Prognostic factors of low bone mineral density in systemic sclerosis

P.D. Sampaio-Barros, L. Costa-Paiva[1], S. Filardi, Z. Sachetto, A.M. Samara, J.F. Marques-Neto

Unit of Rheumatology, Department of Internal Medicine; [1]Department of Gynecology and Obstetrics, State University of Campinas, Campinas, Brazil

Abstract

Objective

To analyse the results of bone densitometry in patients with systemic sclerosis (SSc), evaluating the prognostic factors of low bone mineral density (BMD) in fertile and postmenopausal patients, and comparing to a control healthy group.

Methods

Cross-sectional study analysing 61 female SSc patients, aged 25 to 51 years, who performed a bone densitometry using dual x-ray absorptiometry. BMD values (lumbar spine, femoral neck, Ward and trochanter) in fertile and postmenopausal patients were compared according to SSc clinical variant (limited and diffuse), race, previous use of drugs (corticosteroids and cyclophosphamide) and bone mass index (BMI). These results were compared with 47 fertile and 60 postmenopausal healthy women; multivariate linear regression analysis was used to study the influence of the variables of interest in the BMD results.

Results

Twenty-seven SSc patients presented osteopenia and 14 densitometric osteoporosis. No statistical association was found between BMD values and SSc clinical variants, race and previous use of corticosteroids and cyclophosphamide, in the fertile and in the postmenopausal groups. Fertile SSc patients were paired by age and race with the control group, but BMI ($p = 0.035$) was significantly lower in the SSc group. BMD values of lumbar spine ($p = 0.070$, statistical trend), femoral neck ($p = 0.003$), Ward ($p < 0.001$) and trochanter ($p = 0.003$) were significantly lower in the SSc group. Postmenopausal SSc patients were paired by age and race with the control group, but BMI ($p < 0.001$) was also significantly lower in the SSc group. Age at menopause ($p = 0.006$) was also significantly lower and time from menopause ($p < 0.001$) was significantly higher in the SSc group. BMD values of femoral neck ($p < 0.001$), Ward ($p < 0.001$) and trochanter ($p = 0.001$) were significantly lower in the SSc group. Multivariate linear regression analysis showed that BMI was the main variable influencing BMD in the fertile and postmenopausal groups.

Conclusion

In the present study, BMD results in fertile and postmenopausal SSc patients were independent of the SSc clinical variants, race and previous use of corticosteroids and cyclophosphamide. A low BMD in appendicular sites was observed in fertile and postmenopausal SSc patients when compared to a control healthy group, associated to a low BMI.

Key words

Systemic scleroderma, bone mineral density, osteoporosis, menopause.

Percival D. Sampaio-Barros, MD, PhD; Lúcia Costa-Paiva, MD, PhD; Silvana Filardi, MD; Zoraida Sachetto, MD; Adil M. Samara, MD, PhD; João Francisco Marques-Neto, MD, PhD.

Please address correspondence to: Dr. Percival D. Sampaio-Barros, Disciplina de Reumatologia, Departamento de Clínica Médica, Faculdade de Ciências Médicas, Universidade Estadual de Campinas (UNICAMP), Barão Geraldo, Campinas SP, Brazil CEP 13081-970.
E-mail: psbarros@fcm.unicamp.br

Received on February 12, 2004; accepted in revised form on January 21, 2005.

Introduction

Osteoporosis is defined as a systemic skeletal disorder characterised by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture risk (1). Autoimmune rheumatic diseases, like systemic lupus erythematosus (SLE) (2, 3), rheumatoid arthritis (RA) (4, 5) and ankylosing spondylitis (AS) (6, 7), as well the treatment with corticosteroids and immunosuppressive drugs, represent important risk factors to the development of secondary osteoporosis.

Systemic sclerosis (SSc) is a chronic systemic disease that affects predominantly the female sex, and this higher female prevalence is somewhat more marked in the child-bearing years compared with older age groups (8). There are a few studies analysing bone mineral density (BMD) in SSc patients (9-13).

