



Vertebral fracture prevalence and measurement of the scanographic bone attenuation coefficient on CT-scan in patients with systemic sclerosis

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Abstract

To study vertebral fracture (VF) prevalence and the scanographic bone attenuation coefficient of the first lumbar vertebra (SBAC-L1) on computed tomography scans (CT-scans) in systemic sclerosis patients. This monocentric retrospective study included patients followed from 2000 to 2014 and fulfilling ACR/EULAR 2013 criteria for systemic sclerosis and who underwent a thoracic or thoraco-abdomino-pelvic CT-scan during their follow-up. Clinical characteristics for sclerosis and osteoporosis risk factors were collected. For CT-scan, the VFs were determined according to Genant's classification, the SBAC-L1 was measured in Hounsfield Units (HU), and a SBAC-L1 \leq 145 HU (fracture threshold) defined patients at VF risk. Predictive factors for SBAC-L1 \leq 145 HU were studied. A total of 70 patients were included [mean age, 62.3 (\pm 15.6) years, women 88.5%, diffuse sclerosis 22.9% (n = 16)]. On CT-scans, three VFs were detected in three patients (4.3%). The mean SBAC-L1 was 157.26 HU (\pm 52.1), and 35 patients (50%) presented a SBAC-L1 \leq 145 HU. In multivariate analysis, only age (especially patients older than 63 years, OR = 1.08, CI 95% 1.04–1.13, p = 0.001) and calcinosis (OR = 6.04, CI 95% 1.27–28.70, p = 0.02) were independently associated with a SBAC-L1 \leq 145 HU. On a large sample of patients with systemic sclerosis, the VF prevalence on CT-scan was low (4.3%) while 50% of the patients presented a SBAC-L1 \leq 145 HU. Interestingly, the presence of calcinosis, periarticular calcifications or acro-osteolysis was linked with low SBAC-L1 and should lead to an osteoporosis screening, especially for patients under 63 years old.

Keywords Sclerosis · Osteoporosis · Vertebral fracture · Bone mineral density · Tomodensitometry/CT scan

Introduction

Systemic sclerosis is a multi-systemic disease and its prognosis depends on cardiac, pulmonary and vascular impairments. The improvement of life expectancy (survival at 10 years, 80–90% for the limited cutaneous disease and 60–80% for the systemic disease) [1–3] requires better management of comorbidities [4], especially for osteoporosis in this population, which is mainly composed of women (3–8 women for every man) with a disease beginning between 45 and

64 years. Until now, osteoporosis screening in sclerosis was conducted in a subgroup of patients for whom Dual Energy X-ray Absorptiometry (DEXA) and/or radiographic assessment were available. The studies based on DEXA found a large range of osteoporosis prevalence varying from 3–60% [5–7]. In comparison with the general population, some authors found an increased risk for osteoporosis, but other authors did not confirm this increased risk [5–22]. Some studies comparing patients with rheumatoid arthritis and with systemic sclerosis (adjusted for age and sex or without differences between the two groups), demonstrated a similar risk of osteoporosis [5, 11, 21]. Concerning the vertebral fractures (VFs) on radiography, studies showed also a varying prevalence of VF ranging from 0 to 38% [5, 7, 18, 20, 23] with a relative risk of 1.78 compared to healthy paired patients [23]. Osteoporosis in this population was multifactorial and the proposed physiopathological mechanisms were: loss of mobility and strains on bone in severe systemic

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sclerosis [6, 10, 11, 15, 19–22], displacement of calcium stocked in bone towards vascular and soft tissues (which is responsible for calcinosis), periarticular calcifications and ectopic calcifications [11, 19], and finally, digestive malabsorption related or not to a loss of vitamin D activity [6, 10, 11, 15, 19, 21, 22].

Thoracic or thoraco-abdomino-pelvic (TAP) computed tomography scan (CT-scan), classically performed in the follow-up of sclerosis and mainly to evaluate lung involvement, allowed both an evaluation of VF and of the first lumbar vertebra bone attenuation coefficient (SBAC-L1) [24]. Recently, Pickhardt et al. showed that a measurement of the SBAC-L1 was a good alternative to identify patients at risk of VF in general population. These authors demonstrated that a SBAC-L1 ≤ 145 HU (Hounsfield Units) permitted to identify 96.6% of the patients with VF, whereas DEXA [with a T score ≤ -2.5 standard deviation (SD)] identified only 39% of them. The primary objective of this study was to evaluate the prevalence of VF on CT-scan and to measure the SBAC-L1 and its reliability (intra- and inter-reader) and to determine the proportion of patients at the fracture threshold (≤ 145 HU) in a large sample of sclerosis patients who were assessed or not by DEXA. The secondary objectives were to determine the prevalence of osteoporotic risk factors and to identify factors associated with VF and SBAC-L1 ≤ 145 HU in this population.

