Bone disease in systemic sclerosis: outcomes and associations

M.A. Omair[1,2], H. McDonald-Blumer[1,3], S.R. Johnson[1,4]

[1]Toronto Scleroderma Program, Division of Rheumatology, Department of Medicine, Mount Sinai Hospital, Toronto Western Hospital, University of Toronto, Toronto, ON, Canada; [2]Division of Rheumatology, Department of Medicine, King Saud University, Riyadh, Saudi Arabia; [3]Osteoporosis Program, Toronto General Hospital, University of Toronto, Toronto, ON, Canada; [4]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada.

Mohammed A. Omair, MD
Heather McDonald-Blumer, MD, MSc
Sindhu R. Johnson, MD, PhD

Please address correspondence to:
Sindhu Johnson, MD, PhD,
Toronto Scleroderma Program,
Division of Rheumatology,
Ground Floor, East Wing,
Toronto Western Hospital,
399 Bathurst Street,
Toronto,
M5T 2S8 Ontario, Canada.
E-mail: sindhu.johnson@uhn.ca

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ABSTRACT

Objective. *The relationship between systemic sclerosis (SSc) and low bone mineral density (BMD) is poorly understood. The aim of this study is to improve our understanding of low bone density in SSc and its potential consequences.*

Methods. *Fifty consecutive unselected SSc patients were approached. Demographics, disease manifestations, BMD (lumbar spine and femoral neck) were collected at baseline and occurrence of fracture and death were collected over 2 years. The 10-year risk of osteoporotic fracture was estimated using the fracture risk assessment tool (FRAX) v2.0 with the Canadian population reference. Fisher's Exact and Student's t-tests were used to evaluate differences between patients with and without low BMD. Logistic regression was used for multivariate analysis.*

Results. *Forty-five patients had complete BMD data. Twenty-eight patients (62%) had low BMD, of those 10 (36%) had osteoporosis. There was no difference in age, sex, or disease duration between both groups. Low BMD was associated with non-Caucasian race (57% vs. 18%, p=0.01), postmenopausal status (83% vs. 47%, p<0.01), low body mass index (24.5 vs. 26.2, p=0.05). The mean 10-year risk of developing a major osteoporotic fracture and a femoral neck fracture was higher in the low BMD group (10.2% vs. 4.8%, p=0.12) and (4.1% vs. 0.5%, p = 0.16) respectively. Fourteen percent (4/28) of SSc patients with low BMD had a fracture, compared to 6% (1/17) SSc patients without low BMD. Fracture-related mortality did not occur in any patients.*

Conclusion. *Low BMD and fracture are frequently seen in SSc patients. A number of clinically relevant factors are associated with low BMD. Further research is needed to evaluate these factors and the role of bone-specific treatments in SSc.*

Introduction

Systemic sclerosis (SSc) is an autoimmune disease characterised by progressive fibrosis of the skin and internal organs. Low bone density, and in particular osteoporosis, are common conditions characterised by a systemic impairment of bone mass, microarchitecture, and strength which increases the propensity of fragility fractures. Several risk factors, such as age, low body mass index (BMI), previous fragility fractures, a family history of fractures, use of glucocorticoids, physical inactivity, excess alcohol consumption and active cigarette smoking are classically associated with osteoporosis (1).

There have been conflicting data whether or not SSc by itself increases the risk of low BMD (2). In our systematic review of the published literature (3), the prevalence of low bone density ranged between 27%–53.3%, and the prevalence of osteoporosis ranged between 3%–51.1% (4-12). Ten studies reported a lower bone density in SSc patients compared to matched controls (5, 7-9, 12-17), whereas 2 studies reported no difference (6, 18). Two studies only described findings without a comparison group (11, 19). Zurek *et al.* compared a group of patients with connective tissue disease (which included 20 SSc patients) and found that the SSc patient group had a lower BMD (20). D'Amore *et al.* compared bone density at the hip and lumbar area, and found the hip density lower (21). Proposed risk factors for low bone density in SSc include family history of osteoporosis, age, menopause, diffuse cutaneous subtype, presence of internal organ involvement, low vitamin D levels and calcinosis. However, the studies supporting these factors were conflicting. Vitamin D plays a complex role in bone metabolism in addition to its immunomodulatory effect (22). Rios-Fernandez *et al.* reported a high prevalence of low vitamin D in patients with SSc in 2 different Spanish regions, but these factors did not sig-

nificantly influence bone density (23). Hagdrup *et al*. evaluated at the effect of penicillamine on BMD and found no significant reduction in patients treated with penicillamine (24).

