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ORIGINAL ARTICLE

Distal radius and tibia bone microarchitecture impairment in female patients with diffuse systemic sclerosis

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Abstract

Summary Radius and tibia bone microarchitecture, analyzed through a high-resolution peripheral quantitative computed tomography, were significantly impaired in female patients with diffuse systemic sclerosis compared with healthy controls. Acroosteolysis, quality of life-grip strength, hand disability, and disease duration were significantly associated with this bone deterioration.

Introduction The effect of diffuse systemic sclerosis (dSSc) on the bone is not completely understood. The objective of this study was to analyze the volumetric bone mineral density (vBMD), microarchitecture, and biomechanical parameters at the distal radius and tibia using high-resolution peripheral quantitative computed tomography (HR-pQCT, XtremeCT) in female patients with dSSc and identify clinical and laboratory variables associated with these parameters.

Methods Thirty-eight women with dSSc and 76 healthy controls were submitted to HR-pQCT at the distal radius and tibia. Clinical and laboratory findings, bone mineral density(BMD), nailfold capillaroscopy (NC), total passive range of motion(ROM), and quality of life (health assessment questionnaire—HAQ) were associated with HR-pQCT (Scanco Medical AG, Brüttisellen, Switzerland) parameters. Multiple linear regression models adjusted for clinical and laboratory variables, ROM and HAQ, were performed.

Results Density, microarchitecture, and biomechanical parameters at the distal radius and tibia were significantly impaired in dSSc patients compared with healthy controls ($p < 0.001$). Multiple linear regression models showed that lower trabecular density (Tb.vBMD) (radius $R^2 = 0.561$, $p = 0.002$; and tibia $R^2 = 0.533$, $p = 0.005$), and lower trabecular number (Tb.N) (tibia $R^2 = 0.533$, $p = 0.005$) were significantly associated with acroosteolysis. Higher trabecular separation (Tb.Sp) was associated with disease duration and higher HAQ-grip strength (radius $R^2 = 0.489$, $p = 0.013$), while cortical density (Ct.vBMD) was associated with ROM (radius $R^2 = 0.294$, $p = 0.002$).

Conclusion Bone microarchitecture in patients with dSSc, analyzed through HR-pQCT, showed impairment of trabecular and cortical bone at distal radius and tibia. Variables associated with hand involvement (acroosteolysis, quality of life-grip strength, and ROM) and disease duration may be considered prognostic factors of this bone impairment.

Keywords Acroosteolysis · Grip strength · HR-pQCT · Radius · Range of motion · Systemic sclerosis · Tibia

Introduction

Systemic sclerosis (SSc) is a chronic autoimmune disease characterized by vasculopathy of the small vessels, excessive collagen synthesis, and activation of the immune system. Impaired hand function is considered a major source of disability in SSc patients; the large number of variables associated with this disability includes skin sclerosis, microvascular lesions, tendon retractions, the bone and articular involvement, acroosteolysis, and subcutaneous calcinosis [1–4]. Flexion contractures are commonly observed in patients with SSc [5] and can significantly affect the range of motion (ROM) of the fingers, leading to functional limitations in activities of daily living (ADLs) [6] and contributing to disease severity and progression [7].

Osteoporosis (OP) is a condition characterized by systemic impairment of bone mass, strength, and microarchitecture, increasing the propensity for fragility fractures.

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Dual-energy X-ray absorptiometry (DXA) is a valid method to measure BMD, diagnose OP, and help to predict the risk of fracture [8], but it is not useful for analyzing the bone microarchitecture. High resolution peripheral quantitative computed tomography (HR-pQCT) is a new method for assessing the bone microarchitecture and volumetric bone mineral density (vBMD) in high-quality 3D images, and it allows for the estimation of the bone functional properties based on finite element analysis (FEA) [9].

Although the effect of SSc on the bone is not completely understood, recent publications have shown an increased risk of osteoporotic fractures in patients with SSc [10, 11]. A study from Taiwan, analyzing 1712 SSc patients (with 77.8% females and mean age 50 years) compared with controls, found a significantly higher incidence rate (IR) of vertebral (1.78) and hip (1.89) fractures; the main risk factors for fractures were female gender, older age, high dose of glucocorticoid use, and bowel dysmotility [10]. Interestingly, a French study compared the risk of osteoporotic fractures in 71 females with SSc, 139 with rheumatoid arthritis (RA) and 227 healthy controls; the prevalence of osteoporosis (30% in SSc, 32% in RA, and 11% in controls) and fractures (35% in SSc, 33% in RA, and 10% in controls) showed comparable frequency of fractures in SSc and RA patients (35% in SSc vs. 33% in RA vs. 10% in controls) [11]. Low BMD and poor quality of life in SSc can be associated with internal organ involvement [12], acroosteolysis [2], disease duration [13], and low serum levels of vitamin D [14, 15].

In this setting, studies focusing the bone microarchitecture are necessary for a better comprehension of these factors that can potentially affect the bone metabolism in SSc. In RA, a disease with significant hand involvement, studies analyzing HR-pQCT were focused in the distal radius [16, 17]. In SSc, the only study analyzing HR-pQCT at the distal radius and tibia included predominantly patients with limited SSc [18]. Faced with the hypothesis that SSc patients have a higher risk of low bone mass [8, 10, 11, 19] and that skin thickening and hand joint involvement can induce local bone loss and contribute to functional disability in SSc patients, the aim of this study was to evaluate vBMD, microarchitecture, and biomechanical bone properties at the distal radius and tibia using HR-pQCT in women with diffuse SSc (dSSc) in comparison with healthy controls (HC) and to correlate these bone alterations with clinical and laboratory variables, nailfold capillaroscopy (NC), ROM, and quality of life.

Methods

Patients and controls

A total of 107 female patients classified as dSSc according to the criteria of LeRoy et al. [20] were attending the Scleroderma Outpatient Clinic of the Hospital das Clínicas da Universidade de Sao Paulo from May 2012 to May 2013. Inclusion criteria were female gender, age between 18 and 50 years, and the capacity to understand the study and sign the informed consent. Exclusion criteria included diagnosis of another connective tissue disease (CTD), severe organ involvement (renal, lung, cardiac, or gastrointestinal), gastric surgery, pregnancy, breastfeeding, severe infection, and severe chronic comorbidities. Severe organ involvement was defined according to a previous publication [21]: (1) kidney—scleroderma renal crisis; (2) lung—pulmonary fibrosis with a forced vital capacity $\leq$ 55% of predicted; (3) heart—symptomatic pericarditis, congestive heart failure, or arrhythmias requiring treatment; (4) gastrointestinal—malabsorption (chronic diarrhea, with hypomotility at the small bowel, contrasted radiographic study) or pseudoobstruction.

Forty-six patients were invited to participate, and 38 completed the study. All the patients and controls were non-smokers.

Seventy-six healthy females matched for age, height, and weight, constituted the control group. They were employees of the university or their family members. Exclusion criteria were bone-associated metabolic diseases, prior non-traumatic fracture, chronic diseases (diabetes mellitus, renal or liver failure, hyperthyroidism, hypothyroidism, and malabsorption), use of any medication that could interfere with the bone metabolism (bisphosphonates, teriparatide, anticonvulsants, anticoagulants), smoking, and drinking (considered significant if $\geq$ 3 U/day). Few patients were using low doses of prednisone ($\leq$ 10 mg/day) for a short period of time. Despite its effects on bone metabolism, proton pump inhibitors (PPI) were not excluded from the study, as they were necessary for the treatment of the esophageal involvement of the SSc patients.