La Montagna *et al*., studying bone mineral content (BMC) and BMD in 90 female SSc patients and comparing to 90 age- and sex-matched controls, found that both were significantly lower in SSc patients than in controls, and that menopause had occurred significantly earlier in the patients, without a relationship with the extent of skin or internal organ involvement (9).

Di Munno *et al*., analysing 43 female SSc patients and 50 sex and age-matched healthy controls, showed a lower BMD at the radial, lumbar and total body determinations, more significant in the diffuse clinical variant (10). Silva *et al*., analysing 25 female Caucasian patients, did not find statistically significant differences in BMD, compared to healthy controls paired by age (11).

Carbone *et al*. studied 15 female SSc patients and 15 healthy controls paired for age, race, menopausal status and use of exogenous estrogens, and found lower BMD in SSc patients at the spine, femoral neck, trochanter and total hip (12).

Frediani *et al.*, analysing 55 SSc patients and 60 age-matched healthy controls, found that BMD (measured by fan-beam x-ray densitometry) and Stiffness Index (measured by ultrasonometry of the heel) were lower in scleroderma patients with the diffuse clinical variant and one or more internal organ involvement (13).

The aim of the present study was to analyse the results of bone densitometry in a female group of 61 SSc patients, evaluating the importance of the SSc clinical variant, race, previous use of drugs and bone mass index (BMI) in the determination of the BMD in fertile and postmenopausal patients, and comparing to a control healthy group (fertile and postmenopausal).

Material and methods

Patients

This cross-sectional study analysed 61 female SSc patients, aged 25 to 51 years, diagnosed according to the American College of Rheumatology classification criteria (14), and followed at the Scleroderma outpatient clinic of the Hospital de Clínicas of the State University of Campinas between 1997 and 1999. The patients were classified as having the diffuse (dSSc) or limited (lSSc) clinical variants according to LeRoy *et al*. (15). Patients with organ failure (renal, pulmonary or cardiac), esophageal stenosis or intestinal malabsorption were excluded from the study; treatment with hormone replacement therapy, thyroxine, and bone regulating drugs, as well as the presence of demineralising diseases were exclusion criteria. According to the menopausal status, patients were divided into fertile and postmenopausal; age at menopause and time from menopause were recorded.

Regarding race, patients were divided into Caucasians and African-Brazilians (black patients of unmixed ancestry and Mulattos, i.e. originating from the genetic admixture of white and black populations). Patients were also subdivided according to the previous use of corticosteroids (≥ 5 mg daily oral dose of prednisone or equivalent, for at least 60 days) and cyclophosphamide (at least 12 intravenous monthly doses of 15 mg/kg).

The results were compared with a group of 107 healthy female controls, divided into a fertile (47 patients) and a postmenopausal (60 patients) subgroup.

Table I. Demographics – fertile vs. postmenopausal patients.

		Fertile (n = 33)	Postmenopausal (n = 28)
Clinical variant	– Diffuse (%)	17 (52)	4 (14)
	– Limited (%)	16 (48)	24 (86)
Race	– Caucasoid (%)	28 (85)	26 (93)
	– African-Brazilian (%)	5 (15)	2 (7)
Corticosteroids (%)		12 (36)	11 (39)
Cyclophosphamide (%)		19 (42)	14 (50)
Lumbar	– Osteopenia (%)	10 (30)	10 (36)
	– Osteoporosis (%)	- (0)	9 (32)
Femoral neck	– Osteopenia (%)	5 (15)	17 (61)
	– Osteoporosis (%)	3 (9)	5 (18)
Ward	– Osteopenia (%)	8 (24)	12 (43)
	– Osteoporosis (%)	3 (9)	10 (36)
Trochanter	– Osteopenia (%)	10 (30)	14 (50)
	– Osteoporosis (%)	2 (6)	5 (18)

Osteopenia was considered when values for the T-score were between –1.0 and –2.5 SD; Osteoporosis was considered when values for the T-score were below –2.5 SD.

