Low Bone Density in Systemic Sclerosis. A Systematic Review

Mohammed A. Omair, Christian Pagnoux, Heather McDonald-Blumer, and Sindhu R. Johnson

ABSTRACT. ***Objective.*** The effect of systemic sclerosis (SSc) on bone density is not well understood. Through systematic review of the literature, the objectives of this study were to synthesize data about the prevalence of low bone mineral density (BMD), risk factors for low BMD, and occurrence of fracture and fracture-related mortality in SSc.

Methods. A search was conducted of MEDLINE (1948–2012), Evidence Based Medicine Reviews (1991–2012), EMBASE (1980–2012), and CINAHL (1981–2012). Abstracts were screened to identify studies that evaluated low BMD in patients with SSc. Two investigators independently used a standardized form to abstract prevalence of osteopenia and osteoporosis (OP); risk factors for low BMD, BMD measurements, frequency of fracture, and fracture-related mortality.

Results. Screening of 1032 citations identified 19 articles. Fifteen studies compared patients with SSc to controls. Most patients were white, female (prevalence 74%–100%), and postmenopausal (prevalence 45.9%–100%). The prevalence of low BMD and OP was 27%–53.3% and 3%–51.1%, respectively. Ten studies reported a lower BMD in patients with SSc compared to matched controls, whereas 2 studies reported no difference. Candidate risk factors for low BMD in SSc include family history of OP, age, menopause, diffuse subtype, presence of internal organ involvement, low vitamin D levels, and calcinosis. However, the studies supporting these factors were conflicting. Fracture rate ranged between 0% and 38%. No study reported OP-related fracture mortality.

Conclusion. The data suggest that patients with SSc are at risk of low BMD and fracture, especially when other risk factors for OP are present. The interaction of SSc manifestations, traditional OP risk factors, and clinically relevant outcomes is complex and warrants further research. (First Release Sept 15 2013; J Rheumatol 2013;40:1881–90; doi:10.3899/jrheum.130032)

Key Indexing Terms:

SYSTEMIC SCLEROSIS	SCLERODERMA	OSTEOPOROSIS
OSTEOPENIA	BONE DENSITY	FRACTURE REVIEW

Systemic sclerosis (SSc) is an uncommon connective tissue disease characterized by progressive fibrosis of the skin, vasculopathy, and immune activation. Internal organs such as the gastrointestinal tract, lungs, and kidneys may become affected. Inflammation evidenced by elevation of acute phase reactants early and late in the disease (most probably occurring secondary to infection) is an increasingly recognized feature of the disease[1].

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Dr. Johnson has been awarded a Canadian Institutes of Health Research Clinician Scientist Award and is supported by the Norton-Evans Fund for Scleroderma Research.

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Accepted for publication July 16, 2013.

Skeletal manifestations of SSc may include fibrosis of the joint capsule, flexion contractures, thickened tendons, or inflammatory, erosive, and nonerosive arthritis[2]. These skeletal manifestations of SSc have been shown to affect quality of life[3], and may be amenable to treatment[4]. The effect of SSc on bone is less well understood. Osteopenia and osteoporosis (OP) are conditions characterized by a systemic impairment of bone mass, strength, and microarchitecture, which increase the propensity for fragility fractures. Bone mineral density (BMD) is commonly measured by dual-energy x-ray absorptiometry (DEXA). OP is defined by a T score of –2.5 or lower, i.e., more than 2.5 SD below the average density of a young adult. When the T score is –1 to –2.5 SD below the average density of a young adult, the term low bone density (formerly osteopenia) is applied, recognizing that osteopenia technically refers only to postmenopausal white women with low bone mass. The measurement of BMD by DEXA is a valid method to diagnose OP and help to predict the risk of fracture[5].

There have been conflicting data reporting whether SSc increases the risk of OP[6]. Risk factors, such as age, low body mass index (BMI), previous fragility fractures, a family history of fractures, use of glucocorticoids, early menopause, systemic inflammatory disease, and active

cigarette smoking are classically associated with OP[5]. Whether these classical risk factors are also associated with SSc-related OP is unclear. SSc-specific factors that may increase the risk of OP include chronic inflammation, early menopause, immobilization, soft tissue calcification depleting calcium stores, and disturbance of vitamin D metabolism in the skin, kidney, and gastrointestinal tract[6]. Hypothyroidism, a common feature associated with SSc, can contribute to the low bone mass[7,8]. The goal of OP therapy is prevention of fractures. Early assessment and stratification of an individual's risk using validated tools of OP is therefore important to prevent the first fracture[9]. The first line of management includes lifestyle modification (cessation of smoking, reduction of alcohol consumption, and increased physical activity). Vitamin D supplementation and adequate calcium intake are recommended as preventive treatment in patients at risk of or with OP. Despite the conflicting results of clinical trials assessing the efficacy of vitamin D supplementation and calcium in the prevention of fractures, the efficacy of specific OP drugs has been shown only if these supplements were concurrently given[10]. Specific treatments include estrogen (for women)[11], bisphosphonates[12], selective estrogen receptor modulators[12], recombinant parathyroid hormone[12], strontium ranelate[13], and monoclonal antibodies against receptor activator of nuclear factor-κB ligand (RANKL)[14]. Challenges unique to the use of bisphosphonates in SSc include the significant esophageal involvement precluding the use of oral form[13]. Additionally, with the bisphosphonates and potentially with other agents such as denosumab, the high prevalence of vitamin D deficiency found in SSc individuals[15,16] can negatively influence the response to these medications.