SSc clinical manifestations

An interview and physical examination were performed to analyze the presence of ischemic ulcers, calcinosis, and visceral involvement (esophageal dysmotility, bowel involvement, interstitial lung disease (ILD), pulmonary hypertension, scleroderma renal crisis, peripheral neuropathy). A modified Rodnan skin score (mRSS) was used to determine the extension of the skin involvement, classifying 17 anatomical sites from 0 (no skin involvement) to 3 (severe skin involvement), with a maximal score of 51 [22]. Scleroderma hand contracture was considered when the joint involvement score of the Medsger severity index [23] was $\geq$ 1, corresponding to finger-to-palm distance $\geq$ 1.0 cm. Acroosteolysis was determined by physical examination and confirmed by radiographic findings.

Range of motion

The total passive ROM in each finger was measured and calculated from the angle between maximal flexion and maximal extension of each joint using a stainless JAMAR goniometer. The total passive ROM of each finger was measured as follows: ROM of metacarpophalangeal (MP,°), ROM of proximal interphalangeal (PIP,°), and ROM of distal interphalangeal joint (DIP,°), according to a previously published protocol [24]. The same professional gauged passive ROM for all patients.

Laboratory data

Blood was collected in the morning, following a 12-h fasting period. Laboratory parameters of bone metabolism included calcium, parathormone (PTH), and 25OHD serum levels; serum and plasma were aliquoted and kept at − 80 °C in the Bone Metabolism Laboratory of Rheumatology Division for further analysis. The analysis of autoantibodies included antinuclear antibodies (ANA) and anticentromere antibody (ACA), by indirect immunofluorescence with Hep-2 cell, and anti-topoisomerase I (anti-Scl-70) antibody, by immunoblotting.

Bone mineral density

BMD was analyzed by dual-energy X-ray absorptiometry (DXA; Hologic; QDR 4500, Bedford, MA, USA) at the lumbar spine (L1-L4), femoral neck, total hip, and 1/3 radius.

Quality of life

This study performed the HAQ disability index, validated to the Brazilian–Portuguese language [25]. It contains eight domains of activity (dressing, raising, eating, walking, personal hygiene, reach, grip strength, and usual daily activities), each of which has at least two questions, for 20 items. For each item, patients report the amount of difficulty experienced performing the activity. A mean score was calculated for each domain. This score ranges from 0 (can do without difficulty) to 3 (unable to do).

Nailfold capillaroscopy (NC)

NC was performed and graded by the same rheumatologist for all participants. Eight digits (all of the fingers except thumbs) were examined using a bifocal stereomicroscope (Zeiss, Germany). Abnormal findings were nailfold microhemorrhages, reduced capillary density, enlarged loops, and avascular areas. The severity of the abnormalities was quantified as between 0 and 3, with 3 considered as the worst stage. NC was also classified as "early" (presence of giant capillaries without loss of capillaries), "active" (presence of combination of giant capillaries and avascular areas), and "late" (predominance of avascular areas) [26].

HR-pQCT parameters

Volumetric density, structural, and biomechanical parameters were analyzed by HR-pQCT (XtremeCT, SCANCO Medical AG, Brüttisellen, Switzerland) at the non-dominant distal radius and tibia. The measurements included 110 slices with a length of 9.02 mm (voxel size of 82 μm) from the distal end, positioned 9.5 mm proximal to the reference line. The following settings were used: effective energy of 60 kVp, X-ray tube current of 95 mA, and matrix size of 1536 × 1536. A single operator performed all HR-pQCT scans. The entire volume of interest (VOI) was automatically separated into cortical and trabecular regions using a threshold-based algorithm. To access the different bone parameters, the XtremeCT system automatically creates different compartments (total bone, trabecular, and cortical bone) based on image processing. These scripts include the definition of volumetric density parameters (mg HA/cm^3) for trabecular (Tb.vBMD) and cortical (Ct.vBMD) regions; trabecular structure parameters for number (Tb.N, 1 mm), thickness (Tb.Th, mm), separation (Tb.Sp, mm), and cortical structure parameters for cortical thickness (Ct.Th, mm); and cortical porosity (Ct.Po). The measurement of Ct.Po, a validated auto-segmentation method, was applied to separate the cortical and trabecular compartments. Ct.Po was calculated as the percentage of void space in the cortex [27]. This method has been validated for accuracy and reproducibility and is distributed by the manufacturer (Scanco Medical).

The biomechanical properties are established by a finite element analysis (FEA), also calculated by the software (Finite Element Soft-ware, V.1.13, Scanco Medical AG, Switzerland, January 2009, Manufacturer Handbook) and are represented by bone stiffness (S, n/mm) [9]. The precision of HR-pQCT for the distal radius (DR) and distal tibia (DT) presented a coefficient of variation ranging from 0.93 to 1.41% (DR) and 0.25 to 1.16% (DT) for density measurements and 1.49 to 7.59% (DR) and 0.78 to 6.35% (DT) for morphometric measurements in our laboratory [28].

Ethical approval

All patients gave their written informed consent and the Ethics Committee of the University of Sao Paulo approved the study (research protocol 0294/11).

Statistical analysis

Results were reported as the mean ± standard deviation and as percentages. Data with normal distributions were expressed as the mean ± standard deviation and were compared using an independent Student's *t* test. Non-parametric variables were

analyzed by the Mann-Whitney test. Categorical variables are expressed as absolute (n) and relative (%) frequencies. Pearson analysis was used to analyze the correlation between HR-pQCT parameters and clinical and laboratory variables, total passive ROM, and HAQ. Multiple linear regression analysis was performed and adjusted for the significant variables observed in the univariate analysis at the distal radius and tibia. The level of significance was 5%. The R^2-adjusted values highlights the quality of the model, and p values for each variable showed significant β coefficients.

Results

Diffuse SSc patients and healthy controls

After applying inclusion and exclusion criteria, 38 patients agreed to participate and signed the informed consent. Moreover, 76 healthy subjects, paired by gender, age, and BMI, were also selected; none of them had osteoporosis by DXA nor have altered laboratory exams. Patients with dSSc showed significant lower age of menopause compared with HC. The demographic and clinical characteristics of the patients with dSSc are described in Table 1. The mean mRSS for the 38 dSSc patients was 20.8 at initial diagnosis and 6.6 at study entry, after a mean of 8.3 years of disease duration.

Regarding treatment, 16 patients (42%) were currently using monthly doses of intravenous cyclophosphamide, while 18 (47%) patients referred previous use, and four (11%) had never used it. Among the 18 patients who previously used cyclophosphamide, 15 (39%) were currently using azathioprine and three (8%) were using mycophenolate mofetil. Sixteen patients (42%) also referred previous use of methotrexate. All the patients were using at least one vasodilator drug (predominantly nifedipine or diltiazem) and one proton bomb inhibitor (predominantly omeprazol). Nine patients (24%) were currently using corticosteroids (prednisone, in a daily dose $\leq$ 10 mg) and eight (21%) referred daily use of calcium tablets. Only three patients referred previous use of bisphosphonate for a short period of time, and none were currently using any bisphosphonate.

There was no significant difference between the ROM of dominant hand compared with the non-dominant hand in all of the five fingers (Table 2). The intraclass correlation coefficient (ICC) of intraobserver variability of mean total passive ROM in each finger was 0.968 ± 0.06; an excellent ICC was considered when > 0.8.

