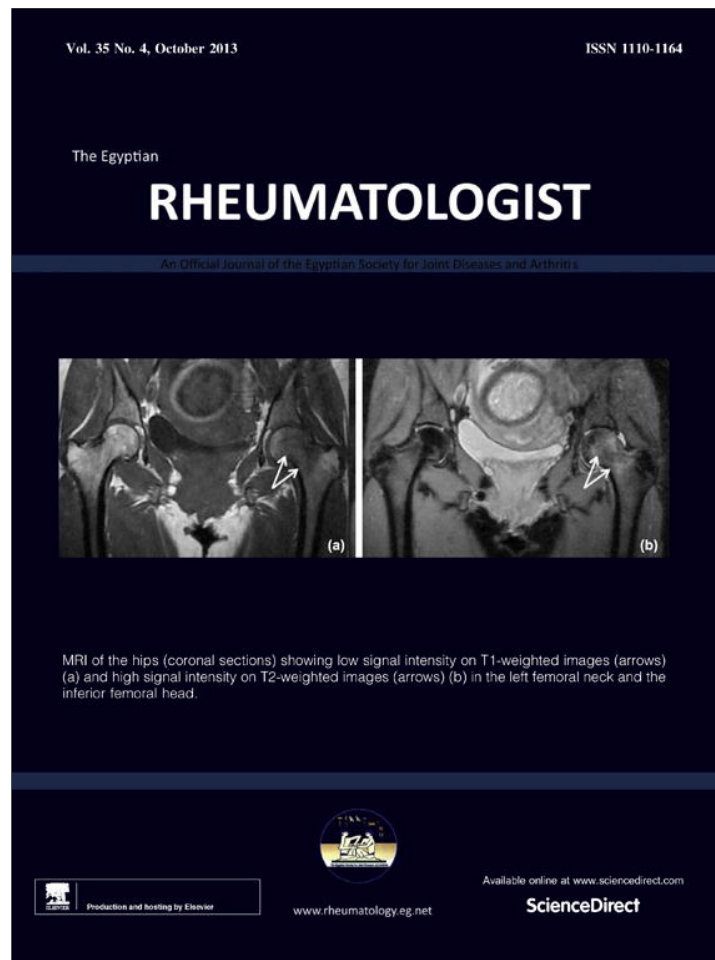


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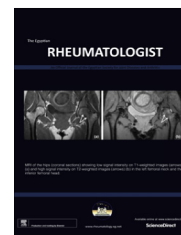
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## ORIGINAL ARTICLE

# Bone mineral density in patients with systemic sclerosis and its association with hand involvement



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Received 7 August 2013; accepted 10 August 2013

Available online 26 September 2013

## KEYWORDS

Systemic sclerosis;  
 Bone mineral density;  
 Hand involvement

**Abstract** *Aim of the work:* The aim of the present study is to assess bone mineral density (BMD) in systemic sclerosis (SSc) patients and to determine associated factors.

*Patients and methods:* Sixty-five female SSc patients (mean age  $39.5 \pm 13.5$  years, disease duration  $7.3 \pm 5.9$  years), and forty age- and sex- matched controls were included. Forty-seven patients had limited SSc and 18 had diffuse type. Patients were subjected to clinical and functional assessment. BMD was quantified at the distal radius, femoral neck and lumbar spine (L2–4) by dual energy X-ray absorptiometry.

*Results:* SSc patients had a higher frequency of osteoporosis at the distal radius and osteopenia at the lumbar spine ( $p = 0.001$  and  $0.002$ , respectively), but the BMD at the femoral neck was not significantly different from the control group. Patients with osteoporosis at the distal radius had a significantly higher frequency of hand deformities ( $p < 0.05$ ) and higher functional scores reflecting more disability than patients without ( $p = 0.01$ ), while patients with osteoporosis at the lumbar spine were significantly older ( $p < 0.001$ ) and had a longer disease duration than those without ( $p = 0.001$ ). No associations were found between menopausal status, SSc subtype, skin score, internal organ affection and osteoporosis at the three skeletal sites.

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Peer review under responsibility of Egyptian Society for Joint Diseases and Arthritis.



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**Conclusion:** Patients with SSc have lower bone mineral density than controls at the distal radius and lumbar spine. Osteoporosis at the distal radius is associated with the presence of hand deformity and functional disability, while osteoporosis at the lumbar spine is associated with older age and longer disease duration.

