Original Research Article

Change in bone mineral density in premenopausal women with rheumatoid arthritis managed with or without prednisolone

Deepak Kumar[1], Sanjay Kumar Pandey[2], Sanyal Kumar[3*], Ashok Kumar[4], Deependra Rai[5], Kavita Munjal[6], Madhulika Rani[7], Shivlok Narayan[8]

[1]Associate Professor, Department of Physical Medicine & Rehabilitation, AIIMS, Patna,Bihar,India
[2]Additional Professor & Head, Department of Physical Medicine and Rehabilitation, AIIMS, Patna,Bihar,India
[3]Senior Resident, Department of P M &R, AIIMS, Patna,Bihar,India
[4]Senior Research Fellow, Department of Neurosurgery, PGIMER, Dr. R.M.L. Hospital, New Delhi-110001, India.
[5]Additional Professor & Head, Department of Pulmonary Medicine, AIIMS, Patna,Bihar,India
[6]Senior Research Fellow, Department of Pharmacognosy & Phytochemistry, Jamia Hamdard,New Delhi,India
[7] Consultant (Obstetrics & Gynaecology),Geeta Clinic,Patna, India
[8]Associate Professor, Department of General Medicine, VMMC Hospital, New Delhi, India

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Abstract

Background: Osteoporosis (OP) is being increasingly recognized in inflammatory rheumatic diseases like rheumatoid arthritis (RA), characterized mainly by low bone mass, reduced bone strength, and an increased risk of fractures affecting bone metabolism influencing bone mineral density (BMD) and fracture risk.**Results :**Women in the RA with PRED group did not show lower BMD values than those in the RA without PRED group at baseline, in both lumbar spine L1-L4 (P=0.691), in femoral neck (P=0.332), in radius total (P=0.564) and radius UD (P=0.941). Women in the RA without PRED group had lower T score (Radius UD**)** (P=0.015) value than those in the RA with PRED group. However, during 12 months follow ups there was no statistically significant difference between the two groups in the change in BMD or projection area in the lumbar spine, femoral neck and radius UD.**Conclusion:** Premenopausal RA women with or without prednisolone treatment lost their bone mass statistically similar. Study assumes role of RA on axial bone mass development will be less important with better treatment of RA than our patients received.

Keywords: Bone Mineral Density, Premenopausal, Rheumatoid Arthritis

Introduction

Rheumatoid Arthritis (RA), a chronic systemic inflammatory disease, its prevalence is approximately 1-3% of the population. Inflammatory synovitis which leads to articular cartilage damage with bone erosion & joint space narrowing. Rheumatoid arthritis (RA) is a usual risk associated with osteoporosis its investigation benchmarks dual energy X-ray absorptiometry (DEXA) for calculating bone mineral density (BMD) in RA [1, 2].Early phase of rheumatoid arthritis occurs with loss of periarticular bone [3, 4]. As stated, RA leads to bone loss; however contribution of multiple factors speculates its generalized bone loss [5-7]. Multifactorial postulates like functional loss and long time span of illness imposes a negative effect on bone mineral density (BMD) in case of both axial and peripheral bones. In early stage of RA, the disease activity relates more with functional capacity; though joint damage becomes severely indisposed in later stages. Bone loss may be controlled with effective

**Correspondence*
Dr. Sanyal Kumar
Senior Resident, Department of P M &R, AIIMS, Patna,Bihar,India
E-mail: kumar.sanyal@gmail.com

treatment for RA [8-11].In RA patients, Prevalence of low BMD variably reported in published literature from 25% to 91% [12, 13]. Further, the major site/s of significant BMD loss in RA have also been variably reported in literature like - lumbar spine, distal forearm/lumbar spine, hip or all sites except lumbar vertebrae [14-16].

The corticosteroids-induced bone loss still pendulates around proportion of risk versus benefit ratio among individual RA patients [17]. However, major confounding factor underlying axial bone loss among women with RA is postmenopausal bone loss leading to reduced BMD in them [18].

