Trabecular Bone Score in Female Patients with Systemic Sclerosis: Comparison with Rheumatoid Arthritis and Influence of Glucocorticoid Exposure

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ABSTRACT. ***Objective.*** Systemic sclerosis (SSc) is associated with an increased risk of osteoporosis and fractures. To date, the etiology of bone loss in SSc is unclear. Trabecular bone score (TBS) provides an indirect measurement of bone microarchitecture, independent of areal bone mineral density (aBMD). The aims were to assess bone involvement in SSc using TBS in comparison with a "high-risk" population with rheumatoid arthritis (RA) and controls, and to investigate the determinants of a low TBS.

Methods. This was a cross-sectional study of 65 women with SSc, 138 age-matched female patients with RA, and 227 age-matched female controls. Spine and hip aBMD were assessed using dual-energy X-ray absorptiometry. TBS was calculated from the anteroposterior image of the spine aBMD.

Results. TBS was significantly lower in SSc compared to controls ($p < 0.0001$) and did not differ from RA ($p = 0.128$), despite lower cumulative and daily glucocorticoid (GC) dose ($p < 0.0001$). Further, patients with SSc receiving GC ≥ 5 mg/day had a significantly lower TBS than those receiving GC < 5 mg/day ($p = 0.001$). Multivariate analysis revealed that a low TBS was independently associated with daily GC dose (OR 5.6, 95% CI 1.7–19.2) and a T score ≤ –2.5 SD (OR 5.0, 95% CI 1.5–7.0) in SSc. No association between GC and TBS was found in RA.

Conclusion. Our results support the development of a combined approach using both TBS and aBMD for the assessment of bone microarchitecture in inflammatory rheumatic diseases. Our study showed that SSc-related bone involvement is characterized by an impairment in bone quality in addition to reduced bone quantity, and highlights that TBS can identify the negative effect of GC on bone microarchitecture. (First Release Dec 1 2014; J Rheumatol 2015;42:228–35; doi:10.3899/jrheum.140752)

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Osteoporosis (OP) and fractures are major causes of morbidity in subjects with rheumatic inflammatory diseases[1]. The etiology of bone loss in rheumatic diseases is multifactorial, involving age, disability, low body mass index (BMI), longstanding disease, disease-related systemic inflammation, and longterm glucocorticoid (GC) exposure[2,3,4].

Systemic sclerosis (SSc) is an orphan and severe connective tissue disorder causing vascular, immune, and fibrotic changes in the skin and some internal organs[5]. Bone involvement has been reported in numerous studies and is a major cause of morbidity in patients with SSc[6]. It is now clearly established that patients with SSc have lower areal bone mineral density (aBMD) than do healthy subjects[6,7,8,9,10,11,12]. Moreover, a higher prevalence of fractures in patients with SSc than in healthy patients was also shown[6,13]. In addition, our group recently demonstrated that the prevalence of OP and of fractures in SSc reached those observed in rheumatoid arthritis (RA), a typical rheumatic disease associated with secondary OP and considered as an independent OP risk factor[6,14]. Strikingly, one of the main findings was that the proportion of patients with fractures and/or OP was similar between patients with SSc and RA, despite milder GC exposure and shorter

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disease duration in SSc. Several candidate risk factors for OP in SSc have been suggested, including early menopause, low vitamin D status, intestinal malabsorption, systemic inflammation, GC exposure, and calcinosis[7,8,15,16]. To date, however, the determinants of bone loss in SSc are still not understood and the need to develop novel strategies for the prevention and treatment of SSc-associated OP are evident.