Materials and methods

Population

This descriptive analytical and retrospective study was conducted in patients who were followed at Nancy University Hospital between January 2000 and April 2014 for diffuse or limited systemic sclerosis. We chose medical records with codes M34.0, M34.1, M34.8 and M34.9 of the International Classification of Diseases and corresponding to the classification of ACR/EULAR (American College of Rheumatology/European League Against Rheumatism) 2013 for systemic sclerosis. Patients were included if they had a thoracic TAP CT-scan during the follow-up. Patients were excluded if they did not satisfy ACR/EULAR criteria for systemic sclerosis and without thoracic or TAP CT-scan during their follow-up.

Demographic (age, gender, and disease duration), clinical (medical history, arthralgia, modified Rodnan score, and Raynaud Syndrome) and biological [C-reactive protein (CRP), erythrocyte sedimentation rate, antinuclear antibodies (ANA), phosphoremia and calcemia] characteristics and treatments concerning sclerosis were collected on all of the medical records (anterior to the CT-scan). A biological inflammation was defined either a CRP ≥ 5 mg/L or a

ESR \geq age/2 for a men and (age + 10)/2 for women. The selected complementary exams (radiographs of the hands, Pulmonary Function Testing (PFT) and cardiac echography) had to be conducted one year before or after CT-scan evaluation. Hand structural damages were studied on the radiographs of the hands and according to the Erre Score [25] by a senior rheumatologist with much experience scoring. Pulmonary involvement was studied functionally with PFT and morphologically with thoracic or TAP CT-scan [non-specific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP) and interstitial lung disease (ILD)] by a senior radiologist (MD). Pulmonary arterial hypertension (PAH) was detected on cardiac echography and confirmed by right heart catheterization.

For the assessment of osteoporosis, clinical risk factors (gender, age, chronic biological inflammation, smoking, and corticosteroid therapy) were recorded during the entire follow-up. Data about DEXA and anti-osteoporotic treatments were recorded 2 years before or after the CT-scan. For DEXA, osteoporosis was retained for a T score ≤ -2.5 SD on the spine and osteopenia with $-2.5 < T$ score ≤ -1 SD.

Morphological and densitometric scanographic bone evaluation (scanographic bone attenuation coefficient of L1: SBAC-L1)

During the period of follow-up, all of the CT-scans were conducted in the same department of Radiology and thus 43 TAP, 26 thoracic and one lumbar CT-scans were selected. From the axial acquisitions, sagittal reconstructions in bone window permitted a study of the vertebral morphology from C7 to L1 for thoracic CT-scan and from C7 to S1 for TAP CT-scan based on OSIRIX software (v6.5.1–64 bits).

- *VF assessment* The VFs were analysed manually, on sagittal sections of CT-scan, according to an adaptation of the Genant's classification, which was usually used on spine radiographs [26]. The vertebrae were scored on visual inspection as normal (grade 0), mildly deformed (grade 1, 20–25% reduction of the anterior, middle or posterior height), moderately deformed (grade 2, 25–40% reduction in any height) or severe deformed (grade 3, over 40 reduction in any height). The grade was determined on the most severe lesion observed on one of the sections
- *SBAC-L1 measurement* The SBAC-L1 study was conducted on L1 axial sections through the pedicles on the bone window. The largest elliptical Region of Interest (ROI) was drawn in trabecular bone and provided the average bone mineral density (in HU). If there was a VF on L1 vertebra, the measurement could be performed on the adjacent vertebrae (CT-scan performed similarly from T12 to L5 [24]). The intra-reader reliability was

evaluated on two measurements performed with a delay of 2 weeks and using the same reader for all patients. The inter-reader reliability was evaluated on 30 CT-scans by two independent readers.

- *Choice of the threshold* Pickhardt et al. showed that a SBAC-L1 ≤ 145 HU identified 96.6% of the patients with VF in a general population, whereas DEXA (with T score ≤ -2.5 SD) identified only 39% of the VF in the same population. A SBAC-L1 ≤ 145 HU allowed a good compromise between sensitivity and specificity to identify patients at risk of VF in a population with an unknown risk of osteoporosis. Other thresholds were also studied: 110 HU with moderate sensitivity (52.1%) and excellent specificity (91.3%) in a population without risk factors of osteoporosis and 160 HU with an excellent sensitivity (90%) but a moderate specificity (52.3%) in a population with risk of osteoporosis [24].

Ethics approval and consent to participate

All data were available from usual care in patients with sclerosis. The ethics committee of Nancy hospital agreed with this study (referral file number 166). This study was designed in accordance with the general ethical principles outlined in the Declaration of Helsinki, patients gave their consent to use their medical data when they were cared at the university hospital.

