Hand bone densitometry associates with nailfold capillaroscopic severity of microvascular damage in systemic sclerosis: a pilot study

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Abstract

Objectives

Patients with systemic sclerosis (SSc) exhibit systemic and more pronounced micro- and macro-architectural bone damage compared to healthy subjects (HS). The extent of the microvascular damage in SSc may be associated with the severity of compromised systemic bone integrity.

The aim of this study is to investigate and score the status of the hand bone mineral density (BMD) in patients with SSc, using a new dedicated hand software and to score the microvascular status of the same hands by using nailfold videocapillaroscopy (NVC).

Methods

Bone mineral density (BMD/g/cm^2) and bone mineral content (BMC/g) of left and right hand using a new hand dedicated software (enCore, GE Lunar Prodigy Bone Densitometer, BMD hand software, USA), as well total BMD of the skeleton (GE Lunar Prodigy Bone Densitometer), were measured in 32 SSc patients classified according to the 2013 ACR/EULAR criteria (mean age 61±14 years, 94% women, 47% (n=13) dcSSc and in 27 age-matched HS. Quality of peripheral microvascular involvement (NVC patterns) was evaluated via standardised NVC analysis including capillary number scoring. SSc organ involvement was evaluated according to the 2023 EULAR recommendations. Statistical analysis included non-parametric and multivariable regression analyses to explore the relationship between capillary density and hand bone status.

Results

A multiple regression analysis demonstrated that left- and right-hand BMD was significantly associated with capillary loss after adjustment for age, sex, BMI, osteoporosis history, grip strength, immunosuppressive therapy and bone-specific treatments ($p=0.02$ and $p=0.03$). Interestingly, BMD values were found positively correlated with the absolute number of capillaries per linear millimetre (left hand $r=0.6893$, $p<0.001$; right hand $r=0.45$, $p=0.03$). A significant negative correlation was also found between left hand BMD ($r=–0.5752$, $p=0.001$) with the presence of "late" NVC scleroderma pattern. A significant negative correlation was finally observed between left hand BMD and the presence of dcSSc ($r=–0.3836$, $p=0.036$) and the modified Rodnan skin score ($r=–0.5811$, $p=0.002$). Moreover, SSc patients exhibited significantly lower hand BMD compared to HS even adjusted for age, sex, BMI and history of osteoporosis.

Conclusion

For the first time, hand local bone status was found significantly associated with hand/fingers NVC microvascular damage in SSc patients, emphasising the effects of capillary loss/local hypoxia on the observed bone loss. At the same time, the results of the regression model reinforced the role of capillary loss as a potential predictor of hand bone quality in SSc patients.

Key words

nailfold capillaroscopy, connective tissue disease, microvascular circulation, bone density, systemic sclerosis

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Introduction

Systemic sclerosis (SSc) is an autoimmune connective tissue disorder involving a complex interplay of genetic predisposition and an altered immune system response (1, 2). This complex interaction in the presence of Raynaud's phenomenon (RP) triggers a sequence of pathological events, starting with progressive microvascular damage, abnormal activation of both the innate and adaptive immune systems, and the transition of fibroblasts into myofibroblasts, ultimately leading to tissue fibrosis (3-5). Among connective tissue diseases, SSc has also been identified as a risk factor for osteoporosis (6).

Osteoporosis is a systemic skeletal disorder characterised by low bone mass and bone microarchitectural deterioration, resulting in increased susceptibility to fractures (7). Key risk factors contributing to reduced bone mineral density include hormonal changes following menopause or early menopause, advanced age, glucocorticoid therapy, endocrine disorders (hyperthyroidism or hyperparathyroidism), and chronic systemic inflammation (7).

Patients with SSc, including men and younger women, exhibit lower bone mineral density (BMD) compared to the general population, emphasising the importance of comprehensive bone health assessment in all SSc patients (8, 9). In some cohorts, the prevalence of low BMD ranges from 27% to 58%, despite normal calcium metabolism (10). Already in 1995, a study identified correlations between BMD values and SSc clinical features such as calcinosis, diffuse cutaneous subtype, and disease duration (11).

More recently, a correlation between impaired microvascular status assessed by nailfold capillaroscopy (NVC) analysis and an increased prevalence of systemic osteoporosis was reported, along with significant changes in body composition in SSc patients (12, 13). Notably, microvascular alterations in SSc lead to local tissue hypoxia and contribute to the deterioration of bone trabecular architecture (14). Building on this evidence, the present study aims to further investigate the interplay between vascular damage and bone health in SSc. Specifically, the objective was to assess the relationship between local hand bone quality using a dedicated software and peripheral microvascular status assessed by a detailed NVC analysis.

Material and methods

Study design and study population

The present study was conducted in the Division of Rheumatology at the University of Genova, Bone Research Unit (managed by SP) using an observational cross-sectional design. The study was reported in accordance with the STROBE checklist for observational studies (Supplementary Table S1). Additionally, a CONSORT-style flow diagram was used to illustrate patient recruitment (Supplementary Fig. S1).

