Original Article

Lean Mass and Disease Activity are the Best Predictors of Bone Mineral Loss in the Premenopausal Women with Rheumatoid Arthritis

Meha Sharma, Urmila Dhakad, Anupam Wakhlu, Danveer Bhadu, Deep Dutta[1], Siddharth K. Das

Department of Rheumatology, King George's Medical University, Lucknow, Uttar Pradesh, [1]Department of Endocrinology, Post Graduate Institute of Medical Education and Research, Dr. Ram Manohar Lohia Hospital, New Delhi, India

Abstract

Background and Objectives: Factors determining bone mineral (BM) loss in rheumatoid arthritis (RA) are not well known. This study aimed to determine the occurrence and predictors of BM loss in the young premenopausal women with RA. **Methods:** Ninety-six females with RA and 90 matched controls underwent clinical, biochemical, BM density (BMD), and body composition assessments. RA disease activity was assessed using disease activity score-28 (DAS-28) and hand X-ray. **Results:** In the young premenopausal females with RA having median symptom and treatment duration of 30 (18–60) and 4 (2–12) months, respectively, with moderate disease activity (DAS-28, 4.88 ± 1.17), occurrence of osteoporosis and osteopenia was 7.29% and 25% at spine, 6.25% and 32.29% at hip, and 17.7% and 56.25% at wrist, respectively (significantly higher than controls). RA patients had lower BMD at total femur, lumbar spine (LS), radius total, and radius ultra-distal. Total lean mass (LM) and BM content were significantly lower in RA ($P = 0.022$ and <0.001, respectively). In RA, BMD at majority of sites (LS, neck of femur, greater trochanter, radius total, and radius 33%) had the strongest positive correlation with LM followed by body fat percent. RA patients with most severe disease had lowest BMD at different sites and lowest LM. Stepwise linear regression revealed LM followed by DAS-28 to be best predictors of BMD. RA patients receiving glucocorticoids did not have significantly different BMDs from patients not taking glucocorticoids. **Interpretation and Conclusion:** BM loss is a significant problem in the young premenopausal women with recent-onset RA. LM and disease severity were the best predictors of BMD.

Keywords: Bone mineral density, disease activity score, lean mass, osteoporosis, rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is an established risk factor for osteoporosis with all major guidelines recommending dual-energy X-ray absorptiometry (DEXA) for bone mineral density (BMD) assessment in RA.[1,2] However, factors which determine this bone mineral (BM) loss in RA have not been well determined. Data on osteoporosis in RA are predominantly available from postmenopausal women, which is often complicated by coexisting postmenopausal osteoporosis.[1,2] Data on BMD from young premenopausal women with RA are scant. Data on the pattern, severity, and predictors of BM loss in these patients are scant. Furthermore, impact of Vitamin-D deficiency on BMD in RA has not been evaluated. This study was done in a population where Vitamin-D deficiency/insufficiency is common.[3,4] Glucocorticoid use has conventionally been associated with adverse impact on bone health. There are conflicting data available on the impact of glucocorticoid use on bone health in RA. Hence, the aim of this study was to quantify the occurrence of osteopenia and osteoporosis in the young premenopausal women with RA; to determine the clinical, biochemical, and radiological predictors of BM loss; and to assess the impact of treatment on bone health in RA.

Methods

Consecutive ambulatory premenopausal females, 20–45 years of age, attending the outpatient services of

Access this article online

Quick Response Code:

Website: www.ijem.in

DOI: 10.4103/ijem.IJEM_665_17

Address for correspondence: Dr. Meha Sharma, Department of Rheumatology, King George's Medical University, Lucknow, Uttar Pradesh, India.
E-mail: docmsharma@gmail.com

How to cite this article: Sharma M, Dhakad U, Wakhlu A, Bhadu D, Dutta D, Das SK. Lean mass and disease activity are the best predictors of bone mineral loss in the premenopausal women with rheumatoid arthritis. Indian J Endocr Metab 2018;22:236-43.

the Department of Rheumatology, King's George Medical University, who fulfilled the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria for RA were considered.[5] Patients with previous history of any secondary cause of osteoporosis (e.g., celiac disease, type-1 diabetes), hyperparathyroidism, severe Vitamin-D deficiency (25-hydroxyvitamin-D [25OHD] <10 ng/ml), history of use of drugs which interfere with BMD (antiepileptics, bisphosphonates), postmenopausal state, liver disease, renal disease, or any severe comorbid state were excluded. The study protocol was explained to those who fulfilled all criteria, and only those who gave informed written consent were included. The institutional ethics committee approved the study. The study duration was from March 2015 to July 2016.

