Clinical determinants of bone mass and bone ultrasonometry in patients with systemic sclerosis

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Abstract

Objective

The aim of this study was to evaluate bone mass and bone ultrasonometry in patients affected with systemic sclerosis (SSc).

Methods

Fifty-five patients (mean age 54.1 ± 14.1 years; 25 premenopausal, and 30 postmenopausal women) affected with SSc (in a limited, intermediate or diffused form) and 60 age-matched healthy controls (30 premenopausal, and 30 postmenopausal women) were studied for Bone Mineral Density (BMD) measured by fan-beam x-ray densitometry, Stiffness Index (SI) measured by ultrasonometry of the heel, inflammation indices (erithrocyte sedimentation rate, C-reactive protein), and autoantibodies (ANA, ENA). Examinations were also carried out in order to determine any internal organ involvement. None of the patients had previously received steroid treatment.

Results

BMD was significantly lower in the SSc group than in the control group, whether it was expressed in g/cm^2 (lumbar spine: 0.980 vs 1.241, $p < 0.01$; femoral neck: 0.832 vs 0.955, $p < 0.05$; total body 1.050 vs 1.168, $p < 0.01$) or by T- and Z-score (lumbar spine: T = -2.48; Z = -1.10; femoral neck: T = -1.69; Z = -0.55; total body: T = -1.11; Z = -0.48). SI was also altered (75.8 vs 96.2, $p < 0.01$; T = -2.10, Z = -1.12). BMD and SI were lower in women with the diffuse form of skin involvement. BMD and SI were lower in women in whom one or more internal organs were involved.

Conclusion

SSc patients had reduced BMD and SI that was more marked in the diffuse form and in those with internal organ involvement and that became more marked with age and estrogen deficiency. This demineralisation was not related to the inflammation indices, disease duration, or to the immunological pattern.

Key words

Osteoporosis, systemic sclerosis, dual x-ray absorptiometry, quantitative ultrasound.

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Introduction

Systemic Sclerosis (SSc) is a disease characterised by fibrosis, degenerative changes and vascular lesions in the skin, synovium, muscles and internal organs such as lungs, heart, gastrointestinal tract and kidneys.

Less is known about bone involvement in this disease. Generalized osteopenia, as detected by radiological investigations, has been seen to occur in a significant percentage of SSc patients (1, 2). Little information is available concerning bone mass evaluated by absorptiometry in SSc patients; dual energy x-ray absorptiometry (DXA) is a quantitative, accurate and reproducible method of measuring the bone mineral content of the spine, femur and the body as a whole (3,4). In SSc patients, bone mineral content evaluated by DXAwas found to be reduced at the radius (5-7), of the lumbar spine and in the total body (7). In most cases the pathogenesis of osteopenia is unknown: the bone mass in SSc patients may be negatively influenced by factors such as reduced physical activity, decreased sun exposure, use of corticosteroids, and involvement of the intestinal tract and kidneys that may alter calcium metabolism.

No data are available about regarding bone quality in patients with SSc. Many studies have suggested that quantitative ultrasound (QUS) measurements may be useful for investigating bone quality (8). The aim of this study was to evaluate bone mass, bone ultrasonometry and some clinical determinants in non-steroid treated pre-menopausal and post-menopausal women with SSc using DXAand QUS.

Patients and methods

Study population

SSc group. In this retrospective study, 55 women (age range 31-78 years; mean age 54.1 years, 25 premenopausal and 30 postmenopausal subjects) affected with SSc were investigated. All of the patients satisfied the preliminary LeRoy (9) criteria indicated in the classification of progressive SSc. The exclusion criteria were current or previous treatment with corticosteroid, immunosuppressants, hormone replacement therapy, thyroxine, bone regulating drugs and/or the presence of demineralising diseases. Twenty-five patients had not received any previous treatment; 20 patients had occasionally received Iloprost for no more than 6 months; and 10 patients had received griseofulvin.

Control group. This group was made up of 60 healthy female subjects recruited from volunteers: 30 of them were in premenopausal and 30 were postmenopausal. None of them presented any pathology, nor were they taking demineralising drugs, and they did not have any form of phlogistic or degenerative disease. The exclusion criteria were the same as that of the SSc groups.

