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Original Research Article

To study the bone mineral density and vitamin D in patients suffering from rheumatoid arthritis irrespective of duration in comparison to age and sex-matched controls who were not having any musculoskeletal disorder

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ABSTRACT

Background: Rheumatoid arthritis is a chronic inflammatory disease of synovial tissue of joints of unknown etiology marked by a symmetric, peripheral, polyarthritis. Osteoporosis is a progressive systemic skeletal disease characterised by reduced bone mass/density and micro-architectural deterioration of bone tissue. Osteoporosis is more common in patients with rheumatoid arthritis than an age and sex-matched population. Chronic use of glucocorticoids and disability-related immobility also contributes to osteoporosis.
Methods: The present study was conducted at Department of Medicine, Dr. S. N. Medical College, Jodhpur, India. Case control study was conducted to determine bone mineral densities (BMD) and vitamin D levels among patients with rheumatoid arthritis attending the medicine OPD and IPD, Dr. S. N. Medical College, Jodhpur, Rajasthan, India. 25 patients with rheumatoid arthritis and 25 age and sex-matched controls were studied. All known cases of Rheumatoid Arthritis attending Medicine outdoor and patients who are admitted indoor. Patients with co-morbidities like diabetes mellitus, coronary artery disease, hypertension, chronic kidney disease and pre-existing osteoporosis.
Results: Mean age of the study population was 49.68±8.4 yrs; most of the subjects were females. Vitamin D levels were found to be comparatively lower in females. Vitamin D deficiency was more prevalent of in urban population. As the age increased the levels of vitamin D and BMD decreased. Inadequacy in vitamin D levels was more prevalent in Rheumatoid arthritis patients, 74.99% females had low BMD values. Correlation of low BMD with RA was statistically significant. The duration of Rheumatoid arthritis was related to vitamin D levels significantly ($p<0.013$). The longer the duration of disease more number of RA patients had vitamin D deficiency. All patients with RA for more than 4 years had osteoporosis. The duration of Rheumatoid arthritis was related to low BMD significantly ($p<0.025$). The correlation of HAQ (health assessment questionnaire) with BMD is statistically significant; the correlation of DAS score with RA duration is statistically significant. The correlation of DAS score with BMD is statistically significant. The lesser the BMD more number of RA patients had moderate or severe scores.
Conclusions: Vitamin D levels were found to be comparatively lower in females especially in urban areas. Vitamin D deficiency and low BMD is more prevalent in Patients of rheumatoid arthritis in comparison to controls. High index of suspicion is required during follow-up of rheumatoid arthritis patients.

Keywords: BMD, Osteoporosis, Osteopenia, Rheumatoid arthritis, Vitamin-D

INTRODUCTION

Rheumatoid arthritis is a chronic inflammatory disease of synovial tissue of joints of unknown etiology marked by a symmetric, peripheral, poly-arthritis. It is the most common form of chronic inflammatory arthritis and often results in joint damage and physical disability.[1]

Rheumatoid arthritis affects approximately 0.5-1% of the adult population worldwide. The overall incidence of Rheumatoid arthritis has been decreasing in recent decades, whereas the prevalence has remained the same because individuals with rheumatoid arthritis are living longer. Like many other autoimmune diseases, Rheumatoid arthritis occurs more commonly in females than males, with a 2-3:1 ratio.[2]

Osteoporosis is a progressive systemic skeletal disease characterised by reduced bone mass/density and micro-architectural deterioration of bone tissue. Bone formation initially exceeds bone resorption, but by the third decade this has reversed resulting in a net loss of bone mass. This leads to an increased bone fragility and susceptibility to mechanical forces that would not ordinarily result in fracture. Osteoporotic fractures are defined as fractures associated with low bone mineral density (BMD) and include cervical spine, forearm, hip and shoulder fractures.