Statistical analysis

Both descriptive and comparative analyses were conducted by accounting for the nature and distribution of the variables. Qualitative variables were described with frequencies and the percentage; quantitative variables were evaluated with the mean \pm SD (standard deviation) or with the median and interquartile range (IQR). The Kolmogorov–Smirnov test showed that among the continuous demographic and clinical variables, only age followed a normal distribution as a result the Student's t test was used for the age and the Mann–Whitney U test for the other variables. For qualitative variables, the Chi-square test and/or the exact calculation of Fisher was used. The Spearman's rho allowed for the analysis of the correlations for quantitative variables. The paired t test was used to compare the differences used in Bland–Altman analysis to 0 for intra-reader and inter-reader-reliability with concordance verified by the Cohen's test. Significant results (univariate and multivariate analysis) are presented with the odds ratio (OR) and its 95% confidence interval (CI 95%). A logistic regression was performed for the variables significantly associated with the SBAC-L1 145 HU threshold and not correlated with each other (age, calcinosis and the binary outcome being SBAC-L1 145 HU). To identify the profiles of the subjects, a classification system displayed

in a decision tree, i.e., the Chi-square automatic interaction detection (CHAID), was used to select the successive split variables associated with the SBAC-L1 145 HU threshold.

The risk α was established as 0.05, except for the inter-reader reliability study, where it was established at 0.01 given the repetition of the tests. IBM SPSS Statistics V22 was the software used for the data analysis.

Results

Demographic and clinical data

One hundred patients were selected from our request: 70 of them met the ACR/EULAR 2013 criteria and all of them were evaluated by a CT-scan during their follow-up. The population characteristics are presented in Table 1. Sixteen patients (22.9%) had diffuse cutaneous disease and 54 (77.1%) had limited cutaneous disease. Concerning the known clinical risk factors of osteoporosis: 47 women (67.1%) were menopausal (> 50 years), 17 (24.3%) patients smoked, 20 (28.6%) presented biological inflammation and 28 (40%) received corticosteroid treatment (average posology: 3.8 ± 6.6 mg/day). The differences between patients according to sclerosis clinical forms (diffuse or limited) are presented in Table 1.

Osteoporosis assessment

Sixty patients (85.7%) had at least one clinical risk factor for osteoporosis. The biology (calcemia and phosphoremia) was normal for all of the patients. During their follow-up, 30 patients (42.8%) had a DEXA: 5 (16.7%) were classified with osteoporosis, eight (26.7%) with osteopenia and 17 (56.7%) with normal bone density. Finally, for the 70 patients with systemic sclerosis, 18 patients (25.7%) received a supplementation with calcium and/or vitamin D and 10 (14.3%) a specific treatment for osteoporosis (antiresorptive therapy). For the 10 patients who received antiresorptive therapy, two had vertebral fracture and the others presented low T -score values on DEXA (≤ -2.5 SD) or high risk of fracture at 10 years (FRAX).

Vertebral fracture (VF) evaluation on CT-scan

For CT-scan, three women presented a vertebral fracture (4.3%): two on dorsal localizations (T10 and T11) and one on the lumbar spine (L2). The 3 VFs were classified as Genant 2 ($n=2$) and Genant 3 ($n=1$). Patients with VF were older (71.7 years versus 62.3 years) and had a lower disease duration (7 years versus 10.2 years). DEXA was available for only one of these three patients and was normal, while her SBAC-L1 was measured at 102.5 HU.

Table 1 Characteristics of the 70 patients with systemic sclerosis according to the clinical form (diffuse or limited sclerosis)