In this study a cohort of 32 consecutive Caucasian SSc patients were recruited during routine clinical assessment at the Scleroderma Clinic of Rheumatology Division, University of Genova (Italy). All patients fulfilled the 2013 American College of Rheumatology (ACR)/European League against Rheumatology (EULAR) classification criteria (15). Additionally, 27 sex-matched and age-matched healthy subjects (HS) with no history or clinical signs of connective tissue diseases were enrolled. All patients and controls were aged over 18 years.

Patients with a medical history of overlap with other autoimmune diseases (such as Rheumatoid arthritis, Sjögren's disease, Systemic Lupus Erythematosus and inflammatory myositis) or with other possible causes of osteoporosis (such as severe neurological, pulmonary, cardiac and endocrine diseases) were not included. Furthermore, patients with comorbid conditions known to significantly interfere with bone metabolism or microvascular function were not included. These conditions comprised chronic kidney disease, uncontrolled thyroid or parathyroid disorders, severe chronic pulmonary disease, severe cardiovascular involvement, major neurological disorders, presence of malignancies, and chronic use of glucocorticoids. All medical treatments were recorded. As

this was a real-life investigation patients treated with bone repairing drugs for osteoporosis or with supplementation on calcium and vitamin D were not excluded. The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki, following approval from the Ethics Committee of the Ospedale Policlinico San Martino (N. CET - Liguria: 16/2025 - id 14273- 22/04/2025), and after obtaining written informed consent from all participants.

Clinical and functional parameters

All SSc patients met 2013 ACR/EULAR classification criteria for SSc and were treated with standard therapies, mainly immunosuppressors, according to their organ involvement and disease severity (Table I) (15, 16).

Data on the following variables were collected in SSc patients: gender, age, smoking condition, alcohol consumption, prior fragility fractures, family history of fragility fractures, menopausal status, body weight and height [with body mass index (BMI)], subset of SSc according to the extent of skin fibrosis (lcSSc or dcSSc), disease duration (time from first symptom to baseline in years), antibody profile, organ involvement (RP, digital ulcers (DUs), pulmonary arterial hypertension (PAH), interstitial lung disease (ILD), oesophageal involvement and musculoskeletal (MSK) involvement), and ongoing treatment, including vasodilators and immunosuppressors.

Skin involvement was assessed by the modified Rodnan skin score (mRSS) to evaluate skin thickness performed by the same experienced rheumatologist (SP) (17).

Diagnosis of limited cutaneous (lcSSc) and diffuse cutaneous (dcSSc) systemic sclerosis was made according to the LeRoy classification (18).

Pulmonary involvement was defined by evidence of ILD on high-resolution computed tomography and reporting by pulmonary function tests (PFT) with the determination of forced vital capacity (FVC) and diffusion for carbon monoxide (DLCO/VA% and DLCOAdj%) and 6-minute walking test (6MWT) (19).

Table I. Descriptive statistics of the demographic, clinical and NVC parameters in SSc patients.

	SSc (n 32)
Age (years, M ± SD)	61.7 ± 14
Gender (Female/Male)	30/2
BMI (g/cm^2, M ± SD)	22,3875 ± 3,9172
Disease duration (years, M±SD)	10 ± 7.4
Antibody profile n (%)	
Anti-centromere	12 (37.5)
Anti-Scl70	13 (40)
Anti-RNA polymerase III	1 (3)
Clinical manifestations n (%)	
Skin involvement (lcSSc / dcSSc)	13/19
RP	29 (90.5)
DUs	13 (40.6)
PAH	8 (25)
ILD	22 (68.7)
GI involvement	14 (43.7)
Kidney involvement	12 (37.5)
mRSS (M±SD)	7.6 ± 9.8
Osteoporosis	14 (43.7)
Osteoporosis with fracture	5 (15.6)
Laboratory results (M ± SD)	
Calcemia (mg/dL)	9.5 ± 1.9
25-hydroxivitamin D (ng/mL)	40.6 ± 21.9
Bone alkaline phosphatase (U/L)	15.1 ± 6
Parathyroid hormone level (pg/mL)	54 ± 27
Therapy n° (%)	
	MMF=12 (37.5)
	MTX=8 (25)
	RTX=0(0)
	AZA=0
	CYC=2 (6.3)
	HCQ=5 (15.6)
	Ca-ant =6 (18.8)
	ACEi=7 (21.9)
	PDE5i=4 (12.5)
	Bosentan=12 (37.5)
	Macitentan=1 (3.1)
	Prostanoids=27 (84.4)
	Selexipag =0 (0)
	Riociguat =0 (0)
	Nintedanib=5 (15.6)
	IPP=20 (62.5)
	PDN=3 (9.4)
	Vitamin D supplementation=22 (61.1)
	Calcium supplementation=5 (15.6)
	Oral bisphosphonates= 7 (21.9)
	Intravenous bisphosphonates= 1 (3.1)
	Denosumab=3 (8.3)
	Romosozumab=1 (3.1)
Absolute number of capillaries M±SD (1 linear mm)	4.7 ± 1,97
Absolute number of capillaries right hand M±SD (1 linear mm)	4.57 ± 2.04
Absolute number of capillaries left hand M±SD (1 linear mm)	4,68 ± 2,03
Normal	0 (0)
Non-specific alterations	4 (12.5)
"Early" SSc	1 (3.13)
"Active" SSc	9 (28.13)
"Late" SSc	16 (50)
Missing	2 (6.25)
Hand grip strength (M±SM)	
Hand dynamometer	49.6 ± 18.4
Duruöz Hand Index (DHI) 0-90	7.6 ± 10.2
HAMIS test	3.9 ± 4.7
HAQtot	8.3 ± 11.5

