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Overview of osteo-articular involvement in systemic sclerosis: specific risk factors, clinico-sonographic evaluation and comparison with healthy women from the French OFELY cohort.

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Abstract

Osteoarticular involvement in Systemic Sclerosis (SSc) is frequent and varied. Data are scarce about prevalence and risk factors of osteoporosis (OP). We aim to assess clinical, radiological, US articular involvements, the frequency of osteoporosis and evaluate SSc-specific risk factors. In a prospective cohort of 54 SSc patients, data on OP risk factors, SSc organ involvements, tender and swollen joint counts, DAS28-CRP, hand US sonographies, X-ray hand views, bone mineral density (BMD) were assessed. BMD values were compared to that from a healthy female population (OFELY cohort). Nineteen patients (40%) had OP. SSc was a risk factor of lower BMD compared to the control group. OP was associated with SSc-related risk factors, and not with usual OP risk-factors. 9 patients had clinical synovitis (16%), 23 (68%) patients had at least one US-synovitis. No correlation was found with articular destruction, disease severity auto-antibody profile or other organ impairment.

A. Introduction:

Systemic Sclerosis (SSc) is a rare auto-immune disorder characterized by a vascular and fibrosing involvement of the skin and internal organs [1]. Osteoarticular involvement is frequent and includes osteoporosis, arthritis, tenosynovitis, tendon friction rubs, flexion contractures and acroosteolysis [2-4].

Articular pain is one of the highest rated symptoms impacting the quality of life of SSc patients [5]. Clinical synovitis are found in 16% of SSc patients [6] and was proven as being associated with cutaneous, cardiac and micro-vascular involvements [7]. US synovitis are a less studied entity, the prevalence varying between 6 and 58 % [8] (**Table 1**). It is described as being significantly more frequent than clinical synovitis [9]. The significance of infra-clinical synovitis and its relation with SSc organ involvement and subtypes remain to be determined.

Osteoporosis (OP) is characterized by a qualitative and quantitative impairment of the bone, due to low bone mineral density (BMD) and microarchitectural deterioration; its risk factors are well studied in general population [10,11]. Links between OP and SSc are well established [12-15], yet it is unclear whether it is disease-specific, or due to confounding factors that are common with all chronic diseases such as malnutrition [16], premature menopause induced by cyclophosphamide [17], proton-pump inhibitor consumption (PPI) [18] and dysthyroidism [19].

In this prospective study, we aimed to describe osteoarticular involvement of SSc and compare with data in literature. We study the prevalence of US synovitis and osteoporosis, its correlation with clinical and radiographical findings, and identify disease specific risk factors.

B. Patients and methods:

All consecutive patients with SSc were prospectively included between January 2017 and July 2017 in an Internal Medicine department of a university hospital. All patients fulfilled 2013 American College of Rheumatology (ACR)/ European league against rheumatism (EULAR) criteria for SSc [20]. Patients with associated rheumatoid arthritis, systemic lupus erythematosus or mixed connective tissue disease, microcrystalline arthritis, infectious arthritis were excluded. Internal medicine practitioners and rheumatologists reviewed all patients. All patients included in the database granted their informed consent to participate. The study complied with the recommendations of the Declaration of Helsinki, and being non-interventional in those patients with SSc, ethics committee approval was not necessary according to the French local law. The OFELY cohort has been approved by the CPP Lyon Sud-Est 2.

a) Data about the systemic sclerosis.

Clinical and paraclinical evaluation was performed blinded to the US, radiographical and BMD results. Data were collected as follows: age, sex, SSc duration, SSc subtype, Rodnan score, presence of digital ulcers, calcinosis, dyspnea, presence of heart involvement,

interstitial lung disease, arterial pulmonary hypertension, gastrointestinal and joint involvements. Current and past treatments were collected. Laboratory data included the C-reactive protein, creatinine, urea and CPK levels; antinuclear antibodies (anti-centromere, anti-topoisomerase, ARN polymerase 3 antibodies), anti-citrullinated protein (ACPA) antibodies and rheumatoid factor. All patients underwent heart echocardiography, pulmonary function tests, chest and hand radiographs.

b) Articular assessment.

Clinical articular assessment was done on 28 joints including bilateral proximal interphalangeal joints (PIJ), metacarpophalangeal joints (MCP), wrists, elbows, glenohumeral joints and knees. Tender joint count, swollen joint count, visual analog scale (VAS) of pain and VAS of disease activity was assessed. Clinical synovitis was defined as the presence of at least one swollen and tender joint at the time of inclusion in the study. DAS28 CRP was assessed just like in rheumatoid arthritis.

The joint hand sonographies were performed by one of two rheumatologists, expert in US examination that were blinded to clinical, biological and radiographical findings. US examination was performed using a Samsung UGEO H60 model. The examination was done on both hands, including proximal interphalangeal, metacarpophalangeal, radiocarpal, ulnocarpal and distal radioulnar joints. Joints were evaluated using B-mode and power Doppler mode. The presence, number and the grade OMERACT of synovitis, tenosynovitis, calcinosis was assessed, as well as the B-mode grade and power-doppler signal using the Outcome Measures in Rheumatology (OMERACT) definitions [21]. Joint synovitis was defined as the presence of intraarticular effusion and/or synovial hypertrophy. Active synovitis was defined as the presence of a power Doppler signal.

All patients underwent a posteroanterior X-rays of both hands. X-rays were evaluated by an experienced internal medicine doctor, specialized in rheumatology, blinded of the clinical and US findings. The presence of erosions, calcinosis, acro-osteolysis were assessed. Calcinosis was defined by the presence of calcification in soft tissues. Acro-osteolysis was defined as bone resorption of distal phalanx.