Table 1 Demographic and anthropometric data in patients with diffuse systemic sclerosis (dSSc) versus healthy controls (HC)

	dSSc $n = 38$	HC $n = 76$	P
Age, years	40.2 ± 7.3	38.9 ± 8.9	0.45
BMI, kg/m^2	25.5 ± 5	26.1 ± 3.6	0.45
Lean body mass, kg	38.4 ± 7.1	41.2 ± 4.8	0.02*
Menopausal age, years	37.6 ± 6.8	43.3 ± 7.5	< 0.001*
Postmenopausal, n (%)	23 (61)	04 (5)	< 0.001*
Disease duration, years	8.3 ± 5	_	NA
Modified Rodnan skin score	6.6 ± 4.7	_	NA
Digital scars, n (%)	24 (63)	_	NA
Active ulcers	0	_	NA
Calcinosis, n (%)	05 (13)	_	NA
Acroosteolysis, n (%)	23 (61)	_	NA
Hand contracture, n (%)	21 (55)	_	NA
Esophagus (dysmotility and GERD), n (%)	31 (82)	_	NA
ILD, n (%)	30 (79)	_	NA
Active NC, n (%)	18 (47)	_	NA
Late NC, n (%)	20 (53)	_	NA
Anti-Scl70, n (%)	19 (50)	_	NA
ACA, n (%)	02 (05)	_	NA
Calcium, mg/dL	9.2 ± 0.61	_	NA
25-hydroxivitamin D, ng/mL	20.7 ± 8.2	_	NA
Parathyroid hormone level, pg/mL	49.9 ± 20	_	NA
PTH ≥ 65 (pg/ml), n (%)	08 (21)	_	NA

ACA anticentromere antibodies; *BMI* body mass index; *GERD* gastroesophageal reflux disease; *ILD* interstitial lung disease; *NA* not applied; *NC* nailfold capillaroscopy; *PTH* parathyroid hormone

*p-value < 0.05

Table 2 Comparison between patients with diffuse systemic sclerosis (dSSc) and healthy controls (HC) regarding areal bone mineral density (aBMD) at the lumbar spine (L1–L4), femoral neck, total hip, and 1/3 distal radius, and comparison between range of motion (ROM) of dominant versus non-dominant hands of dSSc patients

DXA aBMD	dSSc $n = 38$	HC $n = 76$	P	Segment	dSSc Non-dominant hand ROM (°)	dSSc dominant hand ROM (°)	P
aBMD L1-L4, g/cm^2	0.92 ± 0.16	1.04 ± 0.08	< 0.001	Radius-carpal	100.79 ± 35.19	95.13 ± 30.12	0.45
aBMD femoral neck, g/cm^2	0.71 ± 0.13	0.84 ± 0.11	< 0.001	Thumb	120.26 ± 34.42	118.02 ± 28.03	0.76
aBMD total hip, g/cm^2	0.79 ± 0.17	0.96 ± 0.12	< 0.001	Indicator	205.47 ± 62.76	119.79 ± 64.33	0.35
aBMD 1/3 radius, g/cm^2	0.52 ± 0.08	0.58 ± 0.04	< 0.001	Medium	227.32 ± 64.81	205.34 ± 71.82	0.17
				Ring	239.42 ± 57.38	222.95 ± 62.88	0.24
				Minimum	237.37 ± 65.37	200.13 ± 76.12	0.29

aBMD areal bone mineral density; *dSSc* diffuse systemic sclerosis; *DXA* dual-energy X-ray absorptiometry; *HC* healthy control; *L1–L4* lumbar spine; *ROM* range of motion

DXA results showed that there was a significant difference among dSSc patients and controls regarding areal BMD (aBMD) at lumbar spine ($p < 0.001$), femoral neck ($p < 0.001$), total femur ($p < 0.001$), and 1/3 radius ($p < 0.001$) (Table 2).

Regarding HR-pQCT parameters at distal radius, Pearson correlation showed that Tb.vBMD was correlated with aBMD L1-L4 ($r = 0.75$, $p < 0.001$), aBMD femoral neck ($r = 0.77$, $p < 0.001$), and aBMD total hip ($r = 0.85$, $p < 0.001$). Moreover, Ct.vBMD values of patients showed also correlation with aBMD L1-L4 ($r = 0.33$, $p = 0.03$), aBMD femoral neck ($r = 0.35$, $p = 0.03$), and aBMD total hip ($r = 0.36$, $p = 0.02$).

HR-pQCT parameters in dSSc patients vs. healthy controls

The analysis of volumetric density, structure, and biomechanical properties at distal radius showed lower density parameters including Tb.vBMD ($p < 0.0001$) and Ct.vBMD ($p < 0.0001$) in dSSc patients compared with HC. Regarding the structure parameters in the trabecular compartment, dSSc patients showed lower Tb.N ($p < 0.0001$), and Tb.Th ($p < 0.0001$) and higher Tb.Sp ($p < 0.0001$) compared with HC. Ct.Th was decreased in dSSc patients ($p < 0.0001$), but Ct.Po was comparable between the groups ($p = 0.15$). Stiffness was significantly lower in dSSc patients compared to controls ($p < 0.0001$) *(*Table 3*)*. HR-pQCT parameters at distal tibia presented similar results as the distal radius, with the only exception of Ct.Po, which was higher in SSc patients compared to controls ($p < 0.001$).

Radius

Volumetric bone mineral density parameters using HR-pQCT vs. anthropometric, clinical and laboratory variables, and total passive ROM In the univariate analysis, Tb.vBMD values were lower in patients with acroosteolysis ($p < 0.001$), ILD ($p = 0.01$), and esophageal dysmotility ($p = 0.01$). Tb.vBMD was also positively correlated with total passive ROM ($r = +0.39$, $p = 0.02$) and negatively associated with disease duration ($r = -0.43$, $p = 0.007$). Ct.vBMD was also correlated with ROM ($r = +0.49$, $p = 0.001$). dSSc patients with late pattern NC had lower Ct.vBMD values ($p = 0.03$) compared with patients with the active pattern. Laboratory parameters (serum calcium, 25OHD, and PTH) did not influence the volumetric bone density parameters (Table 4).

Structural parameters using HR-pQCT vs. anthropometric, clinical and laboratory variables, and total passive ROM In the univariate analysis, patients with esophageal dysmotility presented lower Tb.N ($p = 0.006$) and higher Tb.Sp ($p = 0.02$) values, compared with patients without esophageal dysmotility. Moreover, patients with acroosteolysis showed lower Tb.N ($p = 0.006$) and higher Tb.Sp ($p = 0.02$) values compared with patients without acroosteolysis. There was a positive correlation between Tb.N and ROM ($r = +0.44$; $p = 0.006$) and a negative correlation between Tb.N and HAQ-grip strength ($r = -0.33$; $p = 0.04$) and disease duration ($r = -0.43$; $p = 0.007$). Tb.Sp was inversely correlated with ROM ($r = -0.40$; $p = 0.01$) and showed a positive correlation with HAQ-grip strength ($r = +0.37$; $p = 0.02$), HAQ-reach ($r = +0.34$; $p = 0.03$), and disease duration ($r = +0.46$; $p = 0.003$). Lower Tb.Th was observed in dSSc patients with acroosteolysis ($p = 0.01$), with positive anti-Scl70 ($p = 0.03$), and with late pattern NC ($p = 0.03$) compared with patients without these parameters. Lower Ct.Th was observed in dSSc patients with acroosteolysis ($p = 0.007$), positive anti-Scl70 ($p = 0.03$) and late pattern NC ($p = 0.03$), and ILD ($p = 0.009$) when compared with patients without these parameters. Lower Ct.Th also showed a positive correlation with ROM ($r = +0.42$; $p = 0.008$) and a negative correlation with disease duration ($r = -0.35$; $p = 0.03$) at the distal radius. There was no association or correlation between Ct.Po and these variables at the distal radius (Table 4).