	Total population <i>n</i> = 70	Limited disease <i>n</i> = 54	Diffuse disease <i>n</i> = 16	<i>p</i>
Demographic/clinic				
Age (SD, years)	62.4 ± 15.6	62.9 ± 14.9	60.4 ± 18	0.57
Disease duration (years)	10 (5–13)	10 (5–13)	10 (5–13.8)	0.81
Women	62 (88.6)	50 (92.6)	12 (75)	0.07
Smoking	17 (24.3)	11 (20.4)	6 (37.5)	0.19
Obesity (BMI > 30 kg/m ²)	9 (12.9)	8 (14.8)	1 (6.3)	0.67
Digital ulcers	36 (51.4)	26 (48.1)	10 (62.5)	0.31
Capillaroscopy (<i>n</i> = 52)	46 (65.7)	35 (64.8)	11 (68.8)	0.99
Arthralgia	58 (82.9)	44 (81.5)	14 (87.5)	0.72
Rodnan score	6 (2–11)	4.5 (0–8)	13.5 (7.3–25.8)	0.0001
Dyspnoea stage III–IV	28 (40)	23 (42.6)	5 (31.3)	0.42
Death	9 (12.9)	7 (13)	2 (12.5)	0.99
Dyslipidaemia	29 (41.4)	21 (39)	8 (50)	0.43
Gastroesophageal reflux	42 (60)	32 (59)	10 (62.5)	0.82
Biology				
ESR (mm)	16.5 (10–32)	15 (10.0–30.0)	24.5 (10.0–48.0)	0.18
C reactive protein (mg/L)	4.4 (1.6–7.1)	4.5 (1.5–6.7)	3.6 (1.8–8.8)	0.99
Anticentromere antibodies (<i>n</i> = 63)	38 (54.3)	37 (68.5)	1 (6.3)	0.0001
Anti-SCL-70 antibodies (<i>n</i> = 63)	11 (15.7)	2 (3.7)	9 (56.3)	0.0001
Radiography and CT scan				
Calcinosis	16 (22.9)	13 (24.1)	3 (18.8)	0.75
Periarticular calcifications	20 (28.6)	17 (31.5)	3 (18.8)	0.53
Acro-osteolysis	14 (20)	10 (19)	4 (25)	0.72
Pulmonary involvement				
NSIP	9 (12.9)	6 (11.1)	3 (18.8)	0.42
UIP	5 (7.1)	3 (5.6)	2 (12.5)	0.32
Interstitial lung disease	18 (25.7)	11 (20.4)	7 (43.8)	0.10
DLCO/VA (<i>n</i> = 66)	18 (25.7)	14 (25.9)	4 (25)	0.99
PFT Restrictive respiratory disorder (<i>n</i> = 66)	6 (8.6)	3 (5.6)	3 (18.8)	0.15
PFT Obstructive respiratory disorder (<i>n</i> = 66)	14 (20)	13 (24.1)	1 (6.3)	0.16
PAH (<i>n</i> = 66)	8 (11.4)	6 (11.1)	2 (12.5)	0.68
Treatment				
Corticosteroid therapy	28 (40)	20 (37)	8 (50)	0.39
DMARD	19 (27.1)	14 (25.9)	5 (31.3)	0.75
Immunosuppressive drugs	6 (8.6)	3 (5.6)	3 (18.8)	0.13
Osteoporosis				
≥ 1 Osteoporosis risk factor	60 (85.7)	46 (85.2)	14 (87.5)	0.85
Number of DEXA	30 (42.8)	23 (42.6)	7 (43.8)	0.93
Osteoporosis on DEXA	5 (7.1)	3 (5.6)	2 (12.5)	0.57
VF	3 (4.3)	3 (5.6)	0 (0)	0.99
SBAC-L1	145.6 (120.9–189)	144.2 (120.9–177)	155.4 (114.7–219.3)	0.36
Calcium or vitamin D supplementation (<i>n</i> = 40)	18 (25.7)	16 (29.6)	2 (12.5)	0.15
Specific treatment for osteoporosis (<i>n</i> = 40)	10 (14.3)	8 (14.8)	2 (12.5)	0.99

The data in bold correspond to the results statistically significant

Qualitative data are described by headcount (percentage), whereas quantitative data are described by average ± SD for age or by median and interquartile index. Pulmonary involvement was determined by a specific CT scan evaluation for interstitial lung disease (ILD) in two categories: usual interstitial pneumonia (UIP) and non-specific interstitial pneumonia (NSIP). The duration of disease progression corresponded to the time between the date of diagnosis and the date of the imaging examinations

SD standard deviation, BMI body mass index, ESR erythrocyte sedimentation rate, DLCO/VA CO lung diffusion capacity, PFT pulmonary function testing, PAH pulmonary arterial hypertension, DMARD disease-modifying antirheumatic drugs, DEXA dual-energy absorptiometry, VF vertebral fracture, SBAC-L1 scanographic bone attenuation coefficient of the first lumbar vertebra

Reliability of the SBAC-L1 measurement

Intra-reader ($n = 70$) and inter-reader ($n = 30$) reliabilities are represented in Fig. 1a, b, respectively. For each of the analyses, the mean difference between the two measurements did not differ from 0 and were -0.79 HU ($t = -1.07$, $p = 0.29$) and 0.20 HU ($t = 0.11$, $p = 0.91$). In each analysis, the Bland–Altman method showed 95% confidence intervals of the mean of the differences with limits that could be considered acceptable in the context under study. We do not observe a trend in the differences as these differences seem to be constant according to the increasing values of the x -axis.

Considering the threshold at 145 HU, Cohen's Kappa resulted in an intra-reader value of 0.94 ($p = 0.0001$) with 68 concordant observations out of 70 and an inter-reader value of 0.93 ($p = 0.0001$) with 29 concordant observations out of 34. For the measurements available for the three readings ($n = 30$), the intra-class correlation coefficient was equal to 0.99 (CI 95% 0.995–0.998, $p < 0.0001$).

Evaluation of the SBAC-L1

The mean of the two intra-reader values was used to calculate the SBAC-L1. In our patients, the mean SBAC-L1 was 157.3 ± 52.2 HU and 35 patients (50%) had an SBAC-L1 ≤ 145 HU. The SBAC-L1 of the three patients with VF were 102.5, 131.4 and 171 HU.