2.3 Osteoporosis assessment.

Data on OP risk factors were collected as follows: patients were weighed, measured and body mass index (BMI) was calculated, personal and family history of fractures, active smoking, daily calcium consumption according to the «Groupe de Recherche et d'Information sur l'Ostéoporose» score (GRIO) [22], alcohol consumption (gram/day), insulin dependent diabetes, menopause and age of menopause, chronic liver diseases, coeliac disease, thyroid disease, long-term steroid treatment (> 7.5mg/day during 3 months or more), repeated falls (2 falls/year or more) with a standardized questioner. Patients underwent spine radiographs, to detect the presence of vertebral fractures. Laboratory data included: serum calcium, phosphate, albumin, 25-hydroxyvitamin D3, parathyroid hormone (PTH), C-terminal telopeptides of type I collagen (CTX), Hemoglobin A1c, thyroid-stimulating hormone (TSH), hepatic function.

The OFELY cohort [23] is a prospective cohort of 1039 volunteer women, aged 31 to 89 years, recruited between February 1992 and December 1993 from the Rhône district, randomly selected from a health insurance company (“Mutuelle Générale de l’Education Nationale”). The cohort was completed between 2005 and 2007 for young women data with 168 women aged 25 to 42 years old [24]. Forty-one females were selected from the OFELY cohort at their 14th annual visit, matched for age and BMI with the forty-one female patients from our cohort.

Bone mineral density (BMD) was measured using a dual X-ray absorptiometry (DXA) with a Prodigy GE LUNAR (GE Corporate, Madison, WI, U.S.A). BMD of the OFELY cohort was measured by DXA with a Hologic QDR-4500 device (Hologic, Bedford, MA, U.S.A). BMD was measured at various skeletal sites: lumbar spine (LS) including antero-posterior incidence from L1-L4, femoral neck (FN) and total hip (TH). Results are expressed in g/cm². In order to compare the BMD of both cohorts, cross-calibration was used to obtain Standardized BMD (sBMD) [25-27]. Osteoporosis was defined as having a femoral or L1-L4 lumbar spine BMD T-score inferior to -2.5. The WHO Fracture Risk Assessment Tool (FRAX®) score for major fracture risk and hip fracture risk was calculated using BMD results, for patients aged of 40 years and more.

2.4 Statistical analysis.

Data were presented as mean with standard deviation for gaussian continuous variables, medians with 1st and 3rd quartile for non-gaussian continuous variables, and numbers with frequencies for qualitative variables. Mann-Whitney U-tests have been used to compare the values for continuous variables, and a Fisher test for discrete variables. Correlation was analyzed using the Spearman test. A p value under 0.05 was considered as statistically significant. The statistical analysis was done using a Graphpad Prism 5 Project program.

C. Results:

3.1 Patient characteristics.

Fifty-four SSc patients were included during the study period with median age 59 years [49.75-64] at inclusion, of whom 45 (83%) were women. The median disease duration (from the date of first non-Raynaud symptom) was 12.6 [8.5-23.3]. Patients had diffuse cutaneous SSc in 13 cases (24%), with a median Rodnan score of 12 [6-18]. All patients’ characteristics are described in **Table 1**.

3.2 Osteoporosis in SSc patients and “OFELY” controls.

3.2.1 DXA findings.

Forty-eight SSc patients underwent DXA. Osteoporosis affected 19 patients (40%) in our SSc population, with average BMD of 0.98 [0.86-1.09] at LS, 0.84 [0.75-0.94] at FN and 0.86 [0.78-1.02] at TH. Six patients (32%) had a history of OP fractures (including vertebral fractures seen on vertebral radiographs), against 4 (14%) in the non-OP group (p = 0.16). The WHO Fracture Risk Assessment Tool (FRAX®) score for major fracture risk was 5.6% [4-15] in the OP group versus 3.5% [2.6-4.4] in the non-OP group (p<0.01). FRAX® hip

fracture risk was also significantly higher ($p < 0.01$): 1.4 [0.7-5.2] in the OP group versus 0.2 [0.2-0.6] in the non-OP group.

In comparison to OFELY healthy females, sBMDs of total and femoral neck were significantly lower in the 41 women from the SSc group. The values of sBMD of respectively total hip and femoral neck were 0.79 [0.71-0.94] in the SSc group (versus 0.93 [0.86-1.03] in the control group, $p < 0.01$), and 0.75 [0.67-0.82] (versus 0.81 [0.72-0.87] in the control group; $p = 0.03$). No difference was found in sBMD of the lumbar spine in the two groups (**Table 2**).

3.2.2 Osteoporosis SSc-specific risk factors.

Among patients with OP ($n=19$), an associated auto-immune disease was found in 13 patients (68%) versus 10 patients (34%) in the non-OP group ($p = 0.04$) (**Table 3**). A digestive SSc-related sub-occlusion was found in 4 patients (21%) in the OP group (versus none in the non-OP group; $p = 0.02$). No difference was found in the frequency of dysphagia, anal incontinence, and gastrointestinal reflux. Respiratory explorations found a diffusing capacity of the lungs for carbon (DLCO) of 12.7% [10.9-15.2] versus 15.6% [13-17.8] ($p < 0.01$), and a forced vital capacity (CVF) of 2.47 mL [2.3-3.0] versus 3 mL [2.6-3.3] ($p = 0.03$). DAS28-CRP was significantly higher (2.3 [2.0-3.6] in the OP group versus 1.9 [1-2.8] in the non-OP group, $p = 0.02$); with a higher frequency of hand X-ray erosions (6 OP patients (32%) versus 2 non-OP patients (7%), $p = 0.04$). No difference was found in Rodnan score, SSc subtype, SSc duration, calcinosis, malnutrition, treatments (proton pump inhibitors, cyclophosphamide, steroids), and autoantibody profiles.