Methods

A detailed history of each patient was recorded, with particular reference to age, menopausal status, disease duration (evaluated by anamnestical data), current and/or previous treatments and current or previous pathologies; their height and weight were measured and analysed by the body mass index (BMI) ratio. Blood samples were taken for the determination of the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The following serological markers were performed using standard techniques in all patients: antinuclear (ANA) antibodies by indirect immunofluorescence on Hep-2 cell line at end point dilution, anticentromere antibody, antiextractable nuclear antigen (ENA) antibodies by the Ouchterlony method of immunodiffusion and by EIA immunodiffusion, including anti-Scl 70, -Sm, -RNP, -SSB, -SSAand Jo-1.

Examinations were also carried out to determine the extent of any internal organ involvement (heart, lung and kidney). Lung involvement was assessed by high resolution QCT and respiratory tests, including DLCO. Kidney involvement was assessed by ultrasonography, evaluating creatinine clearance, creatininemia and urinary sediment. Heart involvement was assessed by echo color doppler and ECG. The gastrointestinal tract was assessed by endoscopy and x-ray using barium. The patients were divided into three groups based on the extent of cutaneous involvement (10): limited (L-SSc, 15 pa-

tients), intermediate (I-SSc, 14 patients) and diffuse (D-SSc, 18 patients).

BMD was evaluated by means of fan-beam x-ray densitometry, using a Lunar Expert version 1.72. The following regions were evaluated: total body, lumbar spine (L2-L4) and femur (neck, Ward's triangle and trochanter). The results were expressed as g/cm^2. Bone was evaluated by means of QUS of the heel using the Lunar Achilles Plus, and the results were expressed in terms of a Stiffness Index (SI) (theoretical entity matching both previous measurements). T-scores (the difference between the BMD of the patients and that of young healthy adults corrected for the standard deviation) and Z-scores (the difference between the BMD of the patient and that of healthy subjects of the same age) were used in the DXA and QUS.

Statistical analysis

Analysis was performed by subgroups based on BMD status. The mean BMD and SI were compared with those of the age-matched control group (Z-score) and young adults (T-score). The parametric tests included the analysis of variance, Pearson's correlation coefficient and the t-test for unpaired data. The non-parametric test included Spearman's correlation coefficient and Mann-Whitney's U-test.

In addition to the univariate analysis, a multivariate analysis was carried out in order to establish the independent effects of the different covariates on bone mass: a linear model was adopted in which BMD and SI were used to identify the independent variables predictive of osteoporosis.

Results

Table I shows the characteristics of the SSc group, including age, years since menopause, height, weight, BMI and disease duration, and those of the various subgroups based on menopausal status, and controls. BMD, expressed in g/cm^2, was significantly lower in the SSc group than in controls: the SSc lumbar spine BMD was 0.980 g/cm^2 vs 1.241 in controls ($p<0.01$), the femoral neck BMD was 0.832 vs 0.955 ($p< 0.05$) and total body BMD was 1.050

Table I. Characteristic and epidemiological features of the SSc patients and controls.

	Premenopausal patients		Postmenopausal patients		Total	
	Controls	SSc patients	Controls	SSc patients	Controls	SSc patients
Number	30	25	30	30	60	55
Age	37.5 ± 6.6	36.9 ± 4.6	64.7 ± 5.9	64.3 ± 14.1	53.9 ± 13.5	54.1 ±14.1
Years of menopause	-	-	10.8 ± 4.8	10.5 ± 7.1	10.8 ± 4.8	10.5 ± 7.1
Height (cm)	159.2 ± 4.1	160 ± 3.1	157.1 ± 4.9	157.9 ± 7.7	158.1 ± 5.4	158.8 ± 6.9
Weight (kg)	57.4 ± 4.2	57.6 ± 5.6	56.8 ± 5.5	56.5 ± 5.7	57.0 ± 4.8	57.2 ± 5.9
BMI (kg/m^2)	22.5 ± 2.6	22.7 ± 2.5	23.4 ± 2.9	22.9 ± 3.6	22.8 ± 2.7	22.5 ± 2.9
Disease duration (months)	- -	65.4 (6-84)	- -	175.1 (18-244)	- -	130.8 (6-244)

Table II. Bone mineral density (g/cm^2) and ultrasonometry results (stiffness) in healthy control subjects and patients with SSc.