Osteoporosis is more common in patients with Rheumatoid arthritis than an age and sex-matched population, with prevalence rates of 20-30%. The inflammatory milieu of the joint probably spills over into the rest of the body and promotes generalized bone loss by activating osteoclasts. Chronic use of glucocorticoids and disability-related immobility also contributes to osteoporosis.[3]

Bone remodelling in rheumatoid arthritis has been investigated in some large, case-control cohort and longitudinal studies. Bone mass was found to be lower in Rheumatoid arthritis, compared with non-rheumatoid arthritis controls. Low bone mass at the femoral neck was particularly noted in non-treated patients with rheumatoid arthritis and in those with prolonged disease course. Presumably, patients with a longer disease duration present with a lower bone mass and a greater risk of fractures compared with a short duration. The relationship between disease duration and bone mass has not been thoroughly investigated in rheumatoid arthritis. In particular, the effect of disease duration on bone mass in rheumatoid arthritis, independent of a variety of confounding factors, has not been determined.[4]

BMD categories proposed by the World Health Organization (WHO) and the International Osteoporosis Foundation (IOF). [5]

- *Osteoporosis*: hip BMD 2.5 SD or more below the young adult reference mean (T-score ≤-2.5)
- *Severe osteoporosis:* hip BMD 2.5 SD or more below the young adult reference mean in the presence of one or more fragility fractures (T-score ≤-2.5 PLUS fracture).

Other possible BMD results:

- *Low bone mass (osteopenia)**:*** hip BMD between 1 and 2.5 SD below the young adult reference mean (T-score less than -1 but above -2.5)
- *Normal**:*** hip BMD greater than the lower limit of normal which is taken as 1 SD below the young adult reference mean (T-score ≥-1)
- Bone density scanning, also called dual-energy x-ray absorptiometry (DXA) or bone densitometry, is an enhanced form of x-ray technology that is used to measure bone loss. DXA is today's established standard for measuring bone mineral density (BMD)
- An x-ray (radiograph) is a non-invasive medical test that helps physicians diagnose and treat medical conditions.

METHODS

An informed consent was taken from the patients regarding participation in the study. In the selected patient's history regarding duration of disease and treatment was elicited. Detailed clinical examination was performed. HAQ (Health Assessment Questionnaire) and DAS score were calculated according to ACR guidelines. The patients were subjected to DEXA scan at lumbar spine (L1-L5) by the machine available with the Department of Medicine and Serum Vitamin D2 levels were analysed.

Exclusion criteria

Patients with co-morbidities like diabetes mellitus, coronary artery disease, hypertension, chronic kidney disease and pre-existing osteoporosis.

Laboratory investigations

DEXA scan, serum 25-hydroxy vitamin D assessment using chemiluminescent immunoassay (CLIA), Serum calcium and phosphorus levels, Haemogram, ESR, liver function test, blood urea, serum Creatinine were performed.

Number of cases studied- 50 (25 rheumatoid arthritis and 25 controls), (28 females and 22 males).

Comprehensive clinical evaluation, general physical examination and physical strength assessment, HAQ and DAS score, relevant laboratory investigations, DEXA scan at lumbar spine, vitamin D level estimation were performed at MDM hospital.

HAQ- (as per ACR guidelines)

- Dressing and grooming
- Arising
- Eating
- Walking
- Hygiene
- Reach
- Grip.

The four possible responses for each variable

- without any difficulty=0
- with some difficulty=1
- with much difficulty=2
- unable to do=3.

Disability index is given by summing up all the variables' score and dividing by seven.

DAS (Disease Activity score as per ACR criteria)

- Number of joints involved, tender (total 28)
- Number of joints involved, swollen (total 28)
- ESR in mm/hr
- Global health (pain scale) 1 to 10(10 cm line).

$$DAS=0.56\times\sqrt{t28}\ +\ \sqrt{sw28}\ +0.70\times ESR+0.014\times GH$$

Data evaluation

Data were analyzed by Epi info statistical and multivariate analysis methods with the help of statistician.