3.2.3 Usual-OP risk factors.

No difference in the usual OP risk factors were found between patients with and without OP: age, smoking, personal or family history of OP fractures, alcohol consumption, weight, BMI, long term steroid treatment, early menopause and thyroid disease. No differences in serum vitamin D, calcium, albumin, TSH, PTH, CTX and CRP levels were found between OP and non-OP groups (**Supplementary Data 1**).

3.3 Articular involvement in SSc

3.3.1 Clinical articular involvement

Arthralgia affected 23 patients (43%), of which 9 (16%) had clinical synovitis. Synovitis were symmetric in 5 (55%) cases, with MCP synovitis in 7 (78%) cases, and PIJ in 6 (67%) cases. Articular involvement was polyarthritis in 6 cases (66%), with median number of tender joints of 6 [2-8.5], swollen joints of 3 [1.5-10.5] and with a DAS28 CRP at 3.7 [3.4-4.3].

Amongst the 9 patients having clinical synovitis, US synovitis were present in 4 patients (50%), and X-ray erosion was present in 1 patient (11%). No association was found between clinical synovitis, US-synovitis or X-ray erosion, with 81% of patients without clinical synovitis had US synovitis. Clinical synovitis tended to be more frequent in limited SSc subtypes and older patients ($p = 0.09$) and, as expected DAS28 CRP was higher in the presence of synovitis. No significant association was found with gender, disease duration,

Rodnan skin score, immunosuppressive treatment, pulmonary, cardiac and renal involvement and antibody profile (**Table 4**).

3.3.2 US articular involvement.

Thirty-four patients underwent joint hand sonographies. US-synovitis was present in 23 patients (68%), with a median number of synovitis of 2 [1-4]. The B-mode grades distributions were as follows: at least one grade I in 14 (60%) cases, grade II in 5 (22%) cases, grade III in 1 (4%) case. One patient (4%) had a positive doppler signal. Tenosynovitis was found in 12 patients (35%).

US synovitis tended to be more frequent in women (21 (91%) versus 7 (64%); $p = 0.07$). There was no significant difference of clinical synovitis, DAS28-CRP, and X-ray erosions between patients having US-synovitis and the other patients (**Table 5**). No significant difference of age, illness duration, SSc subtype, Rodnan skin score, other organ involvements, calcinosis and antibody profile was demonstrated between the two groups. A higher use of immunosuppressant treatments (cyclophosphamide, mycophenolate mofetil, azathioprine, biotherapies, intravenous immunoglobulins) was noted in the group without US-synovitis (7 patients, 64%) than the group with US-synovitis (5 patients, 22%) ($p = 0.03$).

3.3.3 X-ray articular involvement.

Hand X-rays were done in 52 patients, of which 8 (15%) had articular erosions. Patients having erosions were more elderly: 66.50 [64-72.8] years versus 56.50 [48.3-62.8] in the non-erosion group ($p < 0.01$), with no significant difference in disease duration (14.4 [12.2-26] in the erosion group, versus 11.4 [7.0-22.9]; $p = 0.12$). No difference in SSc subtype, cutaneous and organ involvement, treatments and autoantibodies profile were noted between the 2 groups. Only one patient of the erosion-group had clinical synovitis (14%). No significant difference was found in the frequency of clinical synovitis, DAS28-CRP levels, US synovitis, number of clinical synovitis (**Supplementary Data 2**). Joint space narrowing was significantly more important in the erosive group (5 patients, 62%; versus 6 patients, 13%; $p < 0.01$); as well as the prevalence of acro-osteolysis (7 patients, 87%; versus 17 patients, 68%; $p = 0.02$).

3.4 Articular involvement.

Articular involvement, defined as having clinical synovitis and/or US synovitis and/or hand X-ray erosions, was found in 39 patients (72%). Patients having articular involvement were significantly older: 61 years [56-65] versus 49 years [39-53] ($p < 0.01$); without any significant difference of disease duration. The diffuse cutaneous SSc was less frequent in the articular involvement group (4 patients, 10% versus 9 patients, 60%; $p < 0.01$). Anti-centromere autoantibodies were also more frequent in the articular involvement group (23 patients, 60% versus 3 patients, 20%) ($p = 0.01$) (**Supplementary Data 3**).

D. Discussion.

In this study, Systemic Sclerosis was significantly associated with lower BMD in comparison to healthy controls, and some SSc specific features, in particular gastrointestinal, pulmonary

and joint involvements tended to be associated with low BMD. The significantly higher FRAX score in OP SSc patients should be taken into account to manage and prevent better the risk of fractures in SSc patients, particularly when associated with other OP risk factors. Another observation was that US synovitis were more frequently found than clinical synovitis but were faintly active: 60% had a B-mode grade I, and only one synovitis had a positive power Doppler signal. All our patients had negative anti-citrullinated protein antibodies [28,29] and patients with other connective tissue diseases were excluded.

We found that SSc may be a risk factor of low BMD, with no significant association with the usual OP risk factors. Multivariate analysis was not done because of the number of patients included was not sufficient. Several studies previously assessed the prevalence of OP in SSc, using healthy controls or rheumatoid arthritis (RA) [15,30], but controls were only selected by age and sex. In our analysis, we used the well characterized prospective OFELY cohort, so SSc patients were matched for age and BMI, considering them as important factors associated with OP. In our study, OP was associated with SSc severity such as: articular, digestive and respiratory involvements, and associated auto-immune diseases. Other studies have found significant correlations between BMD and diffuse cutaneous subtype, severe joint involvement, malabsorption syndrome and anti-topoisomerase antibody positivity [31,32]. On the other hand, most studies have not found any correlation between disease severity and BMD, like Mok *et al.* [33]. Even though disease duration was previously shown to be related to OP prevalence in SSc [31,32], a recent study by Avouac *et al.* has found a significantly lower disease duration in their SSc patients (10 years) than their RA patients (18 years), with similar prevalence of OP [15]. Thus, SSc could be associated with OP in particular in some subsets of patients with severe disease and specific impairments.

