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CASE CONTROL STUDY OF BONE MINERAL DENSITY (BMD) IN PATIENTS WITH RHEUMATOID ARTHRITIS AND CO-RELATION BETWEEN DURATION AND SEVERITY OF THE DISEASE

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ABSTRACT **Introduction:** Rheumatoid arthritis (RA) is a chronic inflammatory disease causing symmetric, peripheral polyarthritis.1-3 People with rheumatoid arthritis are at increased risk of osteoporosis. Hence this study shows the importance of Bone Mineral Density (BMD) measurement in patients with RA as a tool for assessment of disease activity and severity.

Objectives: To evaluate Bone Mineral Density in patients of Rheumatoid Arthritis on treatment and its corelation with duration and severity of disease.

Materials and Methods: Heel bone density was measured on the right heel using DEXA scan. This BMD was correlated with markers of disease activity and RA positivity.4

Results: In our study, there were 50 patients with equal number of controls. 18 patients in study group and 33 patients in control group were <45 years and had normal Z-score while in age group >45 years, 7 and 5 cases in study and control groups respectively had their Z-score within normal range. There were 9 and 2 cases in study and control groups respectively with osteopenia and age <45 years and 10 and 7 cases in study and control group respectively with osteopenia and age > 45 years. There were total 4 and 1 cases of study and control groups respectively (age <45 years) who had osteoporosis while in age group >45 years,3 and 1 cases in study and control groups respectively had osteoporosis. Among the cases who received steroids,14 cases developed osteopenia and 25 had osteoporosis,1 case with normal BMD.

Conclusion: Patients with RA are more susceptible for bone loss in comparison to normal age and gender related subjects. Patients with longer disease duration and positive rheumatoid factor with other markers of disease activity (seropositive RA) are more prone to osteopenia and osteoporosis. Occurrence of joint deformities increases with longer disease duration. Limitation of physical activity and anti-rheumatic therapy (steroids and Disease-modifying antirheumatic drugs) increases the risk of bone loss. All these factors contribute to bone loss independent of each other. Thus, decreased BMD is commonly seen in patients with early, active, erosive disease.

Limitations of the study-Due to COVID-19 pandemic, sample size for cases and control is inadequate.

KEYWORDS : rheumatoid arthritis, bone mineral density, osteopenia, osteoporosis

INTRODUCTION:

Rheumatoid arthritis (RA) is the prototype of the polyarticular, inflammatory, peripheral arthritis, accounts for about one fourth of all patients referred to rheumatologists.1Typically beginning in multiple small joints of the hands and feet in a symmetric fashion, RA has many variations, including months or years of recurrent monoarthritis (palindromic rheumatism) before a typical pattern evolves.2 The symmetry of RA is sometimes overemphasized, and it must be appreciated that this is a general, rough symmetry. The arthritis of RA is typically additive, with sequential involvement of groups of joints. Most joints remain more or less symptomatic as new joints are involved. The earliest joints involved are usually small joints of the hands and feet, but the distal interphalangeal joints are spared until late in the course. Although arthritis is usually the presenting feature of RA, occasional patients have extra-articular features of the disease at roughly the same time or even earlier. Episcleritis, subcutaneous nodules, and pleural effusions are the most frequent early extra-articular features of the disease.

The incidence increases between 25 and 55 years of age, after which it plateaus until the age of 75 and then decreases. The presenting symptoms typically result from inflammation of the joints, tendons, and bursae. Patients often complain of early morning joint stiffness lasting more than 1 hour that decreases with physical activity.

Increased bone loss and decreased bone formation plays a crucial role in bone remodelling at sites of inflammation. Recent evidence shows that inflammation suppresses bone formation. The proinflammatory cytokine -Tumour necrosis factor-α plays a key role in actively suppressing bone formation by enhancing the expression of dickkopf-1 (DKK-1) which is an important inhibitor of the Wnt pathway, which acts to promote osteoblast differentiation and bone formation.3

Osteoporosis is a condition in which the bone becomes less dense and more likely to fracture. The World Health Organization (WHO) operationally defines osteoporosis as a bone density that falls 2.5 standard deviations (SD) below the mean for young healthy adults of the same gender-also referred to as a T-score of 2.5, as measured by DEXA; the term "established osteoporosis" includes the presence of a fragility fracture.8 Studies have found an increased risk of bone loss in individuals with rheumatoid arthritis.(Figure-1) The glucocorticoids often prescribed for the treatment of rheumatoid arthritis can trigger significant bone loss Disease duration of 12 weeks or more is strongly predictive of persistent RA.9. In addition, pain and loss of joint function caused by the disease can result in inactivity, further increasing osteoporosis risk.

AIMS AND OBJECTIVES:

To evaluate bone mineral density in patients of Rheumatoid arthritis and equal number of controls.

Correlation of BMD with severity of the disease.