Fracture rates in SSc range between 0%–38% (4-12, 17, 19). Carbone *et al*. estimated that bone density is 9.4% lower in SSc patients compared to controls, and they suggest that this confers a 2.6 fold increase in fracture risk (15) Weiss *et al*. described comparable odds ratios for osteoporotic and femoral neck fracture in a large case-control study (25). Clinical practice guidelines recommend the use of 10-year risk of fracture to guide therapeutic decision-making (26). However, there are no published data about the 10-year risk of developing osteoporotic fractures in SSc, nor are there any published data about osteoporosis-associated fracture mortality in SSc.

The aim of this study is to improve our understanding of low bone density in SSc and its potential consequences. This is needed as musculo-skeletal manifestations of SSc are a significant determinant of quality of life for these patients (27). The objectives of this study were to estimate the prevalence of low bone density and/or osteoporosis, evaluate risk factors for low bone density, evaluate the 10-year risk of osteoporotic fractures, and evaluate the occurrence of fracture and fracture-related mortality in SSc patients.

Methods

Patients

The Toronto Scleroderma Program is a large, scleroderma care and research cohort which operates through two University of Toronto affiliated teaching hospitals (Mount Sinai Hospital and Toronto Western Hospital, Toronto, Canada) (28). Fifty consecutive unselected SSc patients seen in the Toronto Scleroderma Program were asked to participate in this study in 2010, and prospectively followed until 2012. Patients were included if they: 1) fulfilled 1980 the American College of Rheumatology classification criteria for SSc (29), 2) were 18 years of age or older, and 3) had been followed for three months or more.

Candidate risk factors

Using a standardised data collection form, patient demographics (sex, age at diagnosis of SSc, age at menopause, age at time of BMD), SSc disease manifestations (subtype, organ involvement, autoantibodies), investigations, (calcium, phosphate, 25-hydroxyvitamin D, B12, folate, ferritin), medication use (corticosteroids, cyclophosphamide, selective serotonin reuptake inhibitors, vitamin D and calcium supplements, hormone replacement therapy, antiresorptive or anabolic bone therapies), history of falls, history of height loss >2 inches/6 centimeters(of the historical height), history of 10 kg/25 lbs. weight loss from usual adult weight, history of kyphoscoliosis, and smoking status were collected. Organ involvement was defined as: (pulmonary arterial hypertension: mean pulmonary arterial pressure ≥25 mmHg by right heart catheterisation, interstitial lung disease: forced vital capacity <70%, diffusing lung capacity <70% with evidence of lung fibrosis on CT scan; cardiac involvement: electrocardiogram evidence of conduction block or left ventricular systolic pressure ≤49 mmHg (30), renal involvement: creatinine >1.3 mg/dl (115 umol/L) or presence of +2 proteinuria (30); arthritis: presence of swollen joints on clinical examination or effusion/synovitis on imaging).

Risk of fracture

The 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder); and the 10-year probability of a femoral neck osteoporotic fracture were calculated using the WHO fracture risk assessment tool (FRAX) version 2.0, using the Canadian population dataset (31). As per FRAX user guidelines, the age of 40 was used when calculating the risk for younger patients.

Exposure

Bone mineral density was assessed using dual energy x-ray absorptiometry bone densitometer (Hologic Discovery model A-84248 for most patients). Low bone density was defined as a T score 1.1 standard deviations or more below the average value for a young healthy woman at either the femoral neck or lumbar spine (32). Osteoporosis was defined as a T score 2.5 standard deviations or more below the average value for a young healthy woman (32). Using a standardised data collection form, bone mineral density and T-score from lumbar spine and femoral neck were recorded.

Outcomes

Fracture was defined as a break in the continuity of a bone. A fragility fracture was defined as a fracture occurring spontaneously or following minor trauma such as a fall from standing height or less (26). Death was defined as all-cause mortality. Fracture-associated mortality was defined as death occurring after a fragility fracture. Cause of death was obtained from the patient hospital electronic record.

