ORIGINAL ARTICLE

A meta-analysis of fracture risk and bone mineral density in patients with systemic sclerosis

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Abstract

Introduction Osteoporosis and fractures are important public health issues that impose serious burdens on patients. Patients with systemic sclerosis (SSc) have low bone mineral density (BMD) and increased risk for fracture. We aimed to explore the association between SSc and BMD and fracture risk.

Methods For this meta-analysis, we analyzed data from articles that reported mean differences in BMD or fracture risk between patients with SSc and controls. We undertook a systematic literature search of the PubMed, Web of Science, and Cochrane Library databases. The pooled weighted mean difference (WMD) was used to estimate the mean difference in BMD between patients with SSc and controls. Pooled odds ratios (ORs; with 95% confidence intervals [95% CIs]) were used to assess the association between SSc and fracture risk.

Results Analysis of the results from 18 studies showed that patients with SSc had significantly lower BMD than controls in the following categories: whole body (WMD -0.07, 95% CI -0.1 to -0.04, $p < 0.00001$), lumbar spine (WMD -0.08, 95% CI -0.11 to -0.05, $p < 0.00001$), femoral neck (WMD: -0.28, 95% CI: -0.46 to -0.10, $p = 0.002$), total hip (WMD -0.10, 95% CI -0.14 to -0.06, $p < 0.00001$), and femoral trochanter (WMD -0.06, 95% CI -0.09 to -0.03, $p < 0.0001$). Moreover, patients with SSc had an increased risk of vertebral fracture (OR 10.38, 95% CI 1.19 to 90.58, $p = 0.03$). We did not find a significant difference in the risk of osteoporotic fracture between patients with SSc and controls (OR = 2.24, 95% CI 0.58 to 8.59, $p = 0.24$).

Conclusion Patients with SSc have a significant reduction in bone mass, and these patients have an increased risk of vertebral fracture. The early monitoring of BMD in patients with SSc is recommended for the prevention of osteoporosis and fracture.

Key points
• SSc patients have a significant low BMD
• SSc patients also have an increased risk of vertebral fracture

Keywords Bone mineral density · Fracture risk · Systemic sclerosis

Introduction

Systemic sclerosis (SSc) is an autoimmune condition characterized by vasculopathy, inflammation, and fibrosis. In

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addition to effects on the skin, vascular structures, and internal organs, pathogenesis in the musculoskeletal system is associated with disability. The skeletal manifestations of SSc include synovial thickening, tendon friction rubs, flexion contractures, joint deformities, articular erosions, and inflammation [1]. These issues negatively affect quality of life among patients with SSc [2]. Bone damage occurs quite early in SSc disease progression, leading to ischemic gangrene and acro-osteolysis. The effect of SSc on bone remains unclear, and risk for osteoporosis is not necessarily increased among patients with SSc. However, the prevalence of osteoporosis in SSc is likely to be underestimated [3].

Systemic skeletal diseases such as osteoporosis/osteopenia (OP) reduce bone mass and cause damage to the bone microarchitecture, with a consequent increase in

bone fragility [4]. Bone mineral density (BMD) is usually measured by dual-energy X-ray absorptiometry (DXA), with OP defined by a T-score of < 2.5—that is, > 2.5 standard deviations below the average T-score of a young adult. The measurement of BMD by DXA is a valid method for the diagnosis of OP and for the prediction of fracture risk [5]. Moreover, low BMD is common in patients with SSc. A previous study reported that the prevalence rates of low BMD and OP ranged from 27 to 53.3% and from 3 to 51.1%, respectively [6]. However, the SSc-specific factors that may be related to low bone mass remain unclear. Several risk factors, such as SSc subtype, extent of skin involvement, low body mass, internal organ involvement, calcinosis, and malabsorption of calcium, may be associated with low BMD; hypothyroidism can also contribute to low bone mass [6]. The fracture risk of a patient with OP is increased, with fractures occurring most commonly in the spine and hip [7–9], although sites such as the femoral neck and trochanter may also be affected. An increased fracture risk has been noted in patients with rheumatic disorders [10] such as systemic lupus erythematosus and SSc [11, 12]. One nationwide population-based study reported a high fracture risk (incidence 9.50%) in patients with SSc [12]. Moreover, patients with SSc and vertebral fracture have a higher 1-year mortality rate than controls (13 vs 3%). Previous studies have emphasized the extent of bone loss in SSc; in these patients, the prevalence of low BMD ranges from 27 to 53.3% [12].