Table 3 Comparison of HR-pQCT parameters of the distal radius and tibia in patients with diffuse systemic sclerosis (dSSc) and healthy controls (HC)

Distal radius	dSSc $n = 38$	HC $n = 76$	P
Density			
Tb.vBMD (mg HA/cm^3)	123.2 ± 45.6	172.2 ± 33.1	< 0.0001*
Ct.vBMD (mg HA/cm^3)	836.61 ± 100.1	898.4 ± 60.9	< 0.0001*
Structure			
Tb.N (1 mm)	1.6 ± 0.43	2.0 ± 0.3	< 0.0001*
Tb.Th (mm)	0.06 ± 0.01	0.07 ± 0.01	< 0.0001*
Tb.Sp (mm)	0.62 ± 0.30	0.44 ± 0.08	< 0.0001*
Ct.Th (mm)	0.59 ± 0.22	0.76 ± 0.18	< 0.0001*
Ct.Po (−)	0.015 ± 0.007	0.013 ± 0.006	0.15
Biomechanical			
S (n/mm)	58,394.98 ± 19,337.13	78,462.07 ± 14,470.35	< 0.0001*
Distal tibia	dSSc $n = 38$	HC $n = 76$	P
Density			
Tb.vBMD (mg HA/cm^3)	121.91 ± 45.28	157.80 ± 36.85	< 0.0001*
Ct.vBMD (mg HA/cm^3)	905.92 ± 46.95	948.16 ± 34.98	< 0.0001*
Structure			
Tb.N (1 mm)	1.51 ± 0.44	1.72 ± 0.32	0.003*
Tb.Th (mm)	0.07 ± 0.01	0.08 ± 0.02	0.0006*
Tb.Sp (mm)	0.67 ± 0.27	0.53 ± 0.13	0.0002*
Ct.Th (mm)	1.08 ± 0.28	1.25 ± 0.19	0.0002*
Ct.Po (−)	0.040 ± 0.01	0.028 ± 0.01	< 0.0001*
Biomechanical			
S (n/mm)	175,509.36 ± 47,492.05	199,573.57 ± 36,752.43	0.004*

Ct.Po cortical porosity; *Ct.Th* cortical thickness; *Ct.vBMD* cortical volumetric bone mineral density; *dSSc* diffuse systemic sclerosis; *HC* healthy control; *HR-pQCT* high-resolution peripheral quantitative computed tomography; *Tb.v BMD* trabecular volumetric bone mineral density; *Tb.N* trabecular number; *Tb.Sp* trabecular separation; *Tb.Th* trabecular thickness; *S* stiffness

*p-value <0.05

Biomechanical parameters using HR-pQCT vs. anthropometric, clinical and laboratory variables, and total passive ROM No association or correlation was found between bone stiffness and these examined variables (Table 4).

Tibia

Volumetric bone mineral density parameters using HR-pQCT vs. anthropometric, clinical and laboratory variables, and total passive ROM In the univariate analysis, Tb.vBMD values were lower in patients with acroosteolysis ($p < 0.001$). Tb.vBMD was also negatively associated with disease duration ($r = -0.32$; $p = 0.04$). Ct.vBMD was not associated with ROM ($r = -0.07$, $p = 0.67$), nor with late pattern NC values ($p = 0.51$). Laboratory parameters (serum calcium, 25OHD, and PTH) did not influence the volumetric bone density parameters in the tibia (Table 5).

Structural parameters at distal tibia using HR-pQCT vs. anthropometric, clinical and laboratory variables, and total passive ROM In the univariate analysis, patients with or without esophageal dysmotility presented no difference with Tb.N ($p = 0.36$) nor Tb.Sp ($p = 0.14$) values. Moreover, patients with acroosteolysis showed lower Tb.N ($p < 0.001$) and Tb.Th ($p = 0.045$) and higher Tb.Sp ($p = 0.003$) values compared with patients without acroosteolysis. There was not a positive correlation between Tb.N and ROM ($r = +0.26$; $p = 0.11$) nor correlation between Tb.N and HAQ-grip strength ($p > 0.05$) nor disease duration ($r = -0.25$; $p = 0.13$). Tb.Sp was also not correlated with ROM ($r = -0.26$; $p = 0.11$) nor with HAQ-grip strength ($p > 0.05$), nor HAQ-reach ($p > 0.05$) nor disease duration ($r = +0.19$; $p = 0.25$). Lower Tb.Th was observed in SSc patients with acroosteolysis (p = 0.045) and with late pattern NC ($p = 0.03$) compared with patients without these parameters. Lower Ct.Th was observed in SSc patients with ILD ($p = 0.01$) when compared with patients without these parameters (Table 5).

Biomechanical parameters using HR-pQCT vs. anthropometric, clinical and laboratory variables, and total passive ROM No association or correlation was found between the bone stiffness and the examined variables at tibia (Table 5).

Table 4 Univariate analysis of HR-pQCT parameters (volumetric density, structure and mechanical) at the distal radius and clinical and laboratory variables of patients with diffuse systemic sclerosis (dSSc)

Distal radius	Interstitial Lung Disease		Esophageal Dysmotility		Acroosteolysis		Anti-Scl70
	(+) $n = 30$ p	(−) $n = 8$	(+) $n = 24$ p	(−) $n = 14$	(+) $n = 23$ p	(−) $n = 15$	(+) $n = 19$ p
Density							
Tb.vBMD [mg HA/cm^3]	113.8 ± 40.9* 0.01*	158.5 ± 47.7*	109.2 ± 45.5* 0.01*	147.1 ± 35.7*	103.6 ± 36.6* 0.0004*	153.3 ± 42.4*	114.5 ± 41.3 0.25
Ct.vBMD [mg HA/cm^3]	823.8 ± 103.1 0.12	884.8 ± 74.4	819.0 ± 102.7 0.15	866.8 ± 90.9	814.9 ± 77.9 0.09	869.8 ± 122.2	811.9 ± 113.3 0.13
Structure							
Tb.N [1 mm]	1.57 ± 0.42 0.06	1.9 ± 0.40	1.50 ± 0.44* 0.006*	1.88 ± 0.27*	1.49 ± 0.44* 0.006*	1.87 ± 0.31*	1.63 ± 0.44 0.90
Tb.Th [mm]	0.059 ± 0.01 0.06	0.07 ± 0.01	0.059 ± 0.01 0.29	0.064 ± 0.01	0.058 ± 0.01* 0.01*	0.07 ± 0.01*	0.057 ± 0.008* 0.03*
Tb.Sp [mm]	0.64 ± 0.31 0.17	0.48 ± 0.17	0.69 ± 0.34* 0.02*	0.47 ± 0.11*	0.70 ± 0.35* 0.02*	0.48 ± 0.12*	0.63 ± 0.34 0.71
Ct.Th [mm]	0.54 ± 0.19* 0.009*	0.76 ± 0.21*	0.54 ± 0.20 0.07	0.67 ± 0.22	0.52 ± 0.15* 0.007*	0.70 ± 0.25*	0.52 ± 0.18* 0.03*
Ct.Po [−]	0.01 ± 0.007 0.98	0.01 ± 0.005	0.014 ± 0.007 0.97	0.015 ± 0.006	0.015 ± 0.007 0.35	0.013 ± 0.005	0.014 ± 0.006 0.92
Biomechanical							
S [n/mm]	59,544.2 ± 20,768.8 0.48	54,085.6 ± 12,750.6	56,219.5 ± 16,060.6 0.37	62,124.4 ± 24,169.6	57,911.69 ± 17,251.25 0.85	59,136.03 ± 22,794.54	56,591.9 ± 18,245.8 0.57