Dexa scan

The most accurate and convincing measure of BMD is DXA (Dual Energy X-ray Absorptiometry). Results of DXA are reported in form of T-score (compares BMD with healthy young) and Z score (compares BMD with other people of same age, gender and ethnicity). In this study, DXA scan was performed using Hologic bone densitometer machine AERB/44/01 Discovery QDR Series.

Estimation of serum vitamin D levels

It is done by a direct competitive chemiluminescence immunoassay (CLIA) for quantitative determination of total 25-hydroxy vitamin D in serum.

RESULTS

We observed that 74.99% females had low BMD values and only 25% females had normal BMD. 31.82% males and 39.28% females had osteopenia while 31.82% males and 35.71% females had osteoporosis. This correlation was statistically significant (p=0.013).

Vitamin D levels were also found comparatively lower in females. 31.82% males had normal vitamin D levels but only 25% females had normal vitamin D levels.36.36% males and 32.14% females had insufficient while 31.82% males and 42.86% females had deficient vitamin D levels. Difference in vitamin D levels in both sexes were found to be statistically significant (p value=0.0025).

Table 1: Correlation of BMD according to population.

Population	Urban	Rural
BMD		
Normal	5 (20%)	10 (40%)
Osteopenia	10 (40%)	8 (32%)
Osteoporosis	10 (40%)	7 (28%)

In this study group 80% subjects from urban areas had BMD values below normal limits while 60% subjects from rural areas had subnormal BMD values. 32% rural and 40% urban had osteopenia while 28% rural and 40% urban population had osteoporosis. Difference between urban and rural areas was statistically significant (p value=0.0116).

Table 2: Correlation of vitamin D according to population.

Population	Urban	Rural
Vitamin D		
Normal	4 (16%)	10 (40%)
Insufficient	11 (44%)	6 (24%)
Deficient	10 (40%)	9 (36%)

Prevalence of vitamin D deficiency was more in urban population in comparison to rural population. 16% urban and 40% of rural population were having normal vitamin D levels. 24% rural and 44% urban people had insufficient, while 36% rural and 40% urban population were vitamin D deficient.

Table 3: Correlation of age with BMD.

Age group	35-44 yrs	45-54 yrs	55-65 yrs
BMD	**(n=16)**	**(n=17)**	**(n=17)**
Normal	6 (37.5%)	7 (41.17%)	2 (11.76%)
Osteopenia	7 (43.75%)	4 (23.53%)	7 (41.17%)
Osteoporosis	3 (18.75%)	6 (35.29%)	8 (47.06%)

37.5% patients in age group 35 to 44 years had normal BMD while 43.75% had osteopenia and 18.75% had osteoporosis. 41.17% patients in age group 45 to 54 years had normal BMD while 23.53% had osteopenia and 35.29% had osteoporosis. 47.06% patients in age group 55 to 65 years had osteoporosis. BMD decreases as age group increased p<0.013.

37.5% patients in age group 35 to 44 years had normal vitamin D while 62.5% had low vitamin D. 29.41% in age group 45 to 5 years had normal while 70.59% had

low vitamin D levels. 83.33% in age group 55 to 65 years age group had low while only 16.67% had normal vitamin D levels.

Table 4: Correlation of age with vitamin D.

Age group	35-44 yrs	45-54 yrs	55-65 yrs
Vitamin D	**(n=16)**	**(n=17)**	**(n=17)**
Normal	6 (37.5%)	5 (29.41%)	3 (16.67%)
Insufficient	6 (37.5%)	4 (23.53%)	7 (41.18%)
Deficient	4 (25%)	8 (47.06%)	7 (41.18%)

Table 5: Correlation of vitamin D and BMD.

BMD	Normal	Osteopenia	Osteoporosis
Vitamin D			
Normal	9 (60%)	4 (22.22%)	1 (%)
Insufficient	4 (%)	9 (50%)	4 (%)
Deficient	2 (13.33%)	5 (27.78%)	12 (70.59%)

Correlation of vitamin D levels with BMD was found to be statistically very significant (p value=0.000). 70.58% osteoporotic subjects were vitamin D deficient. 22.22% osteopenic subjects were in vitamin D sufficient category while 60% subjects with normal BMD had normal vitamin D levels. So, BMD was found to be correlated directly with vitamin D levels.