Fractures occurring due to OP are an important issue in public health and incur substantial healthcare costs. From a patient's perspective, a fracture often has serious effects on the patient's quality of life and causes significant economic burden. Very little is known about bone mass and fracture risk in the setting of SSc. Therefore, it is necessary to undertake a basic assessment of low BMD and fracture risk in patients with SSc. A previous meta-analysis [13] evaluated BMD levels in patients with SSc; however, it included a limited number of studies and did not investigate the relationship between fracture risk and SSc. The present study was conducted to more comprehensively assess the association between BMD and fracture risk in SSc.

Methods

Compliance with PRISMA guidelines

This meta-analysis was conducted in accordance with the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analyses [14].

Search strategy

A systematic literature search was conducted to identify reports on mean differences in BMD or fracture risk between patients with SSc and controls. The search included articles published in PubMed (January 1966–December 2018), Web of Science (January 1986–December 2018), or the Cochrane Library Database (January 1991–December 2018). The following search terms were used: ("systemic sclerosis" OR "systemic scleroderma" OR "scleroderma") AND ("osteopenia" OR "osteoporosis" OR "bone mineral density" OR "fracture risk" OR "fractures" OR "metabolic bone disease"). We imposed no language restrictions on the literature search. The reference lists of all included studies were manually searched to identify additional relevant articles. Two reviewers screened the titles and abstracts of the identified articles to delete duplicates, unrelated reports, and animal studies from the list. Potentially eligible records were identified by screening the full-text articles.

Inclusion and exclusion criteria

Studies were included if they (1) included a cohort with SSc as well as healthy controls without a history of SSc; (2) reported the mean difference in BMD between patients with SSc and controls or the association between fracture risk and SSc; (3) were cohort, cross-sectional, or case–control studies on SSc; (4) reported data on the mean and standard deviation of BMD at the measured sites or the likelihood of fracture events in patients with SSc and controls; (5) measured BMD using DXA. We excluded (1) case reports, review articles, and letters; (2) studies without clear diagnostic criteria for SSc; (3) studies with missing data; and (4) studies that reported overlapping data. All potentially eligible records were independently screened by two investigators who selected studies and extracted data according to the eligibility criteria. Any differences in opinion between the two investigators were resolved by discussion.

Extraction of data and quality assessment

We extracted the following data: first author, year of publication, study design, country, sample size of the case and control groups, mean age of participants, menopausal status, use of glucocorticoids, fracture site, mean and standard deviation of BMD at the measured site, and the incidences of fracture events in patients with SSc and controls. Study quality was assessed using the Newcastle–Ottawa Scale (NOS; total score: 9, high quality: ≥ 7, moderate quality: 4–6) for case–control and cohort studies and using the Agency for Healthcare Research and Quality (AHRQ; total score: 11, moderate quality: ≥ 4) scale for cross-sectional studies [15].

Statistical analysis

We used pooled OR (with 95% confidence intervals [95% CI]) to assess the association between SSc and fracture risk. The weighted mean difference (WMD) was used to assess the mean BMD difference between patients with SSc and controls. Heterogeneity among the studies included in this meta-analysis was assessed using the I^2 test [16]. We used a fixed-effect or random-effect model, respectively, to combine the extracted data when the I^2 value was ≤50% (non-obvious heterogeneity) or >50% (marked heterogeneity). We conducted sensitivity analyses to detect the effect of each study on heterogeneity. The overall combined effect was determined by excluding one study at a time when heterogeneity was significant. Publication bias was assessed with Begg's funnel plot and Egger's test in Stata 12 software (StataCorp). Statistical significance was set at $p < 0.05$. All analyses were conducted using Review Manager 5.3 software (Cochrane Collaboration).