Very little is known about bone quantity or quality in the setting of SSc. Before a therapeutic program of research is undertaken, a basic understanding of the epidemiology of low bone density in the setting of SSc is needed, namely the prevalence, determinants of the occurrence of low bone density, and its effect on clinically relevant outcomes. Knowledge of these factors and an awareness of knowledge gaps are important to inform SSc patient care and further research. Using Hayden's framework of an explanatory approach to studying prognosis, a phase I study is needed to survey the literature and identify proposed associations[17]. A systematic review of the literature was conducted to synthesize data evaluating the prevalence, risk factors for low bone density, and clinically relevant outcomes in patients with SSc.

MATERIALS AND METHODS

Literature search. Searching the literature was done through the University Health Network library with the assistance of an information specialist. The search included Ovid MEDLINE from 1948 to 2012 (Week 52), Evidence Based Medicine Reviews — Cochrane Central Register of Controlled Trials from 1991 to 2012 (4th Quarter), EMBASE from 1980 to 2012 (Week 52), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) from 1981 to 2012. The following keywords with mapping of term to subject headings were used in the database search: (systemic scleroderma or systemic sclerosis or diffuse scleroderma) and (metabolic bone disease or bone demineralization or decalcification or osteopenia or osteoporosis or bone loss or fracture or bone density or bone resorption or osteolysis). The search was restricted to humans, but no language restriction was applied.

Study selection. Titles and abstracts were screened to identify studies that described low bone mass in patients with SSc. Inclusion criteria were (1) peer-reviewed observational studies (cohort and case-control studies) or randomized trials; (2) report of bone mass by BMD in patients with SSc; and (3) age ≥ 18 years. Abstracts, case reports, or case series with fewer than 10 patients with SSc, and studies using only conventional radiograph, were excluded. Machine translation software was used to translate non-English language articles.

Data abstraction. Two investigators (MO, CP) independently inspected the abstract of each citation identified by the search and applied the inclusion and exclusion criteria to identify relevant studies for full review. A standardized data abstraction form was used to collect study design, sex, age, ethnicity, menopause status, age at menopause, SSc disease duration, SSc subtype, autoantibodies, organ involvement, medications, intervention(s), BMD, T score, risk factors of low bone mass, and occurrence of fracture.

Outcomes. A standardized form was used to abstract the prevalence and incidence of osteopenia, OP; frequency of OP-related and -unrelated fractures; site of fractures; and fracture-related mortality.

Analysis. Descriptive statistics were used to summarize the data.

RESULTS

The search strategy identified 1032 citations. Citations were excluded if they were duplicate citations (n = 307), did not report patients with SSc (n = 427), did not report osteopenia or OP (n = 222), did not measure bone density by DEXA (n = 34) or did not report original data (n = 14). Nineteen articles fulfilled the inclusion and exclusion criteria. (Figure 1).

Patient characteristics. Fifteen studies compared patients with SSc to controls[18,19,20,21,22,23,24,25,26,27,28,29,30,31,32]. The sample sizes were relatively small with a median sample size of 43 (interquartile range: 25, 57.5). Seven studies reported ethnicity, in which most patients were white[19,22,24,26,28,33,34]. The majority of participants were female (proportion ranging 74%–100%) and postmenopausal (prevalence ranging 45.9%–100%[16,18,19,20,21,22,25,26,27,28,29,30,33,34]; Table 1). The presence of calcinosis was assessed in 5 studies, with an estimated prevalence ranging from 8%–54%[25,26,27,32,35]. Joint involvement was described in 4 studies (prevalence ranging 20%–36%)[18,19,25,27]. Percentage of patients with internal organ involvement ranged from 22%–84%[20,21,24,26,27]. Frediani, *et al* reported that 55% of patients had Scl-70 or anticentromere (ACA) antibodies[21]. Rios Fernandez, *et al* reported that 49% of the patients were ACA-positive and only 6.4% were Scl-70-positive[16]. Dovio, *et al* reported the rate of autoantibody positivity was 40% for both types[27]. Calcium and phosphorus levels were normal in 6 studies[25,26,27,34,35,36].