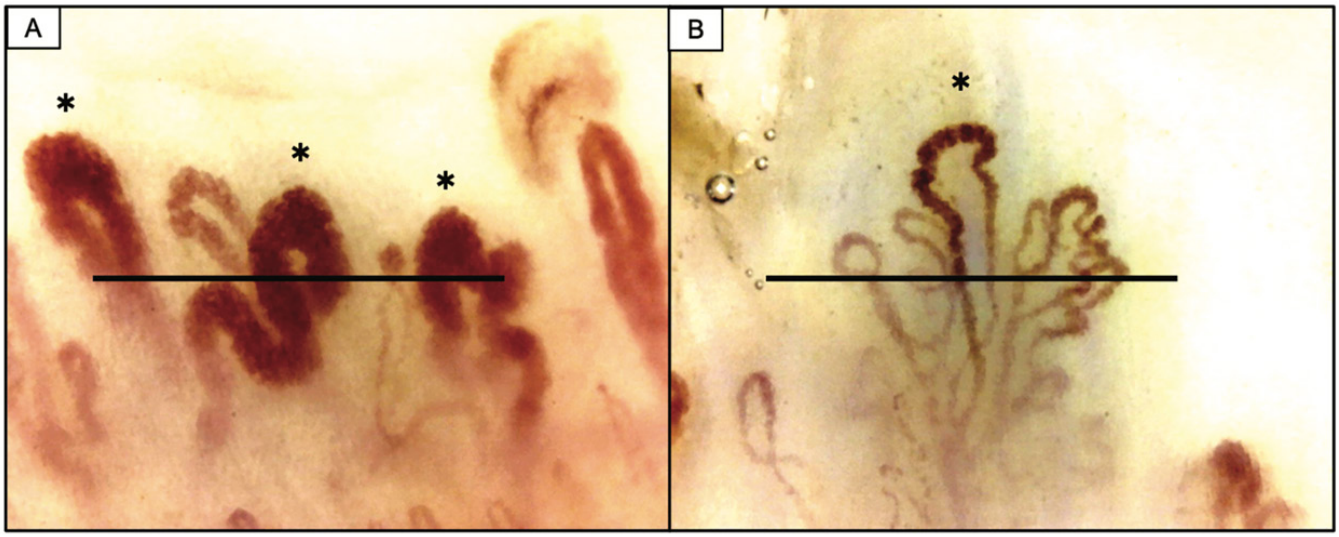

Fig. 1. Nailfold videocapillaroscopy picture of SSc patients.
A. "Active" scleroderma pattern: 3 giant capillaries (diameter >50 μm) highlighted by asterisks, microhaemorrhages deposit, loss of capillaries (5 capillaries per linear mm).
B. "Late" scleroderma pattern is shown: no giant capillaries, no microhaemorrhages, one abnormal shape (neoangiogenesis) highlighted by asterisks and capillary density is reduced (1 capillary per linear mm).
In each image, the black horizontal line represents a linear millimetre. Magnification 200×. Original images from M. Cutolo and Genova team, Laboratory of Experimental Rheumatology and Academic Clinical Division at University of Genova.

Pulmonary arterial hypertension (PAH) was screened as proposed by 2022 European Society of Cardiology/European Respiratory Society guidelines and a non-invasive sonographic assessment of increased systolic pulmonary arterial pressure (sPAP) was made with a cut-off of 25 mmHg (20).
Gastrointestinal (GI) involvement was defined as distal oesophageal hypomotility or aperistalsis documented by manometric study and/or presence of upper and lower GI tract symptoms including reflux, vomiting, early satiety, bloating, diarrhoea, constipation, a diagnosis of malabsorption syndrome, or episodes of pseudo-obstruction after excluding other non-SSc related causes (1).

Laboratory tests
Bone metabolism laboratory tests were performed, such as bone alkaline phosphatase, calcium, phosphorus, 25-hydroxyvitamin D [25(OH)VitD]. Detection of anti-nuclear antibodies (ANA) is performed on HEp-2 cells using indirect immunofluorescence (IFI) (Euroimmun, Lübeck, GE) on sera at screening dilution 1:80. Detection of Extractable Nuclear Antigen (ENA) is performed on sera using FEIA method (Fluorescence Enzyme Immunoassay) in Phadia 250 (Thermofisher). ENA test, called Symphony, is a pool of different antigens: If the test is positive, further analysis is performed to identify the specific antigens (Ro, La, Sm, RNP, Scl-70, Jo-1). The detection of autoantibodies associated with scleroderma is performed on sera using a dot-blot assay (Alphadia, Alifax) searching different antigens: Scl-70, CENP-A, CENP-B, PmScl-100, PmScl-75, Ku, RNA-pol III, U1-RNP, Th/To, Fibrillarin, NOR-90, SS-A 52kDa (Table I).