Results

This systematic database search yielded a total of 1452 articles. After duplicates were excluded, 1085 articles were retained; the duplicates were repeated in these databases and did not present information related to the outcomes of interest. We further excluded 1047 articles after scanning their titles and abstracts. Twenty articles were excluded because they did not meet the inclusion criteria: two studies did not pertain to BMD and fracture risk in SSc; six papers were reviews; seven studies did not use DXA and T-scores to measure BMD; two studies did not have controls; three studies were missing data (two of the three studies did not provide the mean and standard deviation BMD values, and another did not provide information pertaining to the incidence of fracture events among patients with SSc and controls). A manual search of the reference lists of the selected articles did not help to identify additional articles for inclusion in the meta-analysis. Ultimately, 18 studies were included [12, 17–33]. The study flowchart of the literature-screening process is shown in Supplementary Fig. 1. The main features of the included studies are listed in Table 1. Ultimately, data for 2580 patients with SSc and 11,550 controls were reviewed. Female patients constituted 92% of the analyzed population, and 76% of these women were menopausal. Of the 18 studies included, four were conducted in Brazil [19, 22, 23, 33]; three were conducted in the USA [17, 20, 31], France [26, 27, 32], and Italy, respectively [18, 21, 30]; and one study was conducted in each of the following countries: China [24], Taiwan [12], Russia [28], Turkey [25], and Morocco [29]. All included studies were published during the period from 1997 to 2018 (Table 1). Sixteen studies were conducted in women only (patients with SSc, 784; controls, 1194), and two studies included both genders (patients with SSc, 1796; controls, 10,356). Seventeen studies investigated the mean difference in BMD between patients with SSc and controls; 11 were case–control studies, and the rest were cross-sectional studies. Seventeen studies evaluated BMD in the lumbar spine; 15 evaluated BMD in the femoral neck; seven studies evaluated BMD in the hip; five studies evaluated BMD throughout the body; three studies evaluated BMD in the trochanter. Four studies (one case–control, two cross-sectional, and one cohort) evaluated the fracture risk associated with SSc, whereas four studies evaluated the number of fractures at vertebral sites (patients with SSc, 1902; controls, 10,780). One study evaluated each of the following: fractures in the hip, peripheral fractures, and fractures of the radius. Two studies evaluated the total number of osteoporotic fractures.

The NOS and AHRQ scores for each study are shown in Table 1. These scores indicate that all 18 studies included in the meta-analysis were of good quality.

Differences in BMD between patients with SSc and controls

Both Cheng et al. [31] and Carbone et al. [20] presented similar data on BMD in the lumbar spine. As both studies included study populations from the same institution, we decided to retain the study by Cheng et al. because it had more complete data. Differences between patients with SSc and controls in mean BMD of the lumbar spine were reported in 16 studies [17–19, 21–33], which included a total of 851 patients with SSc and 1205 controls. Pooled odds ratios (ORs) initially revealed no significant differences in lumbar spine BMD between patients with SSc and controls (WMD − 0.25, 95% CI − 0.56 to − 0.05, $p = 0.1$) in studies with high heterogeneity ($I^2 = 100\%$); we found this outcome questionable. The results of sensitivity analysis suggested that the results had been skewed by inclusion of the study by Ibn Yacoub et al. [29]. Re-analysis after excluding this particular study showed a significant association between BMD in the low lumbar spine and SSc (WMD − 0.08, 95% CI − 0.11 to − 0.05, $p < 0.00001$). Furthermore, the degree of heterogeneity decreased after exclusion of the Ibn Yacoub study ($I^2 = 72\%$; Fig. 1a).

Fifteen of the included studies [17, 19–33] described femoral neck BMD in patients with SSc ($n = 752$) and controls ($n = 943$). Analysis of data from these studies, which had high heterogeneity ($I^2 = 100\%$), indicated that patients with SSc had low BMD, compared with controls (WMD: −0.28, 95% CI: −0.46 to −0.10, $p=0.002$); Fig. 1b). Sensitivity analysis revealed a slight decline in heterogeneity ($I^2 = 99\%$) after the removal of an outlier study by Carbone et al. [20]; the results indicated that patients with SSc have low BMD (WMD:

Table 1 Characteristics of included studies evaluating the association between SSc and BMD or fracture risk