Bone mass. The prevalence of low bone density scores (Table 2), defined by T scores of –1.1 to –2.5, ranged

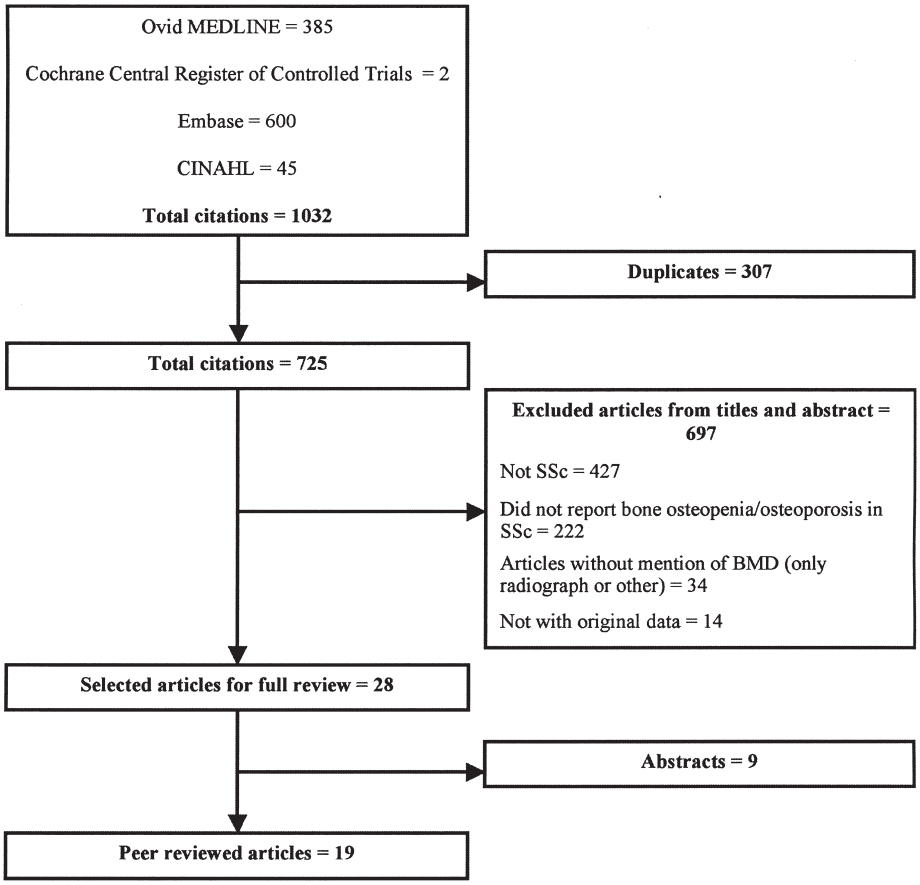

Figure 1. Criteria for selection of study articles. SSc: systemic sclerosis; BMD: bone mineral density.

between 27% and 53.3%. The prevalence of OP, defined by T scores of < –2.5, ranged between 3% and 51.1%[16,21,22,25,27,28,33,34]. Frediani, *et al* stratified patients based on menopausal status. Among premenopausal patients, the prevalence of osteopenia was 36%, and of OP 0%. Among postmenopausal patients, the prevalence of osteopenia was 53.3% and of OP 30%[21].

Ten studies reported a lower bone density in patients with SSc compared to matched controls[18,19,20,21,24,25,27,28,29,30]. Zurek, *et al* compared a group of patients with connective tissue diseases (CTD; which included 20 patients with SSc) to healthy controls, and found patients with CTD have a lower BMD[31]. They compared the BMD values of patients with SSc, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and polymyositis. Except for a significantly lower BMD in postmenopausal patients with SLE, there was no difference between other groups. Neumann, *et al* and da Silva, *et al* reported no difference between BMD values of patients with SSc and controls[22,26]. Yuen, *et al* found a similar rate of OP in SSc compared to patients with RA[30].

The hip was the most reported site of lower BMD (Table 3). Other sites that were found to have lower BMD included total hip, lumbar spine, radius, and total body[16,18,23,24,25,26,29,36]. Souza, *et al* calculated the OR of having OP in the femoral neck to be 4.03 versus 2.75 for the lumbar spine[29]. Carbone, *et al* estimated that BMD is 9.4% lower in patients with SSc compared to controls, which translates to –1 SD. They suggest that this confers a 2.6-fold increase in fracture risk[24].

Traditional risk factors. D'Amore, *et al* found that patients with SSc 45 years or older had a total hip BMD lower than lumbar and total BMD[23]. Six studies excluded patients currently taking corticosteroids[20,21,24,25,29,35]; and 8 studies included these patients (prevalence ranging 14.9%–61%)[16,19,22,27,28,30,33,34]. Hormone replacement therapy was allowed in 1 study[22]. In 2 studies more than half the patients were taking or previously received cyclophosphamide (CYC)[28,33]. Thirteen to 41.8% had family history of OP[22,29,30,34]. Current or previous smoking was reported to range from 3% to 60%[27,30]. In 8 studies, age alone or with the number of years since menopause were risk factors for having a lower BMD[18,20,21,23,25,29,30,33](Table 4 and Figure 2).

SSc-specific risk factors. Three studies reported no difference between SSc subtypes[22,28,29], whereas Carbone reported that the diffuse subtype had lower BMD values than the limited form[24]. Frediani, *et al* identified the diffuse

Table 1. Summary of characteristics of patients with systemic sclerosis.