Details regarding duration of symptoms and diagnosis of RA and duration and nature of medications used were recorded. Modified disease activity score (DAS)-28 was used to assess RA severity.[6] A score <2.6 was considered disease remission, 2.6–3.2 as low disease activity, 3.2–5.1 as moderate disease activity, and >5.1 as high disease activity.[6] The patients were given an appointment to come on a separate day after 12-h overnight fast. Blood samples (8 ml) were collected for biochemical analysis which included rheumatoid factor (RF, IgM, U/L), anti-cyclic citrullinated peptides (anti-CCP) antibody, full complete blood count, erythrocyte sedimentation rate (ESR, mm/h) in the 1st h, C-reactive protein (mg/L), creatinine, fasting blood glucose, liver function tests, calcium profile, and 25OHD. Fan beam DEXA (GE Healthcare, Lunar 05-Prodigy Pro-bone Densitometry System, Batch Number 15643) was used for the estimation of BMD at the lumbar spine (LS; L1–L4), total femur, neck of femur (NOF), greater trochanter (GT), radius total, radius ultra-distal (UD), and radius 33% (g/cm^2) sites.[7] The instrument was calibrated on a daily basis using the phantom provided by the manufacturer, and the coefficient of variation (CV) at different sites was found to be <0.5% over the duration of the study. The manufacturer's appointed service engineer reviewed the calibration data and did scanner maintenance check to ensure the system's performance before at the beginning and at the end of the study to confirm that no instrumentation drift occurred during the study. Osteoporosis at a particular site was defined as Z-score <−2 standard deviation (SD).[8] Patients with Z-score between −1 to −2 SD were defined to have osteopenia.[7] DEXA was also used for the estimation of whole-body bone mineral content (BMC, kg), total body fat (kg), percentage fat mass (FM, %), FM (kg), lean mass (LM, kg), android fat (kg), and gynoid fat (kg). The definition used for android and gynoid regions has been elaborated elsewhere.[9] A single-trained technician in the department performed all the scans. Reproducibility of DEXA measurements was derived from the root mean square SD of two repeat measurements.[10] For body composition variables, technique precision was 12.52 g for BMC (0.97% CV), 166.2 g for LM (0.73% CV), and 156.1 g for FM (0.69% CV).

Clinical, biochemical, and DEXA parameters were also collected from 90 age-, sex-, and body mass index (BMI)-matched healthy controls recruited from nursing staff of the institute. All RA patients in this study received standard medical care for RA.

Statistical analysis

Kolmogorov–Smirnov test was used to check for normality of variable distribution. All continuous variables are expressed as mean ± SD, and nonnormally distributed variables are expressed as median (25th–75th percentile). Student's *t*-test was used for analysis of continuous variables in two groups, Fisher's exact test was used for binary variable, Chi-square test was used for categorical variables, and one-way ANOVA with *post-hoc* analysis was used to study outcomes where three or more groups were present. $P < 0.05$ was considered statistically significant. SPSS version 20 (Chicago, IL, USA) was used for data analysis.

Results

A total of 149 females with RA were screened, of which 96 females (age: 36.90 ± 5.32 years) who fulfilled all criteria and gave informed written consent were included [Figure 1]. The median duration of symptoms and treatment was 30 (18–60) and 4 (2–12) months, respectively. The mean ACR/EULAR RA diagnostic score was 8 ± 1.32. RF and anti-CCP antibody positivity were observed in 78.13% and 69.79% of the study cohort, respectively. X-ray hand was normal in 11 patients (11.45%). Isolated juxta-articular osteopenia (JAO), JAO with joint space narrowing (JSN), and JAO with JSN with erosions were observed in 45 (46.88%), 24 (25%), and 16 (16.67%) patients, respectively. The mean DAS-28 score was 4.88 ± 1.17.

Nonsteroidal anti-inflammatory agents were the most common medications used (93.75%), followed by hydroxychloroquine (90.63%), methotrexate (84.38%), injectable/intramuscular glucocorticoids (64.58%), and oral glucocorticoid (27.11%). The median (25–75th percentile) cumulative dose of methotrexate and oral and injectable/intramuscular glucocorticoids received by the patients was 180 (90–480) mg, 900 (525–1500) mg prednisolone equivalents, and 1270 (640–1420) mg prednisolone equivalent, respectively. Five, three, and one patients were on sulfasalazine, leflunomide, and azathioprine, respectively. None of the patients had received biologics.

The most common site for osteoporosis in RA was wrist, with radius UD being the most commonly involved region (17.7%; $n = 17$), followed by radius total (9.38%; $n = 9$) and radius 33% (5.21%; $n = 5$). Osteoporosis at hip was observed in 6.25% of patients, with GT being the most commonly involved site. Osteoporosis at spine was observed in 7.29% of patients. In contrast, osteopenia was much more common, observed in 24 (25%), 31 (32.29%), and 54 (56.25%) patients at spine, hip, and wrist, respectively. The occurrence of osteopenia and osteoporosis was significantly higher in RA as compared to controls. In controls, none of the individuals had osteoporosis