Our task was to conduct one year follow-up study of BMD in two groups of premenopausal north Indian women suffering from RA distinguishing between patients on continuous corticosteroid treatment and who had not been on systemic corticosteroids prior to the study. Our study generalizes changes in axial BMD prevalence defining to clinical, radiological and biochemical framework of disease.

Methods

This prospective case control study was conducted at the Department of Physical Medicine and Rehabilitation (PMR), in a tertiary care teaching institution in north India. After institutional ethics committee approval for the study and written informed consent taken from subjects, a total of 123 premenopausal females were recruited between February 2018 and January 2020.Our study on 123 cases, we selected 75 premenopausal women on regular menstrual cycles with confirmed cases of RA (28—40 years age) on the basis of eligibility of American college of Rheumatology/ European league Against Rheumatism (ACR/EULAR) 2010 criteria for RA [19] were consecutively follow up for 12 months. All recruited cases we measured BMD twice at the time of recruitment and finally after treatment on 12th month [Fig. 1]. Subjects were divided into two groups: 30 women with RA and without prednisolone and 45 women with RA with PRED group. Women with previous history of any secondary cause of osteoporosis (e.g., celiac disease, type 1 diabetes), hyperparathyroidism, severe vitamin D deficiency (25-hydroxyvitamin-D [25 OHD]<10 ng/ml), history of use of drugs which interfere with BMD (antiepileptics, bisphosphonates), postmenopausal state, liver disease, renal disease, or any severe co morbid state were recognized ineligible for this study.

A detailed medical history, physical examination, BMI, co-morbidities (diabetes mellitus, hypertension and coronary artery disease), history of smoking, regular milk intake ≥300/day and treatment history were noted in all subjects. No compensation was provided for participation in this study.

Measurements

Body weight and height of all women were measured using calibrated scales and standardized stadiometer (nearest 0.1) respectively. They were also examined for swollen and tender joints by an experienced Physician / Physiatrist. Premenopausal women experiencing fragility fractures were evaluated to determine bones fracture despite their adequate estrogenic levels and thereby, other associated environmental factors, such as their diet, smoker or non-smoker etc. were further observed.Diagnosis of RA was done as per 2010 ACR/EULAR criteria [19] and observation was done for joint involvement with scores between 1-5 (1 large joint as 0, 2-10 large joints as 1, 1-3 small joints as 2, 4-10 small joints as 3 and more than 10 joints as 5) and serology score as 0, 2 and 3 (Negative RF and ACPA 0, low titre positive 2, High titre positive 3). Similarly duration of disease and acute phase reactants (CRP and ESR normal 0 and abnormal 1) score was calculated to get the total score. Duration of symptoms and diagnosis (<6 weeks 0 and >6 weeks 1) were also taken into account. Morning stiffness was also measured for its duration of time. Radiographic findings were also been noted.

Blood samples were drawn for measurements of erythrocyte sedimentation rate (ESR, mm/h), ACPA, CRP titre (mg/L), Hb (g/L), TLC, calcium (Ca^{2+}, mmol/L), SGPT/ALT (U/L) and creatitnine (mg/L).In addition, factors such as duration of RA, morning stiffness, joints involvement and other co-morbidities involved if any, had not been evaluated in premenopausal women with RA.BMD measurements in the lumbar spine (L1-L4), total femur, left proximal femur (femoral neck), greater trochancter, radius UD, radius 33 % and radius total were made using dual X-ray absorptiometry (GE, Lunar).In addition, adiposity assessment was also done for measuring total fat mass (kg), total lean mass (kg), android fat (kg), gynoid fat (kg), and total BMC and total fat %.

