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Vertebral fracture prevalence and measurement of the scanographic bone attenuation coefficient on CT-scan in 70 patients with systemic scleroderma

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- Conflict of Interest:

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

Introduction

Systemic scleroderma 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 to 90% for the limited cutaneous disease and 60 to 80% for the systemic disease) [1,2,3] requires better management of comorbidities, especially for osteoporosis in this population, which is mainly composed of women (3 to 8 women for every man) with a disease beginning between 45 and 64 years [4]. Until now, osteoporosis screening in scleroderma was conducted in a subgroup of patients for whom Dual Energy X-ray Absorptiometry (DXA) and /or radiographic assessment were available. The studies based on DXA found a large range of osteoporosis prevalence varying from 3 to 60% [5,6,7]. In comparison with the general population, some authors found an increased risk for osteoporosis, but other authors did not confirm this increased risk [5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22]. Some studies comparing sclerodermic and rheumatoid patients (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 have also shown 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]. The proposed physiopathological mechanisms explain that osteoporosis in this population is multifactorial: loss of mobility and strains on bone in severe systemic sclerosis [6,10,11,15,19,20,21,22], 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 scleroderma and mainly to evaluate lung involvement, allows 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 $SBAC-L1 \leq 145$ HU (Hounsfield Units) permitted to identify 96.6% of the patients with VF, whereas DXA (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 scleroderma patients who were assessed or not by DXA. The secondary objectives were to determine the prevalence of osteoporotic risk factors and to identify factors associated with VF and $SBAC-L1 \leq 145$ 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 scleroderma. 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 scleroderma. Patients were included if they had a thoracic TAP CT-scan during the 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), and phosphocalcic evaluation) characteristics and treatments concerning scleroderma were collected on all of the medical records (anterior to the CT-scan). 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 DXA and anti-osteoporotic treatments were recorded in the two years before or after the CT-scan. For DXA, osteoporosis is classically retained for a T-Score ≤ -2.5 SD on the spine and osteopenia with $-2.5 < \text{T-score} \leq -1$ 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 according to an adaptation of the Genant's classification, which is usually used on spine radiographs [26]. The grade was determined on the most severe lesion observed on one of the sagittal 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 two 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 DXA (with T score ≤ -2.5 SD) identified only 39% of the VF in the same population. A SBAC-L1 ≤ 145 HU allows 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 scleroderma. The ethical committee of Nancy hospital was agree 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 care 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. In the comparisons, 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 with, if necessary, the exact calculation of Fisher was used. The Spearman's rho allowed for the analysis of the correlations and the paired t-test was used to compare the differences to 0. 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. 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.

To analyse the intra-reader and the inter-reader reliability, we used the intra-class correlation coefficient (ICC) and the Bland-Altman limits of agreement (LOA) method. To study the concordance in the context of this study, we also used the Cohen's kappa to analyse the readers' agreement according to the threshold of 145 HU provided by the literature. 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 benefited from a CT-scan. The population characteristics are presented in Table 1. Sixteen patients (22.9%) had diffuse 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 scleroderma 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. Phosphocalcic evaluation was normal for all of the patients. During their follow-up, 30 patients (42.8%) had a DXA: 5 (16.7%) were classified with

osteoporosis, eight (26.7%) with osteopenia and 17 (56.7%) with normal bone density. Finally, for the 70 sclerodermic patients, 18 patients (25.7%) received a vitaminocalcic supplementation and 10 (14.3%) a specific treatment for osteoporosis (antiresorptive therapy).

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). 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). DXA was available for only one of these three patients and was normal, while her SBAC-L1 was measured at 102.5 HU.

Reliability of the SBAC-L1 measurement

Intra-reader (n=70) and inter-reader (n=30) reliabilities are represented in Figures 1a and 1b, 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. There was no trend in the averages of the two measures and their differences. Observations outside the 95% confidence intervals of the mean of the differences were four of the 70 observations (5.7%) and two of the 30 observations (6.7%).

