopy was performed on the first row of capillaries in fingers II-V of both hands, excluding those with recent trauma, after applying a drop of immersion oil for better visibility. The same operator performed the NVC examination and assigned the correct NVC microangiopathy pattern ("early", "active" or "late" NVC pattern) to the SSc patients, according to Cutolo et al.'s classification [19, 20]. In particular, the "early" pattern, is characterized by a limited number of megacapillaries, rare microhemorrhages, absent or mild architectural disorder, and preserved capillary density; the "active" pattern, is characterized by a considerable number of megacapillaries and microhemorrhages, some branched capillaries, a modest reduction in the number of capillaries, and increased architectural disorder; and the "late" or advanced pattern, in which there is total disorganization of the normal capillary architecture, with frequent neoformed capillaries, extensive avascular areas, and almost absent megacapillaries or microhemorrhages [20].

Dual-energy X-ray absorptiometry

In the study population and healthy controls we conducted BMD measurements at the lumbar spine (LS-BMD), femoral neck (FN-BMD), and total hip (TH-MD) using a dual-energy X-ray absorptiometry (DXA) device (Discovery W, Hologic, Waltham, MA, USA). The medical reports included the BMD value obtained from DXA (expressed in g/cm^2) as well as the corresponding T-score value calculated using the Italian reference database [28]. The DXA scans adhered to standard clinical routine procedures. According to the diagnostic criteria recommended by the World Health Organization, a normal BMD score is indicated by a T-score of -1.0 or higher. In comparison, "low bone mass" or osteopenia is defined as a T-score ranging from – 1.0 to -2.5, while a diagnosis of osteoporosis is assigned to those with a T-score of < -2.5 or lower. The classification of severe or established osteoporosis applies to individuals with a T-score of <-2.5 or lower who also have one or more fragility fractures [29].

Laboratory investigation

Additionally, in SSc patients, morning fasting blood samples were collected to measure serum levels of calcium (Ca), phosphate (P), creatinine (Cr), alkaline phosphatase (ALP), intact parathyroid hormone (PTH), bone-specific alkaline phosphatase (B-ALP), and 25-hydroxyvitamin D (25OHD). Serum PTH was assessed by an immunoradiometric assay (Total Intact PTH Antibodies Lab. Inc.; Santee, CA, USA) and the intra- and inter-assay coefficients of variation were 3.6 and 4.9%, respectively. Serum B-ALP was measured by a chemiluminescence immunoassay method (LIAISON BAP Ostase, DiaSorin Inc., Stillwater, MN, USA). In our institution the intra- and inter-assay coefficients of variation for B-ALP were 4.2% and 7.9%, respectively. Serum 25OHD was determined by a chemiluminescence immunoassay (LIAISON 25OHD Total Assay, DiaSorin Inc, Stillwater, MN, USA). In our institution the intra- and inter-assay coefficients of variation were 6.8% and 9.2%, respectively. The measurement of all the other lab parameters was carried out with a colorimetric method (Autoanalyzer, Falcor 350 Menarini, Italy).

Pulmonary assessment

All SSc patients had lung volume, spirometry and gas transfer assessment according to the European Respiratory Society/American Thoracic Society guidelines [30]. The pulmonary function test included forced vital capacity (FVC), total lung capacity (TLC), forced expiratory volume in 1 s (FEV1) and diffusion capacity for carbon monoxide (DLCO). Results are expressed as a percentage of the predicted value.

Fracture assessment

During the visit, information on previous fracture history was collected, focusing on major osteoporotic fractures (MOF), specifically those involving the hip, vertebrae, proximal humerus, and forearm. Fracture occurrence was also verified through chart reviews in the Carestream database. Additionally, reports from magnetic resonance imaging (MRI), chest high-resolution computed tomography (HRCT), and computed tomography (CT) were examined for evidence of any vertebral fractures.

Statistical analysis

Values in this study are presented as "mean ± standard deviation (SD)." The Kolmogorov–Smirnov test was used to assess the normality of outcome variable distributions. Clinical data and baseline values of measured variables between study groups were compared using Student's t-test or the Mann–Whitney U-test, depending on data distribution suitability. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. Linear regression models were created to examine factors associated with hip BMD in patients with limited and diffuse SSc. Factors included in these models were age, BMI, menopausal age, 25OHD, DLCO, fracture history, and NVC. All tests were two-sided, with $p < 0.05$ considered statistically significant. All statistical analyses were performed using the SPSS statistical package for Windows version 16.0 (SPSS Inc., Chicago).