Article (Reference)	N (%)	Women (%)	Ethnicity	Age (mean ± SD)	Disease Duration, yrs ± SD	Post (%)	Age at Menopause, yrs ± SD	BMI, mean ± SD	Skin Extent (%)
La Montagna 1995[19]	22	19 (86)	W	Female 48.6 ± 10.7 Male 54.6 ± 7.8	Female 14 Male 3	9 (47)	45.5	NA	D 6 (27) L 5 (23) I 11 (50)
Neumann 2000[22]	30	30 (100)	W	56 ± 10	9.5 ± 7	24 (80)	NA	NA	D 19 (63) L 11 (37)
D'Amore 2005[23]	25	24 (96)	NA	53.28	6.4	NA	NA	NA	NA
Frediani 2004[20]	47	47 (100)	NA	53.9	NA	27 (57)	NA	NA	NA
Frediani 2004[21]	55	55 (100)	NA	54.1	Pre 5.4 Post 14.5	30 (55)	NA	22.5 ± 2.5	D 18 (33) L 23 (42)
Carbone 1999[24]	15	15 (100)	W 10 B 5	NA	9.87	NA	NA	NA	D 9 (60) L 6 (40)
Di Munno 1995[25]	43	43 (100)	NA	54.8	5.9	36 (84)	46.4 ± 6.4	L 23.7 ± 2.9 I 23 ± 2.6 D 19.4 ± 1.5	D 9 (21) L 25 (58) I 9 (21)
Hagdrup 1983[35]	35	28 (80)	NA	54.9	10	NA	NA	NA	NA
Dovio 2008[27]	60	48 (80)	NA	58	3	37 (77)	NA	25	D 13 (22) L 47 (78)
Alexandersson 2007[34]	24	18 (74)	W	60 ± 15	15 ± 10	16 (89)	NA	27 ± 5	NA
La Montagna 1991[18]	90	90 (100)	NA	48*	9*	56 (62.2)	45.5*	NA	D 34 (37) L 34 (37) I 19 (23) SSS 3 (3)
Souza 2006[29]	43	43 (100)	NA	62.3 ± 7.7	13.2 ± 8	43 (100)	46.6 ± 6.6	24.01 ± 3.7	NA
Serup 1983[32]	37	30 (81)	NA	55.7	8.9	NA	NA	NA	NA
Sampaio-Barros 2005[28]	61	61 (100)	54 W 7 B. Brazilian	Pre 35.79 ± 6.77 Post 54.21 ± 6.43	NA	28 (45.9)	46.7 ± 4.26	Pre 23.34 ± 4.48 Post 23.35 ± 4.98	D 21 (34.4) L 40 (65.6)
da Silva 1997[26]	25	25 (100)	W	48 ± 12	7 ± 7	13 (52)	NA	27 ± 4	D 4 (16) L 19 (76) I 2 (8)
Yuen 2008[30]	159	130 (82)	NA	58.3 ± 0.98	11.5 ± 0.7	63/79	46 ± 1.7	25.9 ± 0.6	NA
Sampaio-Barros 2000[33]	74	74 (100)	64 W 10 non W	D 40 L 50	10.7	40 (54)	45 ± 5.7	NA	D 24 (32) L 50 (68)
Zurek 2003[31]	20	20 (100)	NA	54.2 ± 11.0	5.8 ± 6.6	NA	NA	NA	NA
Rios Fernandez 2010[16]	48	48 (100)	NA	59.1 ± 11.7*	NA	(75.8)	NA	27.7 ± 5	D (8.5) L (91.5)

* Median values. NA: not available; D: diffuse; L: limited; I: intermediate; Pre: premenopausal; Post: postmenopausal; W: white; B: black; SSS: scleroderma sine scleroderma; BMI: body mass index.

subtype and the presence of internal organ involvement, but not autoantibodies nor inflammatory markers as risk factors for a lower BMD[20,21]. Medications such as penicillamine, corticosteroids, and CYC did not increase the risk of OP[16,28,33,34,36]. The prednisone dose was < 10 mg/day[19,28,33]. Carbone, *et al* found that physical activity was significantly less in patients with SSc when assessed by self-reports[24]. Conversely, Alexandersson, *et al* reported that 15 of 24 patients were exercising regularly 5 times per week[34]. In the same paper, physical disability was reported to be as high as 35%[34]. BMI and lean body weight positively correlated with BMD values in both femoral and lumbar areas[16,20,21,28,29]. In the report by Carbone, *et al,* although BMI was lower in SSc compared to controls, and even lower in the diffuse subtype compared to the limited, they did not find a significant correlation between BMD and BMI[24]. Serup, *et al* reported lower total bone mineral content in patients with calcinosis[32]. This finding was not observed by Carbone, *et al*[24] (Table 4 and Figure 2).