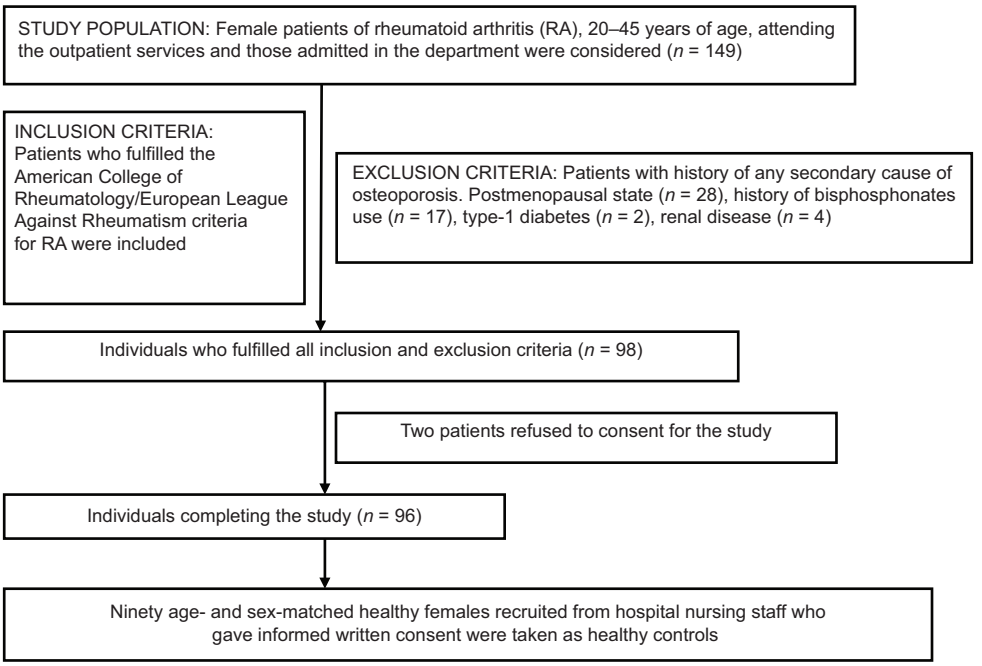

Figure 1: Flowchart elaborating the study protocol

at NOF or spine, and three individuals (3.3%) had osteopenia at wrist. The occurrence of osteopenia at spine, hip, and wrist in controls was 11.11%, 4.44%, and 7.78%, respectively.

Patients with RA had significantly lower total femoral BMD (0.89 ± 0.10 g/cm^2) as compared to controls (0.96 ± 0.92 g/cm^2; $P < 0.01$). BMD at radius UD (0.40 ± 0.07 g/cm^2 vs. 0.45 ± 0.06 g/cm^2), LS (1.05 ± 0.1 g/cm^2 vs. 1.08 ± 0.15 g/cm^2), and radius total (0.60 ± 0.07 g/cm^2 vs. 0.64 ± 0.06 g/cm^2) was also lower, which approached statistical significance ($P = 0.068$, 0.084, and 0.097, respectively) [Table 1]. Total LM (29.71 ± 3.32 kg vs. 31.29 ± 5.05 kg) and bone BMC (1.91 ± 0.31 kg vs. 2.10 ± 0.32 kg) were significantly lower in RA as compared to controls ($P = 0.02$ and < 0.01, respectively) [Table 1]. Both android fat (median: 1.92 kg vs. 4.48 kg) and gynoid fat (3.96 kg vs. 4.57 kg) were significantly lower in RA as compared to healthy controls ($P < 0.01$), with a greater reduction in android as compared to gynoid fat [Table 1].

In RA, BMD at all sites (LS, total femur, NOF, GT, radius total, radius UD, and radius 33%) had a significant positive correlation with LM and body fat percent. For majority of the sites (LS, NOF, GT, radius total, and radius 33%), the correlations were stronger for LM as compared to body fat percent [Table 2]. The correlations between LM and FM with BMD at different sites were significantly stronger in patients with RA, as compared to controls [Table 2]. RA patients with JAO with JSN with erosions on hand X-ray had significantly lower BMD at LS, total femur, NOF, radius total, radius UD, radius 33%, and total body BMC, as compared to those with JAO with JSN, only JAO, and normal hand X-ray. LM was also lowest in patients with JAO + JSN + erosions, which approached statistical significance ($P = 0.053$) [Table 3].

Eight (8.3%), 42 (43.75%), and 46 (47.92%) patients had mild (2.6–3.2 score), moderate (3.2–5.1 score), and severe (>5.1 score) RA disease activity as measured using DAS-28 score, respectively. None of the patients were in remission (DAS-28 score <2.6) during the evaluation for this study. Patients with increased disease activity had significantly lower BMD at total femur, NOF, GT, radius total, radius UD, and whole-body BMC as compared to patients in remission. Among body composition parameters, only total LM was significantly lower in RA patients with higher disease activity [Table 4]. The clinical and biochemical profile of RA patients receiving glucocorticoids (oral and/or intra-articular) were comparable to those not receiving glucocorticoids. BMD at different sites, BMC, and body composition parameters were comparable between the groups [Table 5]. Stepwise linear regression analysis revealed that total LM was consistently the best, independent, and significant predictor of BMD at all the different sites [Table 6]. Following LM, DAS-28 score was the second best, independent, significant predictor of BMD at GT and NOF. Age was the second best, independent predictor of BMD at the three different sites evaluated at wrist. Android/gynoid (A/G) ratio and BMI were independent predictors of BMD only at radius UD [Table 6].

Discussion

Low BMD is a major problem with osteopenia documented in nearly half of the RA patients at wrist in this study. Osteoporosis in contrast was observed in 17.7%, 6.25%, and 7.29% patients at wrist, hip, and spine, respectively. In 30 Egyptian RA patients (aged 35.7 years), osteopenia and osteoporosis were reported in 50% and 13.3%, respectively.[11] In a Finnish study in premenopausal women with RA ($n = 78$),

Table 1: Clinical, biochemical, bone mineral density, and body composition profile of patients with rheumatoid arthritis as compared to controls