Currently, the gold standard for the diagnosis of OP, including secondary causes of OP, has been based on the use of aBMD[17]. However, one of the main pitfalls of aBMD is the considerable overlap between aBMD values in patients with and without fractures[18]. This observation is common in GC-related OP[19]. Indeed, epidemiological data indicate that fractures occur at higher T scores in patients exposed to GC compared with patients not exposed to GC[20,21,22]. Some explanations for the limitation in aBMD sensitivity are that (1) aBMD evaluates both the trabecular and cortical compartments, and (2) aBMD does not identify all of the factors contributing to bone strength, such as bone quality[23]. Bone microarchitecture has emerged over the past few years as a key determinant of bone strength[24]. To date, high-resolution computed tomography and magnetic resonance imaging are the only *in vivo* imaging techniques that can give direct information on trabecular bone microarchitecture. However, these techniques are not available in routine practice and can only be used at peripheral bone sites (i.e., radius or tibia). A novel clinical tool was developed to assess bone texture at the axial skeleton: the trabecular bone score (TBS)[25]. Although not a direct physical measure of microarchitecture, TBS measures spatial grey-level variations within the 2-dimensional projection of lumbar spine dual-energy X-ray absorptiometry (DEXA) image[23,25,26] that correlate with bone microarchitecture variables. A high TBS reflects a dense trabecular network, thus stronger and more fracture-resistant bone structure, whereas lower TBS reflects weaker bone[27]. In postmenopausal subjects, there is evidence showing that TBS is able to discriminate between subjects with versus without fractures and that it can predict incident fractures[27]. In addition, TBS has been used to study bone quality in secondary causes of OP, including RA[28], primary hyperparathyroidism, and hypercortisolism[29,30]. To the best of our knowledge, bone quality and its determinants have not been investigated in SSc.

The aims of our study were to assess bone quality in SSc using TBS in comparison with a "high-risk" population with RA and healthy controls, and to investigate the determinants of a low TBS in SSc as compared to RA.

MATERIALS AND METHODS

Study population. We performed a single-center cross-sectional study, including consecutive female patients with SSc and RA who had been hospitalized in the Rheumatology Department (Rheumatology A, Cochin Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France) for systematic followup on an 18-month period, as previously described[6]. All patients with SSc were classified as limited or diffused cutaneous SSc according to the LeRoy criteria[5]. All patients with RA fulfilled the American College of Rheumatology classification criteria for RA[31]. The local ethics committee approved the study and all subjects gave written informed consent. We also included a control group consisting of consecutive age-matched women addressed to our outpatient clinic by their gynecologist for suspicion of postmenopausal OP. These women were not affected by secondary causes of OP, including inflammatory rheumatic diseases, metabolic and endocrinological diseases known to induce OP, and drug-induced OP.

Clinical and radiographic assessment. Detailed information regarding medical history and medications was recorded, as previously described[6]. Demographic data included age, sex, height, weight, and BMI. Disease duration was defined as the time elapsed between the onset of the first disease-related symptoms (except for Raynaud phenomenon in SSc) and enrollment. Daily GC dose and cumulative GC dose were documented, as well as the use of biologics. The history of low-trauma osteoporotic major vertebral and nonvertebral fracture(s) was also collected. Vertebral fractures were assessed with lateral spinal radiographs of the thoracic and lumbar spines. Nonvertebral fractures included proximal femur, wrist, pelvis, proximal humerus, distal femur, and ribs fractures.

Bone densitometry and TBS measurement. DEXA measured aBMD at the lumbar spine (L1–L4), total hip, and femoral neck using a Prodigy (GE-Lunar) or QDR 4500 (Hologic) densitometer. Both instruments were cross-calibrated using anthropomorphic phantoms for aBMD. The cross-calibration for TBS was done by the manufacturer on each device before installing the software. TBS was evaluated at the lumbar spine (L1–L4) on the same DEXA acquisition used for aBMD assessment using TBS iNsight software (v1.8.2, Medimaps).

Statistical analysis. Statistical analyses were performed using MedCalc Software (v11.6.1, MedCalc Software). Data were expressed as mean ± SD for continuous variables, and numbers and percentages for categorical variables. Comparisons of group characteristics between SSc, RA, and control groups were evaluated by Mann-Whitney U test for unpaired data. Comparisons of proportions were performed using a chi-square test. Spearman rank correlation test was used to assess the relation between quantitative variables. TBS, aBMD, clinical variables, and fracture prevalence were first compared between the SSc, RA, and control groups. Associations between TBS, aBMD, and GC use or the presence of the fractures (vertebral or nonvertebral) in both SSc and RA groups, as expressed by the odds per SD, were evaluated using backward logistic regression models. Additional adjustments for age and BMI were performed. To assess the potential influence of GC use on TBS, patients were classified into 2 groups according to daily GC dose at the time of evaluation (≥ or < 5 mg/day). This threshold was chosen because it was the median GC dose in the SSc and RA-combined cohorts. For all analyses, a 2-tailed p value < 0.05 was considered statistically significant.