Study	Country	Design	Participants (age: mean ± SD)	Menopause, % (SSc/control)	Glucocorticoiduse in patients with SSc, %	BMD assay sites	Fracture sites	NOS/ AHRQ score
Ruaro et al. 2018 [17]	USA	Cross-sectional	84 SSc patients (65±9); 60 controls (64±11)	100/100	None	Total hip, Lumbar spine, Femoral neck, Ward's triangle, Trochanter	–	6
Alekperov et al. 2016 [28]	Russia	Case–control	56 SSc patients (58.1±7.1); 44 controls (59.2±6.6)	100/100	66	Lumbar spine, femoral neck, proximal femur	–	7
Kilic et al. 2016 [25]	Turkey	Cross-sectional	43 SSc patients (50.3±11.4); 38 controls (50.4±9.5)	51.1/55.2	None	Lumbar spine, femoral neck, total hip	–	6
Koumakis et al. 2015 [26]	France	Cross-sectional	65 SSc patients (61.6±11.0); 227 controls (60.1±7.9)	88.9/95.6	51.6	Lumbar spine, femoral neck, total hip	Vertebral fractures, Peripheral fractures	5
Marot et al. 2015 [27]	France	Case–control	33 SSc patients (63.2±10.2);33 controls (62.9±10.4)	85/85	18.2	Lumbar spine, femoral neck, whole body	–	8
Lai et al. 2014 [12]	Taiwan	Cohort study	1712 SSc patients (50.3±14.4); 10,272 controls (50.3±14.4)	NA/NA	NA	NA	Vertebral, hip, radius	8
Mok et al. 2013 [24]	China	Case–control	84 SSc patients (49.4±11.3); 84 controls (49.0±10.5)	60/49	23	Lumbar spine, femoral neck, total hip, whole body	–	7
Marighela et al. 2013 [33]	Brazil	Cross-sectional	61 SSc patients (50.6±13.0); 67 controls (46.7±14.5)	59/40	17	Lumbar spine, femoral neck, whole body	–	6
Atteritano et al. 2013 [30]	Italy	Case–control	54 SSc patients (54.4±1.73); 54 controls (54.6±2.87)	100/100	None	Lumbar spine, femoral neck, total femur	Vertebral	7
Avouac et al. 2012 [32]	France	Cross-sectional	71 SSc patients (62±12.0); 227 controls (60±8.0)	90/95	58	Lumbar spine, total hip	Vertebral, non–vertebral	5
Ibn Yacoub et al. 2012 [29]	Morocco	Case–control	60 SSc patients (49.44±13.12); 60 controls (49.55±12.11)	43.33/40	None	Lumbar spine, femoral neck	–	7
Souza et al. 2006 [23]	Brazil	Case–control	43 SSc patients (62.2±7.7); 47 controls (60.6±7.3)	100/100	None	Lumbar spine, femoral neck	–	8
Sampaio-Barros et al. 2005 [22]	Brazil	Cross-sectional	Fertile group: 33 SSc patients (35.79±6.7); 47 controls (34.23±5.94) Postmenopausal group: 28 SSc patients (54.21±6.43); 60 controls (52.43±3.67)	0/0 100/100	Fertile: 36; Postmenopausal: 39	Lumbar spine, femoral neck, Ward's triangle, trochanter	–	4
Frediani et al. 2004 [21]	Italy	Case–control	55 SSc patients (54.1±14.1); 60 controls (53.9±13.5)	54.5/50	NA	Whole body, lumbar spine, femoral neck, femur Ward's triangle, trochanter	–	8
Cheng et al. 1999 [31]	USA	Case–control	15 SSc patients (54.1±12.8); 15 controls (53.3±12.1)	100/100	None	Femoral neck, lumbar spine	–	7
Carbone et al. 1999 [20]	USA	Cross-sectional	15 SSc patients (NA); 15 controls (NA)	100/100	None	Femoral neck, lumbar spine, total hip, trochanter	–	7
da Silva et al. 1997 [19]	São Paulo	Cross-sectional	25 SSc patients (48±12.0); 90 controls (NA)	52/NA	None	Lumbar spine, femoral neck, Ward's triangle, trochanter, whole body	–	5
Di Munno et al. 1995 [18]	Italy	Case–control	43 SSc patients (54.8±10.3); 50 controls (53.6±9.1)	84/64	None	Lumbar spine, whole body, radial	–	7

NA data unavailable, – not analyzed

−0.21, 95% CI: −0.37 to −0.04; *p*=0.01), compared with controls.