Bone markers. Regarding bone turnover markers, Dovio, *et al* assessed the level of osteocalcin (OC), alkaline phosphatase (ALP), C-telopeptide of type I collagen (CTX), osteoprotegerin (OPG), soluble RANKL (sRANKL), and sRANKL/OPG. Only the latter 2 were higher in patients compared to controls and correlated negatively with BMD measures. Dovio, *et al* found that there was no difference in the OC and ALP levels between controls and patients[27]. Alexandersson, *et al* found that taking corticosteroids significantly reduced the level of both markers[34]. Additionally, vitamin D levels were lower in patients with SSc. Vitamin D levels correlated with a higher CTX level, which may indicate some level of secondary hyperparathy-

Table 2. Values of BMD, T scores, Z scores of patients with SSc.

Article (Reference)	Lumbar			Total Hip			Neck of Femur		
	BMD, g/cm^2	T score	Z score	BMD, g/cm^2	T score	Z score	BMD, g/cm^2	T score	Z score
La Montagna 1995[19]	NA	NA	NA	NA	NA	NA	NA	NA	NA
Neumann 2000[22]	NA	NA	NA	NA	NA	NA	NA	NA	NA
Rios Fernandez 2010[16]	NA	NA	16.7% had < –1	NA	NA	NA	NA	NA	22.9% had < –1
D'Amore 2005[23]	NA	NA	NA	NA	NA	NA	NA	NA	NA
Frediani 2004[20]	Pre 1.159						Pre 0.938		
	Post 0.952	NA	NA	NA	NA	NA	Post 0.816	NA	NA
Frediani 2004[21]	0.98	–2.48	–1.1	NA	NA	NA	0.832	–1.69	–0.55
Carbone 1999[24]	0.98 ± 0.15	0.87 ± 1.3	0.243 ± 1.3	0.745 ± 0.15	–1.89 ± 1.2	–1.062 ± 1.2	–0.671 ± 0.13	–2.183 ± 1.31	–0.923 ± 1.45
Di Munno 1995[25]	0.974 ± 0.143	NA	NA	NA	NA	NA	NA	NA	NA
Hagdrup 1983[35]	NA	NA	NA	NA	NA	NA	NA	NA	NA
Dovio 2008[27]	0.92	–1.45	–0.47	0.85	–0.82	–0.34	NA	NA	NA
Alexandersson 2007[34]	NA	Female –1.2 ± 1.4	NA	NA	NA	NA	NA	Female –1.4 ± 1.1	NA
		Male –1.1 ± 1						Male –2.1 ± 0.9	
Sampaio-Barros 2000[33]		Pre –0.48 ± 1.04						Pre –0.51 ± 1.51	
	NA	Post –1.84 ± 1.58	NA	NA	NA	NA	NA	Post –1.51 ± 1.18	NA
La Montagna 1991[18]	NA	NA	NA	NA	NA	NA	NA	NA	NA
Souza 2006[29]	0.83 ± 0.11	NA	NA	NA	NA	NA	0.64 ± 0.11	NA	NA
Serup 1983[32]	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sampaio-Barros 2005[28]	Pre 1.15 ± 0.12						Pre 0.92 ± 0.18		
	Post 1.00 ± 0.21	NA	NA	NA	NA	NA	Post 0.81 ± 0.15		
							< 40 yrs (1.24 ± 0.29)		
							40–50 yrs (1.03 ± 0.13)		
da Silva 1997[26]	NA	NA	NA	NA	NA	NA	> 50 yrs (1.03 ± 0.18)	NA	NA
Yuen 2008[30]	NA	–1.011 ± 1.38	NA	NA	–1.52 ± 1.28	NA	NA	–2.067 ± 1.03	NA
Zurek 2003[31]	NA	NA	NA	NA	NA	NA	NA	NA	NA

Pre: premenopausal; Post: postmenopausal; NA: not available; BMD: bone mineral density; SSc: systemic sclerosis.

Table 3. Summary of studies that reported osteopenia, osteoporosis, and fracture.

Article (Reference)	Osteopenia, n (%)	Osteoporosis, n (%)	No. Fractures (%)	Site of Fracture
Neumann 2000[22]	11 (36.7)	1 93)	None	None
Frediani 2004[20]	Pre (36)	Pre none	NA	NA
	Post (53.3)	Post (30)		
Rios Fernandez 2010[16]	Total (47.5)	Total (25)	NA	NA
	Lumbar (43.8)	Lumbar (16.7)		
	Femur (47.9)	Femur (12.5)		
Dovio 2008[27]	16 (30)	14 (27)	NA	NA
Alexandersson 2007[34]	8 (33)	3 (12.5)	18 in 12 patients	Forearm, ribs, humerus, vertebrae, collarbone
Sampaio-Barros 2000[33]	26 (35.1)	14 (18.9)	NA	NA
Serup 1983[32]	10 (27)	NA	None	None
Sampaio-Barros 2005[28]	Lumbar	Lumbar	NA	NA
	Pre 10 (30)	Pre none		
	Post 10 (36)	Post 9 (32)		
	Femur	Femur		
	Pre 5 (15)	Pre 3 (9)		
	Post 17 (61)	Post 5 (18)		
Souza 2006[29]	NA	Total hip 22 (51.1)	(18.6)	NA
		Lumbar 13 (32.5)		
Yuen 2008[30]	NA	NA (19.2)	OP related (4)	NA
			Any fracture (38)	
Di Munno 1995[25]	Total 10 (23.3)	NA	NA	NA
	Lumbar 14 (32.6)			
	Radius 15 (34.9)			

Pre: premenopausal; Post: postmenopausal; NA: not available; OP: osteoporosis.