Risk factors associated with a SBAC-L1 ≤ 145 HU

For the univariate analysis (Table 2), a diffuse form of sclerosis was not significantly associated with a SBAC-L1 ≤ 145 HU in comparison to the localized form. Other known osteoporotic risk factors such as gender, smoking or corticosteroid therapy were not significantly associated with a low SBAC-L1. However, age was significantly associated with a SBAC-L1 ≤ 145 HU ($p = 0.0001$). The mean age was 70 years for patients with SBAC-L1 ≤ 145 HU versus 54.7 years for patients with SBAC-L1 > 145 HU. The odds ratio associated with age was 1.09 (CI 95% 1.40–1.13), which corresponded to a 9% increased risk of SBAC-L1 ≤ 145 HU for one additional year. Calcinosis and periarticular calcifications were also significantly associated with a SBAC-L1 ≤ 145 HU ($p = 0.004$ and 0.03 , respectively). Their presence significantly increased the risk of SBAC-L1 ≤ 145 HU with an OR = 6.30 (CI 95% 1.61–24.75) and 3.22 (CI 95% 1.06–9.77), respectively.

The presence of a highly statistically significant relationship between calcinosis and periarticular calcifications (75% of those with calcinosis (12/16) also had periarticular calcifications (12/20) $p = 0.0001$) on one hand, and between periarticular calcifications and age on the other hand (mean 58.5 ± 14.2 years in the absence of periarticular calcifications versus 72.1 ± 14.9 years, $p = 0.001$), did not allow us to conduct a logistic regression association for them. Age and calcinosis showed no significant relationship (mean 60.9 ± 15.7 years in the absence of calcinosis versus 67.3 ± 14.8 years, $p = 0.2$). A logistic regression with age and calcinosis and the binary outcome being SBAC-L1 ≤ 145 HU, showed an overall significant result ($p = 0.0001$,

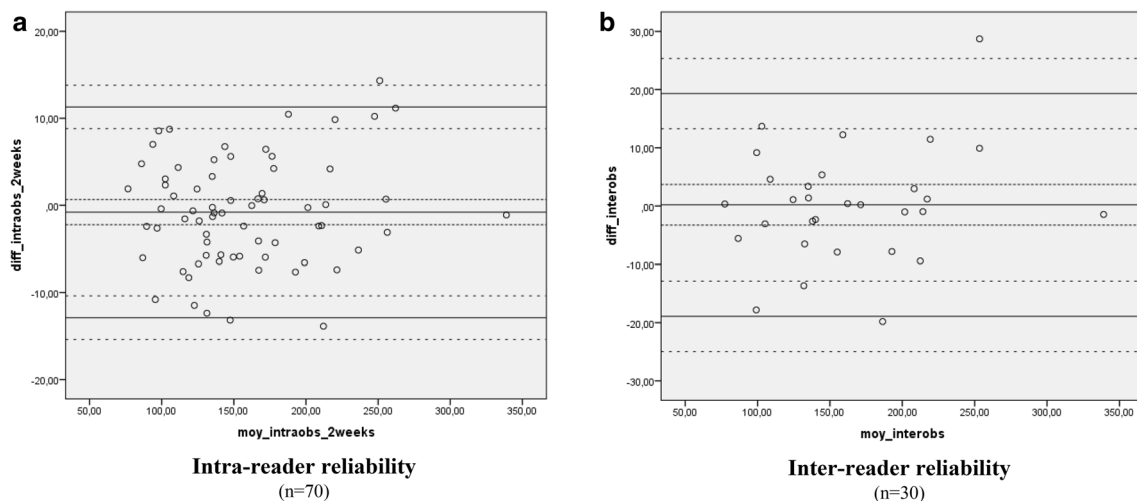


Fig. 1 The Bland–Altman method graph for intra- (a) and inter-reader (b) reliability. The difference between the two measurements for each observation is on the y -axis (HU), the mean of the two measurements for each observation is on the x -axis (HU), and the mean

of the differences between the two measurements with the 95% confidence interval is represented by the solid lines; 95% confidence intervals corresponding to these three values (average of the differences and its two associated limits) are the dotted lines