Statistical analysis

Statically analysis was carried out using statistical software SPSS version 17. The data were presented as no. (%) and median (interquartile ranges). The base line characteristics and other parameters were compared between the groups using Chi-square test for

categorical variable and Mann Whitney U test for continuous variable. The results were reported as difference in proportion (95% CI). P-value <0.05 was considered as statistically significant

Results

The mean ages of subjects at the beginning of the follow-up were 32 years in RA without Prednisalone group and 36 years in RA with Prednisalone groups. Except for marital status there was no statistical difference between the age, weight, menarche age and diet parameters in baseline demographic characteristics table for the two groups (Table 1). Patients in the RA without PRED group had significant higher values of Platelets count (*P*=0.00), ESR rate (*P*=0.05), Blood sugar (*P*=0.04), SGOT (*P*=0.00) and CRP at baseline (*P*=0.00) as compare to RA with PRED group at baseline (Table 2). In comparison of baseline clinical characteristics of diseases between two group rheumatoid factor (*P*=0.05), Joint erosion (*P*=<0.0001) score was higher in RA without PRED group patients than in the RA with PRED group (Table 3). Although in RA without PRED group, the *P* value in duration of symptoms, duration of RA diagnosis, morning stiffness, RA diagnostic factors (Total joint involvement, serology parameter) Joint space narrowing, TJC, SJC, PGH and active co-morbidities was higher though not found statistically significant than the RA with PRED group (Table 3).

During supplementation, sixteen patients (53.3%) doses frequency of once/month and fourteen patients (46.7%) once/week in the RA without PRED group and twenty nine(63.1 %) once/month and seventeen patients (37%) once/month in the RA with PRED group were using vitamin D supplementation (*P*=0.542). Twenty one patients (70%) 500 mg/day and nine patients (30%) 1000 mg/day in the RA without PRED group and Thirty six (78.3 %) 500mg/day and ten (21.7%) 1000mg/day in the RA with PRED group were using calcium supplementation (*P*=0.416).

During treatment profile, patients treated with drug methotrexate in doses regimen of 7.5 mg once/week and 7.5 mg twice/ week in the RA without PRED group were (63.3% and 36.7 %) and in the RA with PRED group were (69.6% and 30.4 %) respectively (*P*=0.572).whereas patients treated with drug hydroxychloroquine in doses regimen of 200mg/OD, 300mg/OD and 400mg/OD in the RA without PRED group were (20%,36.7 %, 43.3%) and in the RA with PRED group were (15.2%,47.8 % ,37%) respectively (*P*=0.622).Other treatment included NSAIDs (90mg, 120mg, and 500mg on OD basis) and Antidepressants (various strength/OD) in the RA without PRED group were (60%, 23.3 %, 16.7), (83.3%) and in the RA with PRED group were (54.3%, 28.3 %, 17.4), (71.7%) with *P* value (0.871, 0.245) (Table 4).None of the patients in the RA without PRED group had previous corticosteroid treatment, all patients out of 45 (100%) in the RA with PRED group had had previous corticosteroid treatment before the outset. Fifteen patients in the RA with PRED group started their use of prednisolone at the beginning of follow-up. Prednisolone in dose strength via Intramuscular (IM) and Intraarticular (IA) (80 mg once /3 month) in the RA with PRED group were (60%, 23.3 %, 16.7), (83.3%) and in the RA with PRED group were (54.3%, 45.7) (Table 4).

Only total lean mass (median: 1.82 kg vs. 2.97 kg) was significantly lower in RA without prednisolone as compared to RA with prednisolone (*P*= 0.01) as comparison of total fat mass, android fat, gynoid fat and in total BMC reduction (Table 5)

Bone mineral results are set out in Table 6.Women in the RA with PRED group did not show lower BMD values than those in the RA without PRED group at baseline, in both lumbar spine L1-L4 (*P*=0.691), in femoral neck(*P*=0.332), in radius total (P=0.564) and radius UD(P=0.941). Women in the RA without PRED group had lower T score (Radius UD**)** (*P*=0.015) value than those in the RA with PRED group. However, during 12 months follow ups there was no statistically significant difference between the two groups in the change in BMD or projection area in the lumbar spine, femoral neck radius total in radius UD.