Parameter	Rheumatoid arthritis ($n=96$)	Healthy controls ($n=90$)	*P*
Age (years)	36.9±5.3	37.77±5.03	0.26
BMI (kg/m^2)	23.3±3.3	22.95±2.62	0.49
Calcium (mg/dl)	9.1±0.5	8.96±0.51	0.39
ALP (U/L)	135.1±52.3	130.43±44.62	0.75
25OHD (ng/ml)	25.5±11.5	20.80±9.03	0.09
BMD (L1-L4) (g/cm^2)	1.05±0.1	1.08±0.15	0.08
T-score (L1-L4)	−1.1±0.9	−0.97±0.95	0.38
Z-score (L1-L4)	−0.6±0.9	−0.52±0.96	0.61
BMD total femur (g/cm^2)	0.89±0.10	0.96±0.92	<0.01
T-score total femur	−0.9±0.8	−0.4±0.9	<0.01
Z-score total femur	−0.4±0.7	−0.1±0.6	<0.01
BMD radius total (g/cm^2)	0.60±0.07	0.64±0.06	0.09
T-score radius total	−1.3±1.1	−0.8±0.8	0.19
Z-score radius total	−1.2±1.0	−0.8±0.8	0.23
BMD radius UD (g/cm^2)	0.40±0.07	0.45±0.06	0.07
T-score radius UD	−1.37±1.6	−0.4±1.3	0.07
Z-score radius UD	−1.11±2.2	−0.4±1.3	0.33
Total fat mass (kg)[a]	20.73 (13.42–27.02)	18.06 (15.49–24.44)	0.11
Total lean mass (kg)	29.71±3.32	31.29±5.05	0.02
Total bone mineral content (kg)	1.91±0.31	2.10±0.32	<0.01
Total fat percentage	40.89±5.99	37.66±9.11	0.02
Android fat (kg)[a]	1.92 (1.18–2.95)	4.48 (3.86–4.96)	<0.01
Gynoid fat (kg)[a]	3.96 (2.76−4.96)	4.57 (3.69–4.86)	<0.01
Android/gynoid ratio[a]	0.48 (0.35–0.57)	1.05 (0.91–1.13)	<0.01

[a]All nonnormally distributed variable expressed as median (25th–75th percentile). 25OHD: 25-hydroxyvitamin-D, ALP: Alkaline phosphate, BMD: Bone mineral density, L1–L4: LS L1–L4, NOF: Neck of femur, BMI: Body mass index, LS: Lumbar spine, UD: Ultra-distal

mean LS BMD was 1.157 g/cm^2, which is slightly higher to that observed in our patients (1.05 g/cm^2).[12] In a Korean study involving 234 RA patients (aged 60 years), osteopenia and osteoporosis were observed in 52% and 39%, respectively.[2] Majority of women being in the postmenopausal state explain this increased osteoporosis occurrence.

Studies have also suggested predominant involvement of the wrist followed by hip, by osteoporosis in patients with RA.[13,14] Increased osteoporosis at wrist in part may be explained by the primary pathology of RA.[13,14] RA is a disease that commonly involves the wrist joints and hands.[13,14] Active RA is commonly associated with osteopenia, JSN, and bony erosions, all of which may contribute to lower BMD at wrist. This hypothesis is supported by the observation of significantly lower BMD at radius total, radius UD, and radius 33% in patients with more advanced X-ray hand features of RA in our study.

RA patients had lower BMD at all sites when compared to controls. The fact that the healthy controls were well matched with RA patients with regard to age, height, and BMI highlights that this lower BMD may be attributed to primary disease state. Further observation of lower BMD at different sites in RA patients with more severe disease highlights the importance of RA *per se* in the genesis of low BMD. RA is a chronic systemic inflammatory disease.[15] Increased systemic inflammation is associated with osteoclast activation, downregulation of osteoblasts, and decreased activity of 1α-hydroxylase, leading to decreased activated Vitamin-D formation, all of which contribute to lower BMD.[16] An inverse correlation was observed between serum tumor-necrosis-factor-α and BMD femur neck in 59 postmenopausal women with RA.[17]

In our study, it was total LM and not FM, which was significantly lower in RA as compared to controls. The observation of LM having the strongest positive correlation with BMD, both LM and BMD being lowest in most severe RA, and regression showing LM to be the best predictor of BMD highlights the importance of LM to bone health in RA. In a study involving 146 RA patients from Japan, LM was demonstrated to be one of the best predictors of BMD at calcaneum and spine.[18] In a Turkish involving 51 postmenopausal women with RA, LM significantly correlated with BMI, waisthip ratio, femoral neck BMD, and BMC.[19] In a study of 36 females with juvenile RA, LM was the best predictor of BMC, accounting for 76.3% of variance in total body BMC.[20]

In a study involving newly diagnosed patients with type-2 diabetes, LM was the strongest predictor of BMC.[21] Increased BMI leads to increased mechanical loading of bone, which explains the higher BMD in heavier individuals.[21] FM is static, viz., it causes mechanical loading of bone by virtue of its mass only. In contrast, LM is dynamic as it is primarily made up of muscles. Increase in muscular mass results to greater movement of the body, which results in additional mechanical loading of the bones. It has been suggested that bone adapts more to dynamic muscle load than to static load, explaining the stronger effect of LM on bone health.[21] Studies have suggested that RA patients with lower physical activity have lower hip BMD.[22] Increase in LM in physically active patients may explain this favorable impact on BMD. However, physical activity was not quantified in our study and this is a limitation. The negative link between A/G ratio and BMD at radius UD highlights the negative impact of increased android fat and decreased gynoid fat on BMD. Android fat primarily represents central adiposity, which is made of subcutaneous and visceral fat. It is this visceral adiposity, which is associated with increased local and systemic inflammation, altered profile of leptin and adiponectin, leading to increased osteoclast activation and bone loss that may explain the lower BMD in these patients.[23]