RESULTS

Study population. During our study period, 65 women with SSc, 138 with RA, and 227 controls with no secondary cause of OP were recruited (Table 1). Among patients with SSc, 21 had the diffuse cutaneous subset (32.3%) and 44 the limited cutaneous subset (67.8%). Pulmonary fibrosis on computed tomography scan was observed in 26 cases (40.0%), and pulmonary arterial hypertension on right heart catheterization in 5 (7.7%). Calcinosis was present in 15 patients (23.1%). Patients with SSc had a higher BMI than the RA and control groups (p = 0.013 and 0.0003, respectively; Table 1). In addition, the age of menopause was lower in the SSc group than in the control group (p = 0.031).

Table 1. Demographic and clinical characteristics of patients with SSc, RA, and controls. Vitamin D insufficiency was defined by a 25-hydroxy vitamin D level < 30 ng/l. Values are % or mean ± SD unless otherwise specified.

Characteristics	SSc, n = 65	RA, n = 138	Controls, n = 227	SSc vs RA, p	SSc vs Controls, p	RA vs Controls, p
Age, yrs	61.6 ± 11.0	61.1 ± 10.7	60.1 ± 7.9	0.654	0.149	0.381
BMI, kg/m^2	26.5 ± 4.8	24.8 ± 4.9	24.2 ± 3.8	**0.013**	**0.0003**	0.391
Menopause	88.9	92.4	95.6	0.591	0.089	0.303
Age of menopause, yrs	48.1 ± 4.6	48.9 ± 5.7	49.5 ± 4.3	0.141	**0.031**	0.573
Early menopause, ≤ 40 yrs	8.3	9.9	3.9	0.990	0.395	0.095
Disease duration, yrs	10.2 ± 8.6	17.3 ± 10.9	NA	**< 0.0001**	NA	NA
GC	51.6	97.8	NA	**< 0.0001**	NA	NA
Cumulative GC dose, mg	8630 ± 14,044	35,522 ± 28,599	NA	**< 0.0001**	NA	NA
GC dose at time of BMD, mg	3.3 ± 3.9	6.8 ± 4.5	NA	**< 0.0001**	NA	NA
C-reactive protein, mg/l	7.0 ± 8.8	11.9 ± 19.4	NA	0.086	NA	NA
Calcium intake, mg/day	723 ± 492	725 ± 344	731 ± 314	0.509	0.28	0.721
Vitamin D supplementation, current	48.1	64.6	24.9	0.091	**0.002**	**< 0.0001**
25(OH)D insufficiency	86.2	85.5	NA	0.93	NA	NA
PTH level above 46 ng/l	37.0	25.4	NA	0.13	NA	NA
Smoking status, current	5.6	6.7	16.7	0.795	0.138	0.141
Alcohol intake, current	5.6	2.7	6.4	0.927	0.851	0.537
Hormone replacement therapy, current	16.0	22.9	29.6	0.432	0.08	0.432
Bisphosphonates, ever	33.8	42.0	4.9	0.336	< 0.0001	< 0.0001

Significant data are in bold face. NA: not applicable; SSc: systemic sclerosis; RA: rheumatoid arthritis; BMI: body mass index; GC: glucocorticoid; BMD: bone mineral density; 25(OH)D: 25-hydroxy Vitamin D; PTH: parathyroid hormone.

Mean disease duration was shorter in SSc than in RA ($p < 0.0001$). Patients with SSc were less likely to receive GC ($p < 0.0001$) in comparison with patients with RA. Both the daily GC dose and the cumulative doses of GC were significantly lower in patients with SSc than in those with RA ($p < 0.0001$ and $p < 0.0001$, respectively). The mean C-reactive protein value at the time of our study tended to be lower in patients with SSc than with RA, although not significantly ($p = 0.086$).