The clinical relevance of low BMDs in SSc is poorly evaluated. Despite significantly lower BMD, the number of fractures in our study was not increased in OP SSc patients, but the very low number of patients with OP fractures and the absence of long term follow-up could probably explain this observation. Mok *et al.* compared 84 SSc patients and healthy controls, and found that BMD and Z-score were significantly lower in the SSc group, with no significant difference in the frequency of fractures [33]. Atteritano *et al.* found a significantly higher prevalence of vertebral fractures in their SSc group (24%), compared to 1.8% in their healthy control group [34]. Lai *et al.* followed during 7 years a cohort of 1712 SSc patients and 10272 control, and found a significantly lower age of first OP fractures in the SSc group [35]. FRAX® fracture risk was significantly higher in our OP patients, but overall was low in our SSc cohort. Prevention of fractures should be included in these patients with low BMD in order to avoid the clinical fractures, especially if they have other added OP risk factors.

Our study has the particularity to have compared systematically the prevalence of clinical synovitis, US synovitis and radiographical erosions. Results of other studies are summarized in **Table 6**. Elhai *et al.* compared the prevalence of US-synovitis in SSc patients and rheumatoid arthritis [36]. More frequent arthritis was detected in patients with disease duration less than 3 years. US-synovitis was detected in 46% of SSc patients with active synovitis in Doppler in 57% of SSc patients. The frequency of positive power-Doppler was

not significantly different with the patients with rheumatoid arthritis, but the Doppler grade was significantly lower: 9% of grade II-III in SSc patients, versus 29% in RA patients. No correlation between US synovitis, clinical synovitis and X-ray erosions was found. Thus, in SSc, US synovitis is more frequent than clinical synovitis, but is weakly active with a low B-mode and power-Doppler grade when US is done in patients with more than 5 years disease duration.

Our study has found no association between synovitis and auto-antibody profile. Avouac *et al* evaluated in a retrospective database of 7286 patients, the association between hand joint involvement and disease phenotype [6]. Patients with clinical synovitis had significantly more anti-topoisomerase antibodies, and less anti-centromere antibodies. Cuomo *et al* described on 45 SSc patients a prevalence of US-synovitis of 58%, of which 42% had positive power-Doppler signal, whereas only 4% have been found in our patients [8]. Their patient characteristics were different, with more frequent diffuse cutaneous subtypes (38% in their study, versus 24% in ours), more anti-topoisomerase antibodies (40% versus 20% in our study), and thus probably less disease duration at the time of US assessment. Our cohort had a longer illness duration, and more limited cutaneous SSc subtypes than the previously described studies, which may explain the difference in our results.

A few hypotheses could be made on why US synovitis were more frequently found than clinical synovitis. A first hypothesis could be that most synovitis in SSc are merely active, and therefore are not clinically apparent. Another suggestion is the difficulty to realize a reliable clinical articular assessment. Gordon *et al.* studied the reliability of the tender and swollen joint count [37] and found a good inter- and intra-observer reliability for tender joint counts, but not for swollen joint counts. However, similarly to our study, US articular evaluation did not correspond to tender nor swollen joint counts. The most striking hypothesis could be that the presence of US synovitis reflects, in patients without clinical synovitis, the inactive state of past inflammatory joint involvement.

US synovitis assessment is recommended in rheumatoid arthritis in the EULAR 2013 recommendations for detecting persistent inflammation, and to assess the risk of progression [38]. In a meta-analysis studying the risk of relapse and structural damage predicted by US, US synovitis was found in 81.8 % of RA patients (40% of negative power doppler signal, 43% of positive power Doppler signal) and determined a risk of structural progression with an OR of 6.95 ($p < 0.01$) [39]. The association with relapse was noted with positive power Doppler synovitis (OR = 3.2; $p < 0.01$), but not with US synovitis alone. A prospective study over 12 months of RA patients showed that active US synovitis was a strong predictive variable of disease activity (DAS 28 CRP), and of progression of radiographic erosions [40]. Even though no studies have assessed the predictive value of US synovitis in SSc patients, considering the data in RA, one can hypothesize that the predictive value of US synovitis in SSc could be low, because US synovitis were less active in SSc than in RA.

A question that remains to be answered is the significance of infra-clinical synovitis in SSc patients. Are infra-clinical synovitis a risk factor of disease severity or other organ impairment? Our study did not find any association between articular and organ involvement. A prospective study with a two-year follow-up of SSc patients found that clinical synovitis

correlated with cutaneous, cardiac, and microvascular progression, but no data were available for infra-clinical US synovitis [7]. Will infra-clinical synovitis evolve towards articular destruction? Infra-clinical synovitis is known to be a risk factor of structural progression in Rheumatoid Arthritis [39]. Our study has found no correlation between US synovitis and X-ray erosions. Hand X-ray studies have found no correlation between articular erosions and disease progression, or organ involvement [41,42]. Only long term prospective studies could determine the risk of structural progression of infra-clinical US synovitis.

E. Summary

SSc was found to be a risk factor of lower BMD at the hip. It did not seem to depend on disease duration nor usual OP risk factors. In our cohort, it was found more frequent in case of SSc severity such as: articular, digestive and respiratory involvements, and the presence of associated auto-immune diseases. The mechanisms of low bone mineral density in these patients are unknown. The clinical relevance of low BMD is poorly studied. US synovitis were found more frequently than clinical synovitis, and were merely active in SSc population. Synovitis was not found to be associated with a particular form of SSc, nor with auto-antibody profile. Further prospective studies are necessary to determine the value of infra-clinical US synovitis and their related outcome, but also its predictive value in early SSc.