Data on impact on the use of glucocorticoids on BMD in RA are conflicting with some, but not all studies suggesting a

Table 2: Correlation between bone mineral densities at different sites with body composition parameters in patients with rheumatoid arthritis (*n*=96) as compared to controls (*n*=90)

Parameters	Lean mass			Fat percentage			Gynoid fat[a]			Android/gynoid ratio[a]		
	RA patients	Controls	*P**	RA patients	Controls	*P**	RA patients	Controls	*P**	RA patients	Controls	*P**
BMD (L1–L4)	0.36[#]	0.07	0.03	0.28[Φ]	0.09	0.18	0.21	0.07	0.34	−0.11	0.01	0.50
BMD total femur	0.42[#]	0.25[Φ]	0.19	0.45[#]	0.02	<0.01	0.16	0.04	0.42	−0.11	−0.21	0.49
BMD NOF	0.52[#]	0.21	0.01	0.37[Φ]	0.20	0.22	0.18	0.25	0.62	−0.13	−0.37	0.08
BMD greater trochanter	0.47[#]	0.02	0.01	0.35[Φ]	0.10	0.07	0.16	0.06	0.49	−0.06	−0.32[Φ]	0.06
BMD radius total	0.42[#]	0.26[Φ]	0.22	0.41[Φ]	0.16	0.06	0.13	0.16	0.83	−0.04	−0.11	0.63
BMD radius UD	0.34[#]	0.10	0.08	0.42[#]	0.13	0.03	0.15	0.25	0.48	0.07	−0.16	0.54
BMD radius 33%[a]	0.50[#]	0.38[Φ]	0.31	0.37[Φ]	0.03	0.02	0.25[Φ]	0.18	0.62	−0.01	0.06	0.73

[a]Spearman's correlation coefficient calculated for nonnormally distributed variable, [#]*P* value of the correlation coefficient <0.01, [Φ]*P* value of the correlation coefficient <0.05, *Represents significance of difference (*P*) of correlation coefficient between patients with RA and healthy controls, *P*<0.05 considered statistically significant, no correlation was found significant with total fat mass and android fat for the different BMD parameters, hence have not been mentioned in the table. BMD: Bone mineral density, All values expressed as correlation coefficient (*P*-value), Pearson's correlation calculated for normally distributed variables, RA: Rheumatoid arthritis, UD: Ultra-distal, NOF: Neck of femur

Table 3: Pattern of bone mineral density and body composition distribution in patients with rheumatoid arthritis as per disease severity assessed by hand X-ray

Parameter	X-ray hand severity of RA				*P*
	Normal (*n*=8)	JAO (*n*=45)	JAO + JSN (*n*=24)	JAO + JSN + erosions (*n*=16)	
BMD (L1–L4) (g/cm^2)	1.14	1.05	1.03	0.99	0.05
BMD total femur (g/cm^2)	0.99	0.91	0.89	0.84	0.03
BMD NOF (g/cm^2)	0.92	0.86	0.84	0.79	0.04
BMD greater trochanter (g/cm^2)	0.76	0.70	0.70	0.64	0.07
BMD radius total (g/cm^2)	0.68	0.61	0.62	0.56	0.01
BMD radius UD (g/cm^2)	0.46	0.41	0.42	0.35	0.01
BMD radius (33%)[a]	0.87	0.77	0.79	0.75	0.01
Total fat mass (kg)[a]	25.20	23.41	21.92	21.2	0.91
Total lean mass (kg)	32.54	29.43	30.51	28.22	0.05
Total bone mineral content (kg)	2.24	1.90	1.97	1.71	<0.01
Total fat percent (%)	42.8	38.11	35.71	38.56	0.44
Android fat (kg)[a]	2.56	1.99	2.72	1.99	0.35
Gynoid fat (kg)[a]	4.77	4.18	4.01	3.65	0.66
Android/gynoid ratioa	0.53	0.46	0.74	0.55	0.25

[a]All nonnormally distributed variable expressed as median, for normally distributed variable *P* value calculated using one-way ANOVA with Dunn's correction, *P* value calculated for the decreasing trend. RA: Rheumatoid arthritis, BMD: Bone mineral density, JAO: Juxta-articular osteopenia, JSN: Joint space narrowing, normally distributed variables have been expressed as mean, UD: Ultra-distal