Nailfold capillaroscopy
To analyse the nailfold capillaroscopy (NVC) characteristics we used the videocapillaroscopy software of the Division of Rheumatology of the University of Genova (Horus, ADAMO srl, Italy). The NVC parameters included the NVC pattern, according to Cutolo *et al*. classification of microvascular damage, in SSc and the EULAR Study Group on Microcirculation in Rheumatic Diseases and Scleroderma Clinical Trials Consortium (SCTC) consensus (21, 22). The mean capillary number per linear mm from both hands was collected in accordance with the 2020 EULAR/SCTC consensus; however, to ensure anatomical consistency during the analysis with hand BMD, capillary counts were also evaluated separately for the right and left hands (21, 22). The NVC images were collected and evaluated by trained rheumatology fellows under the supervision of MC and CP (Table I, Fig. 1).

Bone mineral density
To assess osteoporosis, all patients underwent bone densitometry [DXA Lunar full-Prodigy (GE Lunar, Madison, WI, USA)] and quantitative BMD analysis. BMD of the lumbar spine (L1–L4) and femoral neck was expressed in g/cm^2. Subjects were classified as osteopenic (T score =–1.0 to –2.4 SD) or osteoporotic (T score =–2.5 SD) (23).
For the first time, using a new hand dedicated software (enCore, GE Lunar Prodigy Bone Densitometer, BMD hand software, USA) left and right hand were scanned two times in quick succession, with adjustments made between the scans to assess the local bone status. In addition to the overall BMD of the entire hand as measured by the hand software, ten specific areas of interest (ROI) were chosen for further examination at finger and wrist bone level (23).These areas comprised the articular zones of the total hand; the second (MCP II), third (MCP III), fourth (MCP IV), and fifth (MCP V)

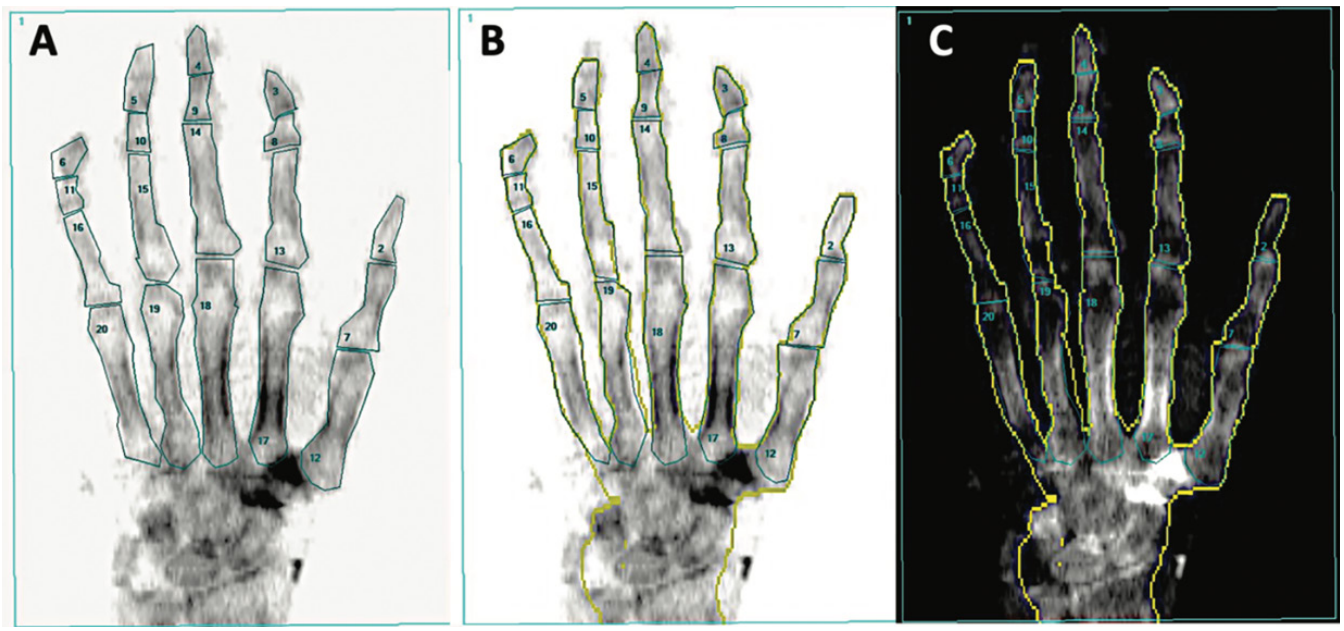

Fig. 2. Hand densitometry of SSc patient.
A Hands regions of interest (ROIs) analysed (blue), **B** ROIs analysed by the hand software (yellow), **C** Same than B with black background (original) Pictures obtained in Genova Division of Rheumatology Centre for Bone Diseases and Metabolism - EULAR Imaging Research and Training Centre.