Seven [17, 20, 24–27, 32] studies reported on total hip BMD in patients with SSc ($n = 395$) and controls ($n = 648$). A meta-analysis of these seven studies showed that patients with SSc had significantly lower total hip BMD than controls (WMD − 0.10, 95% CI − 0.14 to − 0.06, $p < 0.00001$), but with high heterogeneity ($I^2 = 73\%$; Fig. 1c). Sensitivity analysis indicated the heterogeneity was markedly influenced by the study by Ruaro et al. [17]. After excluding the study by Ruaro et al., we found no heterogeneity among studies ($I^2 = 0\%$). Analysis of the modified group indicated that patients with SSc have significantly lower total hip BMD scores than controls (WMD − 0.08, 95% CI − 0.1 to − 0.06, $p < 0.00001$).

Three studies [17, 19, 22] described trochanteric BMD in patients with SSc ($n = 168$) and controls ($n = 199$), without any obvious heterogeneity ($I^2 = 35\%$). A meta-analysis of these studies showed that patients with SSc had lower trochanteric BMD than controls (WMD − 0.06, 95% CI − 0.09 to − 0.03, $p < 0.0001$; Fig. 1d).

Whole-body BMD was reported in five studies [18, 19, 21, 24, 33], which included 266 patients with SSc and 293 controls. A meta-analysis of these studies showed that patients with SSc had decreased whole-body BMD, compared to controls (WMD − 0.07, 95% CI − 0.1 to − 0.04, $p < 0.00001$), but the meta-analysis had substantial heterogeneity ($I^2 = 57\%$; Fig. 1e). We excluded the study by Frediani et al. [21] because sensitivity analysis suggested that this study had a marked effect on the heterogeneity of the results. After exclusion of the study by Frediana et al., we found no heterogeneity ($I^2 = 0\%$), and the earlier results were maintained (WMD − 0.06, 95% CI − 0.08 to − 0.05, $p < 0.00001$).

Difference in BMD between IcSSc and dcSSc subtypes of SSc

Five of the included studies [18, 21, 23, 25, 33] described differences in BMD between limited cutan (IcSSc) and diffuse cutan (dcSSc) subtypes of SSc. Two of those five studies [18, 25] did not provide the mean and standard deviation BMD values. Ultimately, three studies [21, 23, 33] were included to analyze the differences in BMD between IcSSc and dcSSc.

Three studies described lumbar spine and femoral neck BMD in patients with IcSSc ($n = 89$) and dcSSc ($n = 54$). A meta-analysis of these three studies showed that patients with dcSSc had significantly lower lumbar spine BMD than IcSSc (WMD − 0.09, 95% CI − 0.15 to − 0.03, $p = 0.002$), with no heterogeneity ($I^2 = 0\%$; Fig. 1f).

Pooled odds ratios (ORs) initially revealed no significant differences in femoral neck BMD between patients with dcSSc and IcSSc (WMD − 0.06, 95% CI − 0.14 to 0.02, $p = 0.12$) in studies with substantial heterogeneity ($I^2 = 57\%$). We further performed sensitivity analysis; the results suggested

that the results had been skewed by inclusion of the study by Souza RB et al. Re-analysis after excluding this particular study showed patients with dcSSc have low femoral neck BMD (WMD − 0.09, 95% CI − 0.14 to − 0.04; $p = 0.0009$; Fig. 1g), without any obvious heterogeneity ($I^2 = 45\%$), compared with IcSSc.

SSc-associated fracture risk

Four studies (SSc, $n = 1902$; controls, $n = 10,780$) reported the SSc-associated risk of vertebral fracture [12, 26, 30, 32], but we found high heterogeneity among these studies ($I^2 = 92\%$). A meta-analysis of these studies indicated that SSc was associated with an increased risk of vertebral fracture (OR 10.38, 95% CI 1.19 to 90.58, $p = 0.03$; Fig. 2). Sensitivity analysis showed that the study by Lai et al. [12] contributed considerably to heterogeneity, which disappeared ($I^2 = 0\%$) upon removal of this study from the analysis. After removal of the study, SSc was associated with an increased risk of vertebral fracture (OR: 24.89, 95% CI 9.36 to 66.14, $p < 0.00001$).

Two studies described increased risk for osteoporotic fractures in patients with SS, compared with controls [12, 14]. These two studies included a total of 1783 patients with SSc and 10,499 controls. There was obvious heterogeneity between the studies ($I^2 = 93\%$). However, the meta-analysis revealed no significant difference between patients with SSc and controls in the risk for osteoporotic fracture (OR 2.24, 95% CI 0.58 to 8.59, $p = 0.24$; Fig. 1b).