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## 1. Introduction

Systemic sclerosis (SSc) is a disease of unknown cause, the hallmark of which is induration of the skin. It is characterized by a universal functional and structural vasculopathy, inflammation, immunological abnormalities in most cases and ultimately fibrosis due to deposition of extracellular matrix components resulting in tissue destruction and organ dysfunction [1,2]. Osteoporosis and related fragility fractures are among the most common complications that occur in patients who have rheumatic diseases, and they contribute to a dramatic decrease in quality of life [3]. SSc patients suffer from a chronic inflammatory state, are exposed to secondary risk factors for osteoporosis including inactivity, low body mass index, decreased vitamin D synthesis in the fibrotic skin, involvement of the intestinal tract and kidneys that may impair calcium metabolism, earlier menopause in addition to medications used to treat complications of SSc (corticosteroids and cyclophosphamide) [3,4]. Although several authors found lower bone mineral density (BMD) in systemic sclerosis patients in comparison to age and sex matched controls [5–10], this was not confirmed in other studies [11,12]; therefore, whether SSc is associated with an increased risk of osteoporosis remains inconclusive.

The aim of the present study was to assess the BMD status in patients with SSc and its association with disease manifestations and possible confounding factors.

## 2. Patients and methods

Sixty-five female patients with SSc were consecutively recruited from the Rheumatology and Rehabilitation department, Faculty of Medicine, Cairo University. The study was approved by the local ethics committee and conforms with the declaration of Helsinki. All patients satisfied the preliminary American Rheumatology Association criteria for classification of progressive SSc [13]. They had a mean age  $39.5 \pm 13.5$  years, range 17–68 years. Twenty-nine patients were postmenopausal (44.6%); 8 developed menopause before the onset of SSc (preSSc) and 21 after the onset of SSc (post SSc). The control group consisted of 40 age matched healthy females; 22 were postmenopausal (44%). The frequency of menopause was not statistically significantly different between patients and controls ( $p > 0.05$ ).

Patients were classified according to the extent of cutaneous involvement as diffuse and limited SSc using the criteria of LeRoy, et al., [14].

The exclusion criteria were male sex, history of smoking and treatment with hormone replacement therapy and other drugs for osteoporosis.

The following personal and disease parameters were included: age, disease duration, age at disease onset, menopausal status and its relation to disease onset, presence of arthritis and deformities as well as features of hand radiographs. The

involvement of internal organs was determined and current or previous treatment was recorded. Functional assessment was done according to Silman, et al., [15]. This scoring system was developed to assess disability in activities of daily living in SSc patients and contains 11 items; each is given a score from 0 to 3 (0 = able to perform in normal manner, 1 = can manage with some alteration in style, 2 = can only manage with difficulty, 3 = impossible to achieve). The total possible score is 33, with higher scores indicating more disability.

Modified Rodnan Skin Score (mRSS) was used for assessment of skin thickness by palpation at 17 surface anatomical sites, graded from 0 (normal) to 3 (severe thickening) with a maximum of 51 points [16].

The delta finger-to-palm distance (FTP) was used to assess the finger range of motion as described by Torok, et al., [17]. A ruler is used to measure the distance (in centimeters) between the 3rd fingertip and the distal palmar crease while the patient attempts full finger extension minus the standard FTP, which is obtained by measuring the distance between the tip of the pulp of the 3rd finger and the distal palmar crease while the patient attempts to make a full fist (maximal finger flexion at the metacarpo-phalangeal, proximal interphalangeal and distal interphalangeal joints).

The following serologic tests were included: rheumatoid factor, antinuclear antibodies, anticentromere antibodies and anti-Scl 70.

Bone mineral density (BMD) was quantified by dual energy X ray absorptiometry, (Prodigy GE Lunar) at the lumbar spine L2–L4, femoral neck, and distal radius. BMD was measured in  $\text{g}/\text{cm}^2$  and  $T$ -score (deviation with respect to peak bone mass) and was assessed by the same radiologist.

Patients were divided into three groups according to the BMD findings: patients with normal BMD;  $T$  score  $> -1$ , patients with osteopenia;  $T$  score between  $-1$  and  $-2.5$  and patients with osteoporosis;  $T$  score  $\leq -2.5$ .

**Statistical methods:** Data were processed on a personal computer using the statistical package SPSS (version 11) for windows. For descriptive statistics, data were expressed as frequency, range, median, mean  $\pm$  standard deviation (SD). For comparisons between means, two-tailed  $t$ -tests were used. For comparison between categorical variables, the Chi square test was used. Correlations were done using Pearson's correlation coefficient. Statistical significance was set at  $p < 0.05$ .