Correlation between TBS and aBMD. TBS was significantly, but only moderately, correlated with lumbar spine aBMD in all groups: $r = 0.47$ ($p = 0.0002$) in SSc, $r = 0.45$ ($p < 0.0001$) in RA, and $r = 0.38$ ($p < 0.0001$) in controls (Table 2). Similar correlations were obtained between TBS and aBMD at the femoral neck: $r = 0.49$ ($p = 0.0001$) in SSc, $r = 0.32$ ($p = 0.0002$) in RA, and $r = 0.28$ ($p < 0.0001$) in controls.

Comparison of patients with SSc and RA. There was no significant difference in mean lumbar spine TBS between patients with SSc and RA (1.207 ± 0.145 vs 1.247 ± 0.136, $p = 0.128$; Table 3). aBMD at the lumbar spine, femoral neck, and total hip did not differ between groups (Table 3). The prevalence of fractures (29.2% vs 33.3%, $p = 0.682$) was similar in both groups.

Comparison of patients with SSc and controls. Lumbar spine TBS was significantly lower in patients with SSc compared with controls (1.207 ± 0.145 vs 1.294 ± 0.121, $p < 0.0001$; Table 3). This result remained significant after adjustment for age, BMI, and lumbar spine aBMD ($p = 0.002$). Lumbar spine aBMD was also significantly lower in the SSc group ($p = 0.022$), but this result did not remain significant after adjustment for age, BMI, and TBS ($p = 0.150$).

Comparison of patients with RA and controls. Lumbar spine TBS was significantly lower in patients with RA compared with controls (1.247 ± 0.136 vs 1.294 ± 0.121, $p = 0.0009$). Lumbar spine aBMD was also significantly lower in the RA group (1.001 ± 0.202 vs 1.060 ± 0.170, $p = 0.002$). These results remained significant after adjustment for age, BMI, TBS, and lumbar spine aBMD ($p = 0.0284$ for TBS and $p = 0.0483$ for lumbar spine aBMD).

Association of GC daily dose with TBS. In patients with SSc receiving a GC dose of 5 mg/day or more (n = 29), mean TBS was significantly lower than in controls (1.138 ± 0.158 vs 1.294 ± 0.121, $p < 0.0001$; Figure 1). This result remained significant after adjustment for age, BMI, and lumbar spine aBMD ($p < 0.0001$). Lumbar spine aBMD was also significantly different between groups (0.962 ± 0.189 vs 1.060 ± 0.170, $p = 0.003$), but this did not remain significant after adjustment for BMI, TBS, and age ($p = 0.0895$).

Table 2. Spearman rank correlation test between TBS and aBMD.

TBS	Lumbar Spine aBMD	Femoral Neck aBMD
SSc	r = 0.47	r = 0.49
	p = 0.0002	p = 0.0001
RA	r = 0.45	r = 0.32
	p < 0.0001	p = 0.0002
Controls	r = 0.38	r = 0.28
	p < 0.0001	p < 0.0001

TBS: trabecular bone score; aBMD: areal bone mineral density; SSc: systemic sclerosis; RA: rheumatoid arthritis.

Table 3. Comparison of bone involvement assessed by aBMD and TBS in SSc, RA, and controls. Values are n (%) or mean ± SD unless otherwise specified.

Characteristics	SSc, n = 65	RA, n = 138	Controls, n = 227	SSc vs RA, p	SSc vs Controls, p	RA vs Controls, p
Lumbar spine TBS	1.207 ± 0.145	1.247 ± 0.136	1.294 ± 0.121	0.128	**< 0.0001**	**0.0009**
Lumbar spine aBMD, g/cm^2	1.007 ± 0.179	1.001 ± 0.202	1.060 ± 0.170	0.761	**0.022**	**0.002**
Femoral neck aBMD, g/cm^2	0.784 ± 0.142	0.768 ± 0.133	0.842 ± 0.127	0.500	**0.0005**	**< 0.0001**
Total hip aBMD, g/cm^2	0.844 ± 0.137	0.814 ± 0.140	0.902 ± 0.136	0.168	**0.003**	**< 0.0001**
Fracture rate	19/65 (29.0)	46/138 (33.3)	24/227 (10.6)	0.682	**0.0004**	**< 0.0001**
Peripheral fractures	13/65 (20.0)	33/138 (23.9)	23/227 (10.1)	0.649	**0.051**	**0.0007**
Vertebral fractures	10/65 (15.4)	20/138 (14.5)	2/227 (0.09)	0.980	**< 0.0001**	**< 0.0001**
T score ≤ –2.5 SD at 1 site or more	27/65 (41.5)	59/138 (42.7)	39/227 (17.1)	0.993	**0.0001**	**< 0.0001**

Significant data are in bold face. aBMD: areal bone mineral density; TBS: trabecular bone score; SSc: systemic sclerosis; RA: rheumatoid arthritis.