Results

Bone involvement in diffuse SSc and limited SSC

The demographic and clinical characteristics of both the study population and healthy controls are displayed in Table 1. Scleroderma patients have a slightly, but significantly, lower BMI compared to healthy controls. In contrast, healthy controls have significantly higher BMD values at all skeletal sites. As shown in Table 2, the SSc population consisted of subjects with limited cutaneous SSc ($n=41$) and diffuse cutaneous SSc ($n=43$). The levels of total and bone alkaline phosphatase, as well as DLCO, were lower in patients with diffuse SSc compared to those with limited SSc, although the difference was statistically significant only for DLCO. Additionally, patients with diffuse SSc had lower 25OHD values and higher PTH values than those with limited SSc, but these differences did not reach statistical significance; on the contrary, anti-centromere antibodies were more common in limited SSc ($p<0.01$). Moreover, Intestitial lung disease are more frequent in Diffuse SSC ($p<0.05$) (Table 2). Figure 1 shows the mean values of BMD at different skeletal sites, expressed as T-score, in patients with diffuse SSc or limited SSc. It is evident that at lumbar spine there were no differences between the two groups, whereas BMD values at femoral subregions showed T-score values lower in patients with diffuse SSc with respect to those with limited SSc reaching the statistical significance at total hip ($p<0.05$) (Fig. 1).

Figure 2A shows the percentages of patients with diffuse SSc or limited SSc with BMD values indicative of osteoporosis and osteopenia (39.6% and 44.2% vs. 29.2% and 51.3%, respectively). Thirty-two patients with SSc (38.1%) presented a history of major osteoporotic fragility fractures and in particular 22 patients (26.2%) presented vertebral fractures which were mainly located at the dorsal spine level. As expected, the number patients with fractures prevailed in diffuse SSc patients with respect to limited SSc patients (41.9% vs. 34.1%, respectively) (Fig. 2B).

Nailfold videocapillaroscopy patterns and bone mineral density

Figure 3A shows the trend of BMD values at lumbar spine in patients with diffuse SSc and limited SSc divided into three subgroups on the basis of the three categories of capillaroscopic patterns. Patients with a "late" or "active" pattern have a more marked reduction in BMD with respect to those with a "early" pattern. Furthermore, BMD T-scores were lower in patients affected by diffuse SSc with respect to those observed in patients with limited SSc, but the difference was not statistically significant. Figure 3B shows that femoral BMD also presents reduced values in patients with the "active" and "late"

Table 1 Clinical and densitometric characteristics of the patients with systemic sclerosis and controls

	Systemic sclerosis ($N=84$)	Controls ($N=80$)
Gender (F/M)	77/7	66/14
Age (yrs)	64.5 ± 13.7	63.1 ± 10.8
BMI (Kg/m^2)	24.5 ± 5.2	26.4 ± 3.4*
Menopause (years)	52.1 ± 2.8	53.1 ± 3.1
LS-BMD (g/cm^2)	0.960 ± 0.168	1.090 ± 0.117**
LS T-score	-1.4 ± 1.3	-0.8 ± 0.9*
FN-BMD (g/cm^2)	0.759 ± 0.121	0.857 ± 0.111*
FN T-score	-1.6 ± 1.0	-1.1 ± 0.8*
TH-BMD (g/cm^2)	0.820 ± 0.114	0.943 ± 0.124**
TH T-score	-1.5 ± 1.1	-0.7 ± 0.9**

Abbreviations F: female; M: male; BMI: body mass index; LS-BMD: bone mineral density at lumbar spine; FN-BMD: bone mineral density at femoral neck; TH-BMD: bone mineral density at total hip

*$p<0.05$; **$p<0.01$ Systemic Sclerosis vs. Controls

Table 2 Anthropometric, clinical and biochemical characteristics o patients with diffuse SSc and limited SSc