Distal radius	Anti-Scl70	NC		Range of Motion	HAQ	Disease Duration
	(−) $n = 19$ p	Active $n = 18$ p	Late $n = 20$	r, p	r, p	r, p
Density						
Tb.vBMD [mg HA/cm^3]	131.9 ± 49.1 0.25	132.8 ± 40.3 0.22	114.5 ± 49.3	0.39, 0.02*	>0.05	−0.43, 0.0067*
Ct.vBMD [mg HA/cm^3]	861.3 ± 80.4 0.13	873.07 ± 69.75* 0.03*	803.79 ± 112.91*	0.49, 0.001*	>0.05	−0.29, 0.08
Structure						
Tb.N [1 mm]	1.65 ± 0.42 0.90	1.67 ± 0.39 0.65	1.61 ± 0.46	0.44, 0.006*	Grip strength − 0.33, 0.04*	−0.43* 0.007*
Tb.Th [mm]	0.07 ± 0.01* 0.03*	0.066 ± 0.01* 0.03*	0.058 ± 0.01*	0.14 0.41	>0.05	−0.21, 0.21
Tb.Sp [mm]	0.60 ± 0.25 0.71	0.58 ± 0.25 0.52	0.64 ± 0.33	−0.40* 0.01*	Grip strength 0.37, 0.02* Reach 0.34, 0.03*	0.46, 0.003*

Table 4 (continued)

Ct.Th [mm]	0.66 ± 0.22* 0.03*	0.66 ± 0.18* 0.03*	0.52 ± 0.22*	0.42, 0.008*	>0.05		−0.35, 0.03*
Ct.Po [–]	0.015 ± 0.007 0.92	0.014 ± 0.006 0.86	0.014 ± 0.007	−0.01, 0.93	>0.05		0.12, 0.46
Biomechanical							
S [n/mm]	60,197.9 ± 20,708.7 0.57	63,128.97 ± 20,498.44 0.15	54,134.4 ± 17,659.95	0.16, 0.34	>0.05		−0.18, 0.28

Ct.Po: cortical porosity; Ct.vBMD: cortical volumetric bone mineral density; Ct.Th: cortical thickness; dSSc: diffuse systemic sclerosis; HAQ: health assessment questionnaire; HR-pQCT: high-resolution peripheral quantitative computed tomography; NC: nailfold capillaroscopy; S: stiffness; Tb.N: trabecular number; Tb.Th: trabecular thickness; Tb.vBMD: trabecular volumetric bone mineral density

*p-values < 0.05

Multiple linear regression models were performed, adjusted for clinical (ILD, esophageal involvement, and acroosteolysis) and laboratory (anti-Scl70) variables, ROM, and HAQ at distal radius and tibia At the distal radius, this analysis showed that lower Tb.vBMD was significantly associated with acroosteolysis ($R^2 = 0.561$, $p = 0.002$); higher Tb.Sp was associated with disease duration and higher HAQ-grip strength ($R^2 = 0.489$, $p = 0.013$), while Ct.vBMD was associated with ROM ($R^2 = 0.294$, $p = 0.002$) (Table 6). At the distal tibia, the analysis showed that lower Tb.vBMD ($R^2 = 0.533$, $p = 0.005$), and lower Tb.N ($R^2 = 0.533$, $p = 0.005$) were significantly associated with acroosteolysis. (Table 6).

Discussion

This is the first study that demonstrates that microarchitecture and biomechanical bone impairment analyzed through HR-pQCT in dSSc female patients are significantly associated with clinical variables indicative of poor prognosis, mainly at the distal radius. Although some variables related to local hand impairment in dSSc, as ROM and QoL-grip strength, were only associated with bone deterioration at distal radius, acroosteolysis was significantly associated with bone impairment at both peripheral sites at HR-pQCT.

The decision to focus the analysis on dSSc and the female gender was made to select a more homogeneous group of patients, since limited and diffuse SSc subtypes can present distinct profiles of organ involvement, specific autoantibodies, and prognosis [20, 21, 29]. The selection of female patients below 50 years age, without severe organ involvement and current use of bisphosphonates, contributed to standardize a group excluding many potential risk factors for osteoporosis, although it also contributed to the low number of patients able to participate in the study.

Diffuse SSc commonly presents flexion contractures of the hands, leading to functional impairment [1] and reduced health-related quality of life [30]. In the present series, although the skin thickening significantly decreased from a mean mRSS of 20.8 at SSc diagnosis to 6.6 at study entry, hand flexion contractures were still observed in 55% of the patients with dSSc. In many of these patients, despite the decrease in skin thickening, significant limitations in hand function can still persist due to skin atrophy, which is not measured by the skin scores. These findings emphasize the importance of analyzing other hand function parameters in SSc patients besides skin thickening. In this scenario, acroosteolysis can represent an important prognostic factor, as it was associated with localized and systemic bone impairment.

Acroosteolysis was the only variable significantly associated with bone microarchitecture and biomechanical bone impairment in the univariate and multivariate analysis at both

Table 5 Univariate analysis of HR-pQCT parameters (volumetric density, structure and mechanical) at the tibia and clinical and laboratory variables of patients with in diffuse systemic sclerosis (dSSc)

Tibia	Interstitial Lung Disease		Esophageal Dysmotility		Acroosteolysis		Anti-Scl70
	(+) n = 30 *p*	(−) n = 8	(+) n = 24 *p*	(−) n = 14	(+) n = 23 *p*	(−) n = 15	(+) n = 19 *p*
Density							
Tb.vBMD [mg HA/cm^3]	114.9 ± 39.1 0.06	148.1 ± 59.1	118.5 ± 53.2 0.55	127.8 ± 27.8	100.3 ± 33.7* <0.001*	155.0 ± 41.2*	119.9 ± 43.9 0.79
Ct.vBMD [mg HA/cm^3]	903.3 ± 50.8 0.51	915.8 ± 28.4	903.2 ± 44.2 0.65	910.5 ± 52.7	902.6 ± 46.7 0.59	911.0 ± 48.5	900.4 ± 45.9 0.47
Structure							
Tb.N [1 mm]	1.46 ± 0.39 0.18	1.69 ± 0.58	1.46 ± 0.50 0.36	1.59 ± 0.29	1.32 ± 0.38* <0.001*	1.79 ± 0.36*	1.53 ± 0.43 0.73
Tb.Th [mm]	0.065 ± 0.01 0.12	0.072 ± 0.01	0.066 ± 0.01 0.86	0.067 ± 0.01	0.064 ± 0.01* 0.045*	0.072 ± 0.01*	0.065 ± 0.01 0.30
Tb.Sp [mm]	0.68 ± 0.27 0.49	0.61 ± 0.31	0.72 ± 0.32 0.14	0.58 ± 0.12	0.77 ± 0.29* 0.003*	0.51 ± 0.13*	0.66 ± 0.29 0.89
Ct.Th [mm]	1.01 ± 0.22* 0.01*	1.29 ± 0.38*	1.05 ± 0.27 0.43	1.12 ± 0.29	1.01 ± 0.20 0.08	1.17 ± 0.35	1.01 ± 0.18 0.16
Ct.Po [−]	0.04 ± 0.001 0.88	0.04 ± 0.02	0.043 ± 0.02 0.29	0.036 ± 0.01	0.042 ± 0.018 0.44	0.037 ± 0.017	0.046 ± 0.017* 0.049*
Biomechanical							
S [n/mm]	176,743.3 ± 52,359.3 0.76	170,881.8 ± 23,092.2	174,726.6 ± 48,226.8 0.89	176,851.3 ± 47,973.8	173,060.4 ± 37,836.5 0.69	179,264.5 ± 60,715.2	175,521.3 ± 48,247.2 0.99