negative impact.[16,24,25] In a study of 95 Danish RA patients, corticosteroids use was not associated with decreased BMD.[25] Another study evaluating the impact of 1-year glucocorticoid therapy in RA concluded that the anti-inflammatory effect of the low-dose glucocorticoid therapy in RA patients without previous history of glucocorticoid use may balance their direct negative effect on BMC and BMD.[16] In contrast, in a study from Aberdeen evaluating 46 women with RA of whom 25 were receiving low-dose glucocorticoids, BMD was significantly reduced at hip, radius, and calcaneus.[24] Age, female sex, and use of glucocorticoids were risk factors for osteoporosis and fractures in RA patients in a recent Chinese study.[25] Heterogeneity in clinical profile of patients evaluated, disease severity, and dose and nature of glucocorticoids used in different studies may explain this difference. Our study showed that RA patients receiving glucocorticoids did not have significantly different BMD when compared to those not receiving glucocorticoids, in accordance with the previous reports.[18,26] However, it must be stated that the number of RA patients who were not receiving glucocorticoids was small (*n* = 15). Glucocorticoid-induced osteoporosis is a well-known clinical entity. However, the impact of low-dose glucocorticoid use on bone health, in patients with active RA, is more complex. The anti-inflammatory effects of glucocorticoids may have beneficial effect on RA disease activity and course, which may compensate for their direct negative effect on bone health. In 138 postmenopausal Japanese women with long-standing RA, glucocorticoids and biologicals were not associated with bone loss.[27] Engvall *et al*. demonstrated that long-term low-dose prednisolone use in RA was associated with increased FM.[28] Use of nursing staff-based controls instead of population-based controls may

Table 4: Pattern of bone mineral density and body composition distribution in patients with rheumatoid arthritis as per disease severity assessed by disease activity score-28 (7)

Parameter	DAS-28			*P*
	Mild activity (2.6-3.2) (*n*=8)	Moderate activity (3.2-5.1) (*n*=42)	Severe activity (>5.1) (*n*=46)	
BMD (L1–L4) (g/cm^2)	1.11	1.07	1.02	0.07
BMD total femur (g/cm^2)	0.99	0.92	0.86	<0.01
BMD NOF (g/cm^2)	0.92	0.87	0.82	0.01
BMD GT (g/cm^2)	0.80	0.72	0.66	<0.01
BMD radius total (g/cm^2)	0.67	0.61	0.59	0.02
BMD radius UD (g/cm^2)	0.49	0.42	0.38	<0.01
BMD radius (33%)[a] (g/cm^2)	0.82	0.79	0.77	0.20
Total fat mass (kg)[a]	22.01	26.89	20.35	0.13
Total lean mass (kg)	33.74	29.83	29.04	0.01
Total bone mineral content (kg)	2.62	1.95	1.84	0.01
Total fat percent (%)	39.02	40.33	35.09	0.05
Android fat (kg)[a]	2.05	2.38	2.14	0.80
Gynoid fat (kg)[a]	4.27	4.62	3.77	0.20
Android/gynoid ratioa	0.46	0.51	0.60	0.68

[a]All nonnormally distributed variable expressed as median, for normally distributed variable *P* value calculated using one-way ANOVA with Dunn's correction, *P* value calculated for the decreasing trend. NOF: Neck of femur; GT: Greater trochanter, normally distribute variables have been expressed as mean, BMD: Bone mineral density, UD: Ultra-distal, DAS: Disease activity score

Table 5: Clinical, biochemical, disease activity, bone mineral density, and body composition profile of rheumatoid arthritis patients receiving glucocorticoids as compared to those not receiving glucocorticoids

Parameter	RA patients receiving glucocorticoids (oral or injectable) (*n*=81)	RA patients not receiving glucocorticoids (*n*=15)	*P*
Age (years)	37.04±5.47	36.13±4.48	0.54
BMI (kg/m^2)	23.11±3.38	24.07±3.04	0.31
Duration of symptoms (disease duration) (months)[a]	30 (18-48)	36 (24-72)	0.65
Duration of treatment (months)[a]	4 (2-12)	8 (3-12)	0.71
ACR/EULAR RA diagnostic score	8 (7-9)	8 (8-8)	0.40
TJCa	5 (2-8)	3 (1-6)	0.07
SJCa	2 (0-6)	4 (1-6)	0.74
Patient global health (0 mm-100 mm)[a]	40 (20-50)	50 (20-60)	0.33
Erythrocyte sedimentation ratea	60 (30-75)	55 (41-85)	0.36
DAS-28	4.88±1.18	4.86±1.11	0.95
X-ray hand features			
Normal	10	1	0.53
JAO	41	4	0.09
JAO + JSN	18	6	0.14
JAO + JSN + erosions	12	4	0.26
BMD (L1–L4) (g/cm^2)	1.05±0.11	1.05±0.07	0.98
BMD total femur (g/cm^2)	0.896±0.11	0.905±0.11	0.83
BMD NOF (g/cm2)	0.836±0.10	0.844±0.11	0.78
BMD greater trochanter (g/cm^2)	0.690±0.10	0.701±0.08	0.75
BMD radius total (g/cm^2)	0.604±0.07	0.596±0.05	0.74
BMD radius UD (g/cm^2)	0.403±0.07	0.414±0.06	0.70
BMD radius (33%)[a] (g/cm^2)	0.78 (0.75-0.83)	0.76 (0.73-0.78)	0.08
Total fat mass (kg)[a]	18.86 (13.97-30.24)	22.56 (11.01-24.59)	0.31
Total lean mass (kg)	29.90±3.49	28.42±1.47	0.19
Total bone mineral content (kg)	1.92±0.32	1.85±0.22	0.47
Total fat percent (%)	37.44±9.27	39.07±8.24	0.60
Android fat (kg)[a]	1.83 (1.17-2.97)	2.53 (1.87-4.16)	<0.01

Contd...

Table 5: Contd...