Table 4. Proposed risk factors for low bone mass in systemic sclerosis.

Risk Factor	Evidence Supporting Factor (Reference)	Evidence Against Factor (Reference)
Age	> 45 yrs ($p < 0.05$)[23] Association with: Any skeletal region (OR 1.6; CI 1.07–1.93)[28] Lumbar BMD ($r = –0.44$; $p = 0.006$)[28] Femoral neck BMD ($r = –0.46$; $p = 0.007$)[28] Total body BMD ($r = –0.27$; $p = 0.007$)[28] Heel ($r = –0.54$; $p = 0.001$)[28] Lumbar BMD ($r = –0.55$; $p < 0.005$)[25] Radial BMD ($r = 0.46$; $p < 0.0005$)[25] Proximal radius ($r = –0.47$; $p < 0.001$)[18] Distal site ($r = –0.4S$; $p < 0.001$)[18]	None
Duration of menopause/early menopause	Radial BMD ($r = –0.36$, $p < 0.05$)[25] Data not given[20] 46.71 ± 4.26 versus 49.20 ± 3.37 yrs old[33] Souza[29]	None
Diffuse subtype	Lumbar BMD ($p < 0.05$)[20] Femoral neck BMD ($p < 0.05$)[20] Total body BMD ($p < 0.01$)[20] Os calcis ($p < 0.05$)[20]	Yuen[30]; $p = 0.65$ Data not given[28]
Calcinosis cutis	Serup[32] ($p < 0.05$)	Di Munno[25]
Body mass index	Data not given[20] Multivariable model, data not given[28] 23.34 ± 4.48 versus 25.56 ± 4.42, $p = 0.035$[28] Rios Fernandez[16]	Di Munno[25]
Internal organ involvement	Lumbar BMD ($p < 0.05$)[20] Neck of femur BMD ($p < 0.05$)[20] Total body BMD ($p < 0.05$)[20]	Di Munno[25]
Disease duration	Lumbar BMD ($r = –0.37$; $p < 0.05$)[25] Radial BMD ($r = –0.42$, $p < 0.01$)[25]	Yuen[30] Data not given[28]
Calcium metabolism	None	Di Munno[25] Serup[32] Alexandersson 2007[34] Serup[32]
Autoantibodies	None	Data not given[20] Data not given[28]
Vitamin D	None	Rios Fernandez[16]
Corticosteroid therapy	None	Data not given[33] Data not given[28] Alexandersson 2007[34]

BMD: bone mineral density.

roidism[27]. This relationship between CTX levels, vitamin D, and scleroderma is further complicated by the fact that CTX levels can be affected by the extent of skin involvement, and the presence of decreased forced vital capacity[33]. This finding may be explained by the fact that lung and skin are sites of active collagen turnover and CTX might be a possible marker of disease involvement[36]. Alexandersson, *et al* found that a quarter of patients had low vitamin D level and 2 patients had high parathyroid hormone level. Both patients were reported to develop fractures[34]. Rios Fernandez, *et al* found that 81% of patients evaluated were vitamin D deficient even though two-thirds were taking 800 IU daily of cholecalciferol[16].

OP prophylaxis. In the study by Neumann, *et al,* 5 of 30 patients were taking corticosteroids, yet DEXA-defined OP at the lumbar and femoral neck areas was evident only in 1 of 30 patients evaluated. In this study, 50% and 43% of the total patients were taking calcium and vitamin D, respectively; and 60% were taking hormone replacement therapy[22]. Alexandersson, *et al* reported a low rate of OP in a population, of whom 61% were taking current corticosteroids, 33% were taking calcium, and 17% were taking bisphosphonates[34], suggesting a potential care gap.

Outcomes. The rate of fracture ranged from none to 38% (Table 3). No study reported OP-related fracture mortality.

