Patients with Scleroderma May Have Increased Risk of Osteoporosis. A Comparison to Rheumatoid Arthritis and Noninflammatory Musculoskeletal Conditions

SAI YAN YUEN, BRAM ROCHWERG, JANINE OUIMET, and JANET E. POPE

ABSTRACT. ***Objective.*** To investigate if subjects with scleroderma (systemic sclerosis, SSc) have increased risk for developing osteoporosis (OP).

Methods. A survey assessing demographics, diagnosis/investigations for OP, and risk factors for OP was mailed to 129 patients with SSc, 158 controls with noninflammatory musculoskeletal (MSK) disease, and 230 positive controls with rheumatoid arthritis (RA). All available charts were reviewed and results were included in analyses of demographics, OP status, past bone mineral density (BMD), and past steroid use. In addition, we recorded BMD results (T score) of SSc patients with their matched RA controls. Analyses adjusted for age were done for SSc versus MSK and SSc versus RA.

Results. The response rate was 61% for patients with SSc (n = 28 diffuse, 51 limited disease), RA 67%, and MSK 59%; however, through chart review, 159 SSc, 140 MSK, and 235 RA patients were included in the analyses. Mean age and proportion of women did not differ between groups. Disease duration was longer in RA versus SSc group (16.5 vs 11.5 yrs; $p < 0.0001$). The prevalence of OP in SSc was similar to RA controls (19.4% vs 16.7%; $p = 0.38$) but likely higher than MSK controls (12.2%; $p = 0.054$). Subjects with SSc reported a higher rate of disability (41.0% vs 15.6%; $p = 0.0001$) and less family history of OP (22.8% vs 46.7%; $p = 0.0006$) compared with the MSK control group. There were no differences between groups in reports of fracture (35% SSc, 43% MSK, 37% RA; $p = 0.5$) or OP related fractures (4% SSc, 11% MSK, 11% RA; $p = 0.5$). Subjects with SSc were less likely to have had a BMD done in the past compared to RA (40.9% vs 62.6%; $p = 0.0001$). Subjects with RA who reported OP had longer disease duration than RA without OP (18 ± 1.7 yrs vs 12 ± 0.8; $p = 0.0009$). Results from the chart review showed that the T scores of SSc (n = 56, mean age 62.9 ± SD 10.1 yrs) at lumbar spine (SSc –1.01 vs RA –0.97), femoral neck (SSc –2.07 vs RA –1.46; $p = 0.01$, adjusting for age $p = 0.26$), and total hip region (SSc –1.52 vs RA –1.25) were comparable to or even lower than the RA group (n = 56, mean age 62.2 ± SD 10.7 yrs).

Conclusion. The prevalence of OP in patients with SSc was comparable to those with RA, but higher than in the MSK group. Age was found to be an important factor, as expected. Also, our results indicated that BMD (T score) in SSc was similar to or even lower than in patients with RA. Increasing the awareness to order BMD measurements in patients with SSc may be warranted based on our results, especially for older patients. (First Release April 15 2008; J Rheumatol 2008; 35:1073–8)

Key Indexing Terms:

SYSTEMIC SCLEROSIS | RHEUMATOID ARTHRITIS | OSTEOPOROSIS
BONE MINERAL DENSITY | RISK FACTORS | CASE CONTROL

Osteoporosis (OP) is a condition characterized by low bone mass and loss of normal bony architecture and mineralization with an increased risk of fracture. It is a major cause of morbidity and mortality. An individual's bone density and risk of developing OP are influenced by a number of factors, including peak bone mass, race, advanced age, family history of OP, illness, decreased sex-steroid activity, corticosteroid use, certain chronic diseases that affect absorption or vitamin D metabolism, smoking, and excessive alcohol use[1]. Many patients with chronic inflammatory diseases may be exposed to longterm steroid therapy. While chronic steroid use has a number of significant side effects, bone loss resulting in steroid-induced OP and increased fracture risk is serious[2]. Patients with rheumatoid arthritis (RA) have an increased risk of OP that is not sufficiently explained by corticosteroid use[1,3]. In contrast, there is likely no increased risk of OP in osteoarthritis[4].