Table II. BMD results – fertile group.

		SSc (n = 33)	Controls (n = 47)	p
Age (Years)		35.79 ± 6.77	34.23 ± 5.94	0.330
Race	– Caucasoid (%)	28 (85)	36 (77)	0.364
	– African-Brazilian (%)	5 (15)	11 (23)	
Weight (kg)		57.94 ± 10.55	62.75 ± 12.06	0.139
Height (cm)		157.76 ± 6.42	156.53 ± 6.11	0.381
BMI		23.34 ± 4.48	25.56 ± 4.42	0.035
Lumbar		1.15 ± 0.12	1.21 ± 0.15	0.070
Femoral neck		0.92 ± 0.18	1.04 ± 0.12	< 0.001
Ward		0.81 ± 0.19	0.96 ± 0.13	< 0.001
Trochanter		0.75 ± 0.15	0.84 ± 0.11	0.003

BMD: bone mineral density; SSc: systemic sclerosis; BMI: bone mass index.

Bone densitometry

Subjects and controls underwent a dual energy X-ray absorptiometry (DXA) of the lumbar spine (L2-L4), femoral neck, Ward and trochanter using a Lunar DPX (Lunar Corporation, Madison, WI) by trained and certified DXA technicians. In our laboratory, the *in vivo* coefficient of variation (CV) was 2.5% for the femur and 2.0% for the lumbar spine. Values of BMD were considered as g/cm^2 and not as T-score as it was used different comparisons for white and black patients.

Statistical analysis

The $\chi 2$ and Fisher exact tests were used to verify the association of the variables of interest; p values ≤ 0.05 were considered to be significant, and $0.10 \leq p < 0.05$ were considered to be a statistical trend. Non-parametric Mann-Whitney test was used to analyse "continual" variables.

Multivariate linear regression analysis was used to study the influence of the variables of interest in the BMD results.

Results

In the present study, 33 women were fertile (54.1%), while 28 were postmenopausal (45.9%). Forty patients (65.6%) had limited SSc and 21 diffuse SSc (34.4%); although there was a strong predominance of fertile patients in the diffuse SSc group, there was a significant number of postmenopausal patients with limited SSc; no significant difference was observed between the two SSc clinical variants regarding the age at menopause and the duration of the menopause. There were 54 Caucasians (88.5%) and 7 African-Brazilians (11.5%). Twenty-three patients (37.7%) referred previous use of corticosteroids (prednisone doses between 5 and 10 mg for 2 to 8 months), and 33 (54.1%) cyclophosphamide (16 for 12 months and 17 for 24 months); there were a similar number of patients using corticosteroids and/or cyclophosphamide in the fertile and postmenopausal groups. These demographic variables are stated on table I.

Twenty-seven SSc patients presented osteopenia (10 fertile and 17 postmenopausal) and 14 densitometric osteoporosis (4 fertile and 10 postmenopausal). No statistical association was found between BMD values and SSc clinical variants, race and previous use of corticosteroids and cyclophosphamide, in the fertile and in the postmenopausal groups.

Demographic and densitometric features of the fertile SSc and control groups are stated on table II. Fertile SSc patients were paired by age and race with the control group, but BMI ($p = 0.035$) was significantly lower in the SSc group. BMD values of lumbar spine ($p = 0.070$, statistical trend), femoral neck ($p = 0.003$), Ward ($p < 0.001$) and trochanter ($p = 0.003$) were significantly lower in the SSc group. Multivariate linear regression analysis, used to study the influence of the variables of interest in the BMD results, showed

Table III. BMD results – postmenopausal group.