Practice points:

- SSc is a risk factor of low BMD, when compared to a healthy female population (OFELY cohort).
- OP was associated with SSc severity and did not seem to depend on disease duration nor usual OP risk factors.
- Prevention of fractures should be included in severe SSc patients, especially if they have other added OP risk factors.
- US synovitis were more frequently found than clinical synovitis but were not inflammatory: could argue for joint involvement becoming inactive during SSc course.
- Articular involvement was associated with limited cutaneous subtype, older patients and anti-centromere antibody positivity. No association between clinical or US-synovitis and anti-body profile was found.

Research agenda:

- Prospective studies to determine the value of infra-clinical US synovitis to predict articular destruction, and SSc organ involvement.
- Prospective studies to follow up bone demineralization and osteoporotic fracture in SSc patients, in comparison with healthy controls.

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Table 1. Patient's characteristics.

Characteristics N=54	
Age (years)	59 [49.75-64]
Female	45 (83)
BMI (kg/m ²)	22.8 [20.3-27.01]
Menopause	31/41 (76)
Disease duration (year)	12.6 [8.5-23.3]
Diffuse SSc	13 (24)
Modified Rodnan skin score	12 [6-18]
Gastroesophageal Reflux Disease	38 (70)
Intestinal sub-occlusion	4 (7)
Cutaneous calcification	28 (52)
Digital ulcer	31 (57)
Interstitial lung disease	24 (49)
DLCO (% of predicted value)	62.0 [53-74.1]
FVC (% of predicted value)	103.7 [87.5-115]
Pulmonary arterial hypertension (catheter)	4 (8)
sPAP > 35 mmHg	15 (31)
Serum creatinine (μmol/L)	73 [63.8-83.3]
Anti-centromere antibody	26 (48)
Anti-topoisomerase I antibody	12 (23)
Anti-RNA polymerase 3 antibody	3 (5)
Anti-citrullinated protein antibody	0 (0)
Current steroid treatment	9 (17)
Cyclophosphamide	2 (4)
Methotrexate	12 (23)
Proton pump inhibitor treatment	38 (79)

Values are medians [1st-3rd quartile] or numbers with frequencies.

BNP: B-type natriuretic peptide. DLCO: diffusing capacity of the lungs for carbon monoxide. FVC: force vital capacity. sPAP: systolic pulmonary arterial pressure assessed by echocardiography. SSc: systemic sclerosis.

Table 2. BMD values of SSc and OFELY cohort.

DXA results	SSc population	Female SSc		P value
		population	OFELY cohort	
Osteoporosis (%)	19 (40)	18 (44)	NA	
Lumbar spine (L1L4) results				
T-score	-1.55 [-2.50 - -0.70]	-1.60 [-2.6 - -0.75]		
BMD (g/cm ²)	0.98 [0.86-1.09]	1.0 [0.9-1.1]	0.97 [0.87-1.11]	
sBMD (g/cm ²)		0.96 [0.86-1.08]	1.00 [0.89-1.13]	0.95
Femoral neck results				
T-score	-1.15 [-1.85 - -0.53]	-1.20 [-1.95 - -0.70]		
BMD (g/cm ²)	0.84 [0.75-0.94]	0.83 [0.74-0.89]	0.87 [0.80-0.93]	
sBMD (g/cm ²)		0.75 [0.67-0.82]	0.81 [0.72-0.87]	0.03
Total hip results				
T-score	-1.15 [-1.80 - -0.02]	-1.20 [-2.00 - -0.10]		
BMD (g/cm ²)	0.86 [0.78-1.02]	0.84 [0.76-0.99]	0.92 [0.84-1.00]	
sBMD (g/cm ²)		0.79 [0.71-0.94]	0.93 [0.86-1.03]	<0.01
FRAX results				
FRAX Risk of major fracture				
(%)	4.20 [3.07-7.05]	4.40 [3.20-7.30]	4.50 [2.70-6.30]	0.12
FRAX Risk of hip fracture (%)	0.60 [0.20-1.43]	0.60 [0.30-1.5]	0.80 [0.20-1.40]	0.18

Values are medians [1st-3rd quartile] or numbers with frequencies.

BMD: Bone mineral density. sBMD: standardized bone mineral density. FRAX: WHO Fracture Assessment Fracture Tool.

Table 3. SSc specific osteoporosis risk factors.

	Osteoporosis n=19 (40%)	Absence of osteoporosis n = 29 (60%)	P value
General characteristics			
Illness duration (years)	13 [9-24.4]	12.2 [7.4-22.2]	0.52
Diffuse cutaneous subtype	4 (21)	9 (31)	0.52
Modified Rodnan score	15 [3-17.5]	11 [8.2-17]	0.68
Associated autoimmune disorder	13 (68)	10 (34)	0.04
Digital ulcer	12 (63)	15 (52)	0.55
Cutaneous calcification	10 (53)	15 (52)	1
Organ involvement			
Gastroesophageal Reflux Disease	13 (68)	19 (65)	1
Sub-occlusion	4 (21)	0 (0)	0.02
Anal incontinence	6 (32)	4 (14)	0.16
Interstitial lung disease	8 (50)	11 (41)	0.75
sPAP	29 [27.2-34.2]	31 [13-17.8]	0.9
DLCO	12.7 [10.9-15.2]	15.6 [13-17.8]	< 0.01
DLCO (% theory)	55.9 [50.3-69.1]	56.3 [56.3-75.9]	0.07
CVF (L)	2.47 [2.3-3.0]	3 [2.6-3.3]	0.03
CVF (% theory)	100.9 [90.7-113.8]	106 [87.5-116.9]	0.94
TLC (L)	4.7 [3.7-4.9]	4.8 [4.3-5.1]	0.31
TLC (% theory)	102.7 [81.9-102.7]	95.2 [91.6-106.7]	0.44
Clinical synovitis	5 (28)	3 (11)	0.23
DAS 28 CRP	2.3 [2.0-3.6]	1.9 [1-2.8]	0.02
Hand X-ray erosions	6 (32)	2 (7)	0.04
Hand X-ray acroosteolysis	11 (58)	10 (34.)	0.14