Systemic sclerosis (SSc) is a rare connective tissue disease causing fibrosis of the skin and internal organs[5]. Patients with SSc could have an increased risk of osteoporosis (OP), as a result of a chronic inflammatory state,

From the Division of Rheumatology, Department of Medicine, The University of Western Ontario, London, Ontario, Canada.

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S.Y. Yuen, MD, FRCPC; B. Rochwerg, BSc; J. Ouimet, MSc; J.E. Pope, MD, MPH, FRCPC.

Address reprint requests to Dr. J.E. Pope, St. Joseph's Health Care London, 268 Grosvenor Street, Box 5777, London, ON N6A 4V2. E-mail: janet.pope@sjhc.london.on.ca

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occult malabsorption or malnutrition, immobilization, and use of corticosteroid therapy. In addition, SSc is often accompanied by calcinosis; it is possible that the calcium is obtained from our calcium stores (i.e., the skeleton) to be deposited subcutaneously. Many authors have recognized the importance of OP in patients with SSc[6-11]. Several factors have been evaluated as risk factors for developing OP in SSc such as disease duration[6], clinical variant, i.e., diffuse versus limited form[6,8,11], body mass index (BMI)[9,10], earlier menopause[7], and internal organ involvement[8,11]. Certain authors have even stated that SSc might be an independent factor for low bone mineral density (BMD)[6,9]. However, these studies involved different SSc populations, study designs, and generally a relatively small sample size, and some results were conflicting. Therefore the literature does not definitively conclude that OP is increased in SSc. We investigated whether individuals with SSc were at a higher risk of developing OP as compared to a control population with noninflammatory disease as well as compared to a "high risk" (positive control) population with RA.

MATERIALS AND METHODS

Our project was approved by the University of Western Ontario Research Ethics Board. The goal of this case-control study was to determine whether patients previously diagnosed with SSc were at greater risk for OP. All patients were from 1 practice. SSc was defined as meeting the preliminary American College of Rheumatology (ACR) criteria for scleroderma or the presence of calcinosis, Raynaud's, esophageal dysmotility, sclerodactyly, or telangiectasias (CREST) syndrome[12,13]. A 28-question survey was designed to assess demographics, diagnosis, or investigations for OP (e.g., BMD) and the presence of risk factors for OP, including age, menopausal status, calcium intake, vitamin D intake, family history, disease severity, comorbidity, and steroid use. The questionnaire was then mailed to 129 patients with SSc, 158 negative controls with noninflammatory musculoskeletal (MSK) disease (such as OA, tendonitis, and fibromyalgia), and 230 positive controls with RA meeting the ACR criteria for RA[14]. All patients with SSc, RA, and MSK followed by our rheumatology clinic at the study period were invited to participate. A second mailing to all nonrespondents was conducted 6 weeks later in an attempt to increase response rate. OP was considered present if the subject had stated that he/she had OP and/or if a BMD (upon chart review) revealed a T score $\leq$ 2.5 in the lumbar spine, femoral neck, or total hip regions. All available patient charts were reviewed and results were incorporated into the analysis, although not all data were systematically available (such as diet and exercise). If a subject reported OP but no fragility fracture and a BMD did not show OP, they were thought to have been misclassified, and the BMD in the chart was used preferentially. Also, data of nonrespondents from the chart review were analyzed to determine if they differed in terms of demographic information (age, sex, disease, and duration of disease), OP status, past BMD test(s), and prednisone use (ever). In addition, we recorded the T score of the BMD at lumbar spine, femoral neck, and total hip region of SSc and matched RA patients. Patients with RA were selected matching for age, sex, and prednisone use. All BMD reports used dual-energy x-ray absorptiometry (DEXA). Demographic factors and other possible confounders of an association with OP were assessed.

Separate univariate analyses of SSc versus MSK, and SSc versus RA subsets were performed using chi-squared (Pearson) and Fisher's exact tests for frequencies and Student's t-tests or analysis of variance for continuous data, from a SAS-based JMP statistical software package[15]. Risk factors and outcomes were analyzed for statistical significance at $p < 0.05$, between cases and the 2 control groups. For each comparison group, all variables that were significantly different between groups were analyzed in a subsequent multivariate logistic regression model. Age was adjusted for in the final analysis to decrease variability on this important confounder (as not all patients had a BMD). Reduced models were then generated where applicable. It was beyond the scope of our study to determine relationships with low BMD in SSc according to organ involvement. However, in our SSc cohort about 8% have had scleroderma renal crisis and 13% have been in Functional Class III or IV from pulmonary arterial hypertension.