Analysis

SSc subjects with low BMD were compared with SSc subjects with normal BMD. Descriptive statistics were used to characterise the SSc subjects. Fisher's Exact test and Student's *t*-test were used to evaluate differences between patients with and without low BMD. Logistic regression was used for multivariate analysis. Bonferroni correction was used to account for multiple comparisons. A p-value <0.001 was considered statistically significant. All analyses were conducted using R version 2.8.1 (The R Foundation for Statistical Computing).

Institutional research ethics board approval was obtained for the conduct of this study. Patients provided written informed consent.

Results

Prevalence

Of the 50 consecutive subjects who consented to study participation, 45 SSc subjects had complete BMD data. All subject also fulfilled the ACR-EULAR classification criteria for SSc. (33-35) Five subjects did not complete BMD assessment. Demographic, clinical and laboratory characteristics are reported in Table I. Twenty-eight patients (62.2%) had low bone density, of those 10 (35.7%) had osteoporosis.

The median lumbar spine density of the low BMD group compared to the normal density group was 0.921 g/cm^2 (interquartile range (IQR) 0.820 g/cm^2, 1.006 g/cm^2) *vs*. 1.173 g/cm^2 (IQR 1.109 g/cm^2, 1.274 g/cm^2), $p<0.001$. The median femoral neck density of the low BMD group compared to the normal density group was 0.772 g/cm^2 (IQR 0.699 g/cm^2, 0.885 g/cm^2) *vs*. 0.956 g/cm^2 (IQR 0.840 g/cm^2, 0.977 g/cm^2), $p<0.004$.

Risk factors

SSc subjects with low BMD were non-Caucasian (57% *vs*. 18%, $p=0.01$), post-menopausal (83% *vs*. 47%, $p<0.01$), had lower median BMI (24.5 *vs*. 26.2, $p=0.05$), lower median weight (62.3 kg *vs*. 64.5 kg, $p=0.03$) and family history of osteoporosis (18% *vs*. 6%, $p=0.01$). In an adjusted analysis including menopausal status and weight, non-Caucasian race was statistically significantly associated with low BMD (beta estimate -0.36, $p=0.04$). SSc subjects with low BMD frequently had the ScL-70 antibody (29% *vs*. 43%), more lower gastrointestinal involvement (18% *vs*. 6%), small bowel bacterial overgrowth (11% *vs*. 1%), ILD (39% *vs*. 29%), PAH (21% *vs*. 12%), more frequent history of falls (7% *vs*. 0%), ≥10 kg weight loss (32% *vs*. 24%), family history of osteoporosis (18% *vs*. 6%), and kyphoscoliosis (7% *vs*. 0%); however none were statistically significant. (Tables I and II). None of the patients developed cyclophosphamide premature ovarian failure.

Outcomes

All 45 patients were followed for 2 years. Fourteen percent (4/28) of SSc patients with low bone density had a fracture compared to 6% (1/17) of SSc patients without low bone density. The sites of fractures for the low bone density group were femoral neck (n=2), pelvis (n=1) and vertebrae (n=1). The mean FRAX 10-year risk of developing a major osteoporotic fracture was higher in the low bone density group (10.2% *vs*. 4.8%, $p=0.12$). The mean FRAX 10-year risk of developing a femoral neck fracture was higher in the low bone density group (4.1% *vs*. 0.5%, $p=0.16$). One patient died of liver failure. The cause of death was not attributed to fracture-associated mortality.

Table I. Comparison of clinical characteristics between SSc patients with and without low bone density.

