ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 06 | June - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

STUDY OF BONE MINERAL DENSITY IN PATIENTS WITH SYSTEMIC SCLEROSIS.

General Medicine

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ABSTRACT

Background: Systemic sclerosis (SSc) is a chronic, multisystem connective tissue disease characterized by microangiopathy leading to inflammation and fibrosis involving skin and internal organs. The amount of steroid intake in patients of systemic sclerosis is also less as compared to other rheumatological disorders and as such BMD changes may not be much attributable to it. The present study is conducted to correlate disease related variables & BMD and treatment parameters with BMD and the amount of osteoporosis. **Methodology:** The present Observational Cross-sectional study was conducted on 61 diagnosed age more than 16 years, diagnosed cases of systemic sclerosis. Patients' demographics and examination findings, laboratory parameters, DEXA scan findings, disease related variables such as time since diagnosis, disease duration and presence of systemic features such as ILD and PAH were noted. Disease activity scores were obtained using The Rodnan skin score and Medsger disease severity index. Bone mineral density from DEXA scan report were noted in the case record proforma. DEXA Scan was done at two sites-lumbar and hip and BMD was obtained. **Results:** Majority of subjects belonged to 36-45 years (36.07%); mean age was 41.49±9.71 years. 96.72% were females. Skin involvement among all subjects (100%). Hypertension among 18.03% subjects, hypothyroidism and diabetes mellitus among 3.28%. Moderate restriction among 81.97% subjects, followed by mild restriction among 16.39%, severe restriction among 1.64% subjects. 3+ grading among 47.54%, followed by 1+ among 36.07%, and 2+ among 16.39% study subjects. Mean Modified Rodnan Skin Score was 32.47±5.42, and Mean Medsger Disease Severity Index of 10.21±3.42. Majority of the study subjects had total steroid dose between 0 to 5 gms (52.46%), followed by 27.87% subjects with dose between 6 to 10 gm. 18.03% subjects with dose between 11 to 15 gm, and 1.64% study subjects had total steroid dose more than 15 gm. Comparatively higher BMD in both LS and hip in group with total dose between 0 to 5 mg, compared to steroid dose more than 10 mg, where BMD was least (r-value -0.71, p-value <0.001). Comparatively higher BMD in both LS and hip in group with disease duration between 1 to 3 years, compared to disease duration more than 5 years, where BMD was least. The difference was analysed using Pearsons correlation methods (r-value -0.766, p-value: <0.001 & r-value -0.58, p-value <0.001). **Conclusion:** The mean age of subject was 41.49 ± 9.71 years with male: female ratio 1: 29.5. Skin involvement was commonest. Moderate restriction in PFT among 81.97% subjects, followed by mild restriction among 16.39%, severe restriction among 1.64% subjects. Weaker correlations between disease severity indices and BMD/T scores. Inverse correlation between BMD in both LS and hip in the group with total cumulative steroid dose. We also observed inverse correlation between BMD with disease duration.

KEYWORDS

Bone Mineral Density (BMD), Systemic Sclerosis, Rodnan skin score and Medsger disease severity index, Correlation

INTRODUCTION

Systemic sclerosis (SSc) is a chronic, multisystem connective tissue disease characterized by microangiopathy leading to inflammation and fibrosis involving skin and internal organs. Characteristics of systemic sclerosis include essential vasomotor disturbances; fibrosis; subsequent atrophy of the skin, subcutaneous tissue, muscles, and internal organs (eg. gastrointestinal tract, lungs, heart, kidney, CNS); and immunologic disturbances accompany these findings[1].

Chronic inflammatory rheumatic diseases like rheumatoid arthritis and spondyloarthropathies are well recognized risk factors of bone loss and fractures. Currently, there are very few studies regarding effect of systemic sclerosis disease activity on bone mineral density. Osteoporosis is typically diagnosed by dual- energy x-ray absorptiometry (DEXA) measurements of areal Bone Mineral Density (BMD)[2]. Systemic sclerosis can also be subdivided according to different criteria, such as involvement of organs and the presence of specific antibodies which are hallmarks of the disease. These autoantibodies are disease-specific and usually mutually exclusive and correlate with the extent of skin involvement and associated disease manifestations. The most common are DNA topoisomerase (anti-Scl70), and Anti- centromere antibodies.