Parameter	RA patients receiving glucocorticoids (oral or injectable) ($n=81$)	RA patients not receiving glucocorticoids ($n=15$)	*P*
Gynoid fat (kg)[a]	4 (2.69-5.08)	3.59 (3.17-4.2)	0.34
Android/gynoid ratio[a]	0.45 (0.35-0.54)	0.64 (0.49-1.31)	<0.01

[a]All nonnormally distributed variable expressed as median (25th–75th percentile), *P* value calculated using unpaired *t*-test. The small number of patients in the RA patients not receiving glucocorticoids limits this analysis. BMD: Bone mineral density, L1–L4: LS L1–L4, NOF: Neck of femur, DAS: Disease activity score, JAO: Juxta-articular osteopenia, JSN: Joint space narrowing, RA: Rheumatoid arthritis, BMI: Body mass index, LS: Lumbar spine, ACR/EULAR: American College of Rheumatology/European League Against Rheumatism, UD: Ultra-distal, TJC: Tender joint count, SJC: Swollen joint count

Table 6: Stepwise linear regression showing models that predict bone mineral density at different sites in patients with rheumatoid arthritis

Parameter	Unstandardized coefficient (B) (95% CI)	*P*
BMD (L1–L4)		
Lean mass	0.01 (0.01-0.02)	<0.01
BMD GT		
Lean mass	0.01 (0.00-0.02)	<0.01
DAS-28	−0.03 (−0.05-0.00)	0.02
BMD total femur		
Lean mass	0.01 (0.01-0.02)	<0.01
BMD NOF		
Lean mass	0.01 (0.01-0.02)	<0.01
DAS-28	−0.02 (−0.04-−0.01)	0.03
BMD radius total		
Lean mass	0.01 (0.01-0.02)	<0.01
Age	−0.01 (−0.01-0.00)	0.02
BMD radius 33%		
Lean mass	0.01 (0.01-0.02)	<0.01
Age	−0.01 (−0.01-0.00)	<0.01
BMD radius UD		
Lean mass	0.01 (0.01-0.02)	<0.01
Age	−0.01 (−0.01-−0.00)	<0.01
Android/gynoid ratio	−0.26 (−0.42-−0.10)	<0.01
BMI	0.01 (0.00-0.02)	0.02

Stepwise linear regression analysis were done using all clinical, disease activity and body composition parameters which are likely to influence the bone mineral density at different sites (age, BMI, duration of symptoms, duration of treatment, DAS-28 score, CRP titer, Vitamin-D, total lean mass, total fat mass, total fat percent, and android/gynoid ratio). Models constructed using variables that significantly contributed to BMD at different sites have been elaborated in the table. BMD: Bone mineral density, UD: Ultra-distal, GT: Greater trochanter, NOF: Neck of femur, BMI: Body mass index, CI: Confidence interval, DAS: Disease activity score, CRP: C-reactive protein

be a limitation of this study. Lack of follow-up to evaluate long-term outcomes is also a limitation.

Conclusion

This study highlights for the first time that low BMD is a significant problem in young premenopausal women with RA, with osteopenia being the predominant disease type. Hence, interventions for the preservation of bone health should start immediately from RA diagnosis. Our study highlighted RA disease activity to be associated with lower BMD at all sites. Perhaps, the most important observation was that LM was the best predictor of BMD. Additional benefits of increased LM include prevention of falls, thus decreasing fracture risk.

Acknowledgment

We are grateful to the paramedical and nursing staff of the Department of Rheumatology, King George's Medical University, for making this work possible.

Financial support and sponsorship

This study was funded by the Department of Rheumatology, King George's Medical University, Lucknow, India.

Conflicts of interest

There are no conflicts of interest.

References

1. Leib ES, Lewiecki EM, Binkley N, Hamdy RC, International Society for Clinical Densitometry. Official positions of the international society for clinical densitometry. J Clin Densitom 2004;7:1-6.
2. Yoon J, Kwon SR, Lim MJ, Joo K, Moon CG, Jang J, *et al.* A comparison of three different guidelines for osteoporosis treatment in patients with rheumatoid arthritis in Korea. Korean J Intern Med 2010;25:436-46.
3. Dutta D, Mondal SA, Choudhuri S, Maisnam I, Hasanoor Reza AH, Bhattacharya B, *et al.* Vitamin-D supplementation in prediabetes reduced progression to type 2 diabetes and was associated with decreased insulin resistance and systemic inflammation: An open label randomized prospective study from Eastern India. Diabetes Res Clin Pract 2014;103:e18-23.
4. Dutta D, Maisnam I, Shrivastava A, Sinha A, Ghosh S, Mukhopadhyay P, *et al.* Serum Vitamin-D predicts insulin resistance in individuals with prediabetes. Indian J Med Res 2013;138:853-60.
5. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, *et al.* 2010 rheumatoid arthritis classification criteria: An American College of Rheumatology/European league against rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569-81.
6. van Gestel AM, Haagsma CJ, van Riel PL. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. Arthritis Rheum 1998;41:1845-50.
7. Biswas D, Dutta D, Maisnam I, Mukhopadhyay S, Chowdhury S. Occurrence of osteoporosis and factors determining bone mineral loss in young adults with Graves' disease. Indian J Med Res 2015;141:322-9.
8. Dutta D, Dharmshaktu P, Aggarwal A, Gaurav K, Bansal R, Devru N, *et al.* Severity and pattern of bone mineral loss in endocrine causes of osteoporosis as compared to age-related bone mineral loss. J Postgrad Med 2016;62:162-9.
9. Klein S, Fabrini E, Romijn JA. Obesity. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM. Williams Textbook of Endocrinology. 12th ed., Vol. 36. Los Angeles, CA, USA: Elsevier Saunders; 2011. p. 1605.
10. Baim S, Wilson CR, Lewiecki EM, Luckey MM, Downs RW Jr. Lentle BC, *et al.* Precision assessment and radiation safety for dual-energy X-ray absorptiometry: Position paper of the international