	SSc (n = 28)	Controls (n = 60)	p
Age (yrs.)	54.21 ± 6.43	52.43 ± 3.67	0.108
Age at menopause (yrs.)	46.71 ± 4.26	49.20 ± 3.37	0.006
Time menopause (yrs.)	8.50 ± 5.27	3.23 ± 2.25	< 0.001
Race – Caucasoid (%)	26 (93)	55 (92)	1.000
– African-Brazilian (%)	2 (7)	5 (8)	
Weight (kg)	58.14 ± 12.00	65.15 ± 11.47	0.003
Height (cm)	158.00 ± 6.99	155.18 ± 5.56	0.102
BMI	23.35 ± 4.98	26.97 ± 4.09	< 0.001
Lumbar	1.00 ± 0.21	1.05 ± 0.16	0.194
Femoral neck	0.81 ± 0.15	0.92 ± 0.12	< 0.001
Ward	0.67 ± 0.18	0.78 ± 0.13	< 0.001
Trochanter	0.66 ± 0.15	0.76 ± 0.12	0.001

BMD: bone mineral density; SSc: systemic sclerosis; BMI: bone mass index.

that BMI was the main variable influencing BMD in the femoral neck (SE 0.012 (0.004); p = 0.002; R^2 = 24.2%), Ward (SE 0.010 (0.004); p = 0.025; R^2 = 22.2%) and trochanter (SE 0.010 (0.003); p = 0.002; R^2 = 24.8%).

Demographic and densitometric features of the postmenopausal SSc and control groups are stated on table III. Postmenopausal SSc patients were paired by age and race with the control group, but BMI (p < 0.001) was also significantly lower in the SSc group. Age at menopause (p = 0.006) was also significantly lower and time from menopause (p < 0.001) was significantly higher in the SSc group. BMD values of femoral neck (p < 0.001), Ward (p < 0.001) and trochanter (p = 0.001) were significantly lower in the SSc group. Multivariate linear regression analysis showed that BMI was the main variable influencing BMD in lumbar spine (SE 0.013 (0.004); p = 0.001; R^2 = 22.5%), femoral neck (SE 0.011 (0.003); p < 0.001; R^2 = 35.3%), Ward (SE 0.011 (0.003); p = 0.001; R^2 = 35.3%) and trochanter (SE 0.013 (0.003); p < 0.001; R^2 = 31.7%).

Discussion

Although osteoporosis can be observed early in the course of auto-immune rheumatic diseases, like SLE, RA or AS, it is not yet defined how and when it may occur in SSc. The present study shows that a low BMD may be observed in fertile and postmenopausal SSc patients, compared to a control group; SSc patients presented an early menopause, and BMI represented a strong risk factor for a low BMD, while race, SSc clinical variant and previous use of corticosteroids and cyclophosphamide were not risk factors for the development of osteoporosis.

In the fertile group (paired by age and race), BMD values were significantly lower in the SSc patients than in the control group in the axial and appendicular sites. BMI represented the main factor involved in the low BMD observed in these patients; although the exclusion criteria tried to select patients without potential bias in the measurement of BMD, the BMI values persisted lower in the SSc patients. The finding of a lower BMD at the hip is similar to that observed by Carbone et al (12) in scleroderma patients compared to age and sex-matched controls.

Menopause was referred by 45.9% of the patients; there was predominance of patients with lSSc, and the low frequency of postmenopausal dSSc patients (only 4) could be associated to the exclusion criteria of severe organ involvement, more frequent in the dSSc group. The age at menopause was significantly lower in the SSc group (46.71 years) compared to the controls (49.20 years). The postmenopausal group also presented lower BMD values in the appendicular sites (femoral neck, Ward and trochanter). BMI was the main factor influencing BMD results in postmenopausal patients, as it was in fertile patients. La Montagna *et al*. pointed out that the earlier menopause could have a role in the osteopenia observed in SSc (p < 0.001) (9); BMI was not calculated in that study. Although the previous use of cyclophosphamide could be related as a factor influencing early menopause in SSc, it was not a significant statistical determinant of BMD results in the present study .