MATERIAL AND METHODS:

The case control study was conducted in the Department of Medicine, Smt. Kashibai Navale Medical College and General Hospital, Pune during February 2021 to August 2021 after explaining the objectives of the study and taking an informed consent from the patients. Right heel bone density was measured on the using DEXA scan (Dual energy x ray absorptiometry). A DXA scanner is a machine that produces two X ray beams, one is high energy and the other is low energy. It measures the amount of X rays that pass through the bone from each beam which varies depending upon the thickness of the bone. Based on the difference between the two beams, bone density can be measured. A standard graph with T score is obtained. This BMD was correlated with markers of disease activity and RA positivity.9 Other laboratory investigations (eg. Complete blood count, renal function test, liver function test, random blood sugar, serum lipid profile, thyroid function test, erythrocyte sedimentation rate, Rheumatoid factor, C-reactive protein etc.) were done. Data was compiled and tabulated. Statistical analysis was done using IBM software and methods like t-test, chi-square test as and when required. Results were considered to be statistically significant when p value was <0.001.

Number of patients: 50 cases recruited as per the following inclusion and exclusion criteria and equal number of controls with no known history of disease.

INCLUSION CRITERIA:
Patients of rheumatoid arthritis diagnosed as per American College of Rheumatology (ACR) criteria 1987 were included in the study.

EXCLUSION CRITERIA:
Patients of RA with other connective tissue disorders like scleroderma, systemic lupus erythematosus, poliomyelitis etc. (overlap syndrome).
All pregnant and lactating mothers having RA.
All patients of RA who smoke.

Observations:
Mean age in study group was 40.59+11.00 and in control group 41.79+13.87 years. Mean haemoglobin was 9.67+1.54 and 10.03+1.24 in study and control groups respectively. Mean BMD was 0.55+0.11 and 0.59+0.05 in study and control groups respectively while mean T-score was -1.32+1.84 in study group and -0.14+0.09 in control group. Mean Z-score in study group was -0.40+1.69 and in control group 0.41+1.44. On statistical comparison, the difference was statistically highly significant in BMD, T-score, Z-score between study and control groups ($p<0.001$) while it was insignificant in age, haemoglobin and platelet count ($p>0.05$).

Among the male, there were 3 and 14 patients each in study and control group respectively with normal Z-score while among females, 5 and 12 cases in study and control groups respectively had Z-score within normal range and there were 10 and 4 male patients each in study and control group who had osteopenia while among females, 15 and 13 cases in study and control groups respectively had osteopenia.

There were total 7 and 2 patients each in study and control group who had osteoporosis in male group while among females, 10 and 5 cases in study and control groups respectively had Osteoporosis. On statistical comparison of study vs control groups, there was highly significant difference in Z-score among males and females ($p<0.001$)

Table 1: Distribution of cases and controls according to Z-score in relation to gender

Z -score	Cases		Controls		Total
	Male	Female	Male	Female	
Normal	3	5	14	12	34
Osteopenia	10	15	4	13	42
Osteoporosis	7	10	2	5	24
Total	20	30	20	30	100

There were total 34 cases who had their Z-score within normal range and out of these 34 patients, joint deformity was present in 9 patients. Out of these 9 patients, 2 had their disease duration <1 year while 7 patients had their disease duration more than 1-5 years.

In osteopenia group, there were total 42 patients and out of them joint deformity was present in 23 patients. Out of these 23 patients,18 patients had their disease duration >10 years while 1 patient had disease duration between 1-5 years. One patient was found in disease duration groups <1 and 3 patients had their disease duration >5-10 years.

In osteoporosis group, there were total 24 patients and out of them joint deformity was present in 12 patients. Out of these 12 patients, 6 patients had their disease duration >10 years while 4 patients had their disease duration >5-10 years and 2 patients had their disease duration between 1-5 years while no patient was found in disease duration <1 year. There were total 34 cases who had their Z-score within normal range and out of these 34 patients, joint deformity was present in 2 males and 7 females.

Out of these 44 patients with deformities, 12 were males and 32 were females. In osteoporosis group, total 24 patients were found and out of them joint deformity(Figure-2) was present in 12 patients. Out of these 12 patients, 4 were males and 8 were females.

Rheumatoid factor was positive in total 37 patients out of them 58% patients had osteopenia, 41.6% had osteoporosis while in patients with negative rheumatoid factor,16% had osteopenia and 8% had osteoporosis. Among the cases who received steroids, 35% and 62.5% patients developed osteopenia and osteoporosis respectively while 2.5% had normal BMD. On statistical comparison 't' test was applied and the difference was statistically highly significant between Z-score and rheumatoid factor ($p<0.001$). All the co-relations are depicted and presented in Tables 1-5

Table 2: Distribution of cases and controls according to Z-score in relation to rheumatoid factor

Z -score	Rheumatoid factor	
	Positive	Negative
	No. of patients (%)	No. of patients (%)
Normal	1(8)	10(1.25)
Osteopenia	21(58)	2(16)
Osteoporosis	15(41.6)	1(8)
Total	37(100)	13(100)

Table 3: Distribution of cases and controls according to Z score in relation to presence of deformities and duration of disease