metacarpophalangeal joints; the second (PIP II), third (PIP III), fourth (PIP IV), and fifth (PIP V) proximal phalangeal joints; the radiocarpal (RC) joint; and the carpo-ulnar (CU) joint at the wrist. Additionally, the overall average BMD of four groups of subregions was computed: MCPII–V, PIPII–V, RC+ CU, along with the total average of all ROIs. The assessment of the finger joints was conducted with the height of the subregions established at 10 mm in line with the methodology of the Murphy model, meaning that the chosen subregion encompassed 5 mm of articular bone on either side of the joint line (24).

Finally, the evaluation of the wrist joints was first carried out with the subregions' height set at 10 mm, then repeated after adjusting the measurement to match each patient's individual anatomical characteristics. All scans were performed on the same machine by the same operator (AC) (Fig. 2) and were analysed by a dedicated physician (SP) (Table III). The reproducibility of the hand-DXA software measurements was considered high, with a reported precision error of 0.7% and an observed inter-scan coefficient of variation (CV%) of 0.24%. Body weight and body height were also recorded, and body mass index (BMI) was calculated.

Disease-specific questionnaires and hand strength evaluation

In 26 SSc patients of our cohort quality of life (QoL) was assessed using the Health Assessment Questionnaire (HAQ), while hand function and mobility specific to SSc were evaluated via the HAMIS (Hand Mobility in Scleroderma) test in 18 SSc patients (25). In this context, HAMIS comprises nine performance-based tasks (*e.g.*, finger/thumb movements, wrist and forearm manoeuvres), each rated on a scale from 0 (no impairment) to 3 (complete inability to perform), for a maximum score of 27 per hand.

A higher HAMIS score therefore indicates greater hand disability, and this metric has been validated as both reliable and sensitive in distinguishing various degrees of hand dysfunction in SSc patients (26).

A total of 26 SSc patients also underwent a functional assessment of hand performance using the hand grip strength test, which objectively quantifies muscular strength in pounds in both right and left hand. Measurements were obtained using an analogue dynamometer (SMEDLEY DYNAMOMETER, GIMA, Gessate, Italy) (27).

Following the standardised protocol described by Mathiowetz *et al.*, each patient was seated with the arm positioned in abduction, the elbow flexed at 90°, and no external support provided. Three consecutive measurements were taken for each hand, and the average value was used for statistical analysis (28).

Statistical analysis

To determine whether the variables followed a normal distribution and to define parametric versus non-parametric variables, the Shapiro-Wilk test was applied. Statistical analyses were performed using the non-parametric Mann-Whitney U test to compare differences between groups (Table III). Multivariate analysis was performed and adjusted for the significant variables observed in the univariate analysis (Table III). Spearman's rank correlation was used for non-parametric data, while linear and logistic regression analyses were applied where appropriate to assess associations between continuous and categorical variables (Table II). Where appropriate, analyses included correction for multiple comparisons using the False Discovery Rate (FDR).

A p-value of less than 0.05 was considered statistically significant. All analyses were conducted using DATAtab Team software (2025) and R statistical software.

Table II. Statistically significant Spearman correlations between hand BMD and BMC and clinical features, antibody profiles and NVC parameters in SSc patients.

Variables	r	df	*p*-value
Organ involvement			
Left hand BMD and dcSSc	-0.3836	28	0.036
Left hand BMD and mRSS	-0.5811	23	0.002
Left hand BMD and GI	-0.3899	28	0.033
Left hand BMC and GI	-0.3628	28	0.049
Right hand BMD and dcSSc	-0.3836	20	0.633
Right hand BMD and mRSS	-0.36	17	0.125
Right hand BMD and GI	-0.25	18	0.285
Antibody profile			
Left hand BMD and anti-centromere	0.3976	26	0.036
Left hand BMD and anti- Scl70	-0.4522	26	0.016
Right hand BMD and anti- centromere	-0.01	20	0.974
Right hand BMD and anti- Scl70	-0.10	20	0.656
NVC patterns			
Left hand BMD and late pattern	-0.5752	28	0.001
Right hand BMD and late pattern	-0.33	19	0.143
Details on NVC parameters			
Left hand BMD and absolute number of capillaries (1 linear mm)	0.6893	28	<0.001
Left hand BMD and abnormal shapes (neoangiogenesis)	-0.4144	28	0.023
Right hand BMD and absolute number of capillaries (1 linear mm)	0.45	19	0.038
Right hand BMD and derangement	-0.56	19	0.009
Femoral neck BMD and absolute number of capillaries (1 linear mm)	0.39	28	0.031
Femoral total BMD and absolute number of capillaries (1 linear mm)	0.50	28	0.005
Vertebral BMD and absolute number of capillaries (1 linear mm)	0.45	28	0.013
Hand grip strength and HAQ test			
Hand BMD and dynamometer value	0.53	28	0.003
Left hand BMD and left dynamometer value	0.40	24	0.044
Right hand BMD and right dynamometer value	-0.13	17	0.586
Left hand BMD and HAQ test	-0.39	23	0.055
Right hand BMD and HAQ test	-0.04	16	0.882
Left hand BMD and HAMIS test	–0.1829	16	0.468
Right hand BMD and HAMIS test	0.21	10	0.505

