Low Bone Mineral Density in Premenopausal Females with Rheumatoid Arthritis

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ABSTRACT

Introduction: Rheumatoid arthritis is known to negatively impact bone mineral density. This study aimed to evaluate prevalence and pattern of low bone mineral density in premenopausal females with rheumatoid arthritis.

Material and Methods: In this prospective case control study, 113 premenopausal rheumatoid arthritis female patients were assessed and compared to 90 controls. Body mass index, co-morbidities, serum calcium, serum vitamin D and bone mineral density (using dual energy x ray absorptiometry) at lumbar spine (L1-L4), femur and radius were assessed in all subjects. Clinical disease activity index, erythrocyte sedimentation rate and c reactive protein were measured in all patients. Unpaired t test and Chi-square test/fisher exact test were used to analyze the data.

Results: Low bone mineral density (Z-score ≤ -2) was significantly more prevalent in rheumatoid arthritis group as compared to controls (p=0.00019) especially at lower radius (p<0.0001). In rheumatoid arthritis patients, low bone mineral density was significantly more common in those with moderate to severe clinical disease activity, erosive disease and longer disease duration (p values 0.0200, <0.00001 and 0.00244 respectively).

Conclusions: Premenopausal rheumatoid arthritis patients are susceptible for low bone mineral density especially at radius and more often if they have long standing, moderate to highly active and erosive disease. Early adequate treatment of rheumatoid arthritis along with monitoring of bone mineral density at wrist in these patients should be advised.

Keywords: Rheumatoid Arthritis, Bone Mineral Density, Disease Activity.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown etiology characterized by synovial inflammation and destruction. Low bone mineral density (BMD) as one of the extra-articular manifestations of RA[1], may result in increased risk of fractures, morbidity, mortality and financial burden**.** Prevalence of low BMD in RA patients has been variably reported in published literature[2-4] from 25% to 91%. Further, the major site/s of significant BMD loss in RA have also been variably reported in literature like - lumbar spine[5], distal forearm/lumber spine[6], hip[7]or all sites except lumber vertebrae[8]. Ethnic variance, variance in tools used for BMD assessment, stage of disease and variance in disease treatment may explain these conflicting outcomes from different studies. Many of these studies include combined data on premenopausal and post-menopausal patients. As studies on BMD in premenopausal RA patients are limited in published literature and bone loss among Indian RA patients has been sparsely studied, the purpose of present study was to evaluate the prevalence and pattern of low BMD in premenopausal RA patients in India with regard to clinical, radiological and biochemical disease parameters.

MATERIAL AND METHODS

This prospective case control study was conducted at the rheumatology department of a tertiary care teaching institution in north India. After institutional ethics committee approval for the study and written informed consent of subjects, a total of 203 premenopausal females were recruited between August 2015 and January 2018. Of these, 113 were confirmed cases of RA (18-45 years of age) who fulfilled the American College of Rheumatology/European League Against Rheumatism (EULAR/ACR) 2010 criteria for RA[9] and 90 were healthy controls matched for age, menstrual status and socio-cultural status. Inclusion criteria included confirmed cases of RA and those volunteered for participation in the study after explanation of the purpose of the study. Exclusion criteria were: post-menopausal females, autoimmune disorders other than RA, patients with any secondary cause of osteoporosis (e.g. celiac disease, type 1 diabetes mellitus and hyperparathyroidism), severe vitamin D deficiency (25-hydroxy vitamin D <10ng/ml), patients on drugs interfering with BMD (e.g. anti-epileptics, bisphosphonates), previous history of fragility fractures, chronic liver disease and chronic renal disease (CKD stage ≥3). Current or past use of corticosteroids for RA was not an exclusion criterion. A detailed medical history, physical examination, BMI, co-mobidities (diabetes mellitus,