Biological findings			
Creatinine ($\mu\text{mol/L}$)	73 [66-84]	73 [62-84]	0.68
GFR (MDRD mL/min/1.73m ²)	62 [54-86]	79.6 [66-106]	0.34
GFR (cockroft mL/min)	62	81	< 0.01
ANA	1280 [640-1280]	1280 [320-1280]	0.89
Anti-centromere antibody	12 (63)	12 (41)	0.24
Anti-topoisomerase I antibody	3 (16)	6 (21)	1
Anti-RNA polymerase 3 antibody	0 (0)	2 (7)	0.51
Treatment			
Steroid	5 (26)	8 (28)	1
Duration of steroid treatment	2.7 [1.5-4.8]	1.2 [0.4-6.3]	0.41
Cyclophosphamide	0 (0)	2 (7)	0.51
Immunosuppressive treatment	3 (16)	4 (14)	1
PPI treatment	15 (79)	23 (79)	1

Values are medians [1st-3rd quartile] or numbers with frequencies.

ANA: antinuclear antibody. DLCO: diffusing capacity of the lungs for carbon monoxide. FVC: force vital capacity. GFR (glomerular filtration rate), MDRD (modification of renal disease), PPI: proton pump inhibitor. sPAP: systolic pulmonary arterial pressure assessed by echocardiography. SSc: systemic sclerosis. TLC: total lung capacity.

Table 4. Clinical articular findings.

	Clinical synovitis n = 9/54 (17%)	No clinical synovitis n = 45/54 (83%)	p
General characteristics			
Women	7 (78)	39 (87)	0.21
Age (year)	63 [54-67]	57 [47.3-63.3]	0.09
Disease duration (year)	9.0 [5.3-17.8]	12.8 [9.2-24.2]	0.18
Diffuse cutaneous SSc	0 (0)	13 (29)	0.09
Cutaneous involvement			
Modified Rodnan skin score	10 [6-17]	12 [6-18]	0.69
Subcutaneous calcification	4 (44)	24 (53)	0.73
Organ involvement			
Interstitial lung disease	2 (28)	22 (52)	0.4
DLCO (% of predicted value)	59,9 [50.4-72.8]	60,7 [53-74]	0.81
FVC (% of predicted value)	103.7 [86-114.9]	103 [87.3-115.5]	0.75
sPAP > 35 mmHg	2 (22)	15 (33)	0.71
Antibodies			
Anti-Centromere antibodies	7 (78)	17 (41)	0.07
Anti-topoisomerase I antibodies	2 (22)	10 (24)	1
ARN pol 3 antibodies	1 (11)	2 (5)	0.23
Treatment			
Steroids	1 (11)	8 (18)	1
Hydroxychloroquine	2 (22)	5 (11)	0.59

Methotrexate	1 (11)	6 (13)	0.32
History of immunosuppressant treatment	1 (11)	8 (18)	1

Articular characteristics			
DAS 28 CRP	3,7 [3.4-4.3]	2.0 [1.0-2.4]	< 0.01
Hand X-ray : Erosion	1 (11)	7 (16)	1
US synovitis	4 (50)	19 (73)	0.16
Number of US synovitis	2 [0-5]	2 [0-3]	0.94
US tenosynovitis	1 (12)	11 (42)	0.21
US calcinosis	5 (62)	16 (61)	1

Values are medians [1st-3rd quartile] or numbers with frequencies.

DLCO: diffusing capacity of the lungs for carbon monoxide. FVC: force vital capacity. sPAP: systolic pulmonary arterial pressure assessed by echocardiography. SSc: systemic sclerosis.

Table 5. US articular findings.

	US synovitis n = 23/34 (68%)	Absence of US synovitis n = 11/34 (32%)	P
General characteristics			
Women	21 (91)	7 (64)	0.07
Age (year)	61 [57-64]	56 [52-65]	0.52
Disease duration (year)	21.3 [9.3-25.5]	12.1 [2.8-23.1]	0.13
Diffuse cutaneous SSc	3 (13)	4 (36)	0.18
Cutaneous involvement			
Modified Rodnan skin score	15 [5.5-18.5]	16 (0-29)	0.81
Digital ulcer	13 (56)	6 (55)	1
Subcutaneous calcification	13 (56)	4 (36)	0.46
Organ involvement			
Interstitial lung disease	9 (39)	6 (54)	0.70
DLCO (% of predicted value)	60.7 [53-72.4]	55.0 [44.7-76.9]	0.61
FVC (% of predicted value)	109 [89.9-117.5]	100 [75-113]	0.37
sPAP > 35 mmHg	5 (23)	3 (27)	1
Serum creatinine (µmol/L)	78 [71-85]	66 [61-101]	0.15
Antibodies			
Anti-Centromere antibodies	14 (61)	5 (45)	0.47
Anti-topoisomerase I antibodies	3 (13)	5 (45)	0.08
ARN pol 3 antibodies	0 (0)	1 (9)	0.32
Treatment			
Steroids	3 (13)	3 (27)	0.36

Methotrexate	4 (17)	3 (27)	0.66
History of immunosuppressant treatment	5 (22)	7 (64)	0.03
Articular characteristics			
Clinical synovitis	4 (18)	4 (40)	0.22
Athralgia	12 (52)	6 (60)	0.72
Articular swelling	4 (18)	4 (40)	0.22
DAS 28 CRP	2,4 [1.8-3.3]	2,4 [1.5-5.9]	0.76
X-ray Erosions	4 (17)	2 (18)	1
US tenosynovitis	10 (43)	2 (18)	0.25
US calcinosis	18 (78)	3 (27)	< 0.01

Values are medians [1st-3rd quartile] or numbers with frequencies.