These autoantibodies are marker antibodies for relatively distinct clinical phenotypes of SSc where anti-Scl[4] antibodies are a marker for Diffuse cutaneous SSc and SSc patients with clinically significant pulmonary fibrosis with a poor prognosis whereas anti-centromere antibodies typically are associated with Limited cutaneous SSc, uncommon pulmonary fibrosis, and late onset of pulmonary hypertension and generally are associated with an overall good prognosis. Various studies are done in western population but little is known about the bone mineral density in patients with Systemic sclerosis in Indian population. The current study is planned to assess the BMD in Systemic sclerosis in patients presenting to a tertiary care rheumatology clinic[5].

The amount of steroid intake in patients of systemic sclerosis is also less as compared to other rheumatological disorders and as such BMD changes may not be much attributable to it. The present study is conducted to correlate disease related variables & BMD and treatment parameters with BMD and the amount of osteoporosis.

AIMS AND OBJECTIVES

1. To correlate between bone mineral density in Systemic sclerosis and disease activity using Modified Rodnan skin score and Medsger disease severity index.
2. To correlate bone mineral density with age, gender and menopausal status in women, disease duration, time since onset of symptoms and effect of treatment given in Systemic sclerosis on BMD.
3. To study whether changes in bone mineral density as obtained by DEXA Scan is attributable to the physiological factors as mentioned above or to the disease activity per se.

MATERIAL AND METHODS

Study Design

The present Observational Cross-sectional study was conducted on 61 diagnosed cases systemic sclerosis in Department of Medicine (Rheumatology division) - out-patient department and indoor patients of Systemic sclerosis in tertiary care centre between December 2018 to June 2020 (18 months). Patients of age more than 16 years with diagnosed cases of Systemic sclerosis according to the 2013 ACR-EULAR Classification Criteria. Patients on drugs causing loss of BMD with exception of drugs used in the treatment of systemic sclerosis, Pregnant women and Comorbid conditions affecting bone mineral density like malignancy, alcoholism, chronic kidney disease were

excluded.

After getting permission from institutional ethics committee, study was started. Written informed consent of the study subjects was taken. Patients were asked a detailed history and clinical examination with the help of standard, pre- validated, semi-structured case record proforma. Patients' demographics and examination findings, laboratory parameters, DEXA scan findings, disease related variables such as time since diagnosis, disease duration and presence of systemic features such as ILD and PAH were noted. Disease activity scores were obtained using The Rodnan skin score and Medsger disease severity index. Bone mineral density from DEXA scan report were noted in the case record proforma. DEXA Scan was done at two sites-lumbar and hip and BMD was obtained.

Data was analysed using multivariate regression analysis. Bone mineral density was correlated with disease variables. Pearson's correlation method was used to study the correlation between BMD and disease severity, BMD, cumulative steroid dose, BMD and disease duration. Correlation coefficient value near or equal to +/- 1 and p-value less than 0.05 was considered to be of statistical significance.

CRITERIA: ACR/ EULAR Classification criteria for SSC Total score of >/= 9: Definite scleroderma.

1 Item	Sub-item(s)	Weight/Score
Skin thickening of fingers-both hands extending proximal to MCP joint		9
Skin thickening of fingers	Puffy fingers	2
	Whole finger, distal to MCP joint	4
Finger-tip lesions	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia		2
Abnormal nailfolds		2
PAH +/- Interstitial lung disease		2
Raynaud's phenomenon		2
SSc related autoantibodies	Anti-centromere, Anti-topoisomerase-I, Anti-RNA Polymerase-3	3

Disease Activity Indices

Modified Rodnan Skin Score[6]

This score consists of an evaluation of patient's skin thickness rated by clinical palpation using a 0–3 scale (0=normal skin; 1=mild thickness; 2=moderate thickness; 3=severe thickness with inability to pinch the skin into a fold) for each of 17 surface anatomic areas of the body: face, anterior chest, abdomen, (right and left separately) fingers, forearms, upper arms, tights, lower legs, dorsum of hands and feet. These individual values are added and the sum is defined as the total skin score.