DISCUSSION

Our systematic review summarizes the published literature evaluating low bone density in SSc, synthesizes what is known, and identifies knowledge gaps. We found that low

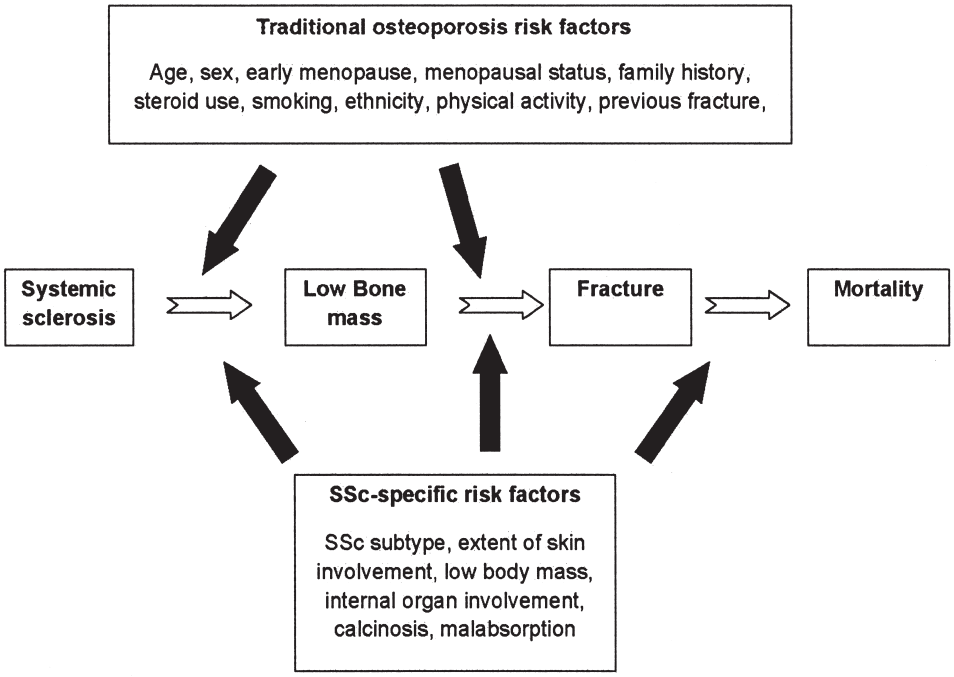

Figure 2. Conceptual framework of relationship of traditional osteoporosis risk factors and SSc-specific factors that may be related to low bone mass and outcomes in SSc. SSc: systemic sclerosis.

bone density in SSc is not infrequent. However, the relationship between SSc and low bone density is poorly understood, potentially important, heavily confounded, yet likely treatable. We found that studies evaluating low bone density in SSc are small and have significant clinical and methodologic variations. More than two-thirds of the studies had sample sizes of fewer than 50 patients. Despite bone health in SSc being the topic of interest, very few studies reported the BMD of the lumbar spine, total hip, or femoral neck. Even fewer studies reported clinically relevant outcomes related to low bone density.

Accelerated bone loss has been well-documented in RA[37] and SLE[38]. The evidence evaluating low bone density in SSc is less clear. Ten observational studies have demonstrated that women with SSc have lower peripheral and axial BMD measurement than matched subjects[18,19,20,21,24,25,27,28,29,30]. Frediani, *et al* reported that not only is bone density reduced, but the quality is altered when assessed by quantitative ultrasound[20,21]. However, 2 observational studies found no difference in BMD between SSc and controls[22,26]. When low bone mass does occur in SSc, it remains uncertain if it is associated with the disease in general or related to specific clinical manifestations[19].

Determinants of low bone density in SSc have been described but not well-studied. Ethnicity was poorly described, and when described, was almost exclusively white. Few studies evaluated low bone mass in male patients with SSc. Frediani, *et al* argue that low bone mass is worse in patients with the diffuse cutaneous subtype and internal organ involvement. However, La Montagna, *et al* did not corroborate these associations[18]. Since SSc is a heterogeneous disease, the heterogenicity can affect the results of various studies. It is also not clear how many patients included in the study suffered from diffuse SSc and localized SSc. There was no correlation between bone density values and HLA classes[23].

Low bone mass appears to be made worse with concomitant traditional risk factors such as increased age and postmenopausal status[21,23,25]. La Montagna, *et al* have suggested that earlier menopause can play a role in the induction of low bone mass in SSc[18]. These data suggest that menopausal status may be a confounder or effect modifier of the relationship of SSc with low bone mass. The same issue pertains to low BMI. Only half the studies reported BMI. In these studies, the average BMI was normal, with the notable exception being patients with the diffuse cutaneous SSc subtype. In 1 study, the diffuse patients with SSc also had an abnormally low BMI. Thus it remains unclear if extent of skin involvement and low BMI are independently related to OP, jointly related, or have a confounded relationship.

Medications that can alter bone density and strength directly (e.g., corticosteroids) or indirectly, by causing premature ovarian failure (e.g., CYC), were evaluated in some studies. The use of corticosteroids did not have a significant effect on bone density results in patients with SSc. Possible reasons for this are that patients with SSc tend not to receive corticosteroids for a long period of time[28], or

the patients were taking some sort of prophylaxis. Premature ovarian failure related to CYC was not reported in any of the studies. The use of steroids might have an effect on reducing inflammation, which could outweigh the risk of developing low BMD. Because steroids are known to cause OP, there might be a detection bias or inadequate followup of patients.