Table 2 Specific risk factors of SBAC-L1 ≤ 145 HU univariate analysis

SBAC-L1 <i>n</i> = 70	> 145 HU <i>n</i> = 35 (50%)	≤ 145 HU <i>n</i> = 35 (50%)	<i>p</i>	OR (CI 95%)
Demographic/clinic				
Age (SD, years)	54.7 \pm 15	70 \pm 12.2	0.0001	1.09 (1.04–1.13)/year
Disease duration (years)	9 (5–11)	10 (8–14.5)	0.06	
Women	32 (91.4)	30 (85.7)	0.71	
Smoking	8 (22.9)	9 (25.7)	0.78	
Obesity (BMI > 30 kg/m ²)	5 (14.3)	4 (11.4)	0.99	
Systemic sclerosis	9 (25.7)	7 (20)	0.99	
Digital ulcers	14 (40)	22 (62.9)	0.06	
Capillaroscopy (<i>n</i> = 52)	28 (80.0)	18 (51.4)	0.08	
Arthralgia	32 (91.4)	26 (74.3)	0.06	
Rodnan score	8 (2–11.5)	6 (2–9)	0.30	
Dyslipidaemia	11 (31)	18 (51.4)	0.09	
Gastroesophageal reflux	17 (49)	25 (71.4)	0.06	
Biology				
ESR (mm)	10 (10–29)	24 (11–34)	0.05	1.01 (0.99–1.03)
Anti-centromere antibody (<i>n</i> = 66)	20 (57.1)	18 (51.4)	0.96	
Anti-Scl70	6 (17.1)	5 (14.3)	0.87	
Radiography and CT scan				
Calcinosis	3 (8.6)	13 (37.1)	0.004	6.30 (1.61–24.75)
Periarticular calcifications	6 (17.1)	14 (40.0)	0.03	3.22 (1.06–9.77)
Acro-osteolysis	4 (11)	10 (28.6)	0.073	
Pulmonary involvement				
NSIP	5 (14.3)	4 (11.4)	0.99	
UIP	2 (5.7)	3 (8.6)	0.61	
DLCO/VA (<i>n</i> = 66)	8 (22.9)	10 (28.6)	0.69	
PFT restrictive disorder (<i>n</i> = 66)	3 (8.6)	3 (8.6)	0.99	
PFT obstructive disorder (<i>n</i> = 66)	5 (14.3)	9 (25.7)	0.28	
PAH (<i>n</i> = 66)	1 (2.9)	7 (20)	0.06	
Treatment				
Corticosteroid therapy	15 (42.9)	13 (37.1)	0.63	
DMARD	11 (31.4)	8 (22.9)	0.42	
Osteoporosis				
≥ 1 clinical risk factor	25 (71.4)	35 (100)	0.001	
Number of DEXA	12 (34.3)	18 (51.4)	0.15	
Spinal osteoporosis on DEXA	0 (0)	5 (14.3)	0.05	
VF	1 (2.9)	2 (5.7)	1	
Calcium or vitamin D supplementation (<i>n</i> = 40)	3 (8.6)	15 (42.9)	0.03	5.0 (1.12–22.30)
Specific treatment for osteoporosis (<i>n</i> = 40)	0 (0)	10 (28.6)	0.02	

The data in bold correspond to the results statistically significant

Qualitative data are described by headcount (percentage), whereas quantitative data are described by average \pm SD (Standard deviation) for age or by the median and interquartile index for other parameters. The duration of disease progression corresponded to the time between the date of diagnosis and the date of the performed imaging examinations. Age and disease duration are in years

SBAC-L1 scanographic bone attenuation coefficient of the first lumbar vertebrae, BMI body mass index, ESR erythrocyte sedimentation rate, NSIP non-specific interstitial pneumonia, UIP usual interstitial pneumonia, DLCO/VA CO lung diffusion capacity, PFT pulmonary function testing, PAH pulmonary arterial hypertension, DMARD disease-modifying antirheumatic drugs, DEXA dual energy absorptiometry, VF vertebral fracture

Hosmer–Lemeshow $p=0.3$, 71.4% ranked) with age and calcinosis, which remained significant when considered together [age, OR = 1.08 (CI 95% 1.04–1.13, $p=0.001$); calcinosis, OR = 6.04 (CI 95% 1.27–28.70, $p=0.02$)]. In the obtained CHAID decision tree, age was the first split variable between the two groups defined by SBAC-L1 145 HU with a threshold at 63 years (83% (29/35) SBAC-L1 \leq 145 HU over 63 years) (Online Resource 1 and 2). Among the 6 SBAC-L1 \leq 145 HU under 63 years of age, 50% (3/6) presented periarticular calcifications and acro-osteolysis.

SBAC-L1 evaluation with 160 and 110 HU thresholds

For a SBAC-L1 \leq 160 HU (a threshold with excellent sensitivity in a population with osteoporotic risk factors), 41 patients (58.6%) and 2 of the 3 patients with VF were under this threshold. For a SBAC-L1 \leq 110 HU (a threshold with excellent specificity), 13 patients (18.6%) were under this threshold. Figure 2 shows the distribution of the SBAC-L1 as a function of the three thresholds. When we look at the coefficient distribution according to age, we noted a decrease of SBAC-L1 with age.