Z -score	No. of pts with deformities	Duration of disease	No. of pts
normal	9	<1 year	2
	Male 2 Female 7	1 to 5 years	0
		>5 to 10 years	7
Osteopenia	23	<1 year	1
	Male 6 Female 17	1 to 5 years	1
		>5 to 10 years	3
		>10 years	18
Osteoporosis	12	<1 year	0
	Male 4 Female 8	1 to 5 years	2
		>5 to 10 years	4
		>10 years	6
Total	Male 12 Female 32		

Table 4: Distribution of cases and controls according to Z- score in relation to age

Normal (>-0.99)	18(58.06)	33(91.66)	7(35)	5(38.46)
Osteopenia (-1to -2.49)	9(29.03)	2(5.55)	10(50)	7(53.84)
Osteoporosis (<-2.5)	4(12.90)	1(2.77)	3(15)	1(7.69)
Total	31(100)	36(100)	20(100)	13(100)
Mean Z score	-0.26	1.09	-0.88	-0.89
SD	1.91	1.08	1.52	1.61
T	-7.179		0.026	
P	<0.001		0.980	
	No.(%)z	No.(%)	No.(%)	No.(%)

Table 5: Distribution of cases according to relation of treatment with steroids and BMD

BMD	Received steroids No.(%)	Not on steroidsNo.(%)
Normal	1(2.5)	5(50)
Osteopenia	14(35)	3(30)
Osteoporosis	25(62.5)	2(20)
Total	40(100)	10(100)

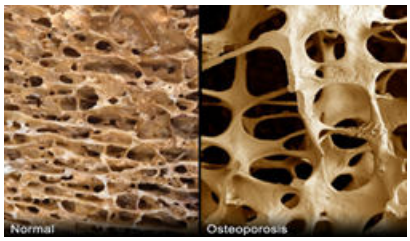

Figure -1. Normal vs Osteoporotic bone

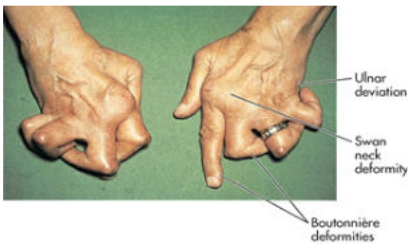

Figure-2. Hand deformities in RA

DISCUSSION:

Osteoporosis and fragility-related fractures are the commonest complications seen in patients with RA and affect the quality of life6. The present study evaluates BMD changes in patients with RA, as well as the effect of severity and drugs (steroids and Disease-modifying antirheumatic drugs) on these changes.

In our study, there were 50 patients with equal number of controls. Total 18 patients in study group and 33 patients in control group who had their age <45 years had normal Z-score while in age group >45 years 7 and 5 cases in study and control groups respectively had their Z-score within normal range.

There were total 9 and 2 cases of study and control groups respectively (age <45 years) who had osteopenia while in age group >45 years 10 and 7 cases in study and control groups respectively had osteopenia. There were total 4 and 1 cases of study and control groups respectively (age <45 years) who had osteoporosis while in age group >45 years 3 and 1 cases in study and control groups respectively had osteopenia.

On the basis of duration of symptoms, patients were divided into 4 groups i.e. <1, 1-5, >5-10 and >10 years. Significant no. of cases showed osteopenia and osteoporosis with disease duration >5-10 years and >10 years. On the basis of age we divided patients into two groups i.e. <45 and >45 years. On statistical comparison of study vs control groups, there was highly significant difference in Z-score in age <45 years group and in age group >45 years. the difference of Z-score between study and control group was insignificant (p>0.05).

It was observed that patients with positive RA factor are more susceptible to osteoporosis as compared to patients with negative RA factor.

These observations supported the fact that patients with RA are more susceptible for bone loss in comparison to normal age and gender related subjects. These findings are in agreement with those of Brand et al10 who reported that patients with RA have a higher risk of low BMD than normal age- and gender matched populations.

Similarly, a study reported by Kim et al11 showed an increased risk of osteoporotic fractures in RA patients in all age groups, regardless of gender, and at various anatomical sites compared with individuals without RA.

In contrast, Curtis et al10 found that the proportion of their RA patients meeting t score criteria for osteoporosis (t score <-2.5 at either the lumbar spine or femoral neck) was only 4%, and Yoon et al1 5 reported that 52% of their patients with early-onset RA had osteoporosis and 39% were classified as having osteopenia.

Our results are also consistent with those of Guler-Yuksel et al11 who reported that RA patients with early, active, erosive disease and a positive rheumatoid factor had more aggressive joint disease and decreased BMD.

CONCLUSION:

Patients with RA are more susceptible to bone loss in comparison to normal age and gender related subjects. Patients with longer duration of disease are more susceptible for developing osteopenia and osteoporosis. Patients with higher disease activity are more susceptible for bone loss. Occurrence of joint deformities increases with longer disease duration. Patients who test positive for rheumatoid factor are also more prone to osteopenia and osteoporosis. Limitation of physical activity impairs the bone mineral density. Patient taking anti rheumatic therapy (steroids and Disease-modifying antirheumatic drugs) are at increased risk of bone loss. All these factors contribute to bone loss independent of each other emphasizing the initiation of osteo-protective therapy in rheumatoid arthritis patients as soon as possible.

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