Discussion

There are few reports establishing the reasons of fall in BMD and fall being linked with menopause [14, 20, 21]. One of the study correlating between spinal and femoral BMD on 456 premenopausal women resulted in stabilized spinal BMD values though there was decrease in femoral BMD in 20-24 years younger group women being in their premenopausal stage [18].Similar findings have been observed in another longitudinal study on premenopausal women where major bone loss occurred in the femoral neck and minimal in the lumbar spine [19, 22-25]. Notably, few variable factors in bone mineral status have found to be nutrient intake and lifestyle changes being listed as one of the healthy strategy in osteoporosis prevention [26]. Although strategies like calcium intake do not result much in changing the outcome in premenopausal women, but change in weight poses positive outcome on bone loss or gain [27-29].In present study, with the

follow up of a year, the mean BMD percentage change in the lumbar spine, total femur, femoral neck, greater trochancter, radius UD and radius was found to be moderate in all groups. The losses in BMD were observed to be more in women without receiving corticosteroid treatment (the RA without PRED group). Study by Shenstone and his coworkers hypothesized that bone loss in RA to be a generalized process as performed on RA patients with less than 6 months disease duration sustaining an increased femoral neck BMD loss over a year [4]. Similar findings observed by Gough and associates on mean percentage bone change in a 12 months follow-up of patients with early RA and corticosteroid treatment [7]. Another investigation on 15 subjects in three groups patients with RA, patients with RA and low-dose corticosteroid treatment, and controls examining mean BMD percentage changes with 2 year follow up observed no statistical differences between the groups being similar to those as in current study. These patients suffered almost over10 years of disease duration [32].In the current study, in women with RA on prednisolone intake (the RA with PRED group) had higher BMD values than those not on the treatment at the start of follow-up. Kalla and coworkers report showed that corticosteroid treated premenopausal RA patients had significantly lower BMD values at the femoral neck in comparison with untreated subjects, but not at the lumbar spine [32]. Tourinho findings showed that premenopausal women with relatively short time span of RA already exhibited significantly lower lumbar spine BMD values and of these 72% were on low-dose corticosteroid treatment [33, 34].We emphasize that in our study that the prednisolone dose was low. There has also been a finding of meta-analysis study done by Van Staa and his research team who found no statistical significant relationship between daily corticosteroid doses with regard to decrease in BMD [35].In our study, women in RA with PRED group were not thriving well during their course of illness resulting in bone loss before the outset. Corticosteroid treatment may limit bone loss owing to very high inflammation [35].

However, it is almost impossible to single out corticosteroids among all possible causes of bone loss in patients with RA. Khaw and associates studied few middle-aged women with their serum concentrations of 25-hydroxyvitamin D supplements relating BMD at the lumbar spine and femoral neck [36].

We observed that25-hydroxyvitamin D levels in the RA with PRED group were higher than those in the RA without PRED group, but the proportion of vitamin D supplementation users was also higher among women in the former group, being in concordance with our results. In both groups, the median level of supplement was same as currently recommended [38].

In current study, the median BMC level with one year follow up was not much changed in the lumbar spine, total femur, left femoral neck, greater trochancter, radius UD and radius total in patients in the RA without PRED group, but there was no statistical difference between the two groups, as subjects in other groups also had bone loss. The mean area percentage loss in the total femur, left proximal femur (femoral neck), greater trochancter, radius UD, and radius total upto12 months was not positively comparable in both groups. Facts leading to realization that the mean BMD change overtime was due to a decrease in both BMC and projection area in the total femur, left proximal femur (femoral neck), greater trochancter, radius UD and radius totalin patients in the RA with PRED group, which defines the statistical difference in BMD change. Reason for low no changes could be short follow-up possibly lower doses and short duration of steroid.