	Diffuse SSc ($N=43$)	Limited SSc ($N=41$)
Age (years)[a]	64.8 ± 12.5	62.4 ± 15.1
Gender (F/M)[b]	40/3	37/4
BMI (Kg/m^2)[a]	24.9 ± 5.5	24.1 ± 5.1
Menopause (years)[a]	51.5 ± 2.8	52.3 ± 2.5
Disease duration (years)[a]	14.4 ± 7.9	13.2 ± 8.1
Creatinine (mg/dl)[a]	0.78 ± 0.19	0.82 ± 0.15
Albumina (mg/dl)[a]	3.6 ± 0.7	3.8 ± 0.6
Calcium (mg/dl)[a]	9.46 ± 0.66	9.26 ± 0.56
Phosphate (mg/dl)[a]	3.56 ± 0.45	3.72 ± 0.63
ALP (UI/L)[a]	67.82 ± 21.96	73.17 ± 25.85
B-ALP (µg/l)[a]	11.27 ± 4.81	12.97 ± 7.86
25OHD (ng/ml)[a]	21.42 ± 15.17	24.66 ± 13.59
PTH (pg/ml)[a]	43.76 ± 11.92	41.37 ± 18.62
mRSS score[a]	17.1 ± 7.9	6.3 ± 2.8**
ANA positive, n/total (%)	41/43(95%)	40/41 (97%)
Anti-Scl-70, n/total (%)	13/43 (30%)	6/41 (15%)
Anti-centromere, n/total (%)	7/43 (16%)	25/41 (61%)**
DLCO (%)[a]	67.10 ± 18.56	72.59 ± 20.91*
Organ manifestation		
Interstitial lung disease, n/total (%)[b]	33/43 (77%)	22/41 (54%)*
Pulmonary hypertension, n/total (%)[b]	8/43 (18%)	4/41 (10%)
Digital ulcerations, n/total (%)[b]	7/43 (16%)	3/41 (7%)
Esophageal atony, n/total (%)[b]	20/43 (46%)	16/41 (39%)

Abbreviation SSc: Systemic sclerosis; F: female; M: male; BMI: body mass index; ALP: alkaline phosphatase; B-ALP: bone alkaline phosphatase; 25OHD: 25-hydroxyvitam D; PTH: intact parathyroid hormone; mRSS: modified Rodnan skin score; ANA: antinuclear antibody; Anti-Scl-70: anti-topoisomerase I; DLCO: diffusion capacity for carbon monoxide

*$p<0.05$ **$p<0.001$ Diffuse SSc vs. Limited SSc

[a]Student's T test

[b]Dichotomous variable, reference NO (chi-square Yates corrected test)

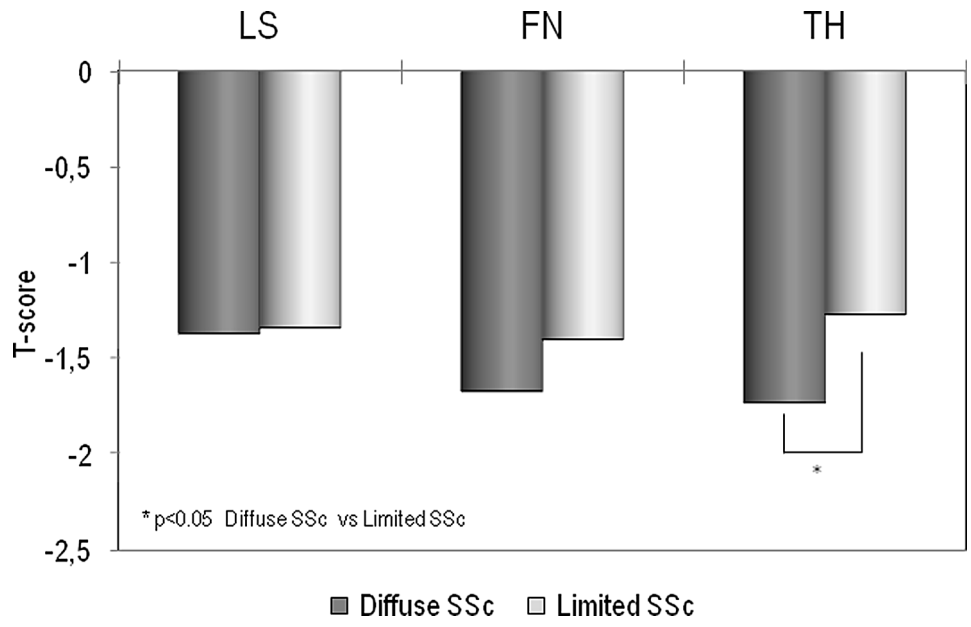

Fig. 1 BMD values, expressed as T-scores at the lumbar spine (LS), femoral neck (FN), and total hip (TH), in patients with diffuse SSc or limited SSc