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 3 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 \leq 145 HU

For the univariate analysis (Table 2), a diffuse form of scleroderma was not significantly associated with a SBAC-L1 \leq 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 \leq 145 HU ($p=0.0001$). The mean age was 70 years for patients with SBAC-L1 \leq 145HU 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 \leq 145 HU for one additional year. Calcinosis and periarticular calcifications were also significantly associated with a SBAC-L1 \leq 145 HU ($p=0.004$ and 0.03 , respectively). Their presence significantly increased the risk of SBAC-L1 \leq 145 HU with an OR=6.30 (CI 95%: 1.61-24.75) and 3.22 (CI 95%: 1.06-9.77), respectively. A higher erythrocyte sedimentation rate was also associated with a SBAC-L1 \leq 145 HU within the limit of the significance level, with an OR of 1.01 (CI 95%: 0.99-1.03). Other factors such as a longer disease duration, digital ulcer, gastroesophageal reflux, pulmonary arterial hypertension, dyslipidaemia and acro-osteolysis tended to be associated with a SBAC-L1 \leq 145 HU. Abnormal capillaroscopy and arthralgia tended to be associated with SBAC-L1 $>$ 145 HU (p are presented in Table 2).

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 vs. 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 vs. 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 ($p=0.0001$, 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 ≤ 160 HU (a threshold with excellent sensitivity in a population with osteoporotic risk factors), 41 patients (58.6%) and two of the three patients with VF were under this threshold. For a SBAC-L1 ≤ 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 note a decrease of SBAC-L1 with age.

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

For the 16 patients who performed a DXA with a delay, which did not exceed two 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

To our knowledge, this is the first study with an evaluation of VF prevalence and a measure of trabecular bone mass (SBAC-L1 in HU) on CT-scans in a sclerodermic population [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 DXA. This percentage is 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 DXA. This result was in agreement with those described in the literature with values ranging from 3 to 60% [5,6,7]. We also observed that vitaminocalcic supplementation and antiresorptive treatment prescription (25.7% and 14.3%, respectively) were low in a population where most of the patients presented with at least one osteoporotic risk factor. Not surprisingly, similar results were found in the literature with vitaminocalcic supplementation 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].

Concerning SBAC-L1 measurement, it is an easily 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 sclerodermic population, that 50% of the patients presented a SBAC-L1 at the VF threshold ($\text{SBAC-L1} \leq 145 \text{ HU}$), which suggests an underestimated risk of VF in sclerodermic patients using DXA.

Similar to DXA, 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 $\text{SBAC-L1} \leq 145 \text{ HU}$ was associated with some severe patterns of disease. Therefore, in younger sclerodermic patients (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 a normal phosphocalcic evaluation. Interestingly, an association between age, calcinosis periarticular calcifications and acro-osteolysis was also described with osteoporosis measured with DXA in other sclerodermic populations [7,17,19,22,31]. We did not find an association between SBAC-L1 and a diffuse form of scleroderma. The literature data with DXA showed an inconsistent association: sometimes the diffuse form was considered a risk factor [7,13,15,20,21,22] 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 tended to be significantly and positively related. In the literature, some of the following parameters, including pulmonary or cardiac involvement [7,13,20,21,22], digital ulcers [8,14,21], and anticentromere antibodies [8,14], are considered risk factors and sometimes they are not related [5,6,10,13,14,17,22,32]. Gender, smoking, and corticosteroid treatment were not associated with a low SBAC-L1 but similar results were found with DXA [5,8,9,10,18,30].

Limitations in this study are 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 [29,30]. 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 are warranted.

In clinical practice, DXA is the gold standard for osteoporosis screening, but according to other studies, our results suggest that this exam is insufficiently performed in the sclerodermic population. Thoracic and TAP CT-scans were usually performed on scleroderma to evaluate pulmonary involvement and were always performed in our population responding to ACR/EULAR criteria for scleroderma. We showed that CT-scan was an alternative method to exclusively explore the trabecular bone without the cortical bone and avoided artefacts due to 2D projection as observed on DXA (osteophyte, bone condensation or disc/vascular calcifications [33,34 ,35 ,36 ,37] or mesenteric adenopathy).

To conclude, we showed, on a large sample of sclerodermic patients with osteoporosis risk factors that only 42.8% were screened for osteoporosis by DXA, 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 is linked with low SBAC-L1 and should lead to an osteoporosis screening, especially for patients under 63 years old.

Compliance with Ethical Standards:

Disclosure of potential conflicts 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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