

## ORIGINAL ARTICLE

## LOW BONE MINERAL DENSITY AMONG PATIENTS WITH NEWLY DIAGNOSED RHEUMATOID ARTHRITIS

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**Background:** Osteoporosis is an early and common feature in rheumatoid arthritis. Apart from other manifestations, Osteoporosis is an extra-articular manifestation of rheumatoid arthritis which may result in increased risk of fractures, morbidity, mortality, and associated healthcare costs. This study evaluates bone mineral density changes in patients with rheumatoid arthritis of recent-onset. **Methods:** This descriptive case series was conducted in the Rheumatology Department of a tertiary care hospital in Karachi. Data was prospectively collected from 76 patients presenting with seropositive or seronegative rheumatoid arthritis. Bone mineral density of these patients measured at lumbar spine and hip by using dual energy x-ray absorptiometry scan. Variables like age, gender, BMI, menstrual status, disease duration, erythrocyte sedimentation rate, vitamin D level, clinical disease activity index and seropositivity for rheumatoid arthritis were measured along with outcome variables. **Results:** A total of 104 patients fulfilling inclusion criteria were registered with 28 excluded from study. Among the remaining 76 patients, 68 (89.50%) were female, with mean age of patients (with low bone mineral density) as  $50.95 \pm 7.87$  years. Nineteen (25%) patients had low bone mineral density, 68.52% had low BMD at spine while 10.52% at hip and 21.05% at spine and hip both. Low bone mineral density was found higher in patients with seronegative 7 (50%) as compared to seropositive patients 12 (19.4%) ( $p$ -value 0.017), whereas low bone mineral density was found higher 12 (70.6%) among post-menopausal women. **Conclusion:** Low BMD was found in 25% of patients at earlier stage of the rheumatoid arthritis with seropositivity, age and menopausal status as significant risk factors.

**Keywords:** Rheumatoid Arthritis, Bone Mineral Density, Seropositivity

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## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory and destructive joint disease that affects 0.5–1% of the world's population and commonly leads to significant disability and consequent impairment of quality of life.<sup>1</sup> Osteoporosis (OP) is an early and common feature in RA and occurs in two forms during the course of the disease.<sup>2,3</sup> Periarticular osteopenia in close proximity to inflamed joints is a typical phenomenon in early and prolonged rheumatoid disease. Generalized osteoporosis affects the axial and appendicular bones.<sup>4</sup> Although the mechanisms of OP in RA are not fully understood, it is thought that osteoclast and its dysfunction with cytokines that mediate them are the principal pathogenesis factors of this bone disease.<sup>5</sup> The prevalence of OP in RA was determined as 2 fold more than controls.<sup>6</sup> Prevalence of OP in RA patients in different parts of the world was reported to be between 22–36%.<sup>7,8</sup>

In one study in Iran, the prevalence of OP in RA patients was 32.3%,<sup>9</sup> but the prevalence of OP in another study on RA patients with the same mean age was 40.4%.<sup>10</sup> Haugeberg showed a twofold increase in osteoporosis in women with RA and a twofold increase of reduced bone mass in men with RA, compared with patients without RA in a population based study.<sup>11</sup>

## MATERIAL AND METHODS

This descriptive case series was conducted in the Rheumatology department, of a tertiary care hospital in Karachi, from July, 2013 to January, 2015, and included all the recently diagnosed patients of Rheumatoid Arthritis (RA).

Data was prospectively collected from 76 patients of age >16 years presenting with seropositive or seronegative RA of less than 6 months duration, diagnosed according to American College of Rheumatology (ACR) criteria.<sup>12</sup> All the patients who had thyroid dysfunctions or patients who were taking steroids >1½ months at the dose of prednisolone  $\geq 7.5$  mg/day, or cyclophosphamide, anxiolytics, antiepileptic, bisphosphonates and heparin were excluded.