Correlation between DEXA and CT-scan (SBAC-L1)

For the 16 patients who performed a DEXA with a delay, which did not exceed 2 years with the CT-scan, the mean bone mineral density of the spine was measured at 0.86 ± 0.16 g/cm², the mean SBAC-L1 was 137 ± 37.4 HU. Spearman's Rho showed no correlation between both modalities (0.2, $p=0.5$).

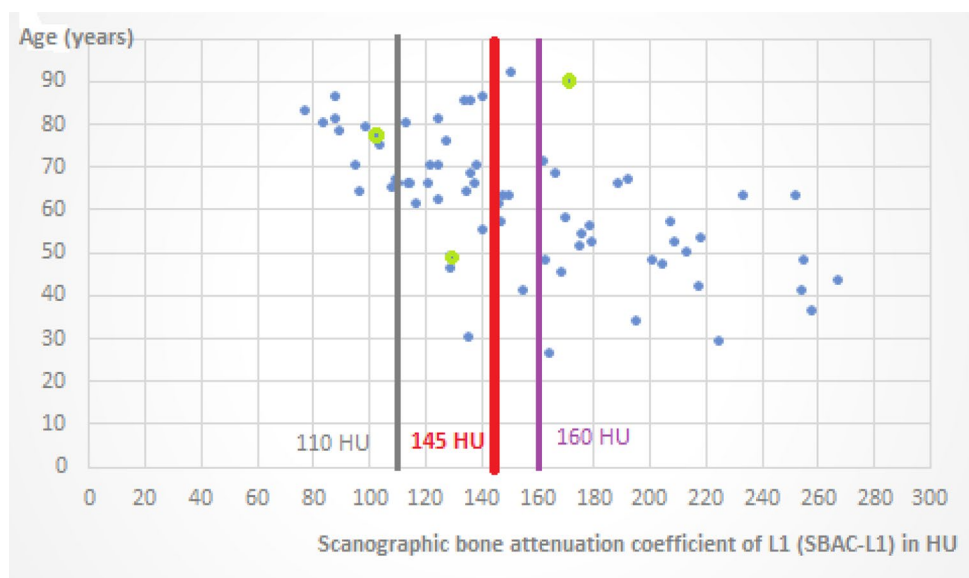
Discussion

In this study, we showed that the prevalence of VF on CT-scan was low (4.3%) whereas most of our patients (85.7%) presented at least one clinical risk factor for osteoporosis. We also showed that the presence of calcinosis, periarticular calcifications and acro-osteolysis on hand radiography was linked with low SBAC-L1, especially for patients under 63 years old.

We demonstrated in this study that we could both assess VF prevalence and measure trabecular bone mass (SBAC-L1 in HU) on CT-scans, with a highly reproducibility, in a population with systemic sclerosis [4, 27]. We showed that most of the patients presented at least one risk factor for osteoporosis (85.7%) but only 30 patients (42.8%) were screened by DEXA. This percentage was lower than those observed in a well-known population with osteoporotic risk, such as rheumatoid arthritis (58.2%) [28]. For these 30 patients, 16.7% ($n=5$) were diagnosed as osteoporotic on DEXA. This result was in agreement with those described in the literature with values ranging from 3 to 60% [5–7]. We also observed that supplementation with calcium and/or vitamin D and antiresorptive treatment prescription (25.7 and 14.3%, respectively) were low in a population where most of the patients presented at least one osteoporotic risk factor. Not surprisingly, similar results were found in the literature with supplementation with calcium and/or vitamin D ranging from 0 to 69% and specific anti-osteoporotic treatment ranging from 6 to 36.4% [8, 10, 14, 18, 21].

On CT-scan, three patients (4.3%) presented a VF. This prevalence was in agreement with data found in the literature and with values ranging from 0 to 38% [5, 7, 18, 20, 23].

Fig. 2 Scanographic bone attenuation coefficient of L1 (SBAC-L1) according to age with the three thresholds. The thresholds are presented on a continuous line (a grey line for the normal population and a threshold at 110 HU, a red line for a threshold at 145 HU, and a purple line for a population at risk and a threshold of 160 HU). The three patients with VF appear as green dots



Concerning SBAC-L1 measurement, it was an easy method, performed with high reliability (both intra- and inter-reader). This measure could also be directly performed by radiologists on the CT-work-station after CT-scan acquisition. We showed, for the first time in a large population with systemic sclerosis, that 50% of the patients presented a SBAC-L1 at the VF threshold ($\text{SBAC-L1} \leq 145$ HU), which suggested an underestimated risk of VF in patients with systemic sclerosis using DEXA.