Tibia	Anti-Scl70	NC		Range of Motion	HAQ	Disease Duration
	(−) n = 19 *p*	Active n = 18 *p*	Late n = 20	r, *p*	r, *p*	r, *p*
Density						
Tb.vBMD [mg HA/cm^3]	123.9 ± 47.8 0.79	123.09 ± 38.6 0.88	120.8 ± 51.6	0.28, 0.08	>0.05	−0.32, 0.04*
Ct.vBMD [mg HA/cm^3]	911.5 ± 48.6 0.47	911.3 ± 40.9 0.51	901.0 ± 52.3	−0.07, 0.67	>0.05	−0.18, 0.27
Structure						
Tb.N [1 mm]	1.48 ± 0.45 0.73	1.45 ± 0.42 0.43	1.56 ± 0.46	0.26; 0.11	Grip strength > 0.05	−0.25;0.13
Tb.Th [mm]	0.069 ± 0.01 0.30	0.071 ± 0.01* 0.03*	0.063 ± 0.01*	0.14; 0.40	>0.05	−0.27, 0.10
Tb.Sp [mm]	0.67 ± 0.25 0.89	0.68 ± 0.22 0.85	0.66 ± 0.32	−0.26; 0.11	Grip strength > 0.05 Reach > 0.05	0.19, 0.25
Ct.Th [mm]	1.14 ± 0.34 0.16	1.13 ± 0.29 0.23	1.02 ± 0.26	0.01, 0.91	>0.05	−0.26, 0.11

Table 5 (continued)

Ct.Po [–]	0.035 ± 0.017*	0.041 ± 0.017	0.039 ± 0.017	−0.03, 0.81	>0.05	0.09, 0.57
	0.049*	0.73				
Biomechanical						
S [n/mm]	175,497.4 ± 48,046.8	176,822.1 ± 39,195.86	174,327.9 ± 54,905.2	0.19, 0.25	>0.05	−0.26, 0.12
	0.99	0.87				

HR-pQCT: high-resolution peripheral quantitative computed tomography; dSSc: diffuse systemic sclerosis; NC: nailfold capillaroscopy; HAQ: health assessment questionnaire; Tb.vBMD: trabecular volumetric bone mineral density; Ct.vBMD: cortical volumetric bone mineral density; Tb.N: trabecular number; Tb.Th: trabecular thickness; Tb.Sp: trabecular separation; Ct.Th: cortical thickness; Ct.Po: cortical porosity; S: stiffness

*p-values < 0.05

sites, distal radius and tibia. It is frequently associated with finger flexion contractures and important functional limitations [1, 31], as well as a more severe disease [2], including esophageal dysmotility and ILD [32]. The frequency of acroosteolysis in our study was 61%, while it ranged from 29 to 80% in international studies [1, 2, 33]. Regarding clinical and laboratory variables specific to dSSc, we also observed that decreased trabecular (Tb.Th) and cortical (Ct.Th) thickness at distal radius were associated with positive anti-Scl70, a known biomarker of ILD in SSc. Similarly, a high prevalence of positive anti-Scl70 was found among SSc patients associated with hand deformity [34].

Previous studies suggested that SSc may be a risk factor for bone loss, particularly in Caucasian patients [12, 35–38]. In this study, DXA results showed a significantly lower BMD in all the sites (the lumbar, hip, and radius) in SSc patients when compared with healthy controls even when they were paired by gender, age, and BMI. Nevertheless, DXA did not analyze volumetric density or structural or biomechanical parameters. A good instrument to better analyze these bone parameters is the HR-pQCT. In the present study, all parameters analyzed by HR-pQCT (density, structural, and biomechanical parameters) at the distal radius and tibia showed a significant decrease in SSc patients compared to controls, demonstrating systemic bone impairment in dSSc patients.

Loss of bone mass in SSc appears to be associated with longer disease duration and severity of joint involvement [39], as well as immobility, ROM impairment, and prolonged menopause [13]. The earlier age at menopause, as observed in the present study and frequently described in other studies analyzing SSc patients [35, 37, 39] can probably be associated with the use of immunosuppressive drugs. Nevertheless, as all diffuse SSc patients are commonly treated with immunosuppressive drugs (methotrexate, cyclophosphamide, azathioprine, or mycophenolate mofetil), according to the recommendations for the treatment of SSc [40], it was not possible to exclude patients with the use of these drugs. And those few patients currently using corticosteroids (prednisone, in a daily dose $\leq$ 10 mg) were using it for less than 12 weeks. Another medication that can potentially affect bone density is the PPI; as most SSc patients have esophageal involvement, the prescription of PPI is mandatory for these patients.

We have not found any association between microarchitecture alterations and digital ulcers. A recent French study, analyzing HR-pQCT in 33 patients (30 limited SSc and three dSSc) and 33 paired controls, found that low lean body mass, anticentromere antibodies, and older age can represent independent factors for decreased BMD at lumbar spine, femoral neck, and total hip; in that series, current or past history of digital ulcers were associated with a lower value of trabecular density and a higher value of trabecular separation at the tibia [18]. Although the percentage of a positive history of digital ulcers was quite similar in both studies (63% in our

Table 6 Multiple linear regression analysis of HR-pQCT parameters (Tb.vBMD, Tb.N, Tb.Sp, Ct.vBMD) at distal radius and tibia, adjusted for clinical and laboratory variables, in patients with diffuse systemic sclerosis (dSSc)

Distal Radius	Tb.vBMD Coefficient (β)	*p*	Tb.N Coefficient (β)	*p*	Tb.Sp Coefficient (β)	*p*	Ct.vBMD Coefficient (β)	*p*
Longer Disease Duration	−2.02	0.165	−0.02	0.164	0.020	0.049*	_	_
ILD	−23.10	0.147	−0.16	0.295	0.016	0.885	_	_
Esophagus (dysmotility)	−13.93	0.332	−0.20	0.151	0.070	0.488	_	_
Acroosteolysis	−34.62	0.019*	−0.25	0.070	0.135	0.176	_	_
Anti-Scl70	7.84	0.562	0.17	0.196	−0.067	0.484	_	_
NC	−0.53	0.968	0.09	0.490	−0.034	0.721	−47.05	0.115
ROM	−0.02	0.872	0.001	0.696	0.000	0.978	0.79	0.006*
HAQ Grip Strength	−16.54	0.080	−0.17	0.069	0.159	0.019*	_	_
Model Value R^2	0.561*	0.002*	0.544*	0.004*	0.489*	0.013*	0.294*	0.002*
Tibia	Tb.vBMD Coefficient (β)	*p*	Tb.N Coefficient (β)	*p*	Tb.Sp Coefficient (β)	*p*	Ct.vBMD Coefficient (β)	*p*
Longer Disease Duration	−1.09	0.460	0.00	0.851	0.0014	0.884	−2.18	0.302
ILD	−20.34	0.210	−0.16	0.306	0.010	0.924	−0.71	0.975
Esophagus (dysmotility)	14.83	0.313	0.02	0.874	0.050	0.641	−4.12	0.843
Acroosteolysis	−51.68	0.001*	−0.44	0.003*	0.24	0.017	−7.39	0.719
Anti-Scl70	18.58	0.186	0.20	0.147	−0.10	0.273	−5.17	0.794
NC	1.98	0.885	0.17	0.212	−0.06	0.503	−6,19	0.752
ROM	0.05	0.723	0.00	0.722	0.0001	0.938	−0.27	0.199
HAQ Grip Strength	−7.38	0.435	−0.10	0.268	0.10	0.115	−12.73	0.348
Model Value R^2	0.533*	0.005*	0.533*	0.005*	0.411*	0.057*	0.114*	0.924*

Ct.vBMD: cortical volumetric bone mineral density; HAQ: health assessment questionnaire; ILD: interstitial lung disease; NC: nailfold capillaroscopy; ROM: range of motion; Tb.N: trabecular number; Tb.Sp: trabecular separation; Tb.vBMD: Trabecular volumetric bone mineral density

*p-values < 0.05

study and 63.6% in the French study), 36.4% of the patients in the French study had current digital ulcers, while our study had none. This finding can possibly explain the results related to vascular alterations observed in our study. Detection of the anticentromere antibody was rare (5%) in our cohort because we only analyzed dSSc patients. Interestingly, while the study focusing patients with predominant limited SSc showed microarchitecture alterations in trabecular bone, our study, focusing on dSSc patients, showed alterations in both trabecular and cortical bone compartments.