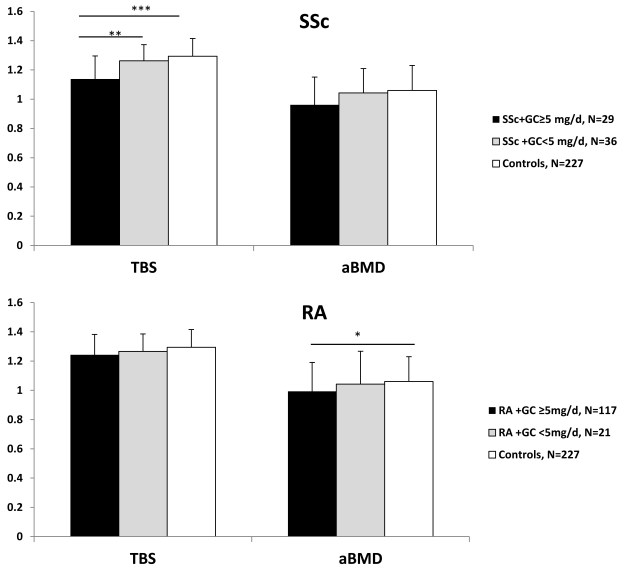

Figure 1. P value adjusted for age, body mass index, lumbar spine TBS, and aBMD. * p = 0.02. ** p = 0.01. *** p < 0.0001. Comparison of TBS and lumbar spine aBMD between patients with SSc, patients with RA, and healthy controls according to daily GC dose. TBS: trabecular bone score; aBMD: areal bone mineral density; SSc: systemic sclerosis; RA: rheumatoid arthritis; GC: glucocorticoid.

On the other hand, there was no difference in TBS and aBMD between patients with SSc receiving less than 5 mg/day and controls (TBS 1.263 ± 0.105 vs 1.294 ± 0.121, p = 0.104 and aBMD 1.043 ± 0.166 vs 1.060 ± 0.170, p = 0.550).

In addition, intracohort analysis showed that TBS was lower in patients with SSc with GC ≥ 5 mg/day (n = 29) compared with patients receiving < 5 mg/day (n = 36; 1.138 ± 0.158 vs 1.263 ± 0.105, p = 0.011). TBS was also significantly lower in patients with SSc who received GC compared with patients with SSc who had never received GC (1.156 ± 0.159 vs 1.256 ± 0.107, p = 0.01). Although a similar trend was observed in the RA group, the association between GC dose and TBS was not significant after adjustment for age and BMI (Figure 1). Intracohort analysis did not reveal any association between GC daily dose ≥ 5 mg/day and TBS in the RA cohort (not shown).

Association of fractures with TBS. In the SSc group, intracohort analysis showed that TBS was lower in patients with SSc with prevalent fractures (n = 19) compared with patients with no history of fracture (n = 46; 1.145 ± 0.166 vs 1.233 ± 0.129, p = 0.019). aBMD was also significantly lower in patients with SSc with fractures versus without fractures (0.893 ± 0.174 vs. 1.054 ± 0.157, p = 0.0001). These results were also observed in the RA population (TBS 1.214 ± 0.131 vs 1.265 ± 0.135, p = 0.045 and aBMD 0.924 ± 0.174 vs 1.043 ± 0.206, p = 0.001).

Factors associated with a low TBS value. To further investigate and compare the determinants of a low TBS in patients with SSc and RA, we divided each of the SSc and RA cohorts into tertiles according to TBS values.

The distribution of TBS values into tertiles was the following in the SSc cohort: 0.725–1.167, 1.175–1.265, and 1.275–1.427. In the RA cohort, the distribution was 0.870–1.196, 1.197–1.315, and 1.316–1.538.