Publication bias

We used a funnel plot and Egger's test to evaluate publication bias. Neither of these statistical methods revealed any risk of publication bias for the association between SSc and BMD or risk for fracture (Fig. 3b).

Discussion

Previous studies have focused on bone loss and risk for fracture in patients with SSc. However, a comprehensive assessment of this association has remained lacking. To the best of our knowledge, this is the first meta-analysis to simultaneously assess the SSc-associated risk for fracture and level of BMD in patients with SSc and controls. We included 18 studies in this meta-analysis, including 17 studies on the mean difference in BMD between patients with SSc and controls, as well as four studies on the risk for fracture associated with SSc. Overall, our meta-analysis showed that lumbar spine, total hip, femoral neck, trochanter, and whole-body BMD were significantly lower in patients with SSc, compared to controls and patients with dcSSc had significantly lower BMD than IcSSc. Moreover, patients with SSc had a higher risk of
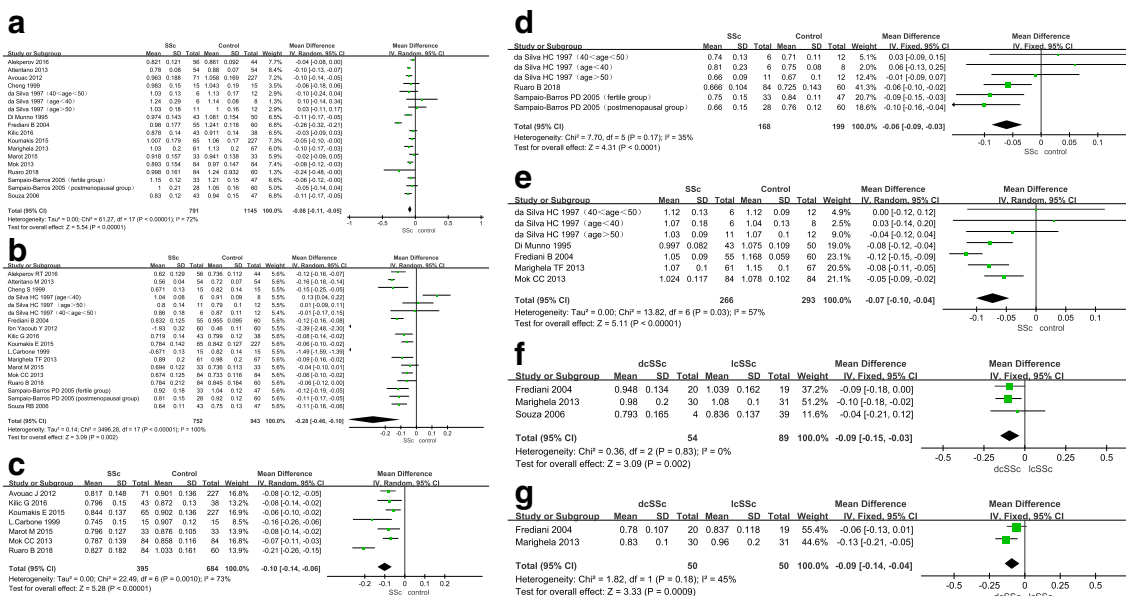
Fig. 1 **a** Forest plot for meta-analysis of the association between SSc and lumbar spine BMD. **b** Forest plot for meta-analysis of the association between SSc and femoral neck BMD. **c** Forest plot for meta-analysis of the association between SSc and total hip BMD. **d** Forest plot for meta-analysis of the association between SSc and trochanteric BMD. **e** Forest plot for meta-analysis of the association between SSc and whole-body BMD. **f** Forest plot for meta-analysis of the association between dcSSc and lumbar spine BMD. **g** Forest plot for meta-analysis of the association between dcSSc and femoral neck BMD

vertebral fracture than did controls. However, the association between SSc and risk of osteoporotic fracture did not reach statistical significance. Advanced age was considered a risk factor for osteoporotic fracture. Most of the subjects in the included studies were postmenopausal women. However, the cohort in the study by Lai et al. [12] had a lower mean age, which may have been associated with decreased risk for osteoporotic fracture. Therefore, we infer that early monitoring of BMD in patients with SSc is important for the prevention of OP and fracture.