## 3. Results

Sixty-five female patients with SSc were involved in this study. The mean age was  $39.5 \pm 13.5$  (range 17–68 years), the mean age at disease onset was  $32.6 \pm 11.5$  (range 16–58 years), and the mean disease duration was  $7.3 \pm 5.9$  (range 0.5–25 years). Forty-seven patients had limited SSc (lSSc), and 18 patients had diffuse type (dSSc). All patients received calcium channel blockers at some time during the course of their

**Table 1** Comparison of bone mineral density between SSc patients and controls at the distal radius, femoral neck and lumbar spine.

	Age	Osteopenia at distal radius (n)	Osteoporosis at distal radius (n)	Osteopenia at femoral neck (n)	Osteoporosis at femoral neck (n)	Osteopenia at lumbar spine (n)	Osteoporosis at lumbar spine (n)
Patients (n = 65)	39.5 ± 13.5	22	34	19	12	26	14
Controls (n = 40)	38.3 ± 13.8	9	3	11	5	5	5
P value	NS	$\chi^2 = 0.084$	$\chi^2 = 0.001$	$\chi^2 = 0.173$	$\chi^2 = 0.162$	$\chi^2 = 0.002$	$\chi^2 = 0.109$

**Table 2** Comparison between patients with osteoporosis at the distal radius, femoral neck and lumbar spine and those without.

	SSc patients (n = 65)	Patients with osteoporosis at the distal radius (n = 34)	Sig.	Patients with osteoporosis at the femoral neck (n = 12)	Sig.	Patients with lumbar osteoporosis (n = 15)	Sig.
		Patients without forearm osteoporosis (n = 31)		Patients without osteoporosis at the femoral neck (n = 53)		Patients without lumbar osteoporosis (n = 50)	
Age (y)**	39.5 ± 13.5	41.8 ± 12.2 36.87 ± 14.67	NS	46 ± 7.04 39.4 ± 13.7	NS	50.14 ± 7.17 36.5 ± 13.5	<i>P</i> < 0.001
Disease duration (y)**	7.33 ± 5.86	8.01 ± 6.3 5.9 ± 4.66	NS	11.75 ± 8.55 6.4 ± 5.1	NS	9.75 ± 6.80 6.3 ± 5.2	<i>P</i> = 0.001
Age at disease onset (y)**	32.6 ± 11.53	34.1 ± 11.1 30.96 ± 11.93	NS	35.9 ± 10.72 31.8 ± 11.3	NS	41.03 ± 9.42 30.3 ± 11	NS
Menopause before onset of SSc: n (%)	8 (12.3)	4 4	NS	1 7	NS	4 4	NS
Menopause now: n (%)	21 (32.3)	13 8	NS	1 20	NS	10 11	NS
DSSc n (%)	18 (27.7)	8 10	NS	5 13	NS	2 16	NS
LSSc n (%)	47 (72.3)	26 21	NS	2 45	NS	13 34	NS
Functional score***	14 (0–33)	18 (0–33) 10 (0–33)	<i>P</i> = 0.01	18.5 (9–23) 12 (0–33)	NS	15 (2–23) 12 (0–33)	NS
Esophageal dysmotility n (%)	44 (67.7)	24 20	NS	10 34	NS	12 32	NS
Interstitial lung disease n (%)	10 (15.4)	7 3	NS	0 10	–	5 5	NS
Heart disease n (%)	15 (23.1)	8 7	NS	5 10	NS	6 9	NS
Raynaud's phenomenon n (%)	63 (96.9)	33 30	NS	5 58	NS	13 50	NS
Skin score***	13 (6–40)	13 (7–40) 15 (6–28)	NS	12.5 (7–40) 13 (6–40)	NS	14 (6–40) 13 (6–36)	NS

\*\* = mean ± SD, \*\*\* = median (range).

disease. Thirty-three patients received corticosteroids in a dose of 5–40 mg/day for 1–72 months. High doses of corticosteroids were needed for patients with interstitial pneumonitis and were gradually tapered during the disease course. Cyclophosphamide IV pulses were given to 4 patients at a dose of 750–1000 mg/m<sup>2</sup> surface area monthly for 6 months then every 3 months over 2 years. Sixteen patients received methotrexate IM 12.5–17.5 mg/week for a duration of 6–24 months.

The bone mineral density (BMD) findings of patients and controls are described in Table 1. The BMD at the distal radius in SSc patients was significantly less than that in controls (0.46 ± 0.40 vs. 0.84 ± 0.18, *p* < 0.001). SSc patients had also a significantly higher frequency of osteoporosis at the distal radius (*p* = 0.001) in comparison to the control group. SSc patients had a higher frequency of osteopenia at the lumbar spine (*p* = 0.002), while the frequency of osteopenia and

osteoporosis at the femoral neck was not significantly different from the control group.