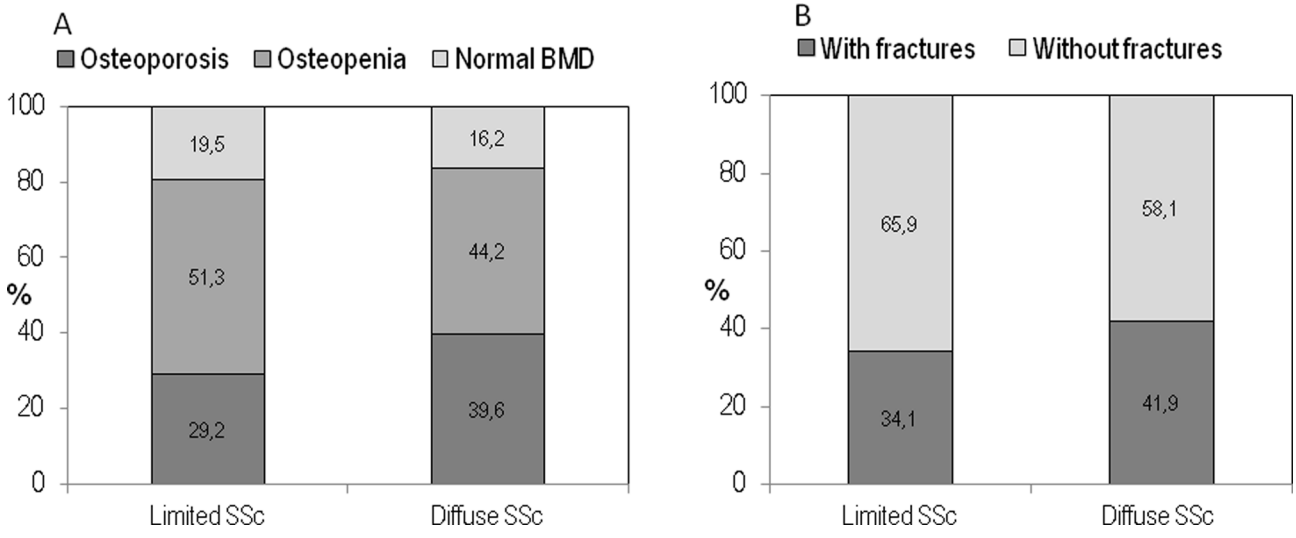

Fig. 2 Prevalence of osteoporosis and osteopenia (**A**) and major fragility fractures (**B**) in patients affected by diffuse SSc or limited SSc

capillaroscopic patterns. In the "active" and "late" capillaroscopic patterns the values of BMD were significantly lower ($p < 0.05$) in patients with diffuse SSc with respect to those observed in patients with limited SSc.

Nailfold videocapillaroscopy patterns and pulmonary involvment

To further evaluate the association between the respiratory parameters and microvascular damage, we compared the three categories of capillaroscopic patterns in the study population according to DLCO. Figure 4 shows that SSc patients exhibit a compromise of DLCO that progressively increases with worsening the capillaroscopic pattern. Moreover, patients with diffuse SSc showed a greater reduction in DLCO values compared to those with limited SSc in all three capillaroscopic patterns (data not shown).

Table 3 reports the linear regression analyses performed for factors associated with BMD at total hip in patients with diffuse SSc and limited SSc. The whole set of variables included into the model comprised age, BMI, menopause, history of osteoporotic fractures, PTH, 25OHD, DLCO and NVC patterns. DLCO and history of previous fractures were independently and significantly associated with low BMD at total hip in diffuse SSc patients.