We omitted an outlier study by Ibn Yacoub et al. from a sensitivity analysis of the association between lumbar spine BMD and SSc. This study mainly included subjects from Africa, whereas the majority of the studies included populations from Europe, the USA, and Asia. There was a possibility that ethnic differences may have been a major contributing factor with regard to study outcome. After exclusion of this study, we found that patients with SSc had significantly lower lumbar spine BMD than controls. The heterogeneity observed may have derived from differences in study design and sample size.

We also excluded an outlier study by Souza RB et al. from a sensitivity analysis of the difference in femoral neck BMD between lcSSc and dcSSc. This study only included four patients with dcSSc. There was a possibility that sample size of dcSSc may have been a major contributing factor with regard to study outcome. After exclusion of this study, we found that patients with dcSSc had significantly lower femoral neck BMD than lcSSc.

Previous studies have shown that OP is relatively common in patients with SSc; among this population, the overall prevalence of low BMD ranges from 27 to 53%; the overall prevalence of OP ranges from 3 to 51% [6]. The specific pathogenic mechanism underlying bone mass reduction in SSc remains unclear. However, common risk factors for bone mass reduction include disease severity, low body mass index, the involvement of internal organs, barriers to mineral absorption, calcinosis, and corticosteroid use [6]. Patients with SSc who have gastrointestinal involvement develop gastrointestinal dysfunction, which affects the absorption of nutrients such as vitamin D and causes malnutrition and low body mass index. Vitamin D may prevent vascular calcification and bone loss. Vitamin D levels are significantly reduced in patients with SSc [34, 35]. It is generally accepted that the main source of vitamin D is the exposure of skin to sunlight, which induces the conversion of vitamin D precursors into active forms of vitamin D. Vitamin D status is also affected by gastrointestinal absorption [36]. In patients with SSc, thickening of the skin or mucosa results in reduced UV penetration and decreased synthesis of pre-vitamin D3. Many SSc patients may lead a sedentary lifestyle with limited exposure to sunlight. In patients with gastrointestinal involvement, the capacity of a thickened intestine to absorb vitamin D may also be reduced [37].

Supplementation with vitamin D is considered beneficial for the prevention and treatment of osteoporosis and for skeletal health among patients vitamin D insufficiency [38]. SSc patients should therefore take vitamin D supplements.

Fig. 2 **a** Forest plot for meta-analysis of the association between SSc and vertebral fracture risk. **b** Forest plot for meta-analysis of the association between SSc and osteoporotic fracture risk
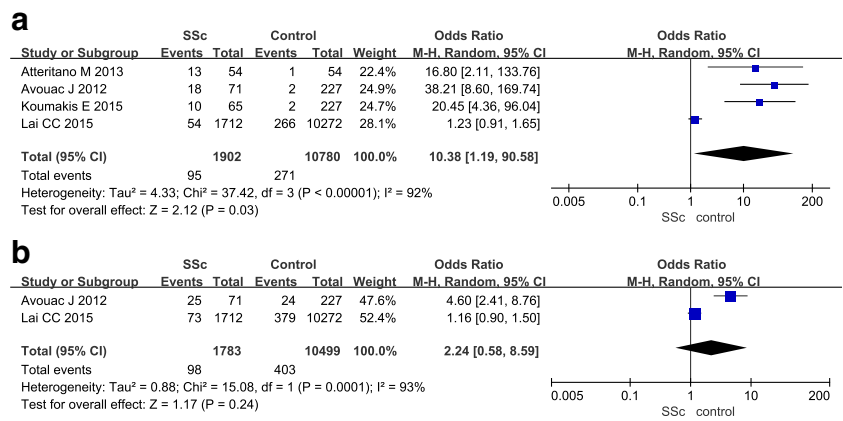
Studies have shown that vascular lesions are associated with low BMD [39, 40]. In SSc, the major manifestations of microvascular disease are Raynaud phenomenon and digital ulcers, whereas the earliest form of macrovascular disease is peripheral vasculopathy resulting in claudication and limb ischemia. The micro- and macrovascular obliterative disease observed in SSc may be attributed to various pathophysiological changes, including endothelial dysfunction, increased collagen deposition, fibrosis, and inflammation [41]; all of these changes may affect the bone [17, 25, 27, 35]. Calcinosis and acro-osteolysis has been associated with the late nail-fold videocapillaroscopy pattern and, particularly, with severe capillary loss, which supports the role of vasculopathy in the pathogenesis of calcinosis [42]. Calcinosis is significantly associated with osteoporosis among patients with SSc [43]. Many studies have confirmed the correlation between vascular calcification and osteoporosis [44]. Chronic inflammation, vascular cell differentiation into osteoblast-like cells, osteoprotegerin, and RANKL are also involved. Osteoprotegerin, which is expressed by osteoblasts, acts as a decoy receptor for RANKL. RANKL mediates osteoclast differentiation and activation, stimulating bone resorption. Osteoprotegerin binds to RANKL, preventing its interaction with RANK, and thus inhibits osteoclast differentiation and prevents bone resorption and bone loss [45]. One study showed that although serum soluble RANKL (sRANKL) levels correlated negatively with BMD measurements in SSc patients, osteoprotegerin levels were higher in those with calcinosis. Elevated osteoprotegerin