Characteristics	Without low bone density n=17	With low bone density n=28	*p* value
Demographic			
Age (years) (median (IQR))	50 (43, 54)	53.5 (48.8, 61.8)	0.15
Female sex	15 (88%)	23 (82%)	0.69
Caucasian	14 (82%)	12 (43%)	0.013
Hormonal			
Menopause (n (%))	7 (47%)	19 (83%)	0.009
Premature menopause (n (%)) [a]	1 (7%)	2 (9%)	0.56
Early menopause (n (%)) [b]	1 (7%)	5 (22%)	0.38
Age of menopause (years)	50.5 (44, 51)	47 (42, 50)	0.79
Hysterectomy (n (%))	0	4 (17%)	0.28
Body habitus			
Height (cm)	162 (156, 165)	161 (157, 167)	0.29
Weight (kg)	64.5 (58, 100)	62.3 (53, 71)	0.034
Body mass index	26.2 (23.1, 30.1)	24.5 (20.3, 26.8)	0.05
Scleroderma specific			
Diffuse subtype (n (%))	8 (47%)	10 (36%)	0.53
Disease duration (months (IQR))	84 (49, 174)	84 (48, 138)	0.83
ScL-70 antibody (n (%))	5 (29%)	12 (43%)	0.52
Anticentromere antibody (n (%))	5 (29%)	7 (25%)	0.99
Upper GI involvement (n (%))	15 (88%)	24 (86%)	0.99
Lower GI involvement (n (%))	1 (6%)	5 (18%)	0.38
Small bowel bacterial overgrowth (n (%))	1 (6%)	3 (11%)	0.99
Myositis (n (%))	3 (18%)	2 (7%)	0.35
ILD (n (%))	5 (29%)	11 (39%)	0.54
PAH (n (%))	2 (12%)	6 (21%)	0.69
Medications			
Vitamin D (n (%))	13 (76%)	23 (82%)	0.71
Calcium (n (%))	11 (65%)	22 (79%)	0.16
Bisphosphonates (n (%))	6 (35%)	15 (54%)	0.22
Prednisone (n (%))	10 (59%)	12 (43%)	0.54
Cyclophosphamide (n (%))	2 (12%)	2 (7%)	0.63
Metabolic indices			
Low vitamin D level (n (%))	7 (41%)	8 (29%)	0.71
Low vitamin B12 (n (%))	3 (18%)	5 (18%)	0.99
Low folate (n (%))	1 (6%)	0	0.41
Low ferritin (n (%))	1 (6%)	0	0.41

IQR: Interquartile range; GI: Gastrointestinal; GAVE: Gastric Antral Vascular Ectasia; cm: centimeters; kg: kilogram; ILD: interstitial lung disease; PAH: pulmonary arterial hypertension; Low vitamin D level: 25-hydroxy vitamin D <75 nmol/L; Low vitamin B12: <198 pmol/L; Low folate: <634 nmol/L; Low ferritin: <4.6 µg/L.
[a]Defined as the occurrence of menopause before the age of 40; [b]Defined as the occurrence of menopause before the age of 45.

Discussion

Our study demonstrates that low bone density is common in SSc patients, highlights clinically relevant risk factors, and indicates that fragility fractures are not uncommon in SSc. Furthermore we demonstrate that the 10-year risk of osteoporotic fractures is increased in SSc patient with low bone density.

The prevalence of low bone density was high in our study. This is a striking finding given that median age in the low bone density group was only 53 years. This is a younger group of patients than is typically seen in bone density studies. The prevalence of low bone density among our SSc patients is also higher than that which has been previously reported. In other SSc studies, the prevalence of low bone density ranges between 27%–53.3% (7-14, 16, 19, 24). The patients included in this study were consecutive patients seen in our program. As such, they were not purposively sampled. However, our center is a tertiary, academic center. It

Table II. Comparison of osteoporotic-fracture risk factors between SSc patients with and without low bone density.

Characteristics	Without low bone mass n=17	With low bone mass n=28	*p*-value
Falls	0	3 (7%)	0.28
Height loss [a]	0	1 (2%)	0.99
Weight loss [b]	4 (24%)	9 (32%)	0.73
Family history of osteoporosis	1 (6%)	5 (18%)	0.39
Kyphoscoliosis	0	2 (7%)	0.52
Previous fracture	1 (6%)	4 (14%)	0.64
Site of fracture	Femoral neck n=1	Femoral neck n=2 Pelvis n=1 Vertebrae n=1	
Mean 10-year risk of fracture [c]	4.8	10.2	0.12
Mean 10-year risk of hip fracture [c]	0.5	4.1	0.16

[a]History of height loss >2 inches/6 centimeters; [b]History of 10 kg/25 lbs. weight loss from usual adult weight; [c]10-year probability of osteoporotic fracture calculated using the FRAX WHO fracture risk assessment tool.

may be that our SSc patients reflect a subset of SSc patients who have more severe disease than the general SSc population. Many SSc patients are followed at specialty academic centers comparable to ours, and therefore such patients should be screened for low bone density.