Table 6: Correlation of RA and BMD.

BMD	Normal	Osteopenia	Osteoporosis
RA	3 (12%)	10 (40%)	12 (48%)
Controls	12 (48%)	8 (32%)	5 (20%)

Only 12% patients with RA had normal BMD,40% patients had osteopenia and 48% patients had osteoporosis.48% controls had normal BMD while 32% where osteopenic and 20% had osteoporosis <0.00. The relation between rheumatoid arthritis and BMD was significant (p=0.001).

Table 7: Correlation of RA duration and BMD.

BMD	Normal	Osteopenia	Osteoporosis
RA duration			
<2 years	1 (33.33%)	1 (33.33%)	1 (33.33%)
2-4 years	2 (15.38%)	9 (69.23%)	2 (15.38%)
>4 years	0	0	9 (100%)

33.33% of patients with RA less than 2 years had normal BMD and 33.33% had osteopenia and similar percentage had osteoporosis. 15.38% patients with RA equal to or more than 2 years and less than 4 years had normal BMD, 69.23% had osteopenia and 15.38% had osteoporosis. All patients with RA more than 4 years had osteoporosis. The duration of rheumatoid arthritis was related to BMD significantly (p).

Only 16% patients with RA were vitamin D sufficient, while 36% had insufficient and 48% had deficient vitamin D levels. 40% controls had sufficient, while 40% had insufficient and 20% had deficient vitamin D levels. This correlation is statistically significant p=0.001.

Table 8: Correlation of vitamin D with RA.

Vitamin D	Normal	Insufficient	Deficient
RA	4 (16%)	9 (36%)	12 (48%)
controls	10 (40%)	10 (40%)	5 (20%)

Table 9: Correlation of RA duration and vitamin D.

Vitamin D	Normal	Insufficient	Deficient
RA duration			
<2 years	1 (33.33%)	1 (33.33%)	1 (33.33%)
2-4 years	3 (23.08%)	7 (53.85%)	3 (23.08%)
>4 years	0	1 (11.11%)	8 (88.89%)

One third of patients with RA less than 2 years had sufficient vitamin D levels and one third had insufficient levels and one third had vitamin D deficiency. 23.08% patients with RA equal to or more than 2 years and less than 4 years had normal vitamin D, 53.85% patients had insufficient and 23.08% patients had Vitamin D deficiency. 11.11% patients with RA more than 5 years had insufficient Vitamin D levels and 88.89% patients had Vitamin D deficiency.

Table 10: Correlation of HAQ score with BMD.

HAQscore	High	Low
BMD		
Normal	0	15 (60%)
Osteopenia	10 (40%)	8 (32%)
Osteoporosis	15 (60%)	2 (8%)

The duration of Rheumatoid arthritis was related to Vitamin D levels significantly (p<0.013).

40% RA patients with high HAQ score had osteopenia and 60% had osteoporosis. Low HAQ score is associated with normal BMD in 60% RA patients. This correlation is statistically significant, p<0.001.

Table 11: Correlation of DAS score with RA duration.

DAS score	Low (<2.5)	Moderate (2.5 to 5)	Severe (>5)
RA duration			
<2 years	1 (33.33)	1 (33.33%)	1 (33.33%)
2-4 years	0	11 (84.62%)	2 (15.38%)
>4 years	0	2 (22.22%)	7 (77.78%)

One third of patients with RA less than two years had low, moderate and severe DAS score respectively.84.62% RA patients with RA equal to or more than 2 and less than 4 years had moderate DAS

score and 15.38% patients had severe DAS score. 22.22% had moderate DAS whereas 77.78% patients with RA more than 4 years had severe DAS score. This correlation is statistically significant p=0.013.

Table 12: Correlation of DAS score with BMD in RA patients.