The general characteristics of all SSc patients, patients with and without detected osteoporosis at the distal radius, femoral neck and lumbar spine are described in Table 2. Patients with osteoporosis at the distal radius had significantly higher functional scores compared to those without (*p* = 0.01), while there was no statistically significant difference in the functional score between patients with and without osteoporosis at the femoral neck and lumbar spine. Patients with osteoporosis at the lumbar spine were significantly older (*p* < 0.001) and had a longer disease duration (*p* = 0.001) than those without, while age and disease duration were not significantly different between patients with and without osteoporosis at the distal forearm and the femoral neck. Age at disease onset, development of menopause before the onset of SSc, menopausal

**Table 3** Comparison between patients with and without osteoporosis at the distal radius concerning hand condition.

	Patients with osteoporosis at the distal radius ( <i>n</i> = 34)	Patients without osteoporosis at the distal radius ( <i>n</i> = 31)	<i>P</i>
BMD at distal radius(g/cm <sup>2</sup> )**	0.318 ± 0.08	0.609 ± 0.54	<i>P</i> < 0.01
Hand deformity	27	16	<i>P</i> < 0.05
Hand arthritis	6	5	NS
RF + ve	3	1	NS
Skin score**	15.62 ± 8.95	15.19 ± 7.93	NS
Delta FTP (cm) ** ****	3.49 ± 2.433 (0.5–11)	4.45 ± 2.39 4 (0–10)	NS

\*\* = mean ± SD, \*\*\*\* = median (range).

status, SSc subtype, esophageal dysmotility, interstitial lung disease, heart affection, Raynaud's phenomenon and skin score did not differ significantly between patients with and without osteoporosis at the three skeletal sites. Furthermore, there was no association between the intake of calcium channel blockers, corticosteroids, cyclophosphamide or methotrexate and osteoporosis at any site (data are not shown).

Since a higher frequency of osteoporosis was found at the distal radius in SSc patients in comparison to the control group, we sought to determine associated factors. The limitation of hand range of motion was measured by delta FTP. Although BMD at the distal radius in all patients ( $3.9 \pm 2.4$  cm) was significantly correlated with delta FTP values ( $r = 0.36$ ,  $p < 0.01$ ), the comparison of delta FTP between patients with osteoporosis at the distal radius and those without revealed no statistically significant difference.

Forty-three patients with SSc had hand deformities in the form of flexion contractures. Deformities were related to skin tightness in 36 patients (83.7%), and related to hand arthritis in 7 patients (16.3%). Hand radiographs revealed erosions in 5 patients (7.7%), resorption of finger tips in 33 patients (50.7%) and calcinosis in 11 patients (16.9%). None of the patients had digital fractures. Patients with hand deformities had a significantly lower delta FTP than those without; mean  $3.3 \pm 2$ , median 3, range 0.5–10 cm versus a mean of  $5.2 \pm 2.7$ , median 4.3, range 0–11 cm,  $p = 0.002$ . Significantly higher functional scores were found in patients with hand deformities as compared to those without; mean score  $15.9 \pm 8.9$ , median 18, range 0–33 versus a mean score of  $8.6 \pm 8.5$ , median 6, range 0–32,  $p = 0.002$ . Hand deformity was detected more frequently in patients with osteoporosis at the distal radius compared to those without ( $p < 0.05$ ), while the frequencies of hand arthritis and RF positivity as well as mean skin scores were not significantly different between both groups, (Table 3).

#### 4. Discussion

Several authors found SSc patients to have lower bone mineral density (BMD) in comparison to age and sex matched controls [5–10,18,19]. Furthermore, the prevalence of osteoporosis in SSc has been found to be comparable to that in positive controls with rheumatoid arthritis [19,20]. In the present study, a higher incidence of low bone mineral density was detected in SSc patients at the distal radius ( $p = 0.001$ ) and lumbar spine ( $p = 0.002$ ).