Interestingly, this study shows that impaired hand function, analyzed by HAQ-grip strength, can be associated with the bone microarchitecture alterations at the distal radius, especially at the trabecular bone. Poole and Steen also found that grip strength was significantly correlated with HAQ scores, suggesting that SSc patients had significant physical disability and finger contractures [6]. According to these findings, an improvement in quality of life in SSc patients should be associated with interventional studies addressing handgrip strength to improve hand function [41].

Our study showed that a significantly lower Ct.vBMD was associated with impairment of finger ROM and that ROM analysis at the dominant hand was similar to those at the non-dominant hand. As hand function in SSc may be affected by several factors, including not only skin thickening but also vascular injury, local tissue, and tendon inflammation, a comprehensive assessment of hand involvement in SSc should include evaluation of mobility, skin thickening, vascular involvement and ADLs capacity. Prophylactic measures such as hand and wrist exercises of self-stretching [24] could help maintain ROM and Ct.vBMD as well as ADL capacity during the first years of SSc [42].

Lower Ct.vBMD, Tb.Th and Ct.Th were associated with the late pattern of NC at distal radius only in the univariate analysis. A recent study analyzing nailfold videocapillaroscopy (NVC) in 155 SSc patients (58% with limited SSc and 42% with diffuse SSc) found that the late pattern of NVC was associated with acroosteolysis and calcinosis; multivariate logistic regression analysis confirmed these associations with history and/or active digital ulcers (referred by 34% of the patients); these findings highlight the association of these variables with severe vasculopathy in SSc [4].

Finally, the density and microarchitecture abnormalities found in our study are likely to lead to the bone fragility,

which was also demonstrated by changes in the biomechanical bone parameters. Interestingly, the cortical porosity of the SSc patients was different from that of controls, but this parameter could be altered by very thin or porous cortices and coarse segmentation [43]. A study that evaluated which structural parameter (cortical thickness, trabecular thickness, number of trabeculae, or overall thinning of structures) was the best predictor of the biomechanical properties of the human radius revealed that most of the load was carried by the cortical bone and that small changes in cortical thickness could cause dramatic bone strength reductions [44]. In our study, the abnormalities in the parameters of the bone fragility are compatible with the altered structures found in the SSc group. Hand involvement should alert us to the significant functional impairment of dSSc patients. Hands and distal forearms represent small proportion of the total area of the body, but they are important in many functions and activities of daily life.

This study has several limitations. First, as the objective of the study was to analyze female patients with diffuse SSc with many exclusion criteria, the number of patients was low. Second, due to the need to treat those diffuse SSc patients, the use of immunosuppressive drugs was not possible to be exclusion criteria. Third, although the use of steroids was at low doses ($\leq$ 10 mg of prednisone or equivalent) in 24% of the dSSc patients, it also may have contributed to these results. Fourth, factors observed in dSSc patients such as early menopause, lower lean body mass and chronic use of PPI may have contributed to the results of the study. Fifth, as hand function impairment represented a significant factor associated with bone microarchitecture impairment, multiple hand outcome instruments should be used in future studies.

In conclusion, this study pointed out that trabecular and cortical bone were significantly impaired at both peripheral sites in dSSc, and clinical parameters indicative of poor prognosis were associated with this deterioration, mainly at the distal radius. Acroosteolysis, related to distal radius and tibia bone damage, should alert us that this manifestation may have implications in local and systemic bone involvement.

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Compliance with ethical standards

Conflicts of interest None.

References

1. Avouac J, Guerini H, Wipff J, Assous N, Chevrot A, Kahan A, Allanore Y (2006) Radiological hand involvement in systemic sclerosis. Ann Rheum Dis 65:1088–1092
2. Koutaissoff S, Vanthuyne M, Smith V, de Langhe E, Depresseux G, Westhovens R, de Keyser F, Malghem J, Houssiau FA (2011) Hand radiological damage in systemic sclerosis: comparison with a control group and clinical and functional correlations. Semin Arthritis Rheum 40:455–460
3. Arslan Tas D, Erken E, Sakalli H, Yucel AE (2012) Evaluating hand in systemic sclerosis. Rheumatol Int 32:3581–3586
4. Morardet L, Avouac J, Sammour M, Baron M, Kahan A, Feydy A, Allanore Y (2016) Late nailfold videocapillaroscopy patterns associated with hand calcinosis and acro-osteolysis in systemic sclerosis. Arthritis Care Res (Hoboken) 68:366–373
5. Bálint Z, Farkas H, Farkas N et al (2014) A three-year follow-up study of the development of joint contractures in 131 patients with systemic sclerosis. Clin Exp Rheumatol 32(6 Suppl 86):S68–S74
6. Poole JL, Steen VD (1991) The use of the health assessment questionnaire (HAQ) to determine physical disability in systemic sclerosis. Arthritis Care Res 4:27–31
7. Medsger TA Jr, Bombardieri S, Czirjak L et al (2003) Assessment of disease severity and prognosis. Clin Exp Rheumatol 21(3 Suppl 29):S42–S46
8. Omair MA, Pagnoux C, McDonald-Blumer H, Johnson SR (2013) Low bone density in systemic sclerosis: a systematic review. J Rheumatol 40:1881–1890
9. Fuller H, Fuller R, Pereira RMR (2015) High resolution peripheral quantitative computed tomography for the assessment of morphological and mechanical bone parameters. Rev Bras Reumatol 55:352–362
10. Lai CC, Wang SH, Chen WS, Liu CJ, Chen TJ, Lee PC, Chang YS (2015) Increased risk of osteoporotic fractures in patients with systemic sclerosis: a nationwide population-based study. Ann Rheum Dis 74:1347–1352
11. Avouac J, Koumakis E, Toth E, Meunier M, Maury E, Kahan A, Cormier C, Allanore Y (2012) Increased risk of osteoporosis and fracture in women with systemic sclerosis: a comparative study with rheumatoid arthritis. Arthritis Care Res 64:1871–1878
12. Frediani B, Baldi F, Falsetti P, Acciai C, Filippou G, Spreafico A, Siagri C, Chellini F, Capperucci C, Filipponi P, Galeazzi M, Marcolongo R (2004) Clinical determinants of bone mass and bone ultrasonometry in patients with systemic sclerosis. Clin Exp Rheumatol 22:313–318
13. Kilic G, Kilic E, Akgul O, Ozgocmen S (2016) Increased risk for bone loss in women with systemic sclerosis: a comparative study with rheumatoid arthritis. Int J Rheum Dis 19:405–411
14. Arnson Y, Amital H, Agmon-Levin N, Alon D, Sánchez-Castañón M, López-Hoyos M, Matucci-Cerinic M, Szücs G, Shapira Y, Szekanecz Z, Shoenfeld Y (2011) Serum 25-OH vitamin D concentrations are linked with various clinical aspects in patients with systemic sclerosis: a retrospective cohort study and review of the literature. Autoimmun Rev 10:490–494
15. Sampaio-Barros MM, Takayama L, Sampaio-Barros PD, Bonfá E, Pereira RM (2016) Low vitamin D serum levels in diffuse systemic sclerosis: a correlation with worst quality of life and severe capillaroscopic findings. Rev Bras Reumatol Engl Ed 56:337–344
16. Zhu TY, Griffith JF, Qin L, Hung VWY, Fong TN, Kwok AW, Leung PC, Li EK, Tam LS (2012) Bone density and microarchitecture: relationship between hand, peripheral, and axial skeletal sites assessed by HR-pQCT and DXA in rheumatoid arthritis. Calcif Tissue Int 91:343–355
17. Kocijan R, Finzel S, Englbrecht M, Engelke K, Rech J, Schett G (2014) Decreased quantity and quality of the periarticular and