RESULTS

The response rate was 61% for SSc (n = 79; 28 diffuse, 51 limited; 89% women), 67% for controls with RA (n = 154, 86% women), and 59% for MSK (n = 93, 88% women). In each of the disease subgroups (SSc, RA, MSK), respondents were not significantly different from nonrespondents in regards to age, sex, or past prednisone use. Disease duration was different between survey respondents and nonrespondents in the MSK group only [mean = 15.02 ± SEM 1.2 yrs (respondents) vs 10.4 ± SEM 1.2 yrs (nonrespondents); p = 0.02]. Ever having had a BMD test done was significantly different in all groups, where BMD were consistently more frequently reported/documented in the respondents versus nonrespondents [46% vs 8%, p = 0.0004 (SSc); 50% vs 19%, p = 0.0005 (MSK); and 62% vs 38%, p = 0.002 (RA)]. However, OP status (as per each nonrespondent's medical chart) was not different between respondents versus nonrespondents in the SSc group (p = 0.7) or the MSK group (p = 0.4) but was borderline in the RA group (21% of respondents reported OP vs 10% of nonrespondents; p = 0.05).

Although the nonrespondents were significantly different in study-related features (BMD, and also OP status was different in RA nonrespondents), we decided to pool the data (obtained from chart review and questionnaire) for the following reasons: (1) given that age is a major factor in OP and the mean age was not different between responders and nonresponders; (2) past BMD may have been overreported by survey respondents (but it is feasible that BMD may not have been available from subject's medical chart if the test had not been ordered by or copied to the rheumatologist carrying out our study); (3) the primary outcome of interest (OP status) was not different between respondents and nonrespondents (except in RA); and (4) in all groups the overall results remained the same whether the nonrespondents were included or not in the analysis for all variables from which data were obtained via chart review. Thus, 159 patients with SSc, 140 with MSK, and 235 with RA were included in analyses of variables obtained via chart review. Table 1 and 2 present the demographic and risk factors related to OP in SSc, RA, and MSK control groups. Mean age, sex, and disease duration did not differ between groups, except for the RA group, which had a disease duration longer than the SSc group (11.5 ± 0.7 yrs vs 16.6 ± 0.7 yrs; $p < 0.0001$). Patients with SSc were more likely than RA or MSK controls to have stopped working due to their illness (41.0% of SSc vs 15.6% of MSK, p = 0.0001; and

Table 1. Demographic and risk factors for osteoporosis (OP) in SSc, RA, and controls with noninflammatory arthritis (MSK). Values are percentage of total or mean ± standard error, where appropriate. All p values are for age-adjusted significance tests.

	SSc, n = 159	MSK Controls, n = 140	RA, n = 235	p (SSc vs MSK)	p (SSc vs RA)
Mean age*, yrs	58.3 ± 0.98	60.2 ± 1.04	60.4 ± 0.80	0.19	0.10
% Female*	81.8	90.0	87.2	0.13	0.14
Disease duration*, yrs	11.5 ± 0.7	13.6 ± 0.8	16.5 ± 0.7	0.06	< 0.0001
% Not working due to illness	41.0	15.6	25.7	0.0001	0.004
% Smoking, ever	60.3	39.0	52.9	0.62	0.10
% Alcohol use, ≥ 1 drink per day	15.7	6.4	9.2	0.054	0.11
% Exercise ≥ twice a week	54.2	57.9	60.5	0.059	0.65
% Steroids*, ever	24.8	23.5	55.8	0.43	0.11
% with family history of OP	22.8	46.7	29.7	0.0006	0.23
% who eat/drink < 2 dairy/day	51.2	66.3	61.4	0.14	0.29
% with past BMD test*	40.9	40.4	62.1	0.65	0.0001
% Osteoporosis*	19.4	12.2	16.7	0.065	0.38
% Osteoporosis†	16.8	11.1	17.3	0.24	0.88

* Reported values include information obtained by chart review, including nonresponders; other results are based on respondents only (SSc, n = 79; MSK, n = 93; RA, n = 154). † Analysis of steroid nonusers only (SSc n = 120; MSK n = 108; RA n = 105). SSc: systemic sclerosis; MSK: controls with noninflammatory musculoskeletal disease; RA: rheumatoid arthritis; BMD: bone mineral density scan.