society for clinical densitometry. J Clin Densitom 2005;8:371-8.
11. Hafez EA, Mansour HE, Hamza SH, Moftah SG, Younes TB, Ismail MA, *et al.* Bone mineral density changes in patients with recent-onset rheumatoid arthritis. Clin Med Insights Arthritis Musculoskelet Disord 2011;4:87-94.
12. Tourinho TF, Stein A, Castro JA, Brenol JC. Rheumatoid arthritis: Evidence for bone loss in premenopausal women. J Rheumatol 2005;32:1020-5.
13. Iwamoto J, Takeda T, Ichimura S. Forearm bone mineral density in postmenopausal women with rheumatoid arthritis. Calcif Tissue Int 2002;70:1-8.
14. Haugeberg G, Green MJ, Quinn MA, Marzo-Ortega H, Proudman S, Karim Z, *et al.* Hand bone loss in early undifferentiated arthritis: Evaluating bone mineral density loss before the development of rheumatoid arthritis. Ann Rheum Dis 2006;65:736-40.
15. Momohara S, Okamoto H, Yago T, Furuya T, Nanke Y, Kotake S, *et al.* The study of bone mineral density and bone turnover markers in postmenopausal women with active rheumatoid arthritis. Mod Rheumatol 2005;15:410-4.
16. Korczowska I, Olewicz-Gawlik A, Trefler J, Hrycaj P, Krzysztof Łacki J. Does low-dose and short-term glucocorticoids treatment increase the risk of osteoporosis in rheumatoid arthritis female patients? Clin Rheumatol 2008;27:565-72.
17. Straburzyńska-Lupa A, Nowak A, Romanowski W, Korman P, Pilaczyńska-Szcześniak Ł. A study of the link between bone turnover markers and bone mineral density with inflammation and body mass in postmenopausal women with active rheumatoid arthritis. J Bone Miner Metab 2013;31:169-76.
18. Shibuya K, Hagino H, Morio Y, Teshima R. Cross-sectional and longitudinal study of osteoporosis in patients with rheumatoid arthritis. Clin Rheumatol 2002;21:150-8.
19. Sahin G, Guler H, Incel N, Sezgin M, As I. Soft tissue composition, axial bone mineral density, and grip strength in postmenopausal Turkish women with early rheumatoid arthritis: Is lean body mass a predictor of bone mineral density in rheumatoid arthritis? Int J Fertil Womens Med 2006;51:70-4.
20. Henderson CJ, Specker BL, Sierra RI, Campaigne BN, Lovell DJ. Total-body bone mineral content in non-corticosteroid-treated postpubertal females with juvenile rheumatoid arthritis: Frequency of osteopenia and contributing factors. Arthritis Rheum 2000;43:531-40.
21. Maisnam I, Dutta D, Mukhopadhyay S, Chowdhury S. Lean mass is the strongest predictor of bone mineral content in type-2 diabetes and normal individuals: An Eastern India perspective. J Diabetes Metab Disord 2014;13:90.
22. Sugiguchi S, Goto H, Inaba M, Nishizawa Y. Preferential reduction of bone mineral density at the femur reflects impairment of physical activity in patients with low-activity rheumatoid arthritis. Mod Rheumatol 2010;20:69-73.
23. Russell M, Mendes N, Miller KK, Rosen CJ, Lee H, Klibanski A, *et al.* Visceral fat is a negative predictor of bone density measures in obese adolescent girls. J Clin Endocrinol Metab 2010;95:1247-55.
24. Martin JC, Munro R, Campbell MK, Reid DM. Effects of disease and corticosteroids on appendicular bone mass in postmenopausal women with rheumatoid arthritis: Comparison with axial measurements. Br J Rheumatol 1997;36:43-9.
25. Ma CC, Xu SQ, Gong X, Wu Y, Qi S, Liu W, *et al.* Prevalence and risk factors associated with glucocorticoid-induced osteoporosis in chinese patients with rheumatoid arthritis. Arch Osteoporos 2017;12:33.
26. Hansen M, Florescu A, Stoltenberg M, Pødenphant J, Pedersen-Zbinden B, Hørslev-Petersen K, *et al.* Bone loss in rheumatoid arthritis. Influence of disease activity, duration of the disease, functional capacity, and corticosteroid treatment. Scand J Rheumatol 1996;25:367-76.
27. Mori Y, Kuwahara Y, Chiba S, Kogre A, Baba K, Kamimura M, *et al.* Bone mineral density of postmenopausal women with rheumatoid arthritis depends on disease duration regardless of treatment. J Bone Miner Metab 2017;35:52-7.
28. Engvall IL, Brismar K, Hafström I, Tengstrand B. Treatment with low-dose prednisolone is associated with altered body composition but no difference in bone mineral density in rheumatoid arthritis patients: A controlled cross-sectional study. Scand J Rheumatol 2011;40:161-8.