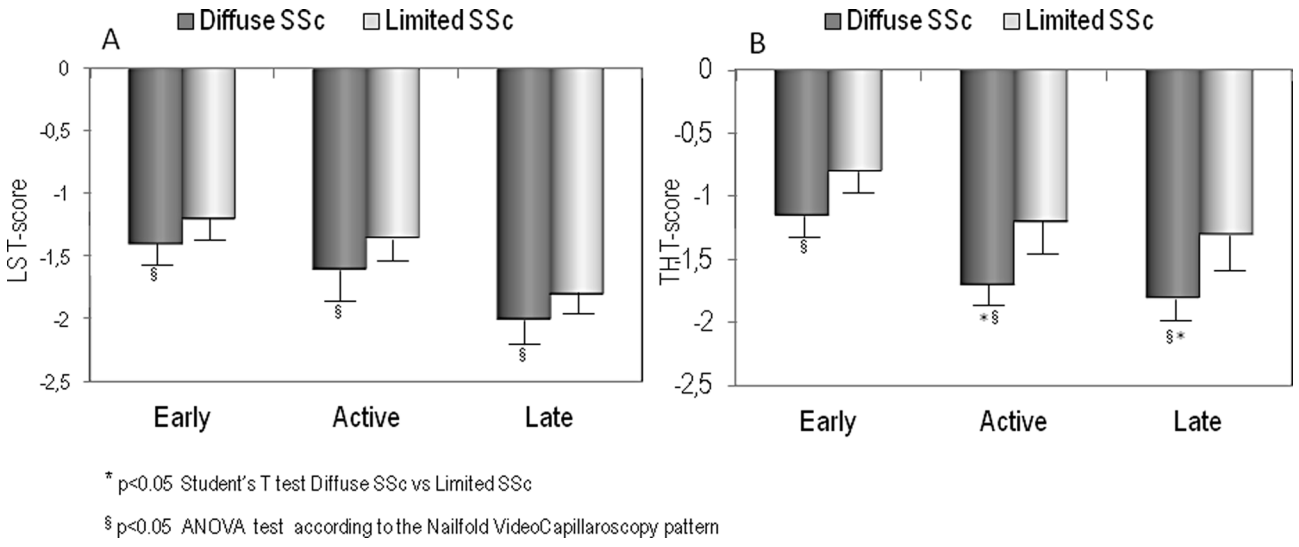

Fig. 3 BMD T-score at lumbar spine (**A**) and at Total Hip (**B**) according to the Nailfold VideoCapillaroscopy pattern in patients with diffuse SSc or limited SSc

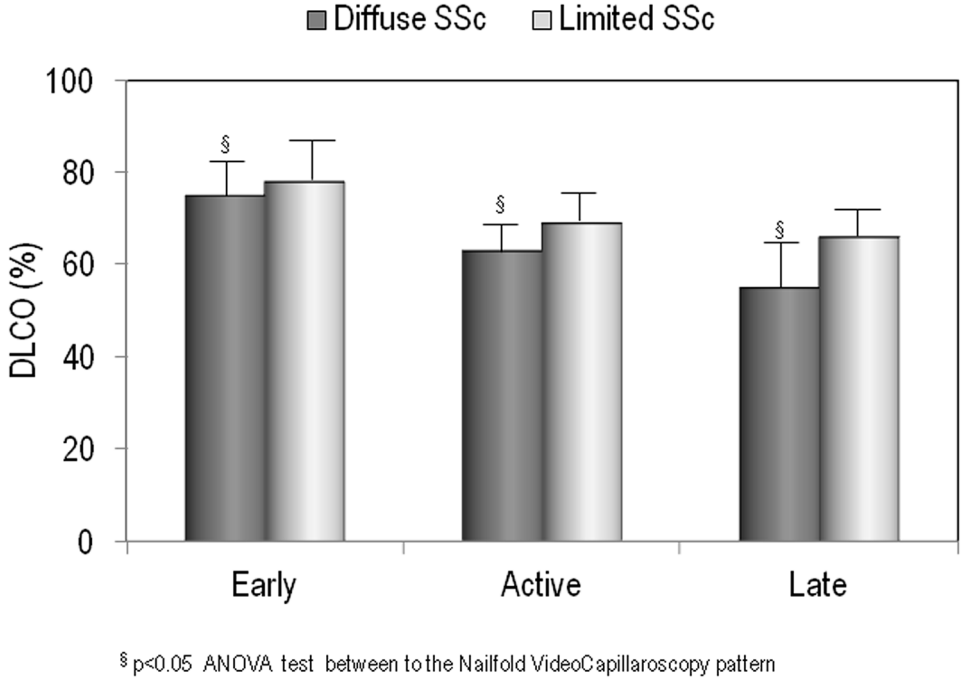

Fig. 4 DLCO values (%) in patients with Diffuse SSc or Limited SSC according to the Nailfold VideoCapillaroscopy pattern