The elevated sRANKL level found by Dovio, *et al* is a potential target of denosumab, which can be an appropriate alternative to bisphosphonates when there is failure or gastrointestinal intolerance. There is an increasing interest in insulin-like growth factor-1 (IGF-1) and IGF binding protein (IGFBP) and their effect on bone mass. IGF-1 is produced by many tissues, including bones under the control of estrogens, growth hormone, and the parathyroid hormone. Correlation studies, which have provided evidence of a relationship between the IGF-1 system and the building of peak bone mass and its subsequent loss, contributed to the understanding of the pathogenesis of OP. A decline of bone IGF-1 in the cortical portion of bones is one of the many mechanisms leading to the development of OP[39]. IGF and IGFBP-3 have been found to be elevated in patients with SSc compared to controls and patients with SLE. This increase correlated with the extent of skin involvement[40]. It has also been hypothesized that calcinosis cutis occurs in part by depletion of skeletal bone calcium stores[6]. This remains a controversial risk factor because its association was supported by 1 study but not by another[25,26]. The contribution of risk factors such as difficulties in physical exercising and malabsorption deficiencies due to bacterial colonization of the intestine was not adequately addressed in the included studies.

Weiss, *et al* assessed the rate of fracture in patients with rheumatic diseases and found that there was increased risk of fracture in all rheumatic diseases when compared to age-matched and sex-matched controls. Yet very few SSc studies reported clinically relevant low bone mass outcomes such as fracture and fracture-associated mortality. The rate of fracture was variable in the 5 studies that assessed this outcome. The OR of developing any fracture and hip fracture has been estimated to be 2.6 (95% CI 1.3, 4.9) and 2.6 (95% CI 1.4, 5.1), respectively[41]. Comparable estimates have been reported by Carbone, *et al* in 1999[24]. Ideally, future studies should include evaluation of 10-year risk of fracture with tools such as the fracture risk assessment tool[42], the Foundation of Osteoporosis Research and Education Fracture Risk Calculator[43], or the Canadian Association of Radiologists and Osteoporosis Canada Risk Assessment Tool[44]. Similarly, no studies evaluated fracture-related mortality. Research is needed to evaluate the significance of fracture, fracture-associated mortality, and the validity of fracture risk indices in the setting of SSc. These may be significant, underrecognized, yet preventable outcomes in SSc.

We present a conceptual framework (Figure 2) that illustrates the relationship between SSc, traditional OP risk factors, SSc-specific factors, low bone density, and outcomes such as fracture and fracture-associated mortality. The role of each factor in the pathway to developing low bone density and its outcomes is unclear. Owing to the complex interactions of many of the factors (e.g., diffuse subtype, extent of skin involvement, low BMI, internal organ involvement), it is unlikely that all the factors are independently associated with low bone density and outcomes. Rather the relationship between factors may be more complex, with some factors being confounders while others are effect modifiers. This conceptual framework is not intended to be static, but rather to be used to guide our thinking, and meant to be revised as our knowledge improves[45,46].

This phase I study was needed to synthesize proposed factors and develop a proposal for a causal pathway[17]. Our synthesis of the data and conceptual framework have laid the groundwork for future research to investigate the interaction of these factors, and the effect of modifying these factors for improved outcome.

A limitation of this work, however, is that it does not provide conclusive information regarding the independence of each examined variable as a valid risk factor. In all of the studies found in our systematic review, risk factors were investigated as one of many factors assessed for their association with the outcome. Although some investigators conducted multivariate modeling, the factors were not chosen *a priori*, but rather only after univariate analysis[21,28]. These studies discuss the finding of factors that are statistically significant. These studies are appropriate when it is unclear which variables are important for predicting an outcome in a population. However, it should be recognized that results from multiple studies in this exploratory phase often have widely varying results. Spurious associations may be found, and real associations may be missed[47]. Our results suggest that this may be the case in evaluation of SSc, low bone mass, and outcomes. This body of work provides the data and justification to proceed with phase II, measurement of the independent effect of these factors while controlling for confounders. Based on this and our other work[48], we hypothesize that the relationship will not be direct and isolated, but rather complex (e.g., some factors mediate the relationship of other factors, the effect of a factor may change over time). The phase III study will evaluate the causal pathway, factors that influence or modify the effect of a factor, factors that are intermediate or a mediator in the pathway toward the outcome, potential confounding variables, and the outcomes[17]. Other potential limitations to consider may include the fact that BMD testing was performed systematically using convenience samples, the studies had very small sample sizes, there was variable length of followup, surrogate outcomes mostly were studied, and standardization of treatment and prophy-

laxis was lacking. Because of the significant heterogeneity across studies and variable study quality, our ability to pool the data into a metaanalysis was limited; it would likely yield biased estimates.

Our systematic review suggests that patients with SSc are at a higher risk of losing bone density, especially when other OP risk factors are present. We describe a conceptual framework synthesizing what is known, and try to unify the complex interaction of SSc disease, its manifestations, traditional OP risk factors, and clinically relevant outcomes. Adequately powered studies with longer followup are required to better delineate the burden of disease, verify these findings, identify predictive clinical and biochemical measures, and assess safety and effectiveness of bone-specific agents in SSc.

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