BMD: bone mineral density; BMC: bone mineral content; dcSSc: diffuse cutaneous ystemic sclerosis; GI: gastrointestinal involvement; HAMIS: Hand Mobility in Scleroderma; HAQ: Health Assessment Questionnaire; mRSS: modified Rodnan skin score; NVC: nailfold videocapillaroscopy; antibodies; Scl70: anti-topoisomerase I.

Results

Nailfold capillaroscopy microvascular alterations and hand bone status

Left hand BMD was assessed in 32 SSc patients and 27 HS, whereas right hand measurements were obtained for only 22 patients; mean values are reported in Table III. The multiple linear regression model showed a high significant association between capillary absolute number at NVC and left-hand BMD in patients with SSc (R^2=0.75, F=5.93, β=0.51, 95% CI 0.01-0.03, p<0.001), indicating a meaningful link between microvascular damage and hand bone deterioration even after the model was adjusted for age, gender, BMI, presence of osteoporosis, grip strength, immunosuppressive treatment, and specific therapies for osteoporosis (p=0.02). Similarly, multiple linear regression model showed a significant association between absolute number of capillaries at NVC of the right hand and right-hand BMD in patients with SSc (R^2=0.76, F=3.59, β=0.50, 95% CI 0.01-0.03, p=0.012) confirmed after adjusting for age, gender, BMI, presence of osteoporosis, grip strength immunomodulating therapy, and specific osteoporosis medications (p=0.033).

The assessment of microvascular damage through NVC revealed significant associations with hand bone health. Specifically, left hand BMD was negatively correlated with the "Late" NVC pattern (p=0.001) and the presence of abnormal shapes (neo angiogenesis) (p=0.023). In the right hand, BMD showed a significant negative correlation with capillary derangement (p=0.009). Notably, a higher absolute number of capillaries per linear mm (capillary density) was consistently and positively associated with BMD in both the left hand (p<0.001) and the right hand (p=0.038). Furthermore, the capillary density was also significantly linked to systemic bone density, including the femoral neck (p=0.031), femoral total (p=0.005), and the vertebral column (p=0.013) (Table II). Of note, SSc patients exhibited significantly lower BMD in the left hand compared to the control group, even after adjusting for age, sex, BMI, and osteoporosis history.

Clinical and laboratory parameters and hand bone status

Analysis of clinical and laboratory parameters revealed significant correlations with hand BMD. Specifically, a moderate negative correlation was observed between left hand BMD and the presence of diffuse cutaneous SSc

(dcSSc; r=-0.3836, p=0.036). Furthermore, left hand BMD showed a strong negative correlation with the modified Rodnan skin score (mRSS; r=-0.5811, p=0.002), and a similar significant association was found for left hand BMC (r=-0.4027, p=0.046). Left hand BMD was also negatively correlated with gastrointestinal involvement (BMD: r=-0.3899, p=0.033) in SSc patients (Table III).

In this cohort of SSc patients, lcSSc patients exhibited higher BMD compared to the dcSSc group (p=0.014). Conversely, BMD values were significantly lower in SSc patients with vs. without: ILD (p<0.001), GI involvement (p=0.03), and 'Late' scleroderma pattern (p=0.002) (Supplementary Table S2). Regarding the immunological profile, anti-Scl70 antibodies showed a significant negative correlation with left hand BMD (r=-0.4522, p=0.016), whereas the presence of anti-centromere antibodies (ACA) correlated positively (r=0.3976, p=0.036) (table II). A similar trend was observed for the right hand, although the results did not reach statistical significance; this may be likely due to the smaller number of DXA analyses available for the right hand. Consistent with these findings, left hand BMD was significantly lower in Anti-Scl70 positive patients compared to ACA positive patients (p=0.01) (Supplementary Table S2). Importantly, SSc patients exhibited significantly lower left-hand BMD and BMC compared to HS (p<0.001). This difference remained statistically significant after adjusting for confounding variables such as age, gender, BMI, and history of osteoporosis (p=0.003), underscoring the independent contribution of SSc to bone loss in the hand (Table III).

Table III. Hand BMD and BMC measured by DXA in SSc patients and HC.