nonperiarticular bone in patients with rheumatoid arthritis: a cross-sectional HR-pQCT study. J Bone Miner Res 29:1005–1014
18. Marot M, Valéry A, Esteve E, Bens G, Müller A, Rist S, Toumi H, Lespessailles E (2015) Prevalence and predictive factors of osteoporosis in systemic sclerosis patients: a case-control study. Oncotarget 6:14865–14873
19. Mok CC, Chan PT, Chan KL, Ma KM (2013) Prevalence and risk factors of low bone mineral density in Chinese patients with systemic sclerosis: a case-control study. Rheumatology (Oxford) 52: 296–303
20. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA Jr, Rowell N, Wollheim F (1988) Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 15:202–205
21. Steen VD, Medsger TA Jr (2000) Severe organ involvement in systemic sclerosis with diffuse scleroderma. Arthritis Rheum 43: 2437–2444
22. Furst DE, Clements PJ, Steen VD, Medsger TA Jr, Masi AT, D'Angelo WA, Lachenbruch PA, Grau RG, Seibold JR (1998) The modified Rodnan skin score is an accurate reflection of skin biopsy thickness in systemic sclerosis. J Rheumatol 25:84–88
23. Medsger TA Jr, Stillman AJ, Steen VD et al (1999) A disease severity scale for systemic sclerosis: development and testing. J Rheumatol 26:2159–2167
24. Mugii N, Hasegawa M, Matsushita T, Kondo M, Orito H, Yanaba K, Komura K, Hayakawa I, Hamaguchi Y, Ikuta M, Tachino K, Fujimoto M, Takehara K, Sato S (2006) The efficacy of self-administered stretching for finger joint motion in Japanese patients with systemic sclerosis. J Rheumatol 33:1586–1592
25. Ferraz MB, Oliveira LM, Araujo PM et al (1990) Crosscultural reliability of the physical ability dimension of the health assessment questionnaire. J Rheumatol 17:813–817
26. Cutolo M, Sulli A, Smith V (2013) How to perform and interpret capillaroscopy. Best Pract Res Clin Rheumatol 27:237–248
27. Vilayphiou N, Boutroy S, Sornay-Rendu E, van Rietbergen B, Chapurlat R (2016) Age-related changes in bone strength from HR-pQCT derived microarchitectural parameters with an emphasis on the role of cortical porosity. Bone 83:233–240
28. Alvarenga JC, Fuller H, Pasoto SG, Pereira RMR (2017) Age-related reference curves of volumetric bone density, structure, and biomechanical parameters adjusted for weight and height in a population of healthy women: an HR-pQCT study. Osteoporos Int 28: 1335–1346
29. Sampaio-Barros PD, Bortoluzzo AB, Marangoni RG et al (2012) Survival, causes of death, and prognostic factors in systemic sclerosis: analysis of 947 Brazilian patients. J Rheumatol 39:1971–1978
30. Maddali-Bongi S, Del Rosso A, Mikhaylova S et al (2014) Impact of hand and face disabilities on global disability and quality of life in systemic sclerosis patients. Clin Exp Rheumatol 32(6 Suppl 86): S15–S20
31. Park JK, Fava A, Carrino J, del Grande F, Rosen A, Boin F (2016) Association of acroosteolysis with enhanced osteoclastogenesis and higher blood levels of vascular endothelial growth factor in systemic sclerosis. Arthritis Rheumatol 68:201–209
32. Erre GL, Marongiu A, Fenu P, Faedda R, Masala A, Sanna M, Soro G, Tocco A, Piu D, Marotto D, Passiu G (2008) The "sclerodermic hand": a radiological and clinical study. Joint Bone Spine 75:426–431
33. La Montagna G, Sodano A, Capurro V et al (2005) The arthropathy of systemic sclerosis: a 12 month prospective clinical and imaging study. Skelet Radiol 34:35–41
34. Radic M, Martinovic Kaliterna D, Ljutic D (2006) The level of anti-topoisomerase I antibodies highly correlates with metacarpophalangeal and proximal interphalangeal joints flexion contractures in patients with systemic sclerosis. Clin Exp Rheumatol 24:407–412
35. La Montagna G, Vatti M, Valentini G et al (1991) Osteopenia in systemic sclerosis. Evidence of a participating role of earlier menopause. Clin Rheumatol 10:18–22
36. Sampaio-Barros PD, Costa-Paiva L, Filardi S, Sachetto Z, Samara AM, Marques-Neto JF (2005) Prognostic factors of low bone mineral density in systemic sclerosis. Clin Exp Rheumatol 23:180–184
37. Souza RB, Borges CT, Takayama L et al (2006) Systemic sclerosis and bone loss: the role of the disease and body composition. Scand J Rheumatol 35:384–387
38. Yuen SY, Rochwerg B, Ouimet J, Pope JE (2008) Patients with scleroderma may have increased risk of osteoporosis. A comparison to rheumatoid arthritis and noninflammatory musculoskeletal conditions. J Rheumatol 35:1073–1078
39. Ibn Yacoub Y, Amine B, Laatiris A et al (2012) Bone density in Moroccan women with systemic scleroderma and its relationships with disease-related parameters and vitamin D status. Rheumatol Int 32:3143–3148
40. Kowal-Bielecka O, Fransen J, Avouac J, Becker M, Kulak A, Allanore Y, Distler O, Clements P, Cutolo M, Czirjak L, Damjanov N, del Galdo F, Denton CP, Distler JHW, Foeldvari I, Figelstone K, Frerix M, Furst DE, Guiducci S, Hunzelmann N, Khanna D, Matucci-Cerinic M, Herrick AL, van den Hoogen F, van Laar J, Riemekasten G, Silver R, Smith V, Sulli A, Tarner I, Tyndall A, Welling J, Wigley F, Valentini G, Walker UA, Zulian F, Müller-Ladner U, EUSTAR Coauthors (2017) Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis 76:1327–1339
41. Poole JL, Santhanam DD, Latham AL (2013) Hand impairment and activity limitations in four chronic diseases. J Hand Ther 26:232–236
42. Sandqvist G, Hesselstrand R, Eberhardt K (2009) A longitudinal follow-up of hand involvement and activities of daily living in early systemic sclerosis. Scand J Rheumatol 38:304–310
43. Zhu TY, Griffith JF, Qin L, Hung VWY, Fong TN, Au SK, Tang XL, Kun EW, Kwok AW, Leung PC, LI EK, Tam LS (2015) Cortical thinning and progressive cortical porosity in female patients with systemic lupus erythematosus on long-term glucocorticoids: a 2-year case-control study. Osteoporos Int 26:1759–1771
44. Pistoia W, van Rietbergen B, Rüegsegger P (2003) Mechanical consequences of different scenarios for simulated bone atrophy and recovery in the distal radius. Bone 33:937–945