The two clinical variants of SSc (limited and diffuse) were not considered risk factors for osteoporosis, when analysed separately. The few previous studies presented diverse results: La Montagna *et al*. found a lower BMD in SSc, independent of the clinical variant (9), while Di Munno *et al*. showed that the lower BMD was predominantly associated to the diffuse SSc (10), and Silva *et al*. did not find significant alterations regarding BMD in SSc (11). The number of diffuse SSc patients in our study was rather small (21 patients) due to the fact that we excluded every patient with any significant organ failure.

Race also did not represent a risk factor for osteoporosis in SSc in this study. It must be noted that there was predominance of Caucasian patients (88.5%) in the present study, and that the African-Brazilian patients were predominantly Mulattos (originating from the genetic admixture of white and black populations) and not pure Blacks; although it was the authors' intention to increase the number of African-Brazilian patients in the study, it is observed a frank predominance of Caucasian patients suffering from auto-immune rheumatic diseases in our country (16,17).

The previous use of medications was referred by a significant number of patients in this study, compatible with re-

ferral bias in a reference tertiary university centre. Previous use of corticosteroids, referred by 37.7% of the patients, did not represent a risk factor for osteoporosis as it represents for RA (4) or SLE (3). The fact that corticosteroids were used in low doses (less than 10 mg/day of prednisone or equivalent) might have contributed to the low prevalence of osteoporosis observed in the present study; patients who used large doses of corticosteroids due to severe organ involvement were excluded from the study. The use of corticosteroids in SSc is commonly indicated in cases of peripheral arthritis or acute pericarditis; one must be careful with the development of a scleroderma renal crisis with the use of large doses of corticosteroids (18).

Cyclophosphamide was previously used by 54.1% of the patients. Its use is common at our institution for treatment of rapidly progressing diffuse SSc and pulmonary restrictive disease (19). Despite cyclophosphamide could be associated to a premature ovarian failure (20-22), we observed only three cases of early menopause during the use of the drug. The previous use of cyclophosphamide was not considered a risk factor for a low BMD in the present study, even after the use of multivariate linear regression analysis.

In conclusion, a low BMD in appendicular sites was observed in fertile and postmenopausal SSc patients when compared to a control healthy group, associated to a low BMI. SSc clinical variants, race and previous use of corticosteroids and cyclophosphamide, were not risk factors for a low BMD in the present study.

Acknowledgements

The authors would like to thank Helymar da Costa Machado and Andreia F. Semolini for the statistical analysis.