In this study, non-Caucasian ethnicity was the strongest factor associated with developing low bone density in our multi-ethnic cohort. SSc patients with low bone density were more frequently postmenopausal, had low BMI, low body weight, were ScL-70 positive, had small bowel bacterial overgrowth, had more lower gastrointestinal involvement, ILD, PAH, more frequent history of falls, ≥10 kg weight loss, family history of osteoporosis and kyphoscoliosis. Similar findings to our study were described in the literature (9-11). La Montagna *et al*. described the role of early menopause in inducing bone loss and osteoporosis. In our cohort there was no difference in the median age of menopause between the 2 groups but the number of patients who developed early menopause was higher in the low BMD group. Low BMI has been associated with low bone density in SSc patients (4, 5, 9, 10, 16). Its presence might be a reflection of disease severity or lower-bowel gastrointestinal involvement. Lower-bowel gastrointestinal involvement is very common in SSc, and is attributed to collagen deposition in the intestinal wall. It can manifest as food intolerance, abdominal distention and diarrhoea leading to malabsorption and weight loss (36). Interestingly, in our study, potential markers of nutritional malabsorption (folate, B12, iron) were not associated with decreased bone density. In our study, the use of corticosteroids was not associated with a lower bone density. This finding may be explained by 2 reasons; first, patients with SSc are usually only on corticosteroids for a short period of time. Second, the majority of our patients were on adequate glucocorticoid-induced osteoporosis prophylaxis.

Our study is the first to report the risk of fracture using a validated, composite risk assessment tool and fracture-related mortality in SSc. The fracture risk using the FRAX tool was increased for patients with low bone density. This suggests that tool may be a helpful measure in SSc patients. How our data suggests that the FRAX tool may *underestimate* the risk of fractures. Our study provides the justification for a larger, adequately powered study to investigate this finding. Outside of SSc, fragility fractures have been associated with an increased risk of subsequent fracture, decreased quality of life, hospitalisation, increased economic burden on the healthcare system and death (26). A large proportion of people with fragility fractures have low bone density. An over reliance in BMD testing to make a diagnosis of osteoporosis has resulted in a missed opportunity to prevent fractures. It has been recommend that initiation of therapy not be based on BMD values alone, but rather through the assessment of 10-year absolute fracture risk using a validated fracture prediction instrument that incorporates both BMD values, as well as important clinical risk factors. Our study demonstrates that SSc patients with low bone density have an increased 10-year risk of both a major osteoporotic fracture and a femoral neck osteoporotic fracture.

Fracture was more common in SSc patients with low bone density than among SSc patients with normal bone density. Our systematic review of the literature found that very few studies evaluating bone density in SSc reported fracture as an outcome (3). When reported, the prevalence of fracture was variable, occurring in up to 38% of patients (4-12, 17, 19). None of the studies evaluated fracture-associated mortality. In this study, fracture-related mortality did not occur. It may be that this is an uncommon outcome. A larger study (*e.g*. large observational cohort or registry data) with a longer duration will be required to appropriately evaluate low frequency, but serious events. Fractures and fracture-associated mortality may be significant, under-recognised yet preventable outcomes in SSc.

Limitations of our study include sample size, lack of a healthy control group, and short duration of follow-up to detect fracture rate or related mortality. Our limited sample size precluded our ability to have the power to detect statistically significant differences. The clinically significant differences we found provide the justification to evaluate these risk factors in a larger, adequately powered study. Secondly, Z scores were not reported for the males and young females. As a result of this systematic difference n reporting, we did not analyse Z scores as this may lead to biased estimation of effects. The next phase of research will require a closer examination of the relationship of SSc, low bone density, fracture and fracture-associated mortality (3). Many of the factors we have identified likely occur at many levels along this pathway. It is unlikely that each factor is independent of each other. It is more likely that they are inter-related (*e.g*.

extent of skin involvement, extent of internal organ involvement, serology) (3). The next phase of research will need to evaluate the directed dependencies among these variable, and quantify the effect each has on the causal pathway. Methodologic approaches to consider include a path analysis, latent variable models or structural equation modelling (37). It is only with this next phase of research can one make definitive conclusions about an explanatory prognostic pathway and make causal inferences. Once the causal pathway is established, targeted behavioural or pharmacologic interventions to prevent adverse outcomes can be appropriately studied.

In conclusion, low bone density and fracture are frequently seen in our SSc patients. A number of clinically relevant factors are associated with low BMD. SSc patients with low bone density have a higher 10-year risk of developing a major osteoporotic fracture, and have a higher 10-year risk of developing a femoral neck fracture.

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