levels indicate an inadequate compensatory response to inhibit calcification [46]. Additional studies are needed to better understand the relationships among RANKL, RANK, and osteoprotegerin in SSc patients with progressing vascular damage.

However, there is no consensus on the mechanism underlying bone loss in patients with SSc. Decreased bone perfusion secondary to poor blood circulation may be one of the mechanisms causing bone loss through regional ischemia and hypoxia; the vascular dysfunction of hematopoietic stem cells may contribute as well [47].

Notably, fractures may have occurred in patients with SSc as a consequence of decreased BMD and OP. Risk for fracture, especially vertebral fracture, was significantly elevated in patients with SSc (fracture prevalence 35%), compared with controls [32]. Our meta-analysis indicated that SSc increases the risk of vertebral fracture. However, studies on the risk for fracture in patients with SSc are limited, and the available data do not allow for an estimation of the non-vertebral fracture risk associated with SSc. For an accurate assessment of risk for fracture, we need additional large-scale studies to supply good evidence of an association between SSc and risk for fracture.

Our meta-analysis has some limitations. Firstly, the study populations investigated were often Caucasian or Asian, rather than African. The association between low BMD and SSc in the African population is uncertain, and more region-specific studies are needed. Secondly, few studies have reported data on risk for osteoporotic fracture in patients with SSc, compared with controls. Additional studies are needed to

Fig. 3 **a** Funnel plot for meta-analysis of the association between SSc and lumbar spine BMD (Begg's test: $p = 0.780$). **b** Funnel plot for meta-analysis of the association between SSc and femoral neck BMD (Begg's test: $p = 0.449$)
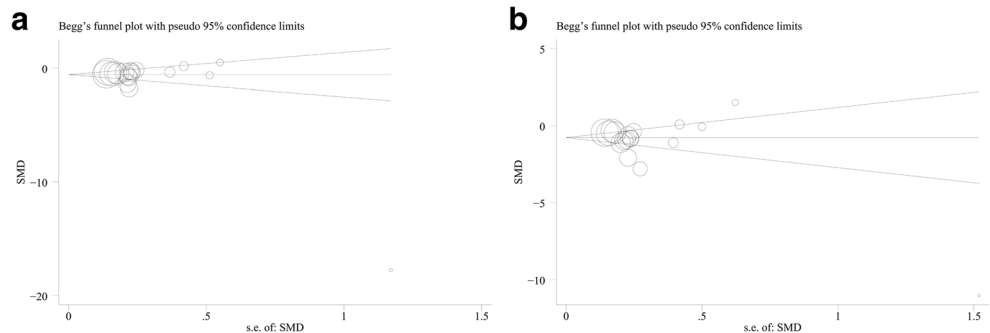
clarify the risk of osteoporotic fracture in patients with SSc. A limited number of studies published to date have investigated SSc-related fractures; however, those studies did not comprehensively evaluate various types of fracture risk in patients with SSc. Thirdly, due to the complexity of the included studies, subgroup analysis was not possible. Lastly, the control group included in one of the studies comprised patients with rheumatoid arthritis, which may have a similar pathogenesis as SSc, but may also differ in important ways.

Conclusion

Patients with SSc, particularly those with OP, may experience a decrease in BMD and an elevated risk for fracture. Routine screening for OP in patients with SSc is a clinical necessity to prevent the considerable disease burden and disability associated with SSc.

Compliance with ethical standards

Disclosures None.

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