	SSc	HC	p-value[a]	p adj. value[b]	p adj. value[c]
Left hand BMD	0.31 ± 0.07 (0.29-0.34)	0.3903 ± 0.06 (0.37-0.41)	p<0.001	p=0.002	p=0.003
Right hand BMD	0.32 ± 0.06 (0.3-0.35)	-	-	-	-
BMD vertebral	0.98 ± 0.2 (0.91–1.05)	1.15 ± 0.13 (1.1–1.12)	p<0.001	p=0.002	p=0.034
BMD femur (neck)	0.75 ± 0.17 (0.69–0.81)	0.85 ± 0.12 (0.8–0.9)	p=0.008	p=0.008	p=0.683
BMD femur (total)	0.83 ± 0.19 (0.76–0.89)	0.97 ± 0.15 0.91–1.03)	p=0.003	p=0.004	p=0.377

[a]p-values Mann-whitney (Univariate analysis).
[b]p-values adjusted for false discovery rate (FDR) Benjamini-Hochberg test.
[c]p-values adjusted for age, gender, BMI, history of osteoporosis (Multiple linear regression analysis).
adj: adjusted; BMC: bone mineral content; BMD: bone mineral density; HC: healthy controls; SSc: systemic sclerosis.

Hand grip strength parameters and hand bone status

The linear regression model showed no statistical evidence that hand grip strength measured by dynamometer explained the variance of Hand BMD (R^2=0.08, F=3.63, p<0.063). Left hand BMD positively correlated with grip strength measured using a dynamometer (r=0.40, p=0.044). The same analysis with the right hand did not reach the statistical significance (r =-0.13, p=0.586). In addition, left and right-hand BMD did not correlate with the HAQ score (left hand BMD: r=–0.39, p=0.055; right hand BMD: r=–0.04, p=0.882). No significant correlations were observed with hand BMD and HAMIS test (left hand BMD: r=–0.1829, p=0.468; right hand BMD: r=0.21, p=0.505).

Discussion

This is the first report about hand bone status in SSc patients and its relationship with microcirculation. Data demonstrate a significant association between absolute number of capillaries, as assessed by NVC and hand BMD values in SSc patients. Multiple linear regression analysis confirmed that nailfold capillary density is independently associated with hand bone quality in both hands. These findings provide novel insights into the pathophysiological mechanisms underlying bone involvement in SSc, specifically highlighting the impact of progressive peripheral microvascular damage. The findings of the present study seem to provide novel insights into the pathophysiological mechanisms underlying bone status in SSc, particularly highlighting the relationship with progressive peripheral microvascular damage. Hand densitometry analysis offers a unique perspective compared to axial scans, as it evaluates the same anatomical district where nailfold capillaroscopy allows for capillary counting. The finding that hand BMD was significantly lower in SSc patients than in HC even after adjusting for confounders such as age, sex, BMI, and history of osteoporosis underscores the distinct nature of skeletal involvement in systemic sclerosis. The anatomical consistency (right and left hand) is fundamental to revealing how capillary density per linear mm acts as a local determinant of bone mass, unveiling a microvascular-bone link. Collectively, these results highlight the interconnected role of microvascular damage, disease severity, together with functional impairment, assessed with hand grip, in SSc-related hand bone involvement. These detailed findings are consistent with previous research suggesting that vascular remodelling leads to localized ischemia, which in turn contributes to microarchitectural bone changes and tissue degeneration in the distal extremities of SSc patients (29).

Indeed, local hypoxia could indirectly influence osteoclastogenesis via autocrine and paracrine secretion of vascular endothelial growth factor (VEGF) under the control of hypoxia-inducible factor 1-alpha (HIF-1α) (30).

Of note, the HIF-1α and VEGF signalling pathways play a crucial role in regulating both osteoclastic bone resorption and angiogenesis (31). Additionally, in SSc elevated Dickkopf-1 and sclerostin levels are likely linked

to skin fibrosis and microvascular damage evaluated by NVC (32, 33).

Therefore, the observed reduction in SSc hands of BMD and BMC, may be partially explained by chronic tissue hypoxia due to microvascular insufficiency, which could impair osteoblast activity and favour bone resorption.

As previously demonstrated, correlations between vertebral and femoral BMD and capillary density were also observed in our cohort of SSc patients, further reinforcing the role of nailfold videocapillaroscopy as a biomarker of systemic bone status (12, 15). Since NVC analysis reflects the status of the microcirculation in SSc as in other connective tissue diseases, it is plausible that bone areas throughout the body may mirror the alterations observed in the hands of SSc patients, depending on the specific vascularization of each skeletal site and the severity of tissue fibrosis and organ involvement, such as lung function (34-36).

In fact, capillary loss, assessed at NVC and resulting from the fibrotic process, is frequently observed in ILD with reduced lung functions, SSc that may contribute to peripheral hypoxia in SSc patients (37).

As matter of fact, the 'Late' NVC scleroderma pattern, observed in patients with advanced SSc, has also been linked to reduced vertebral BMD, indicative of systemic skeletal involvement in the later stages of disease (14, 38).