References

1. CONSENSUS DEVELOPMENT CONFERENCE: Diagnosis, prophylaxis and treatment of osteoporosis. *Am J Med* 1993; 94: 646-50.
2. RAMSEY-GOLDMAN R, DUNN JE, HUANG CF *et al.*: Frequency of fractures in women with systemic lupus erythematosus: Comparison with the United States population data. *Arthritis Rheum* 1999; 42: 882-90.
3. SINIGAGLIA L, VARENNA M, BINELLI L *et al.*: Determinants of bone mass in systemic lupus erythematosus: a cross-sectional study on pre-menopausal women. *J Rheumatol* 1999; 26: 1280-4.
4. DE NIJS RNJ, JACOBS JWG, BIJLSMA JWJ *et al.*: Prevalence of vertebral deformities and symptomatic fractures in corticosteroid treated patients with rheumatoid arthritis. Rheumatology 2001;40:1375-83.
5. KROOT EJJA, NIEUWENHUIZEN MG, MALEFIJT MCW, VAN RIEL PJCM, PASKER-DE JONG PCM, LAAN RFJM: Change in bone mineral density in patients with rheumatoid arthritis during the first decade of the disease. *Arthritis Rheum* 2001; 44: 1254-60.
6. DONNELLY S, DOYLE DV, DENTON A, ROLFE I, MCCLOSKEY EV, SPECTOR TD: Bone mineral density and vertebral compression fracture rates in ankylosing spondylitis. *Ann Rheum Dis* 1994; 53: 117-21.
7. MAILLEFERT JF, AHO LS, EL MAGHRAOUI A, DOUGADOS M, ROUX C: Changes in bone density in patients with ankylosing spondylitis: a two-year follow-up study. *Osteoporos Int* 2001; 12: 605-9.
8. MAYES MD: Scleroderma epidemiology. *Rheum Dis Clin North Am* 1996; 22: 751-64.
9. LA MONTAGNA G, VATTI M, VALENTINI G, TIRRI G: Osteopenia in systemic sclerosis: evidence of a participating role of earlier menopause. *Clin Rheumatol* 1991; 10: 18-22.
10. DI MUNNO O, MAZZANTINI M, MASSEI P *et al.*: Reduced bone mass and normal calcium metabolism in systemic sclerosis with and without calcinosis. *Clin Rheumatol* 1995; 14: 407-12.
11. SILVA HC, SZEJNFELD VL, ASSIS LS, SATO EI: Estudo da densidade óssea na esclerodermia sistêmica. *Rev Assoc Med Bras* 1997;43:40-6.
12. CARBONE L, TYLAVSKY F, WAN J, MCKOWN K, CHENG S: Bone mineral density in scleroderma. *Rheumatology* 1999; 38: 371-2.
13. FREDIANI B, BALDI F, FALSETTI P *et al.*: Clinical determinants of bone mass and bone ultrasonometry in patients with systemic sclerosis. *Clin Exp Rheumatol* 2004; 22: 313-8.
14. LEROY EC, BLACK C, FLEISCHMAJER R *et al.*: Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988; 15: 202-5.
15. SUBCOMMITTEE FOR SCLERODERMA CRITERIA OF THE AMERICAN RHEUMATISM ASSOCIATION DIAGNOSTIC AND THERAPEUTIC CRITERIA COMMITTEE: Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum* 1980; 23: 581-90.
16. CHAHADE WH, SATO EI, MOURA JR JE, COSTALLAT LTL, ANDRADE LEC: Systemic lupus erythematosus in São Paulo/Brazil: a clinical and laboratory overview. *Lupus* 1995; 4: 100-3.
17. SAMPAIO-BARROS PD, BÉRTOLO MB, KRAEMER MHS, MARQUES-NETO JF, SAMARA AM: Primary ankylosing spondylitis: patterns of disease in a Brazilian population of 147 patients. *J Rheumatol* 2001; 28: 560-5.
18. STEEN VD, MEDSGER TA JR: Case-control study of corticosteroids and other drugs that either precipitate or protect from the development of scleroderma renal crisis. *Arthritis Rheum* 1998; 41: 1613-9.
19. MARQUES-NETO JF, SAMPAIO-BARROS PD, SAMARA AM: Intravenous cyclophosphamide for systemic sclerosis. *Clin Exp Rheumatol* 1998; 16: 374.
20. BOUMPAS DT, AUSTIN III HA, VAUGHAN EM, YARBORO CH, KLIPPEL JH, BALOW JE: Risk for sustained amenorrhea in patients with systemic lupus erythematosus receiving intermittent pulse cyclophosphamide. *Ann Intern Med* 1993; 119: 366-9.
21. MARTIN-SUAREZ I, D´CRUZ D, MANSOOR M, FERNANDES AP, KHAMASHTA MA, HUGHES GRV: Immunosuppressive treatment in severe connective tissue diseases: effects of low dose intravenous cyclophosphamide. *Ann Rheum Dis* 1997; 56: 481-7.
22. MOK CC, LAU CS, WONG RWS: Risk factors for ovarian failure in patients with systemic lupus erythematosus receiving cyclophosphamide therapy. *Arthritis Rheum* 1998; 41: 831-7.