	Premenopausal pts. mean (SD)		Postmenopausal pts. mean (SD)		Total mean (SD)	
BMD g/cm^2	Control	SSc patients	Control	SSc patients	Control	SSc Patients
Total Body	1.194 (0.053)	1.159 (0.066)	1.137 (0.065)	1.035** (0.090)	1.168 (0.059)	1.050** (0.090)
Lumbar Spine L2-L4	1.306 (0.129)	1.162* (0.174)	1.197 (0.074)	0.955** (0.221)	1.241 (0.118)	0.980** (0.177)
Femur neck	1.013 (0.103)	0.935* (0.143)	0.906 (0.085)	0.817** (0.111)	0.955 (0.095)	0.832* (0.125)
Femur Wards	0.906 (0.134)	0.811* (0.144)	0.825 (0.073)	0.679** (0.128)	0.862 (0.111)	0.744* (0.137)
Femur troch	0.830 (0.135)	0.753** (0.137)	0.767 (0.117)	0.666** (0.123)	0.788 (0.122)	0.704* (0.134)
Os calcis Stiffness	100 (8.2)	72.1* (14.8)	92 (13.9)	78.1* (12.0)	96.20 (10.9)	75.80** (13.7)

*$p < 0.05$ (SSc vs controls); **$p < 0.01$ (SSc vs controls)

Table III. Bone mineral density and ultrasonometry results expressed as T- and Z-scores in patients with SSc.

	Premenopausal patients		Postmenopausal patients		Total	
	T-score	Z-score	T-score	Z-score	T-score	Z-score
Total body	-0.28	-0.04	-1.26	-0.88	-1.11	-0.48
Lumbar spine L2-L4	-1.12	-0.07	-2.68	-2.09	-2.48	-1.10
Femur neck	-0.65	-0.07	-1.86	-0.97	-1.69	-0.55
Femur wards	-0.99	-0.45	-2.46	-1.77	-2.25	-1.33
Femur troch	-0.89	-0.78	-1.47	-0.87	-1.16	-0.84
Os calcis stiffness	-1.84	-0.58	-2.19	-1.45	-2.10	-1.12

vs 1.168 ($p < 0.01$), respectively (Table II).

Ultrasonometry of the heel was also altered in SSc patients: SI 75.8 vs 96.2, $p < 0.01$ (Table II).

Bone mass was lower in the SSc group than in controls, whether evaluated by the T- or Z-scores (lumbar spine: T = –2.48; Z = -1.10; femoral neck: T = –1.69; Z = -0.55; total body: T = -1.11; Z = -0.48) (Table III).

Bone quality was altered in the SSc group whether evaluated by the T-or Z-scores (T =-2.10; Z = -1.12) (Table III). BMD and SI were significantly lower in the SSc subgroups of premenopausal and postmenopausal women (Tables II and III).

The patients were divided into three groups on the basis of their lumbar and femoral BMD (expressed as the T-score; in cases of disagreement in scores the lower value was taken): group 1 included subjects with a T-score above –1 (normal), while group 2 included those with a T-score between –1 and –2.5 (osteopenic) and group 3 was made up of those with a T-score below –2.5 (osteoporotic). The percentage of patients in each group is shown in Figure 1: demineralisation was observed in at least one skeletal region in 36% of the premenopausal women (osteopenic) affected with SSc and in 83.3% of the postmenopausal subjects (53.3% osteopenic and 30% osteoporotic).

Table IV shows the BMD and SI in the premenopausal women with SSc subdivided on the basis of skin involvement, internal organ involvement, normal or alterated indices of inflammation, and the absence or presence of specific autoantibodies. BMD and SI were reduced in women with the diffuse form of skin involvement. BMD and SI were reduced in women with involvement of one or more internal organs. No correlation was found between skin and internal organ involvement.

In the premenopausal women, BMD and SI correlated only with BMI ($r = 0.33$, $p = 0.004$ for lumbar BMD; $r = 0.30$, $p = 0.005$ for neck BMD; $r = 0.29$, $p = 0.008$ for total body BMD; $r = 0.32$, $p = 0.003$ for heel SI).