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Parameter	Patients (n=113)	Controls (n=90)	p value
Age in years (mean±sd)	33.26±6.78	34.77±8.03	0.148[a]
Body mass index (mean±sd)	21.92±4.67	22.95±3.62	0.087[a]
No. of subjects with co-morbidities	8(7%)	5(5.5%)	0.659[b]
No. of subjects with milk intake ≥ 300ml/day	91(80.5%)	71(78.8%)	0.7721[b]
S. calcium level (mg/dl) (mean±sd)	9.06±0.51	8.96±0.49	0.1595[a]
25(OH) vitamin D (pg/ml) (mean±sd)	25.51±12.92	19.80±10.03	0.0007*,[a]
Duration of disease in years(mean±sd/median)	4.15±3.38/3	-	-
Duration of diagnosis(months)(mean±sd/median)	9.79±19.71/4.5	-	-
Pts. with positive Rheumatoid Factor (No.)	90(79.6%)	-	-
Pts. with positive anti citrullinated protein antibody (No.)	101(89.3%)	-	-
Pts. with findings suggestive of RA on X-ray of hands (No.)	102(90.2%)	-	-
No. of pts. with treatment history with : NSAIDs Methotrexate Hydroxychloroquin Steroids: IM/oral (≤ 15 mg/day, < 6 weeks)	 106(93.8%) 101(89.3%) 103(91.1%) 16(14.1%)	-	-
C-reactive protein (mg/dl), mean	32.85	-	-
ESR (mm/1st hour),mean	60.08	-	-
Clinical disease activity index(CDAI)(mean±sd/median)	15.9±12.9/15	-	-

*p < 0.05, [a]unpaired student t-test, [b]chi-square test/fisher exact test

Table–1: Demography and outcomes: rheumatoid arthritis and control groups

Site of BMD measurement	No. of subjects with low BMD (Z - score ≤ -2)		p value
	Patients	Controls	
Lumbar spine (L1-4)	10 (8.8%)	3 (3.3%)	0.09[a]
Neck of femur (Mean)	5 (4.4%)	0	0.06[a]
Radius lower 1/3rd	17 (15%)	0	<0.0001*,[a]
At any site	24(21.2%)	3(3.3%)	0.00019*,[a]

*p < 0.05, [a]chi-square/fisher exact test, RA; rheumatoid arthritis, BMD; bone mineral density

Table-2: Prevalence & pattern of low BMD in RA group (N=113) as compared to control group (N=90)

Clinical parameter	No. of patients with low BMD (Z - score ≤ -2)				p value
	at lumbar spine (L1-4)	at femur neck	at lower radius	at any site	
Clinical disease activity index (CDAI) Remission (≤2.8,n=15)/Mild (2.8-10, n=32) Moderate to severe (>10, n=66)	 1 9	 0 5	 5 12	 5 19	0.0200*,[a]
Duration of disease ≤5yrs (n= 80) >5 yrs (n=33)	 6 4	 2 3	 6 11	 11 13	0.00244*,[a]
Joint erosions (on X ray hands) With erosion (n=22) Without erosion (n=91)	 5 5	 3 2	 12 5	 15 9	<0.00001*,[a]
25(OH) vitamin D level < 20 pg/ml (n=17) ≥20 pg/ml (n=96)	 2 8	 1 4	 3 14	 5 19	0.37138[a]

*p<0.05, [a]chi-square test/fisher exact test, RA; rheumatoid arthritis, BMD; bone mineral density

Table-3: Low BMD with respect to clinical, radiological & biochemical parameters in RA patients

hypertension and coronary artery disease), history of smoking, regular milk intake ≥300/day and treatment history were noted in all subjects. Complete blood count, erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP), serum creatinine, liver function tests (LFT), rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibody, serum alkaline phosphatase were measured in all patients. Serum calcium, serum 25(OH) vitamin D levels and BMD were measured in all subjects. DEXA machine (GE, Lunar) was used for estimation of BMD at the proximal femur, lumbar spine (L1–L4), and distal radius. For BMD measurement in premenopausal women, the International Society for Clinical Densitometry (ISCD) recommendation[10] was used with Z-scores of −2.0 SD or lower defined as either "low bone mineral density for chronological age" or "below the expected range for age" and those above −2.0 SD being "within the expected range for age". Clinical disease activity index (CDAI) was used to evaluate RA disease activity

in all patients. A score ≤2.8 was considered to be disease remission, >2.8 and ≤10 as low disease activity, >10-and ≤22 as moderate disease activity, and >22 as high disease activity[11].

STATISTICAL ANALYSIS

The results are presented in mean±SD, median and percentages. Chi-square test/fisher exact test was used for comparison between dichotomous/categorical variables. The continuous variables were compared by unpaired t-test. The p value less ≤ 0.05 was considered significant. All analyses were carried out by using SPSS 16.0 version (SPSS Inc., Chicago, IL, USA).