The purpose and procedure of the study was explained to each patient and an informed consent was taken from all the patients. Detailed history including risk factors for low BMD, physical examination especially, examination of the musculoskeletal system, laboratory investigations, including erythrocyte sedimentation rate, serum calcium, serum vitamin D level, X-Rays of both hands and involved joints were obtained from all the patients including in the study.

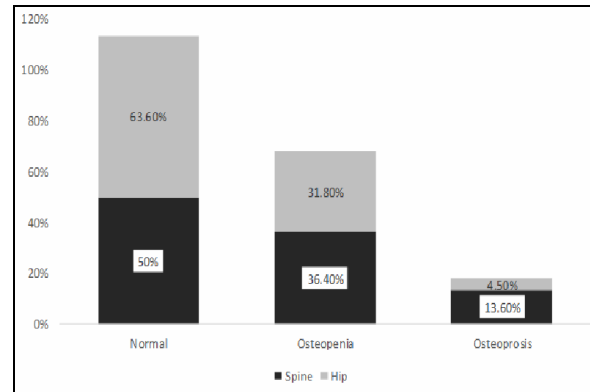
Dual energy X-ray Absorptiometry (DEXA) scan was done in all patients and reported. Demographics variables like age, gender

and menstrual status were noted. Along with these parameters disease activity scoring was also obtained by mean of clinical disease activity index (CDAI).<sup>13</sup> BMD was measured at the postero-anterior (PA) lumbar spine from L1-L4 and hip, by using DEXA machine (Hologic Discovery WI (S/N 86292) USA). For postmenopausal women, BMD was defined according to WHO criteria<sup>14</sup> as follows: (a) Normal bone density (T score >-1.0 both in spine and hip), (b) Osteopenia (T score between -1.0 and -2.5) in the spine and/or hip), and (c) Osteoporosis (T score <-2.5 in the spine and/or hip). For premenopausal women Z-score was used instead of T-score and BMD was defined according to international society for clinical densitometry (ISCD) criteria<sup>14</sup> as follows: (1) low BMD if Z-score ≤2 both in spine and/or hip, (2) Normal BMD if Z-score ≥2 both in spine and/or hip. In males, for above 50 years WHO criteria<sup>14</sup> while for less than or equal to 50 years ISCD criteria was used.<sup>15</sup>

Low BMD was defined as patients have either osteopaenia and/or osteoporosis on DEXA scan.<sup>16</sup> SPSS version 21 was used for data analysis purpose. Mean and standard deviation was calculated for continuous variables and frequencies and percentages for categorical variables. Statistical significance was determined through chi-square test and independent t-test as appropriate with *p*-value ≤0.05 as significant.

**RESULTS**

A total of 104 patients fulfilling the inclusion criteria were registered, but 28 (27%) patients were excluded from study, as 15 (53.6%) patients had systemic lupus erythematosus (SLE), 04 (14.3%) had thyroid dysfunctions, 05 (17.9%) were on Prednisolone for >3 months and 4 (14.3%) had declined DEXA scanning. The final study sample stood at 76 patients fulfilling the criteria. Female preponderance was found to be higher: 68 (89.50%) with male to female ratio of 1:8.5. Mean age of the patients in this study were 42.01±11.01 years. Majority of the patients, 62 (81.6%) were seropositive (positive any one or both of RA factor or Anti-CCP), out of which 55 (80.9%) were females, while only 14 (18.4%) were seronegative, out of which 13 (92.9%) were females (*p*-value 0.648) (Table-1). Low BMD was found in 19 (25%) patients either at spine or hip, while 57 (75%) patients had normal BMD. Low BMD at hip was seen in 10.52%, spine 61.42%, while 21.05% had low BMD at both hip and spine. Mean BMD, T-Score and Z-score at different lumbar spines and hip is shown in Table-2. Osteopenia was predominantly higher at both spine 8 (36.4%) and hip (31.8%) whereas osteoporosis was found in (13.6%) patients at the spine and (4.5%) in the hip (Figure-1).