RESULTS

Demographic And Clinical Characteristics Of The Patients

In the present study we observed that majority of the study subjects belonged to 36 to 45 years (36.07%), followed by 46 to 55 years (32.79%), 26 to 35 years (16.39%). The mean age of the study subject was 41.49 ± 9.71 years. We observed that almost all were female subjects (96.72%), and 3.28% were male subjects. The male: female ratio was 1:29.5.

Skin involvement among all subjects (100%), pulmonary involvement among 95.08% subjects, digital ulcers among 50.82%, Raynauds phenomenon among 39.34%. Rare presentation was joint pain, and GI involvement among 4.92% subjects each. Hypertension among 18.03% subjects, hypothyroidism and diabetes mellitus among 3.28% subjects. IHD among 1.64% study subjects.

PFT findings shows moderate restriction among 81.97% subjects, followed by mild restriction among 16.39%, severe restriction among 1.64% subjects.

Table 1. Demographic And Clinical Characteristics Of The Patients

Patients' Characteristics	Number of subjects	Percentage
Age distribution	16-25 years	5	8.20
	26 to 35 years	10	16.39
	36 to 45 years	22	36.07
	46 to 55 years	20	32.79
	56 to 65 years	4	6.56
	More than 66 years	0	0.00
Gender	Male	2	3.28
	Female	59	96.72
Clinical presentation	Skin involvement	61	100.00
	Pulmonary involvement	58	95.08
	Digital ulcers	31	50.82
	Raynauds' phenomenon	24	39.34
	Joint pain	3	4.92
	GI involvement	3	4.92
Comorbidity	Hypertension	11	18.03
	Hypothyroidism	2	3.28
	Diabetes mellitus	2	3.28
	Ischemic heart disease	1	1.64
	No Comorbidities	41	67.21
PFT findings	Mild Restriction	10	16.39
	Moderate Restriction	50	81.97
	Severe Restriction	1	1.64

Table 2. BMD Scores, T Scores, Modified Rodnan Skin Score And Medsger Disease Severity Index

Parameters		Mean	SD
BMD	Lumbar Spine gm/cm2	0.64	0.09
	HIP gm/cm2	-2.71	0.49
T Score	Lumbar Spine	0.65	0.08
	HIP	-2.69	0.48
Vit. D Levels		23.15	3.96
Mean Modified Rodnan Skin Score		32.47	5.42
Mean MEDSGER Disease Severity Index		10.21	3.42
Mean cumulative steroid dose		5.91	3.82

Mean BMD of lumbar spine (0.64 ± 0.09), and hip (0.65 ± 0.08). We also assessed T score among lumbar spine (-2.71 ± 0.49), and hip (-2.69 ± 0.48). We also assessed vitamin D levels among the study subjects. We observed a mean level of 23.15 ± 3.96. Mean Modified Rodnan Skin Score was 32.47 ±5.42, and Mean Medsger Disease Severity Index of 10.21± 3.42. We also calculated Mean cumulative steroid dose. We observed mean dose of 5.91±3.82 gm (table 2).

Frequency Of Patients With Scleroderma BLOT, Medsger Disease Severity Score And Modified Rodnan Skin Score:

We observed Scl-70 3+ among 47.54%, followed by 1+ among 36.07%, and 2+ among 16.39% study subjects. Mild disease (according to medsgar score) among 44.26% subjects, while moderate disease among 31.15% subjects, and end stage disease among 1.64% subjects. Moderate score(Modified Rodnan skin score) among 78.69% subjects, followed by severe involvement among 19.67% subjects and mild involvement among 1.64% study subjects (Fig 1).