Discussion

This study, consistent with most previous reports, emphasized that SSc patients exhibit lower BMD values and a high prevalence of osteoporosis. Another finding of this study was that BMD values at all skeletal sites were lower in patients with the diffuse subtype and in those with a more altered NCV pattern. Systemic sclerosis itself may be considered an important risk factor for osteoporosis. Previous studies have reported that osteoporosis is relatively common in patients with SSc, with the overall prevalence of low BMD ranging from 27 to 53% and the prevalence of osteoporosis ranging from 3 to 51% [11, 14]. In SSc patients, specific risk factors for osteoporosis include chronic inflammation, early menopause, immobilization, soft tissue calcification, depleting calcium stores, treatments with glucocorticoids and disturbance of vitamin D metabolism in the skin, kidney, and gastrointestinal tract [11, 17]. In agreement with some previous papers the results of this study indicated a more marked reduction in BMD values in patients with diffuse

Table 3 Linear regression analyses of factors associated with BMD at total hip in patients with diffuse SSc and limited SSc

Covariates	Diffuse SSc		Limited SSc	
	β	*p*	β	*p*
Age	0,476	0,250	0,231	0,670
BMI	0,226	0,548	0,391	0,249
Menopause age	-0,064	0,864	-0,230	0,822
25OHD	0,690	0,188	0,536	0,247
NCV	0,613	0,118	0,445	0,335
DLCO %	0,597	0,050	0,243	0,822
History of fractures	-0,825	0,017	0,305	0,175

Variable included in the model: Age, BMI: body mass index; 25OHD: 25-hydroxyvitam D; NCV: nailfold videocapillaroscopy; DLCO %: diffusion capacity for carbon monoxide; History of fractures

$p < 0.05$

SSc compared to those with limited SSc, with a statistically significant difference at total hip [9, 13, 31]. This discrepancy could be attributed to the increased fibrotic and inflammatory activity associated with diffuse SSc, which could have direct impacts on bone density. Furthermore, patients with diffuse SSc may undergo more aggressive therapies to manage systemic involvement, and some of these therapies may affect bone density and fracture risk. However, two recent meta-analyses have reported that patients with SSc have reduced BMD and an increased risk of fractures, regardless of clinical phenotype [13, 32].

In fact, several studies reported higher prevalence of fractures in SSc patients than in healthy controls [10, 17, 22]. The presence of fragility fractures is an important aspect to consider in the management of patients with SSc. A large cohort study conducted using the Taiwan National Health Insurance database reported that SSc patients are at high risk of vertebral and hip fractures, and experience hip fractures at a younger age and exhibit a higher 1-year mortality of vertebral fracture than does the general population [33]. In our study, the percentage of patients with fragility fractures was moderately higher in those with diffuse SSc compared to those with limited SSc (41.9% vs. 34.1%); however, the difference between the two phenotypes was not statistically significant. This finding is consistent with the study by Omair et al., who conducted a systematic review on low bone density in patients with SSc, highlighting an increased risk of fractures even in patients with clinically less severe forms of the disease [11]. A study by Medsger et al. highlighted that patients with diffuse SSc have greater disease activity than those with limited SSc, which may contribute to the more impaired BMD observed in patients with diffuse SSc [34]. In contrast, a recent Korean study did not find any association between vertebral fractures and SSc subtypes [35].

The prevalent distribution of vertebral fractures at thoracic level may negatively influence the course of the disease because these fractures, especially those of moderate/severe degree, have deleterious effects on pulmonary functionally tests by reducing lung volume so contributing to a restrictive ventilatory defect [36].

The present study adds evidence that in both diffuse SSc and limited SSc the extent of microvascular damage is associated with the severity of the impairment of internal organs and in particular with skeletal involvement. In fact, patients with a "late" NVC pattern had lower BMD values at both lumbar and femoral levels than those with an "active" or "early" NVC pattern. Furthermore, some studies have observed a correlation between the progression of microvascular damage and alterations in bone microarchitecture as assessed with the trabecular bone score (TBS) [17, 37]. Therefore, NVC is not only useful for the early diagnosis of SSc but is currently also considered an important indicator of the systemic progression of the disease [19, 38]. However, the pathogenetic mechanisms that can explain the link between the "late" NVC pattern and the greater impairment of bone status have not yet been clarified. Some studies have observed that the progression of microangiopathy from the "early" pattern to the "late" pattern appears to also be associated with a more aggressive autoantibody pattern which could induce an increase in fibrotic activity that may negatively influence bone health [38, 39]. Another study observed that patients with a "late" NCV pattern had a significant increase in serum levels of Dickkopf-1 (Dkk-1) compared to those with "active" or "early" patterns. Since Dkk-1 is a natural inhibitor of the Wnt/β-catenin signaling pathway that promotes osteoblastic activity, its increase could result in reduced bone formation and in a worsening of bone quality [37]. Therefore, the reduced BMD in patients with a more severe NCV pattern may be attributed to increased bone resorption driven by a more aggressive antibody profile, resulting in heightened inflammation, and reduced bone formation mediated by DKK-1 [37–39].