Factors associated with a low TBS value in the SSc cohort. We subsequently compared patients with SSc with a TBS in the lowest tertile (TBS ≤ 1.167, n = 22) with patients with SSc with a TBS value in the 2 upper tertiles (TBS > 1.167, n = 43; Table 4). In univariate analysis, patients with a low TBS value (n = 22) were more likely to have received GC, to have a higher cumulative dose of GC and higher daily GC dose, to have a T score ≤ –2.5 SD, and a history of fracture than patients with SSc with a TBS in the 2 higher tertiles. Daily and cumulative GC doses were highly correlated (r = 0.602, p < 0.001). In logistic regression analysis, including all variables identified with a p value ≤ 0.1, daily GC dose ≥ 5 mg/day and a T score ≤ –2.5 were found to be independently associated with a low TBS (OR 5.6, 95% CI 1.7–19.2 and OR 5.0 95% CI 1.5–17.0, respectively).

No association was observed with disease-specific characteristics, including the cutaneous subtype, the existence of vascular or intestinal involvement, calcinosis, and pulmonary fibrosis (Table 4).

Factors associated with a low TBS value in the RA cohort. In univariate analysis, patients with RA with a low TBS value (TBS ≤ 1.196, n = 46) were significantly older, were more likely to have a T score ≤ –2.5 SD, and to have

Table 4. Factors associated with a low TBS value in the SSc cohort. Values are % or mean ± SD unless otherwise specified.

SSc, n = 65	TBS ≤ 1.167, n = 22	TBS > 1.167, n = 43	p
Age, yrs	63.7 ± 9.8	60.5 ± 11.5	0.5
Disease duration, yrs	11.4 ± 8.4	9.6 ± 8.8	0.2
Diffuse cutaneous subset	31.8	32.6	0.8
Pulmonary fibrosis	36.1	37.2	0.9
Pulmonary arterial hypertension	13.6	4.7	0.4
Calcinosis	31.8	18.6	0.4
Menopause	90.3	88.1	0.9
Age of menopause, yrs	49.1 ± 3.5	47.5 ± 5.1	0.3
GC	72.7	40.5	0.03*
Daily GC dose ≥ 5 mg/day	72.7	30.2	0.003*
Cumulative GC dose, mg	14,359 ± 16,408	5975 ± 12,123	0.04*
C-reactive protein ≥ 10 mg/l	30	13.5	0.2
T score ≤ –2.5 SD at 1 site or more	68.2	27.9	0.004*
Osteoporotic fracture	50	18.6	0.02*
25(OH)D insufficiency	85.7	88.9	0.6
Bisphosphonates	44.4	28.1	0.4

*Variables with p value of univariate analysis ≤ 0.1 included in the logistic regression analysis. TBS: trabecular bone score; SSc: systemic sclerosis; GC: glucocorticoid; 25(OH)D: 25-hydroxy Vitamin D.

received bisphosphonates than patients with RA with TBS in the 2 higher tertiles (n = 92; Table 5). In logistic regression analysis, including all variables identified with a p value ≤ 0.1, age and bisphosphonate exposure were found to be independently associated with a low TBS value (OR 1.11, 95% CI 1.06–1.16 and OR 3.4, 95% CI 1.37–8.46, respectively). No association was observed with disease severity and characteristics including anticyclic citrullinated peptide antibody levels and the presence of erosions (Table 5).

DISCUSSION

Despite the increasing awareness of SSc-related bone loss in recent years, the determinants of bone fragility in this disease still remain largely unknown. We reported that the risk of OP and fractures in patients with SSc reached that of patients with RA and was higher than in healthy subjects[6]. In the same report, age and vitamin D insufficiency were identified as risk factors for fractures in patients with SSc, which was consistent with another study[13]. Results concerning other candidate risk factors, including the age of menopause, low BMI, and GC exposure, have yielded either negative or conflicting results. For example, cumulative GC exposure was not found to be associated with SSc-related OP by several groups[6,10,13]. Over the past few years, it has become clear that bone microarchitecture is an important determinant of bone strength, and that the assessment of bone quality may bring additional information that may have been missed by DEXA evaluation. Indeed, one of the

Table 5. Factors associated with a low TBS value in the RA cohort. Values are % or mean ± SD unless otherwise specified.