**Figure-1: Frequency of Osteopenia and Osteoporosis (n=22)\*, \*Calculated for patients fulfilling ISCD criteria, i.e., male patients with >50 years age and post-menopausal women**

**Table 1: General characteristics of the patients (n=76)**

	n	%
Age, years*	42.01±11.01	
Gender		
Male	8	10.50%
Female	68	89.50%
BMI, Kg/m2*	26.02±5.93	
Duration of Symptoms, months	5.62±2.54	
Menstrual Status		
Pre	51	67.1
Post	17	22.4
ESR*	48.83±28.24	
Creatinine*	0.77±0.16	
Vitamin D level*	28.14±19.48	
Serum Calcium level*	11.50±18.39	
Alkaline Phosphate level*	137.02±70.85	
Sero-positivity		
Sero Negative	14	18.4
Sero Positive	62	81.6

\*mean±SD

**Table-2: Bone mineral density (BMD) measured by Dual X-Ray absorptiometry (DXA) at different skeletal sites and different age groups**

Measurement Site	BMD Mean±SD	T-Score Mean±SD	Z-Score Mean±SD
L1 Vertebrae	0.87±0.14	-1.10±1.26	-0.55±1.67
≤50 years	0.89±0.15	-0.96±1.23	-0.67±1.09
>50 years	0.82±0.13	-1.15±1.26	-0.13±2.84
L2 Vertebrae	0.94±0.16	-0.95±1.35	-0.50±1.15
≤50 years	0.96±0.15	-0.76±1.21	-0.47±1.04
>50 years	0.87±0.17	-1.55±1.61	-0.62±1.47
L3 Vertebrae	0.96±0.20	-1.03±1.52	-0.57±1.35
≤50 years	0.97±0.20	-0.89±1.40	-0.58±1.25
>50 years	0.92±0.20	-1.48±1.84	-0.52±1.66
L4 Vertebrae	0.95±0.21	-1.20±1.41	-0.67±1.32
≤50 years	0.96±0.16	-1.02±1.28	-0.69±1.23
>50 years	0.94±0.34	-1.77±1.66	-0.62±1.64
Total Lumbar Spine Score	0.96±0.23	-1.12±1.32	-0.64±1.19
≤50 years	-0.99±0.24	-0.97±1.22	-0.63±1.13
>50 years	-0.88±0.17	-1.62±1.54	-0.67±1.40
Femur Neck	0.75±0.14	-0.95±1.04	-0.41±0.90
≤50 years	0.76±0.14	-0.79±0.92	-0.42±0.78
>50 years	0.70±0.14	-1.46±1.26	-0.39±1.24
Total Hip	0.87±0.11	-0.61±0.87	-0.26±0.79
≤50 years	0.89±0.08	-0.47±0.73	-0.21±0.68
>50 years	0.82±0.14	-1.04±1.14	-0.42±1.10

SD: Standard Deviation

**Table-3: Comparison of general characteristics with BMD (n=76)**

Variables	BMD	Mean±SD	p-value*	95% CI
Age, years	Normal	39.04±10.33	0.001	-17.07 to -6.75
	Low	50.95±7.87		
BMI, kg/m <sup>2</sup>	Normal	26.12±5.92	0.806	-2.76 to 3.54
	Low	25.73±6.11		
Duration of symptoms, months	Normal	4.32±1.29	0.120	-1.17 to 0.13
	Low	4.84±1.06		
CDAI	Normal	14.09±9.35	0.324	-7.16 to 2.39
	Low	16.47±9.07		
Vitamin D Level, ng/ml	Normal	28.63±20.64	0.495	-6.5 to 13.33
	Low	25.21±11.25		