Similar to DEXA, the SBAC-L1 was strongly dependant on the age ($\text{OR} = 1.09$) and mainly in patients over 63 years old. Interestingly, we showed that $\text{SBAC-L1} \leq 145$ HU was associated with some severe patterns of disease. Therefore, in younger patients with systemic sclerosis (less than 63 years old), a low SBAC-L1 value was strongly associated with calcinosis ($\text{OR} = 6.30$), periarticular calcifications ($\text{OR} = 3.22$), and to a lesser degree, acro-osteolysis. Some authors proposed physiopathological mechanisms to explain calcic deposits in soft tissues and secondary to a displacement of the calcium stocked in bone towards vascular and soft tissues [11, 19]. In our population, calcic deposits were not associated with biologic abnormalities since all of the patients had normal calcemia and phosphoremia. Interestingly, an association between age, calcinosis periarticular calcifications and acro-osteolysis was also described with osteoporosis measured with DEXA in other populations with systemic sclerosis [7, 17, 19, 22, 29]. We did not find an association between SBAC-L1 and a diffuse form of sclerosis. The literature data with DEXA showed an inconsistent association: sometimes the diffuse form was considered as risk factor [7, 13, 15, 20–22] and sometimes it was not related [5, 6, 10, 14, 17, 19]. Due to a lack of power, many specific risk factors tended to be significant: arthralgia and abnormal capillaroscopy seemed to be protective, whereas disease duration, acro-osteolysis, PAH, gastroesophageal reflux and digital ulcers seemed to get worse the risk. In the literature, some of the following parameters, including pulmonary or cardiac involvement [7, 13, 20–22], digital ulcers [8, 14, 21], and anticentromere antibodies [8, 14], were considered as risk factors and sometimes they were not related [5, 6, 10, 13, 14, 17, 22, 30]. Gender, smoking, and corticosteroid treatment were not associated with a low SBAC-L1 but similar results were found with DEXA [5, 8–10, 18, 31].

Limitations in this study were due to the studied segment of spine: for 26 patients (37.1%), the analysis was performed only on the thoracic segment (including L1). As a result, an underestimation of the lumbar VF prevalence should be considered. As described in the literature, two of the three VFs were localized in one of the regions of higher VF prevalence, e.g., the region from the T6 to T8 vertebrae and the region from the T11 to L1 vertebrae [31, 32]. For the patient with a VF and a SBAC-L1 at 171 HU, information concerning

the circumstances of her fracture was unavailable since this patient was dead and the diagnosis of an osteoporotic fracture could not be confirmed.

To be relevant, the threshold depended on one hand on the characteristics of the population studied in terms of osteoporotic risk, and on the other hand, on the VF prevalence in this population. With only three VFs observed, we were unable to calculate the optimum threshold of SBAC-L1 in terms of sensitivity and specificity. Indeed, the 110 HU threshold only permitted the identification of one patient with VF, whereas the 145 and 160 HU thresholds identified two patients with VF. From our point of view, the threshold at 145 HU allowed the best compromise between sensitivity and specificity for an osteoporotic fracture risk screening with SBAC-L1, but further studies would be warranted.

In clinical practice, DEXA is the gold standard for osteoporosis screening, but according to other studies, our results suggest, in a population with systemic sclerosis including 40% of patients with corticosteroid treatment, that this exam is insufficiently performed. The aim was not to substitute the SBAC-L1 measurement to the DEXA, but to obtain information concerning the trabecular bone mineralization of the first lumbar vertebra in patients for whom CT-scan was performed during the follow-up of their disease (according to good clinical practice) whereas DEXA was unavailable. Thoracic and TAP CT-scans were usually performed on sclerosis to evaluate pulmonary involvement and were always performed in our population responding to ACR/EULAR criteria for sclerosis. We showed that CT-scan was an alternative method to exclusively explore the trabecular bone without the cortical bone and to avoid artefacts due to 2D projection as observed on DEXA (osteophyte, bone condensation or disc/vascular calcifications [33–37] or mesenteric adenopathy).

To conclude, we showed, on a large sample of patients with systemic sclerosis and with osteoporosis risk factors that only 42.8% were screened for osteoporosis by DEXA, which classified 16.7% of them as osteoporotic. The VF prevalence was measured at 4.3% in CT-scan and 50% of the population presented SBAC-L1 under the fracture threshold (≤ 145 HU). The presence of calcinosis, periarticular calcifications and acro-osteolysis on hand radiography was linked with low SBAC-L1 and should lead to an osteoporosis screening, especially for patients under 63 years old.

Author contributions FM: corresponding author. Substantial contributions to the study conception and design and to acquisition, analysis and interpretation of the data; CT lectures with VF and SBAC-L1; intra-reader reproducibility; drafting the manuscript. BE: Substantial contributions to the acquisition of clinical data; revising the article critically for important intellectual content; final approval of the submitted version of the article to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. AE: substantial contributions to analysis and interpretation of

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Compliance with ethical standards

Conflict of interest All of the authors declare that they have no conflict of interest.

Research involving human participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.







Informed consent For this type of study formal consent is not required.

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