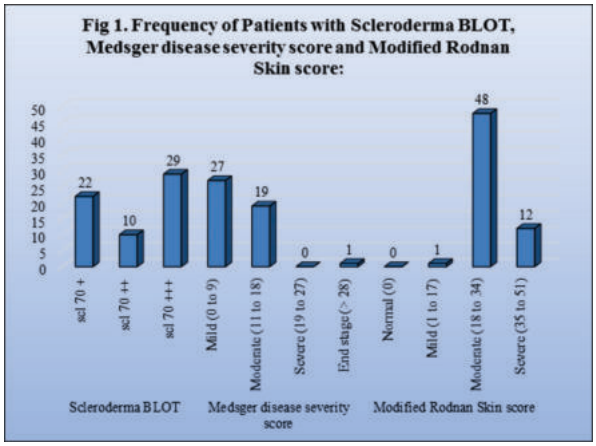
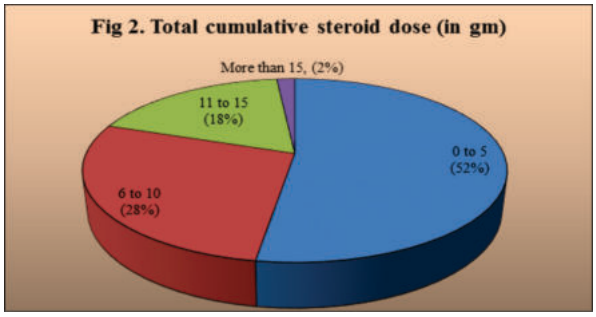


Table 3. Correlation Between Disease Activity Scores And BMD

Parameters	Correlation coefficients	
	Modified Rodnan Skin Score	Medsger Disease Severity Index
BMD LS	-0.2403	-0.0619

BMD HIP	-0.2823	-0.3236
T SCORE LS	-0.303	-0.0954
T SCORE HIP	-0.3405	-0.3351

We assessed correlation between Modified Rodnan Skin Score and BMD LS (-0.2403), BMD Hip (-0.2823), T score LS (-0.303), and T score hip (-0.3405). We also assessed correlation between Medsger Disease Severity Index and BMD LS (-0.0619), BMD hip (-0.3236), T score LS (-0.0954), and T score hip (-0.3351). We observed non-significant correlation between disease severity indices and BMD / T scores. (p value>0.05)



Total Cumulative Steroid Dose (in gm)

In this study we assessed Total cumulative steroid dose (in gm) among the study subjects. We observed that majority of the study subjects had total steroid dose between 0 to 5 gms (52.46%), followed by 27.87% subjects with dose between 6 to 10 gms. 18.03% subjects with dose between 11 to 15 gms, and 1.64% study subjects had total steroid dose more than 15 gms.

Correlation Between BMD & Total Steroid Dose

Our study shows that comparatively higher BMD in both LS and hip in the group with total dose between 0 to 5 mg, as compared to steroid dose more than 10 mg, where BMD was least. The difference was analysed using Pearsons correlation methods. We observed that the difference is statistically significant (r-value -0.71, p-value: <0.001).

Correlation Between Disease Duration And BMD

We observed comparatively higher BMD in both LS and hip in the group with disease duration between 1 to 3 years, as compared to disease duration more than 5 years, where BMD was least. The difference was analysed using Pearsons' correlation methods. We observed that the difference is statistically significant (r-value -0.766, p-value: <0.001 & r-value -0.58, p-value: <0.001).

Table 4. Relation Of BMD With Total Steroid Dose And Disease Duration

Patients' Characteristics		BMD	
		LS	Hip
Total cumulative steroid dose	0 to 5	0.6859	0.6828
	6 to 10	0.6464	0.637
	11 to 15	0.3408	0.31
	More than 15	0.34	0.32
Disease duration (in years)	1 to 3	0.72	0.68
	3 to 5	0.62	0.61
	more than 5	0.34	0.39
r-score (p-value)		-0.766 (<0.0001)	-0.58 (<0.0001)

DISCUSSION

The mechanisms that cause the loss of bone density in autoimmune diseases are very complex: from direct effect of immune cells on cartilage and bone to indirect consequences of the disturbance of systemic control of bone remodeling. Studies in the literature suggested that SSc is a risk factor for bone loss; however, the prevalence of OP was within a wide range from 3 to 51%. This wide dispersion could be attributed to the heterogeneity of the patients studied (e.g., age, gender, menopausal status, geographic location, disease subtype, organ manifestations, and CS exposure).