La Montagna, et al., [5] found that the percentage of SSc patients in menopause was significantly greater than that of

the controls ( $p < 0.001$ ) with menopause occurring in the SSc patients significantly earlier than in controls ( $p < 0.001$ ). It was suggested that earlier menopause can play a role in the induction of osteopenia in systemic sclerosis. Also, lower BMD was more marked with estrogen deficiency in the study by Frediani, et al., [8]. IbnYacoub, et al., [18] also found SSc patients to have an earlier age and longer duration of menopause. On the other hand, another study found no statistically significant differences in age at menarche and menopause and estrogen use between SSc patients and controls [7]. In the present study, the frequency of menopause was not significantly different between SSc patients and age-matched controls and menopausal status was not associated with the presence of osteoporosis, which was also found in a recent study [19]. The development of menopause before the onset of systemic sclerosis was also not associated with osteoporosis at the distal radius, lumbar spine or femoral neck.

In the present study, a higher frequency of osteoporosis was found at the distal radius ( $p = 0.001$ ) in SSc patients as compared to controls, confirming the previous work [5,6,21]. Flexion contractures contributing to decreased hand function, functional disability and work disability in SSc are frequently found [22,23]. In the present study, 43/65 SSc patients with hand deformities had significantly more impaired hand mobility as compared to those without deformities ( $p = 0.002$ ) and higher functional scores, indicating more disability ( $p = 0.002$ ). Osteoporosis at the distal radius was significantly associated with hand deformity ( $p < 0.05$ ), higher functional scores ( $p = 0.01$ ), and the BMD was positively correlated with the delta FTP distance ( $r = 0.36$ ,  $p < 0.01$ ), reflecting the effect of hand immobilization and functional disability on the bone mineral density at the distal radius. Interestingly, the frequencies of hand arthritis and RF positivity were not statistically significantly different between patients with and without osteoporosis at the distal radius.

A higher frequency of low bone mineral density in the form of osteopenia was found at the lumbar spine in SSc patients as compared to controls ( $p = 0.002$ ) which is in agreement with several authors [6,8,10,19,24] but not with others [7,11]. In the present study, patients with osteoporosis at the lumbar spine were significantly older and had a longer disease duration than those without ( $p < 0.001$  and  $p = 0.001$ , respectively), which is in agreement with Avouac, et al., [19]. Frediani, et al., [8], however, stated that the lower BMD in SSc patients was more marked with age but not related to disease duration. In agreement with our results, significant negative correlations were found between BMD and disease duration by Di Munno, et al., [6] and Ibn Yakoub, et al., [18].



On the other hand, the frequency of low BMD at the femoral neck was not significantly different from the control group. This is in agreement with da Silva, et al., [11]. Newman, et al., [12] had also reported that most of their patients had normal or increased BMD, however, several authors found lower BMD at the proximal femur in SSc patients [7–10,19,24]. SSc patients reported significantly less physical activity than controls which could have accounted for the lower BMD at the proximal femur in those patients [7]. Another study also reported more disability in SSc patients compared to control patients with non-inflammatory musculoskeletal disease [20]. In the present study, although functional scores reflecting disability were higher in SSc patients with osteoporosis at the femoral neck compared to those without (median 18.5 and 12, respectively), the difference was not statistically significant.

In the present study, no association was found between patients with and without osteoporosis at the distal radius, lumbar spine and femoral neck and scleroderma subtype. This is in agreement with some authors [9,11,19]. Di Munno et al., [6] and Frediani, et al., [8] found lower BMD in diffuse SSc. Ibn Yacoub, et al., [18] found significant negative correlations between Rodnan score and BMD at the lumbar spine and proximal femur, while in the present study, Rodnan score was not associated with osteoporosis at the three skeletal sites.

Internal organ affection was associated with lower BMD in SSc patients in some studies [8,11,18]. We and others [6,19], however, did not find an association between BMD and internal organ affection. Ibn Yakoub, et al., [18] also found a significant association between BMD and severe joint involvement, which was not confirmed in the present study. These discrepancies could be considered to result from patient selection bias, because the most severe disease is more likely to be influenced by other risk factors for osteoporosis, such as inactivity, poor nutritional state, chronic renal failure, and medications (corticosteroids and cyclophosphamide) [3].

SSc patients were found by some authors to have lower vitamin D levels than controls that were related to the lower bone mass in SSc patients [18,19]. One limitation of the present study is the absence of vitamin D levels in our patients and the control group, however, low vitamin D levels would have been expected to cause generalized osteoporosis which is not the case in this study.

In conclusion, patients with systemic sclerosis have lower bone mineral density than controls at the distal radius and lumbar spine. Osteoporosis at the distal radius is associated with the presence of hand deformity and functional disability, while osteoporosis at the lumbar spine is associated with older age and longer disease duration. Physiotherapy to improve hand mobility and function in SSc patients is recommended.

### Conflict of interest

The authors declare no conflicts of interest.

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