RA, n = 138	TBS ≤ 1.196, n = 46	TBS > 1.196, n = 92	p
Age, yrs	67.2 ± 8.7	58.2 ± 10.5	< 0.0001*
Disease duration, yrs	16.5 ± 10.4	17.8 ± 11.2	0.6
Erosions	82.6	80.4	0.9
Positive anti-CCP antibodies	56.5	59.8	0.9
Menopause	100	89.1	0.07*
Age of menopause, yrs	48.3 ± 4.9	49.1 ± 5.98	0.28
GC, %	97.8	97.9	0.55
Daily GC dose ≥ 5mg/day	85.7	83.4	0.93
Cumulative GC dose, mg	33,891 ± 24,421	36,292 ± 30,504	0.99
C-reactive protein ≥ 10 mg/l	39.3	29.2	0.47
T score ≤ –2.5 SD at 1 site or more	59.1	35.1	0.01*
Osteoporotic fracture	43.2	31.9	0.27
25(OH)D insufficiency	85.7	85.7	1
Biologics	45.2	47.6	0.94
Bisphosphonates	68.4	30.1	0.0002*

* Variables with p value of univariate analysis ≤ 0.1 included in the logistic regression analysis. TBS: trabecular bone score; RA: rheumatoid arthritis; anti-CCP: anticyclic citrullinated peptide antibodies; GC: glucocorticoid; 25(OH)D: 25-hydroxy Vitamin D.

major limitations of DEXA in the management of OP related to chronic inflammatory diseases is the discrepancy between T score values and prevalent fractures[18]. The main aims of our study were, therefore, to increase the understanding of bone loss in SSc by investigating TBS as an indirect marker of bone quality, and to study the clinical variables associated with a low TBS in patients with SSc in comparison with a high-risk control group composed of age- and sex-matched patients with RA.

In our present study, we show that TBS was lower in patients with SSc than in controls. To our knowledge, this indicates for the first time that SSc-related bone involvement could be attributable to an impairment in bone quality, in addition to reduced bone quantity. Further, TBS did not differ between patients with SSc and RA, and was lower in patients with SSc receiving GC compared with patients with RA who received GC, despite lower cumulative and daily GC dose and shorter disease duration, suggesting that the negative effect of GC on bone microarchitecture may be more important in SSc than in RA. This raises the question of the possible mechanisms of such an important bone microarchitecture involvement despite milder exposure to known risk factors for OP. One may hypothesize that GC exposure in SSc directly damages bone microarchitecture, already damaged by SSc-specific pathophysiological processes such as fibrosis and ischemia. Although it would be interesting to have further information on SSc-related bone loss and on the possible contribution of local ischemia and/or fibrosis, there is no histomorphometric description of SSc bone, to our knowledge.

Interestingly, in our study, TBS also helped to discriminate patients with SSc according to daily GC dose, which is consistent with the well-known association between GC and bone microarchitecture deterioration[2], and supports that TBS may be able to detect GC-induced trabecular alterations. Indeed, TBS was significantly lower in patients with SSc receiving GC ≥ 5 mg/day than in healthy controls, whereas there was no difference between patients with SSc receiving less than 5 mg/day and healthy controls. Moreover, TBS was lower in patients with SSc receiving GC ≥ 5 mg/day than in patients receiving < 5 mg/day GC. It should be underscored that GC had been received by only half of the patients with SSc, and that daily GC doses were low at the time of our study, as expected in SSc. Indeed, because the use of GC in SSc is known to increase the risk of renal crisis, this treatment is mainly limited to patients with SSc who have muscular or interstitial lung involvement.