Another interesting finding of this study is represented by the fact that DLCO values, a reliable marker of interstitial lung involvement, were more reduced in patients with diffuse SSc compared to those with limited SSc and in those with a NCV pattern "late" or "active". This finding is in agreement with previous studies that have reported how NVC can be a simple and valuable tool for screening and early detection of SSc organ-based complications, namely, lung involvement [21, 24, 25, 40]. Castellví first reported that capillary loss was associated not only with the interstitial lung disease (ILD) but also with lower FVC and DLCO values [38]. Moreover, the study by Caetano et al. reported that NVC capillary loss and avascular areas were significantly associated with the presence of ILD, and this relation was supported by ROC curve analysis [24]. The importance of predicting pulmonary impairment with NVC in SSc patients was confirmed by

recent studies which showed that the reduction of DLCO, reflecting pulmonary vascular disease, was significantly correlated with diastolic heart failure; moreover, DLCO values ≤ 60%, likely reflecting pulmonary vascular disease, were also independently associated with an increased risk of mortality [41]. Furthermore, this study suggests a significant role of lung involvement in the pathogenesis of osteoporosis in SSc patients; however, a positive relationship between reduced values of DLCO and osteoporosis or fragility fractures has also been found in other ILDs such as sarcoidosis [42]. Finally, another notable finding of this study is that vitamin D levels were within the normal range in patients with both limited SSc and diffuse SSc. Furthermore, no association was observed between vitamin D levels and femoral BMD. These findings contrast with much of the published literature, which typically reports lower vitamin D levels, particularly in patients with diffuse SSc [43]. This discrepancy may be explained by the fact that nearly all of our study participants were receiving vitamin D supplementation.

This study presents some limitations. First, the lack of a control group for comparison may limit the understanding of the specific impact of SSc on the clinical parameters. Second, the cross-sectional design of the study precludes the establishment of causal relationships. But it also has some strong points; these encompass the conduct of the study in a single center, the re-evaluation of the fractures and the assessment of the NVC and DXA exams by two experienced operators (CC and IC, respectively), ensuring reliability in the data collection process.

Conclusion

This study found that patients with systemic sclerosis, and particularly those with a "diffuse" phenotype, have a high prevalence of osteoporosis and major fragility fractures. Furthermore, in both the diffuse and limited phenotypes, the presence of an "active" or "late" capillaroscopic pattern was associated with reduced BMD and DLCO values. Data from this study also suggest that pulmonary involvement may play a role in the pathogenesis of osteoporosis and fractures. These findings, if confirmed in controlled studies, could have significant implications for the clinical management and prevention of skeletal complications in patients with SSc. All patients with systemic sclerosis, especially those with more severe phenotypes, should undergo periodic BMD checks and fracture risk assessments, and receive vitamin D supplementation and appropriate pharmacological treatment when necessary.

Abbreviations

SSc	Systemic sclerosis
NVC	Nailfold videocapillaroscopy
BMD	Bone mineral density
dSSc	Diffuse cutaneus SSc
lSSc	Limited cutaneus SSc
DLCO	Diffusing capacity of carbon monoxide
HR-pQCT	High-Resolution peripheral Quantitative Computed Tomography
TBS	Trabecular Bone Score
LS	Lumbar spine
FN	Femoral neck
TH	Total hip
DXA	Dual-energy B X-ray absorptiometry
ALP	Alkaline phosphatase
PTH	Intact parathyroid hormone
B-ALP	Bone alkaline phosphatase
25OHD	25-hydroxyvitam D
FEV1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
TLC	Total lung capacity
MOF	Major fractures due to osteoporosis

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Author contributions

I.C. design of the study and acquisition of data. C.M: and G.M. and S.B. and M.C. acquisition of data. S.G. and A. A. and L.G. revising the article. C.C. study conception and design, analysis, interpretation of data, revising the article. All authors reviewed the manuscript.

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Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Informed consent was obtained from all patients as appropriate. This study adhered to the principles of Declaration of Helsinki, and was approved by the Institutional Review Board for Human Research of the Siena University Hospital (ID:10412).

Clinical trial number

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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