DAS score	Low (<2.5)	Moderate (2.5 to 5)	Severe (>5)
BMD			
Normal	1 (33.33%)	2 (66.67%)	0
Osteopenia	0	10 (100%)	0
Osteoporosis	0	0	12 (100%)

One third RA patients with normal BMD had low DAS score. All the RA patients with osteopenia had moderate DAS score and all the RA patients with osteoporosis had severe DAS score P<0.001.

Table 13: Correlation of DAS score with vitamin D in RA patients.

DAS score	Low (<2.5)	Moderate (2.5 to 5)	Severe (>5)
Vitamin D			
Normal	1 (25%)	3 (75%)	0
Insufficient	0	7 (87.5%)	2 (18.18%)
Deficient	0	3 (23.08%)	9 (81.82%)

One third had low while two third RA patients with moderate DAS score had normal vitamin D. 87.75% RA patients who had insufficient while 23.08% who had deficient vitamin D levels had moderate DAS score. 81.82% RA patients with severe DAS score had deficient vitamin D levels. This correlation is statistically significant p<0.001.

DISCUSSION

This study was a hospital based case control study. This study describes the vitamin D levels in rheumatoid arthritis patients of Western Rajasthan and association of these levels with bone mineral density. A total number of subjects studied were 50, out of which, 25 patients were Rheumatoid arthritis. Of the 50 peoples, 22 were males and 28 were females.

Demographic distribution in the present study was such that in the study group 50% subjects were from rural areas and 50% subjects were from urban areas. Vitamin D levels were comparatively lower in females. 31.82% males had normal vitamin D levels but only 28.57% females had normal vitamin D levels. 36.36% males and 32.14% females had insufficient while 31.82% males and 39.28% females had deficient vitamin D levels. Difference in vitamin D levels in both sexes were statistically significant (p value=0.0025). Similar results were found in study done by Asghai et al, Goswami et al, Johnson et al, Merlino et al.[6-9]

Prevalence of vitamin D deficiency was more in urban population in comparison to rural population in this study. 16% urban and 40% of rural population were having normal vitamin D levels. 24% rural and 44% urban people had insufficient, while 36% rural and 40% urban population were vitamin D deficient. Indoor spent hours and air pollution is usually considered more common in urban areas so it is usually thought that vitamin D sufficiency is usually less common in urban population.

37.5% patients in age group 35 to 44 years had normal vitamin D while 62.5% had low vitamin D. 29.41% in age group 45 to 5 years had normal while 70.59% had low vitamin D levels. 83.33% in age group 55 to 65 years age group had low while only 16.67% had normal vitamin D levels.

Similar study by Marwaha et al in 2011 in elderly population on urban adults of age>50 years in Delhi showed 91.2% subjects were suffering from vitamin D deficiency.[10]

Similar study by Agarwal et al found 58% vitamin D deficiency incidence rate in their study group (composed of elderly of >50 yrs).[11]

Correlation of vitamin D levels with BMD was found to be statistically very significant (p value=0.000). 70.58% osteoporotic subjects were vitamin D deficient. 22.22% osteopenic subjects were in vitamin D sufficient category while 66.67% subjects with normal BMD had normal vitamin D levels. So, BMD was found to be correlated directly with vitamin D levels. Similar results were obtained in study done by Lips et al.[12]

It was found that 74.99% females had low BMD values and only 25% females had normal BMD. In contrast 36.36% males had normal BMD.

31.82% males and 39.28% females had osteopenia while 31.82% males and 35.71% females had osteoporosis. This finding supports old studies. All postmenopausal females are considered in high risk group of developing osteoporosis in those studies like Jarupanich et al, Paul et al, 59.7% men and 67.5% women had osteopenia.[7,13] 18.39% men and 12.5% women had osteoporosis in a study done on resident doctors in Mumbai by Multani et al, 87.5% subjects were vitamin D deficient.[14]

In the present study, out of 50, 28% of patients were females with Rheumatoid arthritis. The fact that correlation of RA with BMD is significant has contributed to the findings in the present study.