To further assess the determinants of a low TBS in our study population, we compared patients with a low TBS with those with a TBS value in the 2 upper tertiles. We showed that GC exposure was independently associated with a low TBS value in patients with SSc. Conversely, and surprisingly, we did not observe any association between GC exposure and a low TBS value in the RA study population. Although GC have known adverse effects on bone, such as an increase in bone resorption by the upregulation of the receptor activator of nuclear factor-κB ligand and downregulation of osteoprotegerin in osteoblasts, there is increasing evidence that GC suppression of proinflammatory cytokines could be beneficial for bone integrity[32]. These cytokines include tumor necrosis factor, interleukin (IL) 1, and IL-6. Indeed, several studies reported a positive effect of GC and/or biologic therapies on bone[33,34,35]. The negative association between biologic therapies and fracture prevalence observed in patients with RA supports this hypothesis[6]. On the other hand, the benefit of antiinflammatory treatments on bone may not be as relevant in a disease such as SSc, where inflammation is not the prevailing process.

Interestingly, vitamin D insufficiency was not associated with a low TBS, whereas it is known to be associated with low BMD in SSc[6]. This is not unexpected because TBS is mainly known to detect bone microarchitecture deteriorations whereas BMD detects, more specifically, bone mineralization and bone quantity defects, and that vitamin D insufficiency is essentially known to reduce bone mineralization. This highlights the complementarity of TBS and BMD, which assess different aspects of bone.

Importantly, our study also shows that TBS was able to discriminate between patients with versus without fractures, both in SSc and in RA. Indeed, there is accumulating evidence showing that the combined use of aBMD and TBS may improve the evaluation of fracture risk in postmenopausal women, and that the prediction of fracture risk by TBS is independent of aBMD and of clinical factors[27,36]. To date, there are only a few studies investigating TBS in secondary OP, including 1 study on secondary OP related to chronic inflammatory rheumatic diseases[28]. In that study, Breban, *et al* reported that TBS was significantly lower in patients with RA with vertebral fractures as compared with patients without vertebral fractures (1.131 ± 0.195 vs 1.245 ± 0.106, p = 0.0001), which is consistent with our findings in SSc-related OP. Emerging data from several other studies also highly suggest that the evaluation of bone texture by TBS can bring additional information to aBMD on fracture risk in several populations, including adrenal incidentaloma with hypercortisolism[30], primary hyperparathyroidism[29,37,38], and diabetes[39]. The effect of bisphosphonate use on TBS has also been investigated with results indicating an increase in TBS in patients receiving zoledronic acid[40]. Noteworthy, bisphosphonate use was associated with a low TBS in our present study. This result can be explained by the cross-sectional design of our study and reflects the severity of bone involvement in the RA "high-risk" group, which justified the prescription of bisphosphonates because of OP or fractures. Our study also raises the important question of the TBS threshold to use for the decision process, which to date remains unanswered in both postmenopausal and

secondary OP. In our present study, the very close TBS values of 1.167 and 1.196 were found as defining the lowest TBS tertile in the SSc and RA cohorts, and were able to discriminate patients according to daily GC dose in the SSc cohort. Although our study was not designed to answer this specific question, our results suggest that a TBS threshold of around 1.200 may be useful for future clinical applications. This will need to be assessed in prospective studies.

Our study is not without limitations. The most relevant is that ours is a cross-sectional study. Hence, we cannot directly imply a causative association between a low TBS value and the occurrence of fractures. Also, the small number of vertebral fractures in the SSc group led us to take into account both vertebral and nonvertebral fractures, a move that may contribute to the limitations of our study because TBS may have better predictability for vertebral fractures. Further, the evaluation of systemic inflammation by a single measurement of C-reactive protein does not exclude the possible role of inflammation. The vast majority of patients with SSc and RA were in postmenopause and had severe disease related to the fact that they were all hospitalized in a tertiary center at the time of evaluation. Therefore, our data are not applicable to younger and/or male patients with less severe disease.

Our results support the development of a combined clinical approach using both TBS and aBMD for the prediction of fracture risk in SSc, and maybe in all inflammatory rheumatic diseases and in GC-induced OP. Further investigations are required to identify the threshold of TBS, and to further assess the relationship between GC exposure and TBS. Our findings indicate that SSc-related bone involvement may be attributable to bone microarchitecture deterioration and point to a negative effect of GC exposure on bone microarchitecture in SSc, which should further limit the use of GC in SSc. These results also highlight that TBS is able to detect the negative effect of GC on bone microarchitecture, suggesting that TBS, in addition to aBMD, could be a useful tool in the assessment of GC-induced OP.

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