Present study shows skin involvement among all subjects (100%), pulmonary involvement among 95.08% subjects, digital ulcers among 50.82%, Raynauds phenomenon among 39.34%. Ágnes Horváth et al[7], in their study observed the cumulative clinical features of SSc patients, interstitial lung disease (ILD) was most frequently seen (n=35; 79.5%), followed by cardiac involvement (n=29; 65.9%), dysphagia and GERD (n=25; 56.8%), malabsorption syndrome (n=13; 29.5%), digital ulcers (n=13; 29.5%), and PAH (n=3; 6.8%). None of the patients had notable renal involvement.

In the present study, mean level of Vitamin D was 23.15±3.96. Shefali Sharma et al[8], in their study concluded that low bone mass is common in patients with SSc and is associated with elevated Sr. PTH levels. Hypocalcemia is also highly prevalent in such patients and deserves treatment to prevent untoward long-term effects on bone metabolism and quality of life. Recently Caramaschi P et al[9] showed that low levels of vitamin D are very frequent in patients affected by SSc and patients with vitamin D deficiency showed more severe disease in comparison with patients with vitamin D insufficiency only. Reduced sun exposure, as well intestinal involvement, and renal insufficiency are the main factors.

A skin thickening with capillary damage can result in a reduced production of vitamin D3 from 7-dehydrocholesterol after UV-B radiation exposure.

Systemic sclerosis, as it was recently reported by Yuen SY et al[10], should be considered as an important risk factor for osteoporosis. Lateral spine X-ray documented single or multiple vertebral fractures according to Genant's criteria in 13 patients (24%), whereas only one subject had a single mild vertebral fracture in control group (1,8%). It is noteworthy that not all patients with fracture had a osteoporosis and vice versa.

We observed Scleroderma BLOT 3+ grading among 47.54%. Ágnes Horváth et al[7], observed that the prevalence of ANA positivity was 75% (n=33); ACA was present in seven cases (15.9%) and 11 patients (25%) were positive for anti Scl-70 antibodies.

We assessed the correlation between modified Rodnan skin score and BMD LS (-0.2403), BMD Hip (-0.2823), T score LS (-0.303), and T score hip (-0.3405). We also assessed correlation between Medsger disease severity index and BMD LS (-0.0619), BMD hip (-0.3236), T score LS (-0.0954), and T score hip (-0.3351). We observed no correlation between disease severity indices and BMD / T scores. (p value>0.05) HC Da Silva et al[11], in their study concluded that bone mass in different sites was not statistically different from the age-matched control healthy women. Mean bone mass of patients with limited form was not different from patients with diffuse form of systemic sclerosis. Patients with calcinosis had lower bone mass at proximal femur than those without this alteration. Bojana Stamenković et al[12] in their study observed that After comparing BMD of patients with systemic sclerosis and healthy controls, they found a significantly lower value of BMD (in g/cm2 and T-score) in SSc patients, at both spine and hip (all p values<0.01).

Bojana Stamenković et al[12] also observed no significant difference after investigating the relation between BMD and the presence of specific antibodies. SSc patients with positive ACA had no significantly different BMD as compared to patients with positive ATA at both hip and spine (ACA+BMD at lumbar spine, disease duration between ACA+ and ATA+ SSc patients. (all p values >0.01)

We observed that majority of the study subjects had total cumulative steroid dose between 0 to 5 gms (52.46%), followed by 27.87% subjects with dose between 6 to 10 gm. Ágnes Horváth et al[7], observed that 38.6% had ever been treated with CS; however, we did not have an exact data on the cumulative CS dose. Among the 17 patients, 13 (29.5%) received CS for less than 6months.