Table 2. Other factors that may be related to OP in women with SSc, RA, and noninflammatory arthritis (MSK controls). Values are percentage of total or mean ± standard error, where appropriate.

	SSc, n = 73	MSK Controls, n = 87	RA, n = 130	p (SSc vs MSK)	p (SSc vs RA)
% Menopausal/post menopausal status	63	70	63	0.7	0.3
Mean age at menopause*	46 ± 1.7	47 ± 1.7	46 ± 1.3	0.6	0.5
% with hysterectomy	22	41	24	0.3	0.9
% ever pregnant	88	92	94	0.6	0.2
No. of pregnancies	2.4 ± 0.2	2.7 ± 0.1	3.0 + 0.1	0.1	0.0003

* Estimated only from those who were menopausal, so in each group this is an underestimate, as approximately 35% have not experienced menopause.

25.7% of RA, p = 0.004). OP related risk factors including smoking, dairy consumption, decreased vitamin D intake, and age of menopause were not significantly different between SSc and the 2 control groups. However, the SSc group had a trend to consume more alcohol (p = 0.054) and exercise less (p = 0.059) than the MSK group. Past or current use of steroids seemed to be higher in RA; however, when data were adjusted for age, the difference was not significant (p = 0.0001; adjusting for age, p = 0.11). The report of a family history of OP was higher in MSK controls compared to patients with SSc (47% vs 23%; p = 0.0006). Also, we calculated the mean BMI from all available data of each group (SSc n = 86, RA n = 206, MSK n = 91); BMI of SSc and RA groups were similar (SSc = 25.9 ± SEM 0.6 vs RA = 26.5 ± SEM 0.4; p = 0.37), but the MSK group had a significantly higher BMI (29.2 ± SEM 0.8) compared to the 2 other groups (p = 0.001). Among patients with SSc, BMI did not differ between patients with or without OP.

There was a statistical trend in the prevalence of OP; the SSc group obtained a higher prevalence than the MSK group (19.4% vs 12.2%; p = 0.054). No difference was found between the SSc and RA groups in OP prevalence. A subanalysis of the group of nonsteroid users showed that prevalence of OP remained similar in all groups (Table 1). Indeed, only 39 patients with SSc in our cohort have taken prednisone. Through the chart review, the mean duration of steroid use of 35 patients was 3.2 ± SEM 0.8 years. In addition, prednisone dose was available from 25 patients; > 75% of patients took ≤ 10 mg/day and only 16% took > 15 mg/day. There were no differences between groups in reporting a fracture ever (38% SSc, 44% MSK, 36% RA; p = 0.5) or sustaining an OP related fracture (4% SSc, 11%

MSK, 11% RA; p = 0.4), although OP fractures occurred less often in the SSc group. BMD were found to be performed more frequently in patients with RA compared to the subjects with SSc (62% vs 41%; p < 0.0001). In a pooled analysis (SSc, RA, MSK), those with OP had an older mean age than those without (64 ± 1.4 yrs vs 59 ± 0.6 yrs; p = 0.0003). RA subjects with OP had RA disease for longer than RA subjects without OP (20 ± 1.9 yrs vs 15 ± 1.0 yrs; p = 0.006), whereas disease duration was the same in SSc subjects both with and without OP. Additionally, RA controls reported more past pregnancies than SSc (3.0 ± 0.1 vs 2.4 ± 0.2; p = 0.0003).

There was no significant difference in OP diagnosis between SSc subjects with diffuse (22% with OP) or limited disease (18% with OP; p = 0.65). The mean ages were 55.5 ± 1.6 years and 59.8 ± 1.2 years for the diffuse and limited subgroups, respectively (p = 0.03); women composed a larger proportion of the subgroup with limited disease (89%) compared to diffuse (67%) (p = 0.001). A history of steroid use was more common in the diffuse (vs limited) SSc group (33% vs 21%) but the difference was not significant (p = 0.12). Participation in regular exercise was slightly more common in those with diffuse disease (70% vs 52%; p = 0.15).