Notably, hand BMD assessed using dedicated software reveals a distinct pattern of bone loss associated with reduced capillary density, independent of systemic osteoporosis as evaluated by vertebral and femoral BMD in patients with SSc. These findings highlight the distinctive role of hand densitometry and capillaroscopy in identifying local bone damage that may be driven by microvascular alterations characteristic of SSc patients. The earliest microvascular damage in presence of Raynaud's phenomenon could alter the hand bone status in the earliest and most evident manner that the systemic bone involvement. This hypothesis will be explored in future prospective studies. In support of this concept, only a limited proportion of patients in the present cohort exhibited systemic bone involvement, with osteoporosis observed in 43.7% of SSc patients and osteoporotic fractures in 15.6%. Disease phenotype and severity also emerged as important determinants of bone health. In particular, the presence of dcSSc and higher mRSS were both associated with lower hand BMD and BMC values, supporting the hypothesis that more extensive fibrotic tissue involvement contributes to greater skeletal compromise.

These findings are consistent with previous observations linking reduced bone mass to disease severity in SSc (11).

Furthermore, gastrointestinal involvement was also found negatively associated with hand bone parameters, probably reflecting other risk factors like malabsorption, and nutritional deficiencies in SSc (39). Indeed, a recent study demonstrated that SSc patients with malnutrition exhibited significantly lower skeletal trabecular bone scores (TBS), indicating poorer bone quality compared to those with normal nutritional status (40).

Interestingly, the presence of ACA was found positively associated with hand BMD, whereas anti-Scl70 antibodies, commonly linked to a more aggressive disease phenotype, showed a significant negative correlation.

It is agreed that physical exercise and mechanical load influence BMD and hypomobility contribute to bone deterioration (41). As reported in recent studies, functional hand impairment can occur early in the course of SSc causing disability and loss of function (42). However, the linear regression model did not provide statistical evidence that hand grip strength serves as a primary determinant of local bone density variance in this cohort. This indicates that while mechanical loading is a factor, the bone health of the hand may be influenced by a more complex interplay of local and systemic variables. A notable finding was the asymmetry observed between the hands. A significant positive correlation between BMD and grip strength was identified only in the left hand, while the right hand showed no such association. This discrepancy may be attributed to the protective effect of daily mechanical loading on the dominant hand, which might mask the underlying bone loss observed in the non-dominant limb. Finally, the lack of a clear correlation with global disability scores or specific mobility tests (HAQ and HAMIS) suggests that bone density changes might occur independently of a patient's daily functional capacity in SSc. This implies that BMD does not always overlap with the clinical perception of manual dexterity. This study results suggest that local hand DXA may serve as a sensitive tool for detecting localised bone loss associated with microangiopathy, potentially preceding systemic alterations detectable by standard axial DXA. Consequently, hand DXA could represent a valuable instrument for monitoring bone status in SSc, although further longitudinal studies and larger cohorts are necessary to validate these preliminary observations.

Although hypovitaminosis D is frequently observed in autoimmune disease, including SSc, the lack of statistically significant correlations with hand BMD and BMC may suggest that, despite serum vitamin D concentrations being within the normal range due to pharmacological supplementation, indeed impaired microvascular status and microcirculation may limit its effective distribution to peripheral tissues (43-47). This study has certain limitations. Overall, the sample size was relatively small, as this represents a first exploratory evaluation in this field, nevertheless, several observed associations reached statistical significance, supporting the biological plausibility of the findings. The study was designed as a pilot investigation and its cross-sectional design limits the long-term observations for interactions between microvascular damage and hand bone loss in SSc patients. Additionally, the single-centre design represents a limitation, and the findings would benefit from confirmation in larger, multicentre studies to improve external validity. Furthermore, it should be noted that functional assessment data, including grip strength and disability scores, were available for only 26 patients due

to missing data. This reduced subgroup size may limit the statistical power of our correlations between hand function and BMD, and these findings should therefore be considered exploratory. One limitation of the study is that 43.7% SSc patients affected by systemic osteoporosis were already treated according to current guidelines. This reflects real-life clinical practice but may have influenced bone density outcomes over time. However, ongoing prospective studies are currently exploring this relationship further, aiming to better define the progression connection between peripheral microvascular alterations detected through NVC and more detailed structural and compositional changes in hand bone tissue.

Finally, the results of the multivariate regression analysis reinforced the role of reduced capillary density at NVC analysis as a potential biomarker at least of hand bone quality in the same SSc patients.

Conclusions

In conclusion, the results of this detailed investigation suggest that SSc-related microvascular insufficiency, as detected by NVC, may contribute to enhancing local bone damage and loss. For the first time, local bone status of the hand was found to be significantly associated with hand/finger microvascular damage. These data emphasise the impact of microvascular circulation on bone health in SSc patients.

Take home messages

- SSc is associated with severe microvascular impairment and diffuse bone loss, however, the link between altered microcirculation and local bone integrity remains unclear.
- For the first time, BMD and BMC were evaluated solely at the level of the hands in SSc patients, using a dedicated software, and was correlated with local microvascular damage as detected by NVC.
- Capillary loss was associated with impaired hand bone quality.
- Indeed, hand bone quality significantly correlated positively with nailfold capillary density and inversely with "Late NVC" pattern, as well as skin fibrosis (dcSSc and mRSS).
- Finally, SSc patients showed significantly reduced hand BMD *vs*. sex-age-matched healthy subjects.

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