In the postmenopausal women, BMD and SI correlated not only with BMI, but also with age ($r = 0.44$; $p = 0.006$ for lumbar BMD; $r = 0.46$, $p = 0.007$ for neck BMD; $r = 0.27$, $p = 0.007$ for total body BMD; $r = 0.54$, $p = 0.001$ for heel SI) and years since menopause ($r = 0.55$, $p = 0.003$; $r = 0.56$, $p = 0.001$; $r = 0.28$, $p = 0.007$; $r = 0.60$, $p = 0.002$ respectively).

There was no correlation between the ESR, CRP, autoantibody titres or disease duration in the two subgroups.

A multivariate analysis was carried out to analyse the independent effects of the covariates (skin score, years since menopause, height, weight, BMI, and disease duration) on bone mass using a linear model to identify the predictors of osteoporosis in the 55 patients as a whole and in the subgroups. In the group of patients as a whole, age and BMI were significant predictors of bone mass, as were the years since menopause in the postmenopausal women. The only significant predictor among the premenopausal women with SSc was BMI.

In a subsequent phase, a logistic model for the patient group as a whole was

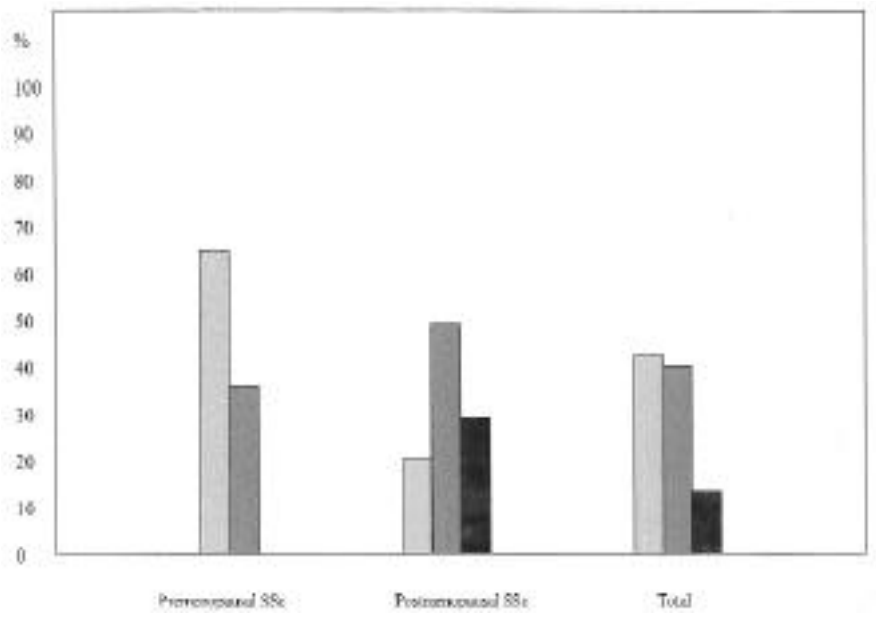

Fig. 1. Percentage of normal (light gray bars), osteopenic (dark gray bars) and osteoporotic (black bars) subjects defined on the basis of T-Scores in patients with SSc.

Table IV. Bone mineral density (g/cm^2) in women with SSc grouped on the basis of their index of inflammation, the presence of autoantibodies and the extent of disease.

	ESR mean (SD)		CRP mean (SD)		Specific autoantibodies mean (SD)		Cutaneous involvement mean (SD)			Internal organ involvement mean (SD)	
BMD g/cm^2	Normal (n = 24)	Altered (n = 31)	Normal (n = 26)	Altered (n = 29)	Absent (n = 25)	Present (n = 30)	Limited (n = 19)	Intermediate (n = 16)	Diffused (n = 20)	Absent (n = 26)	Present (n = 29)
Total body	1.066 (0.075)	1.057 (0.081)	1.074 (0.092)	1.053 (0.072)	1.067 (0.091)	1.059 (0.069)	1.109 (0.090)	1.087 (0.092)	1.025* (0.076)	1.100 (0.087)	1.026* (0.071)
Lumbar spine L2-L4	0.998 (0.122)	0.980 (0.157)	0.985 (0.146)	0.997 (0.147)	0.994 (0.146)	0.985 (0.137)	1.039 (0.162)	1.026 (0.142)	0.948* (0.134)	1.033 (0.137)	0.951* (0.146)
Femur Neck	0.849 (0.134)	0.833 (0.138)	0.835 (0.127)	0.847 (0.121)	0.840 (0.121)	0.832 (0.138)	0.837 (0.118)	0.889 (0.121)	0.780** (0.107)	0.887 (0.138)	0.791* (0.140)
Os Calcis	80 (10.2)	75 (12.9)	78 (13.9)	75 (12.7)	78 (15.3)	74 (14.5)	88 (13.3)	89 (13.7)	63* (11.8)	89 (12.9)	66* (11.8)