Through the chart review, 159 SSc patients' charts were available. Fifty-six patients (35.2%) had a BMD measurement done previously (Table 3). Among the group aged ≥ 65 years, 21 (52.5%) patients had a BMD available in the chart. Table 4 presents results of the T score at lumbar spine, femoral neck, and total hip region of 56 SSc patients with their RA age matched control. We noted that the SSc had a lower BMD than the RA group, especially in femoral neck region; but the difference was not statistically significant when p values were adjusted for age (p = 0.01, adjusted for age p = 0.26). OP was present in 22/56 (39.3%) patients with SSc (Table 5) versus 15/56 (26.8%) patients with RA (p = 0.23). OP was more prevalent in older patients with SSc. Indeed, 12/21 (57.1%) were age > 65 years in the SSc group, and 6/22 (27.3%) were age > 65 years in RA (p = 0.07).

Table 3. Proportion of SSc patients with BMD measurement reported by age group. Data are number (percentage within age group).

	BMD Measurement		Total
	No	Yes	
Age			
≤ 50 yrs	30 (81.1)	7 (18.9)	37 (100.0)
51–64 yrs	54 (65.9)	28 (34.1)	82 (100.0)
≥ 65 yrs	19 (47.5)	21 (52.5)	40 (100.0)
Total	103 (64.8)	56 (35.2)	159 (100.0)

DISCUSSION

We evaluated OP in patients with SSc with self-administered questionnaires and a review of 159 SSc patients' charts. We found that the prevalence of OP of our cohort of patients with SSc was 19.4%, which was similar to our positive control RA group (16.7%; p = 0.38) and likely higher than the MSK group (12.2%; p = 0.054); even the family history of OP was increased 2-fold in the MSK group (22.8% in SSc vs 46.7% in MSK; p = 0.0006). Age was an important factor, as would be expected. Indeed, steroid use, disease duration, and age were included in a multivariate logistic regression model of risk of OP on disease status (SSc vs MSK and SSc vs RA); age was the only statistically significant variable that remained in the model. Frediani, *et al* demonstrated from an analysis of BMD of 47 women with SSc that age was significantly associated with OP[8]. Therefore, the young age of our cohort (mean age 58 to 60 yrs) might partly explain our results; it may be an underestimation of OP prevalence.

Steroid use did not influence the outcome of the diagnosis of OP (Table 1), given that most who took steroids were exposed for a relatively short period and in low doses. This finding is consistent with the results of Sampaio-Barros, *et al* in an analysis of 61 women with SSc; they found no statistical association between BMD values and previous use of corticosteroids[10]. In addition, we did not find an earlier age of menopause in our SSc cohort as compared to La Montagna, *et al*'s study[7].

Our results showed that OP risk factors were not significantly increased in SSc when data were adjusted for age. However, statistical trends were found in alcohol consumption (p = 0.054) and exercise (p = 0.059) compared with the MSK group. Given that the rate of disability due to illness was highly increased in SSc (41% in SSc vs 15.6% in MSK,

Table 4. Results of the BMD measurement of SSc and RA patients. T score, mean age, and mean duration of disease presented as mean ± SD.

Disease	Sex F:M	Mean Age, yrs	Mean Duration of Disease, yrs	Lumbar Spine T score	Femoral Neck T score	Total Hip T score
RA	53:3, n = 56	62.9 ± 10.1 n = 56	16.5 ± 8.06, n = 56	–0.967 ± 1.66, n = 55	–1.456 ± 1.08*, n = 37	–1.246 ± 0.99, n = 50
SSc	53:3 n = 56	62.2 ± 10.7, n = 56	12.7 ± 6.50 n = 52	–1.011 ± 1.38, n = 56	–2.067 ± 1.03*, n = 44	–1.523 ± 1.28, n = 45

* p = 0.01, adjusting for age p = 0.26. BMD: bone mineral density; SSc: systemic sclerosis; RA: rheumatoid arthritis.

Table 5. Results of the BMD measurement of 56 patients with SSc classified by age group.