RESULTS

Table 1 shows demography and outcomes in patients and control groups. Mean age, mean body mass index, co-morbidities, subjects with ≥ 300 ml milk intake/day and mean serum calcium levels were similar in rheumatoid arthritis group and control group (p values 0.148, 0.087, 0.659, 0.772 and 0.159 respectively). Mean vitamin D levels were lower in control group as compared to rheumatoid arthritis group (p=0.0007). Median duration of disease and median duration of diagnosis in RA group were 3 years and 4.5 months respectively. Rheumatoid factor was positive in 79.6% of patients whereas ACPA was positive in 89.3% of patients. On plain X-ray of hands, findings suggestive of RA were observed in a large majority of the patients (90.2%) which included juxta-articular osteopenia (JAO), joint space narrowing (JSN) and erosions. Isolated JAO was the commonest X-ray finding. Non-steroidal anti-inflammatory agents (NSAIDs) were the most common medication used by patients, 93.8% patients were on different NSAIDs. Among the disease modifying agents, 89.3% patients were on methotrexate (MTx) and 91.1% patients were on Hydroxylchloroquine (HCQ). 14.1% patients were taking steroid (≤ 15 mg/day prednisolone or equivalent, either by oral or intramuscular route) for<6 weeks. Mean ESR and CRP were 60.08 mm/1sthr and 32.85 mg/dl respectively. Median clinical disease activity index (CDAI) was 15 with interquartile range of 5-24.

Table 2 shows prevalence and pattern of low BMD (Z - score -2 or less) in RA vs. control groups. Low BMD (Z - score ≤ -2) was significantly more prevalent in rheumatoid arthritis group as compared to controls (p= 0.00019) especially at lower radius (p<0.0001). Wrist was the most common site for low BMD in patients with RA in our study with lower radius being the most commonly involved region in the wrist. Table 3 shows prevalence of low BMD with respect to various parameters in RA group. Prevalence of low BMD was significantly higher in patients with moderate to severe (CDAI >10) disease activity (vs. those with mild disease activity/ those in remission) (p=0.020), in patients with erosions on hand X-ray (vs. those without erosions) (p<0.00001) irrespective of JAO and/or JSN and in patients with long standing (> 5 yrs) disease (vs. those with ≤5 yrs disease duration) (p=0.00244).

DISCUSSION

A link between joint damage at baseline and joint damage progression with degree of BMD loss in RA has been suggested[12] and dual-energy x-ray absorptiometry (DEXA) for BMD assessment has been recommended by International Society for Clinical Densitometry (ISCD) and National Osteoporosis Foundation (NOF) in patients with RA[13]. In present study we noted low BMD in 21.2% of premenopausal females with RA using DEXA. Published literature reports overall prevalence of low BMD between 25 to 91%. Slightly lower prevalence of low BMD in our RA group is well explained in this premenopausal, younger cohort of RA patients in our study. The data on pattern of bone mineral loss in RA and its relation with disease activity, inflammation and treatment is conflicting across the world. Although hypothesized that bone loss in RA may be reflective of the disease activity, the relationship between disease activity and BMD in RA is conflicting[14-16] with few studies reporting a relationship, but others not. In our study prevalence of low BMD was significantly higher among patients with moderate to severe disease activity (CDAI >10) and erosive disease. Consistent with published literature, longer disease duration was associated with low BMD. In present study on younger females with RA, the BMD at radius seem to be most affected by the disease. This is similar to findings of Iwamoto et al[6] who also noted distal forearm to be an important site of bone loss in postmenopausal RA. Vitamin D levels didn't seem to influence BMD loss in premenopausal RA females in our study as majority of these patients were on vitamin D and calcium supplementations and had adequate vitamin D levels. This may also be a reason for higher mean vitamin D levels in RA group as compared to controls in this study. Our study highlights that low BMD is a significant problem (seen in one fifth of the cases) in premenopausal RA patients with maximum impact being at lower radius. One should be particularly vigilant for low BMD in these patients if they have long standing, active and erosive disease.

Our study has some limitations: over representation at tertiary care centre of severe RA cases but with prior treatments including calcium, vitamin D, various NSAIDS and steroids, might have had contradictory unpredictable impacts on BMD. Main strength of this study is: inclusion of reasonable number of premenopausal Indian RA patients. Hence our results may not be generalizable to all patients with RA in the community. In spite of these limitations, this modest size case control study on Asian RA females indicates that low BMD is substantial problems and area of concern in premenopausal RA patients. Avoiding poor bone mineral density related morbidity in this young dynamic population may be very important.

CONCLUSION

Premenopausal females with rheumatoid arthritis are at increased risk of developing low bone mineral density especially in those with moderate to severe disease activity, erosive disease and long duration disease. Lower radius was the most commonly affected site.

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