80% subjects from urban areas had BMD values below normal limits while 60% subjects from rural areas had subnormal BMD values. 32% rural and 40% urban had osteopenia while 28% rural and 40% urban population

had osteoporosis. Difference between urban and rural areas was statistically significant (p value=0.0116).

43.75% patients in age group 35 to 44 years had normal BMD while 31.25% had osteopenia and 25% had osteoporosis. 41.17% patients in age group 45 to 54 years had normal BMD while 23.53% had osteopenia and 35.29% had osteoporosis. 47.06% patients in age group 55 to 65 years had osteoporosis. BMD decreases as age group increased. p<0.013, Study done by Fernando D et al had similar observations.[5]

The relation between rheumatoid arthritis and BMD was significant (p<0.00). Only 12% patients with RA had normal BMD, 40% patients had osteopenia and 48% patients had osteoporosis.48% patients without RA had normal BMD while 32% where osteopenic and 20% had osteoporosis.

The relation between rheumatoid arthritis and vitamin D was significant (p=0.00). Only 16% patients with RA were vitamin D sufficient, while 36% had insufficient and 48% had deficient vitamin D levels.40% patients without RA had sufficient, while 40% had insufficient and 20% had deficient vitamin D levels. Similar results were obtained in study done by Aizer et al, Kim et al.[15,16]

33.33% of patients with RA less than 2 years had normal BMD and 33.33% had osteopenia.15.38% patients with RA equal to or more than 2 years and less than 4 years had normal BMD, 69.23% had osteopenia and 15.38% had osteoporosis. All patients with RA more than 4 years had osteoporosis. A study by RF Laan et al on Bone mineral density in patients with recent onset rheumatoid arthritis also suggested that duration of RA was negatively associated with BMD.[18] Correlation of BMD with RA duration was statistically significant (p value=0.0025). Studies done by Guler et al, Richards et al also had similar results.[19,20]

The duration of rheumatoid arthritis was related to vitamin D levels significantly (p<0.013). One third of patients with RA less than 2 years had sufficient vitamin D levels and one third had insufficient levels. 23.08% patients with RA equal to or more than 2 years and less than 4 years had normal vitamin D, 46.5% patients had insufficient and 30.77% patients had vitamin D deficiency, 11.11% patients with RA more than 5 years had insufficient vitamin D levels and 88.89% patients had vitamin D deficiency.

The duration of rheumatoid arthritis was related to vitamin D levels significantly (p<0.013). Studies done by Craig et al, Braun et al had similar observations and results.[21,22]

40% RA patients with high HAQ score had osteopenia and 60% had osteoporosis. Low HAQ score is associated with normal BMD in 60% RA patients. This correlation is statistically significant, p<0.0001. Similar results were obtained in a multicenter cross-sectional study on bone mineral density in rheumatoid arthritis, Italian Study Group on Bone Mass in Rheumatoid Arthritis, by Sinigaglia et al, El Meidany et al.[17,23]

One third of patients with RA less than two years had low DAS score.84.62% RA patients with RA equal to or more than 2 and less than 4 years had moderate DAS score and 15.38% patients had severe DAS score. All the patients with RA more than 4 years had severe DAS score. This correlation is statistically significant. p=0.013. Study done by Kerr et al show similar results.[24]

One third RA patients with normal BMD had low DAS score. All the RA patients with osteopenia had moderate DAS score and all the RA patients with osteoporosis had severe DAS score. (P<0.001). Study done by Aletaha et al show similar results.[25]

Two third RA patients with moderate DAS score had normal vitamin D. 87.75% RA patients with moderate DAS score had insufficient while 23.08% had deficient vitamin D levels. 76.92% RA patients with severe DAS score had deficient vitamin D levels. This correlation is statistically significant. (p <0.001). Study done by Baker et al had similar results.[26]

Limitation of the study was a small sample size but it will serve as mile stone for further research to study vitamin D levels and bone mineral density in a larger sample longitudinally especially in this region.

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