DLCO: diffusing capacity of the lungs for carbon monoxide. FVC: force vital capacity. sPAP: systolic pulmonary arterial pressure assessed by echocardiography. SSc: systemic sclerosis. US: ultrasonography.

Table 6. Review of previous articles on US-synovitis in SSc.

Authors/Years	N	SSc features Clinical features	US synovitis : - B-mode grade - Power-Doppler signal	X-ray Erosions or MRI synovitis	Comments
Cuomo G 2009 [8]	45	Diffuse SSc: 17 (38%) Disease duration: NA Clinical synovitis: N = 15 (33%)	US synovitis : 26 (58%) Positive PD : 11 patients (24%) B-mode grade : NA	X-ray : 4 (8%)	No correlation between US features and disease duration, SSc type, clinical subset, activity index, HAQ
Chitale S 2010 [22]	13	Diffuse SSc : 3 (18%) Disease duration : NA Clinical synovitis : N = 0	US synovitis : 3 (23%) Positive PD : NA B-mode and PD grade : NA	X-ray : NA MRI synovitis : 8/8 (100%)	US and MRI features not correlated with SSc subtype, CRP, disease duration and antibodies. Percentage of agreement between US synovitis and MRI synovitis: 38%
Elhai M 2012 [9]	52	Diffuse SSc : 21 (40%) Disease duration : 8.6 ± 8.6 yrs Clinical synovitis : N=8 (15 %)	US synovitis: 24 (46%) Positive PD : 39 joints (57%) - PD Grade 1 : 33 joints (85% of US synovitis) - PD Grade 2-3 : 6 joints (15% of US synovitis) B-mode grade : NA	X-ray : 12 (23%)	More clinical synovitis if disease duration < 3 years. Trend of lower disease duration in subgroup with synovitis grade 2-3. X-ray erosion associated with US synovitis.
Iagnocco A 2013 [12]	46	Diffuse SSc : 18 (39%) Disease duration : 11.3 (0.58-44) yrs Clinical synovitis : NA	Hand involvement: 3% Positive PD : 1.7% B-mode Grade 1 : 2% of joints B-mode Grade 2 : 1% of joints	X-ray : NA	No correlation between US features and ulcers, Rodnan, disease duration. Correlation between PD positivity and wrist swelling.

			B-mode Grade 3 : 0.2% of joints Wrist involvement: 46%. Positive PD: 43%		
Abdel-Magied RA 2013 [23]	16	Diffuse SSc: 5 (31.2%) Disease duration: 5.4 ± 3.6 yrs Clinical synovitis : 0	US synovitis: 5 (31%) Positive PD : NA B-mode and PD grade : NA	X-ray : 0 MRI synovitis: 14 (87.5%)	Patients with clinical synovitis were excluded. Correlation between disease duration, patient's age and MRI erosions. Correlation between MRI synovitis and CRP. Correlation between CRP and MRI tenosynovitis and US synovitis.
Freire V 2013 [24]	44	Diffuse SSc : NA Disease duration : NA Clinical synovitis : NA	US synovitis: 17 (39%) B-mode grade 1 : 54% B-mode grade 2-3 : 10% Power doppler : NA	X-ray : NA	Control subjects: no US synovitis.
Stoenoiu MS 2013 [25]	15	Diffus SSc : 15 (100%) Disease duration: 7.5 (2-18) yrs Clinical synovitis : 0	US synovitis : 8 patients (53%) Positive PD : 2 patients (13%) B-mode/PD grade : NA	X-ray: NA MRI synovitis : 8 patients (53%)	NA
Our study	57	Diffuse SSc : 13 (24%) Disease duration : 12.3 (0.3- 41) yrs Clinical synovitis : 9 (16 %)	US synovitis: 23 (68%) Positive PD: 1 patient (1.7%) Grade 1: 14 (60%) Grade 2-3: 6 (26% of US synovitis)	X-ray: 8 (15%)	No correlation with clinical synovitis or erosions More frequent in diffuse SSc

PD: power doppler. HAQ: Health Assessment Questionnaire. N: number of patients. SSc: systemic sclerosis.

US: ultrasonography. MRI: Magnetic resonance imaging. yrs: years.

Supplementary data

Supplementary data 1. Factors usually associated with bone fragility.

	Osteoporosis	Absence of osteoporosis	P value
Clinical risk factors			
Age (year)	63 [57-65]	54 [44.5-62.5]	0.16
Women	18 (95)	23 (79)	0.22
Weight (kg)	58 [44-68]	63 [53.5-77]	0.13
BMI (kg/m ²)	23.5 [18.7-25.6]	23.4 [20.9-28.9]	0.34
Personal history of non-traumatic fracture	6 (32)	4 (14)	0.16
Family history of osteoporosis	4 (21)	3 (11)	0.43
Sedentarity	11 (73)	12 (43)	0.1
GRIIO score	7 [2-11]	8 [6.7-11]	0.25
Sufficient calcium intake	3 (20)	4 (18)	1
Active smoking	4 (21)	2 (7)	0.2
Alcohol consumption (> 30g/day)	1 (5)	1 (3)	1
Insulin dependent diabetes	1 (5)	1 (3)	1
Malnutrition	5/19 (26)	3/28 (11)	0.24
Menopause	16/18 (89)	15/23 (65)	0.14
Early menopause (<45 years)	3/13 (23)	3/14 (21)	1
Chronic liver disease	5 (26)	2 (7)	0.1
Thyroid disease	3 (16)	5 (17)	1
Treatment			
Long term steroid treatment	5 (26)	8 (28)	1
Vitamin D	9 (47)	7 (24)	0.12
Bisphosphonate	2 (11)	3 (10)	1
Calcium	5 (26)	2 (7)	0.1