\*Independent t-test applied

**Table-4: Association of general characteristics with BMD (n=76)**

		Normal n (%)	Low BMD n (%)	p-value*
Menopausal Status (n=68)	Pre	46 (90.2)	5 (9.8)	<0.001
	Post	5 (29.4)	12 (70.6)	
Seropositivity	Sero Negative	7 (50)	7 (50)	0.017
	Sero Positive	50 (80.6)	12 (19.4)	
X-ray Findings	Normal	24 (80)	6 (20)	0.411
	Soft Tissue Swelling	2 (100)	0 (0)	
	Per-articular Osteopenia	22 (75.9)	7 (24.1)	
	Erosions	9 (60)	6 (40)	
ESR	Normal	10 (83.3)	2 (16.7)	0.468
	High	47 (73.4)	17 (26.6)	

\*Chi-square test applied

Significant differences were observed for age ( $p$ -value <0.001), menopausal status ( $p$ -value <0.001) and seropositivity ( $p$ -value 0.017) in this study (Tables-3 and 4).

**DISCUSSION**

The findings of this study revealed that 25% patients with RA had low BMD, which was about one third of the total patients. In this study, we included only those patients who had rheumatoid arthritis of recent onset (<6 months duration), though our findings are somewhat similar to other studies as well.<sup>5,7,8,17</sup>

Prevalence of OP in RA is variable as concluded in different studies.<sup>18,19</sup> The higher prevalence in our patients may be due to the differences in age and other factors such as geography, genetics, behaviour, economy and probably some unidentified factors that may be discovered later. Güler-Yüksel *et al* reported that RA patients with early, active, erosive disease and a positive rheumatoid factor had more aggressive joint disease and decreased BMD.<sup>20</sup>

Age, seropositivity and menopausal status were found significant factors in our study. The significant association of age was also found in another study as well.<sup>9</sup> In another study by Haugeberg on 394 patients with RA, femoral neck BMD was significantly reduced by 4.2% in the age group 50–59 years, and by 5.0% in 60–70 years.<sup>11</sup>

It has been reported that lean body mass and fat mass play a life time positive role in relation to

the bone mass in human. The association between lean body mass and body bone mass could be due to force exerted by mechanical load on bones. Moreover, fat mass is metabolically active, and increases BMD through hormonal metabolism of adipocytes, thereby intervening in osteoblast/osteoclast function.<sup>21</sup>

Older patients have been exposed for greater length of time to underlying risk factors for bone loss such as, lower oestrogen levels, prolonged immobilization, use of corticosteroids and finally inflammatory states. This could be the possible reason behind this bone loss and old age among RA patients. There is disagreement concerning the effects of glucocorticoids on bone mass in RA cases.<sup>22,23</sup>

We did not find any association of male or female gender as a risk factor for OP. However, contrary to this, gender was found significantly associated with osteoporosis in other studies.<sup>18,20,24</sup>

The possibility of this reason may be that, the sample of male patients was very small in comparison to the female patients in our study.

We also did not find any association of low BMD with CDAI, ESR and serum calcium level, while serum vitamin D levels were also not associated with low BMD as well. This was also found similar with other study as well.<sup>25</sup>

At present third world countries are deficient in natural food sources, Pakistan is one of among them where natural food resources are lacking and most foods are not adequately fortified with vitamin D. Studies have observed lower levels of circulating 25(OH)D,<sup>26</sup> thus indicating that sun exposure and diet alone are not enough to maintain vitamin D adequacy. However, prospective follow-up studies are needed in order to determine the calcium and vitamin D intake levels needed to maintain adequate bone metabolism in RA patients.<sup>25</sup>

**CONCLUSION**

Most of the RA patients have low BMD at lumbar spine or femoral neck, which can be detected at earlier stage of the disease, with seropositivity, age and menopausal status as significant risk factors. We recommend early screening of all RA patients by mean of DEXA scan irrespective of gender, age, disease duration and seropositivity, so that timely treatment may alter the natural history of the disease.

**AUTHOR’S CONTRIBUTION**

All the authors contributed equally.

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