*p < 0.05 (SSc vs controls); **p < 0.01 (SSc vs controls)

prepared in which the presence of osteoporosis (a T-score below –2.5) in at least one skeletal site was the dependent variable. In this model the age of the subject, years since menopause and BMI were all significantly associated with osteoporosis. An impared BMI was also significantly associated with osteoporosis after correction for age and the number of years since menopause (Table V).

Discussion

The results of this study show the presence of a bone mass reduction in SSc patients. We confirm a previous report that showed a reduction of bone mass at the peripheral (5-7) and axial (7) levels.

We studied non-steroid-treated patients with SSc, including premenopausal women, in order to exclude the negative effect of estrogen deficiency on bone mass. Compared to young adults (T-score), bone mass was reduced in 35% of premenopausal and 81% of postmenopausal women. Demineralisation was confirmed by comparison with age-matched normal subjects (Z-score).

The reduction in bone mass was more marked at the level of the lumbar spine and heel. It is known that these two sites are partially and completely trabecular, respectively. SSc-related osteoporosis thus seems to have the typical characteristics of postmenopausal osteoporosis. The femur was also greatly involved, but only in the postmenopausal subjects.

This represents, to our knowledge, the first report that has evaluated SSc patients by QUS. Many studies have suggested that QUS could be useful for investigating bone quality (8). In our patients the prevalent impairment of stiffness at the heel also provides an additional indication concerning the presence of a qualitative alteration in the trabecular micro-architecture. This qualitative alteration of bone was present not only in postmenopausal patients but also in premenopausal patients.

However, the T- and Z-scores indicate that the disease was not sufficient to produce severe osteoporosis. The biohumoral indices of inflammation and specific antibodies did not modify the bone mass of our patients and were, therefore, not predictive.

A previous work (5) reported that bone mass was related to the extent of skin involvement, but it did not evaluate the extent of visceral involvement. Many authors have suggested that the extent of skin involvement is directly related to the extent of visceral involvement and to the severity of the disease (10-13). Our data suggest that bone mass and bone quality are altered in SSc patients with the diffuse form of skin involvement and/or the involvement of at least one internal organ. The subgroups were all comparable in terms of mean age, mean menopause duration and disease duration.

Furthermore, bone mass was influenced by both generic risk factors and risk factors that were typical to all primary forms of osteoporosis (BMI, age and years since menopause). In our population, unlike a previous study (5), disease duration did not seem to have any particular influence on the loss of

Table V. Variables associated with a significant relative risk of osteoporosis in at least one skeletal region.

	OR	CI	P	OR (corrected for age and years of menopause)	CI	P
Age	1.6	1.07 - 1.93	0.011	-	-	-
Years of menopause	1.9	1.20 - 2.67	0.006	-	-	-
BMI	0.70	0.55 - 0.90	0.010	0.77	0.59-0.93	0.011

OR: Odds ratio; CI: confidence interval.

bone mass.

In conclusion, our study, based on the use of more sophisticated quantitative and qualitative instrumental evaluations of bone, showed that SSc patients have a reduced total skeleton bone mass and altered bone quality that are more marked in the diffuse form and in patients with internal organ involvement and that this reduction and alteration/ effect becomes more marked with advanced age and estrogen deficiency. Demineralisation and bone quality alterations are not related to inflammation indices, disease duration, nor to any specific immunological pattern. Longitudinal studies are needed to confirm these results.

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