In the present study we observed comparatively higher BMD in both LS and hip in the group with total dose between 0 to 5 mg, as compared to steroid dose more than 10 mg, where BMD was least which was statistically significant (r-value -0.71, p-value: <0.001). there was comparatively higher BMD in both LS and hip in the group with disease duration between 1 to 3 years, as compared to disease duration more than 5 years, where BMD was least which was also statistically significant (both p vaues <0.001). Bojana Stamenković et al[12] in their study observed that Nineteen patients with higher Valentini Disease Activity Index (≥6) had lower BMD as compared to 40 patients with Disease Activity Index ≤6, but without significant difference (p = 0.07). Ageing negatively correlated with significantly lower hip BMD (BMD hip, r =-0.714, p=0.001 and T-score, r= -0.705, p=0.001). Investigation confirmed negative correlation between disease duration and hip BMD; longer disease duration was accompanied by lower hip

BMD in SSc patients (both p values< 0.001)

Ágnes Horváth et al[7], in their study observed that, in DXA, SSc patients exerted significantly lower L2–4 BMD (0.880±0.108 vs. 0.996±0.181g/cm2; p=0.019), as well as FN BMD (0.786±0.134 vs. 0.910±0.090g/cm^2; p=0.007), as determined by DXA. Furthermore, L2–4 (−1.64±1.48 vs.−0.50±0.92; p=0.005) and FN T-scores (−1.78±1.01 vs. −0.44±0.84; p<0.001) were also significantly lower in SSc compared to controls. According to the WHO classification (T-score <2.5), the prevalence of OP in SSc was 22.7% both at the L1–4 and FN region. In contrast, none of the control subject had OP at any measurement site.

A few researchers analyzed the presence of reduced BMD in systemic sclerosis and showed that there was no significant difference in BMD between patients with normal inflammation markers and patients with changed inflammation markers in SSc, i.e., the presence or absence of total antinuclear antibodies. However, the analysis of BMD in SC patients with a specter of specific antibodies, both ACA and ATA which are related with different forms of the disease, has not been carried out yet. It is well known that ACA is frequently present in limited form of SSc, while ATA is present in diffuse form of SSc. This research has not confirmed a significant difference in BMD between the two tested groups with the same disease duration.

Frediani et al. (2004)[13], as well as Umar et al[14], (2014) pointed to the reduced bone density in SSc patients with diffuse form of the disease, diffuse skin lesions, i.e., in patients whose visceral organs, one or more, were affected by the disease. Other studies concluded that bone density correlated with the degree of skin changes.

However, the evaluation of the correlation between BMD and the degree to which visceral organs were affected was not done. Atteritano et al. (2013)[15] proved that patients with systemic sclerosis had a high degree of vitamin D deficiency, which was associated with bone density. Many authors suggested that the degree of skin changes directly correlated with the degree of internal organ deterioration and severity of SSc. Mathilde Marot et al[16], in their study concluded that an increased prevalence of osteoporosis was found and HR-pQCT showed impaired trabecular bone compartment. Also, low lean body mass, high age, digital ulcers and ACAs were identified as independent risk factors for bone damage.

Ά Horváth et al[7] concluded that a high proportion of SSc patients have osteopenia or osteoporosis, as well as low vitamin D levels. As determined by pQCT, trabecular loss is more common. Both total and trabecular bone loss, as well as bone markers may be associated with disease duration, anti-Scl70 and some organ manifestations. SSc patients should be screened and treated for osteoporosis. S Breda et al[17], in their study detected a very high OP frequency in our SSc patients, significantly higher than a control early AR cohort and significantly associated to disease duration. Routine DEXA evaluation and risk factors for OP should always be considered and treated, when possible, in every SSc patient, especially after 5 years of disease duration.

Amira A. Shahin et al[18] in their study concluded that 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. Ageing is related to lower BMD in SSc and longer disease duration, which is in accordance with the results of the research which has been published worldwide.

CONCLUSION

The mean age of the study subject was 41.49 ± 9.71 years. The male: female ratio was 1: 29.5. Skin involvement was the commonest finding followed by, pulmonary involvement, digital ulcers, and Raynauds phenomenon. We observed moderate restriction in PFT among 81.97% subjects, followed by mild restriction among 16.39%, severe restriction among 1.64% subjects.

We observed weaker correlations between disease severity indices and BMD / T scores. We observed inverse correlation between BMD in both LS and hip in the group with total cumulative steroid dose. We also observed inverse correlation between BMD with disease duration.

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