	BMD Measurement			Total
	Normal	Osteopenia	Osteoporosis	
Age*				
< 50 yrs	1 (14.3; 10.0)	4 (57.1; 16.7)	2 (28.6; 9.1)	7 (100.0; 12.5)
51–64 yrs	7 (25.0; 70.0)	13 (46.4; 54.2)	8 (28.6; 36.4)	28 (100.0; 50.0)
> 65 yrs	2 (9.5; 20.0)	7 (33.3; 29.2)	12 (57.1; 54.5)	21 (100.0; 37.5)
Total, n (% of total)	10 (17.9)	24 (42.9)	22 (39.3)	56 (100.0)

BMD: bone mineral density; SSc: systemic sclerosis. Normal: T score > –1, Osteopenia: T score > –2.5 and ≤ –1, Osteoporosis: T score ≤ –2.5. * Data are number (percentage within age group; percentage within BMD measurement).

p = 0.0001, vs 25.7% in RA, p = 0.004), our assumption was that patients with SSc had generally decreased mobility due to their illness, which is another potential risk factor for OP. To our knowledge, no publication has ever reported the prevalence of these risk factors in patients with SSc.

The prevalence of OP of our SSc population was 19.2%, which is consistent with the current literature (6.7% to 51.1%, mean 24.3%)[9-11,16]. As in our subsets, several authors reported no differences in low bone mass between diffuse and limited SSc[10,16]. Di Munno, *et al* found a direct correlation between SSc disease duration and increased OP diagnosis[6]. This lends support to the hypothesis of OP resulting from larger disease effects such as the decreased mobility and impaired health associated with SSc, combined with the increased risk of OP due to advancing age. However, our study found no difference between disease duration of SSc patients with or without OP, but our study participants were still relatively young. We did not observe a correlation between age of menopause (an important risk factor for OP in women) in SSc patients and OP diagnosis (p = 0.4), as observed in a previous study[7], but many of our study participants were premenopausal (37% of SSc).

We found that BMI of the SSc group was similar to the RA group, but significantly lower than the MSK control group. The OP prevalence of our cohort might be affected. Indeed, this finding is in agreement with a previous comparative study of 61 female SSc patients with 107 healthy controls paired by age and race[10]. BMI of the SSc group was significantly lower than the control group and influenced BMD values. Several well known reasons such as immobility and chronic inflammatory gastrointestinal involvement causing malabsorption in SSc may explain a lower BMI. Therefore, it might be an additional factor to consider when evaluating OP in patients with SSc. We had a moderate response rate and we validated the results with charts review, but there was a lack of BMD data for all patients. BMD measurements had been performed on 62.1% of the patients with RA versus only 40.9% of the patients with SSc, which may under- or overestimate the true prevalence of OP in SSc. Also, there may be selection bias with ordering BMD measurements; usually, BMD measurements were requested according to the standard Canadian recommendation[3] for all patients. Any BMD that had been done for any reason was included if available. This may have biased results, as all patients did not have a BMD. However, we obtained a similar rate of BMD tests in the MSK and SSc groups. Surprisingly, the fracture rate in SSc was less than in RA and noninflammatory MSK patients. Thus the increased risk of OP in SSc (similar to RA) may have resulted in underestimation of life fracture risk as our patients were relatively young for an OP study (mean age of 58 to 60 yrs).

Results from our chart review provide evidence that bone density measurements (T score) in patients with SSc were comparable to or even lower than those for patients with RA (Table 4). RA is actually considered as a minor risk factor for OP by the Canadian authority[3]. Several studies have assessed BMD in SSc and healthy control groups[6-10,16-18] and most authors have concluded there is a decreased BMD in patients with SSc[6-10,18]. We found that OP was more prevalent in the age group > 65 years in SSc (Table 5), which is consistent with the literature[19,20], and expected, as age is such an important risk factor. However, only 21/40 (52.5%) patients with SSc aged > 65 years had a BMD measurement available in the specialist's medical record. According to the current Canadian recommendation on the diagnosis and management of OP, bone densitometry should be considered in all patients aged > 65 years[3].

Our study showed that OP prevalence in patients with SSc was similar to that of RA controls but likely higher than that of MSK controls. Patients with SSc had a trend for some increased risk factors such as immobility, alcohol drinking, and less exercise. Also, our results indicated that BMD measurements (T score) in SSc were comparable to or even lower than those for patients with RA. Increasing the awareness of clinicians to order BMD measurements in patients with SSc may be warranted based on our results, especially for older patients. We are uncertain if fracture rates or OP prevalence will increase more in patients with SSc with advancing age compared to controls. Further investigations are needed to allow more definitive conclusions regarding the risk of OP in patients with SSc.

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