Serum biology			
Calcium	2.3 [2.3-2.4]	2.3 [2.3-2.4]	0.82
Albumin	40 [39-42.6]	41.7 [39.1-43.2]	0.44
Phosphor	1.1 [1-1.2]	1.1 [1-1.2]	0.94
Vitamin D	24.4 [15.6-35.3]	19.8 [13.9-27.9]	0.27
Parathormone	57.9 [39.5-75.5]	58 [38.8-92.4]	0.7
CTX	531 [414-778]	434 [264.3-489]	0.17
Uric acid	256 [207-319]	288 [212-355]	0.63
CRP	3 [3-7.2]	3 [3-3]	0.05
TSH	1.36 [0.6-2.6]	1.6 [1.2-3.1]	0.35
HbA1c	5.4 [5.2-5.8]	5.4 [5.2-5.6]	0.69
Urine biology			
Calcium	2.9 [2.5-3.8]	2.49 [0.8-4.5]	0.5
Phosphor	17.9 [9.6-21.3]	10.5 [6.8-27.1]	0.77

Values are medians [1st-3rd quartile] or numbers with frequencies.

CRP: C reactive protein. CTX: C-terminal telopeptides of type I collagen. HbA1c: Hemoglobin A1c. TSH: thyroid stimulating hormone.

Supplementary Data 2. Hand X-ray articular findings.

	Articular erosion n = 8/52 (15%)	Absence of articular erosion n = 44/52 (85%)	p
General characteristics			
Women	7 (87)	39 (89)	1
Age (year)	66.5 [64-72.8]	56.5 [48.3-62.8]	< 0.01
Disease duration (year)	14.4 [12.2-26.0]	11.4 [7.0-22.9]	0.12
Diffuse cutaneous SSc	3 (37)	10 (23)	0.39
Organ involvement			
Digital ulcer	6 (75)	23 (52)	0.28
Modified Rodnan skin score	10.5 [1-24]	8 [8-17]	0.81
DLCO (% of predicted value)	73.2 [62.2-81.5]	60.7 [53.0-74.0]	0.16
FVC (% of predicted value)	116.7 [94.0-151.0]	103.9 [87.3-113.0]	0.14
Interstitial lung disease	4 (50)	18 (46)	1
Pulmonary arterial hypertension	2 (25)	2 (4.5)	0.11
Treatment			
Steroids	0 (0)	9 (20)	0.32
Methotrexate	3 (37)	7 (16)	0.17
History of immunosuppressant treatment	1 (12)	7 (16)	1
Clinical articular characteristics			
Clinical synovitis	1 (14)	8 (19)	1
DAS 28 CRP	2.10 [2.0-3.5]	2.0 [0.96-3.0]	0.42
US articular characteristics			
US synovitis	4/6 (67)	19/26 (73)	1

Number of US synovitis	2.5 (0-9)	1 (0-8)	0.4
Doppler positive synovitis	1/6 (17)	0 (0)	0.17
Tenosynovitis	4/6 (67)	8/28 (29)	0.15
US calcinosis	4/6 (67)	17/28 (61)	1
X-ray articular characteristics			
Joint space narrowing	5 (62)	6 (13)	< 0.01
Acroosteolysis	7 (87)	17 (68)	0.02

Values are medians [1st-3rd quartile] or numbers with frequencies.

DLCO: diffusing capacity of the lungs for carbon monoxide. FVC: force vital capacity. sPAP: systolic pulmonary arterial pressure assessed by echocardiography. SSc: systemic sclerosis.

Supplementary Data 3. Articular involvement.

	Articular involvement n = 39/54 (72%)	Absence of articular involvement n = 15/54 (28%)	P
General characteristics			
Age (year)	61 [56-65]	49 [39-53]	< 0.01
Disease duration (year)	12.4 [8.8-23.8]	10.7 [7.0-14.9]	0.42
Women	34 (87)	14 (93)	1
Diffuse cutaneous SSc	4 (10)	9 (60)	< 0.01
VAS of disease activity	40 [25-50]	0 [0-0]	< 0.01
VAS of pain	30 [0-40]	0 [0-0]	< 0.01
CRP	3 [3-4.1]	3 [3-10.7]	0.61
Cutaneous involvement			
Modified Rodnan skin score	11 [4-18]	12 [8-17]	0.67
Subcutaneous calcification	13 (33)	6 (40)	0.75
Digital ulcer	23 (59)	8 (53)	0.76
Organ involvement			
Serum creatinine	75 [67-84]	63 [59-79]	0.06
sPAP > 35 mmHg	10 (26)	7 (47)	0.19
Interstitial lung disease	15 (44)	9 (60)	0.36
FVC (% of predicted value)	105.4 [91.7-118.5]	90.5 [69.8-106.0]	0.03
DLCO (% of predicted value)	64.0 [53.0-74.9]	57.8 [49.3-72.2]	0.34
Treatment			
Steroids	6 (15)	3 (20)	0.7
Methotrexate	6 (15)	1 (6)	0.66

History of immunosuppressant treatment	4 (10)	5 (31)	0.09
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Antibodies			
Anti-centromere antibodies	23 (60)	3 (20)	0.01
Anti-topoisomerase I antibodies	7 (18)	5 (33)	0.28
Anti-RNA 3 polymerase antibodies	1 (2)	2 (13)	0.19

Values are medians [1st-3rd quartile] or numbers with frequencies.

CRP: C reactive protein; DLCO: diffusing capacity of the lungs for carbon monoxide. FVC: force vital capacity.

sPAP: systolic pulmonary arterial pressure assessed by echocardiography. SSc: systemic sclerosis.