Conclusion

We conclude that according to BMC, premenopausal RA women both with and without prednisolone treatment lost bone statistically similarly. Further, it is assumed that RA role in axial bone mass development during the first decade is not the most important issue. Study assumes that this role will be less important with better treatment of RA than our patients received. The amount of bone loss during treatment with low-grade prednisolone remains controversial.

Abbreviations

OP: Osteoporosis
RA: Rheumatoid Arthritis
BMD: Bone Mineral Density
PRED: Prednisolone
UD: Ultra distal
DEXA: Dual Energy X-Ray Absorptiometry
BMI: Body Mass Index
BMC: Bone Mineral Content
TJC: Total Joint Count
SJC: Swollen Joint Count
PGH: Patient Global Health
ACPA: Anti-Citrullinated Peptide Antibody
ESR: Erythrocyte Sedimentation Rate
Hb: Haemoglobin
TLC: Total Leukocyte Count
NSAID's: Non-Steroidal Anti-inflammatory Drugs
SGPT/ALT: Serum glutamic-pyruvic transaminase / Alanine aminotransferase
SGOT: Serum glutamic-oxaloacetic transaminase

ACR/EULAR: American College of Rheumatology /European League against Rheumatism

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Table 1:Baseline demographic characteristics for RA patients- (without Prednisalone or with Prednisolone)

Demographic parameters		Patient without Prednisolone (n=30) median (IQR)	Patient on Prednisalone (n=45)median (IQR)	*P* Value
Age (years)		32.00 (28.00—39.25)	36.00 (29.50—40.00)	0.512
Weight (kg)		56.50 (45.00—66.25)	52.50 (44.75—58.25)	0.488
Height (Cm)				0.266
Menarche age (years)		14.50 (13.00—15.00)	14.00 (13.00—15.00)	0.174
Marital Status (%)	Married	60	82.6	0.029
	Not married	40	17.4	
Diet (%)	Vegetarian	36.7	30.5	0.629
	Vegetarian+ milk ≥300ml//day	36.7	47.8	
	Non-vegetarian	23.3	15.2	
	Non-Vegetarian + milk ≥300ml//day	3.3	6.5	

Table 2: Baseline hematology and biochemistry characteristics for Patient with RA (without Prednisolone or with Prednisolone

Baseline parameters	Patient without Prednisolone (n=30)median (IQR)	Patient on Prednisolone (n=45)median (IQR)	*P* Value
Heamoglobin (g/l)	10.90 (10.02—12.10)	10.50 (9.70—11.8)	0.190
Platelets count (	1.85 (1.50—2.10)	2.60 (2.10—3.20)	0.000
Total Leucocytes count(/mm^3)	7400 (6360—9100)	8210 (7000—9100)	0.187
Erythrocyte sedimentation rate(mm/hr)	52.00 (28.00—60.00)	62.50(141.00—8500)	0.005
Blood sugar	141.50 (123.00—148.00)	123.00(94.00—145.50)	0.047
SGPT (U/L)	24.00 (19.00—31.15)	27.15 (21.75—35.50)	0.080
SGOT (U/L)	34.00 (25.25—40.00)	21.00 (14.00—27.00)	0.000
C-reactive proteins (mg/L)	6.00 (7.00—22.00)	36.00 (14.00—53.00)	0.000
Anti CCP	81.30 (26.90—222.00)	109.70 (61.00—416.5)	0.294
Serum alkaline phosphate (mg/dl)	112.50(86.00—198.75)	104.00 (86.00—134.00)	0.437
Serum calcium (mg/dl)	9.10 (8.52—9.40)	9.10 (8.90—9.25)	0.625
Serum 25 OH Vit D (ng/ml)	23.00 (14.97—32.00)	24.40 (15.67—32.85)	0.369)
FBG (mg/dl)	87.00 (83.50—89.00)	88.00 (85.00—90.00)	0.478
CRP at baseline	7.00 (6.00—22.00)	36.00 (14.00—53.00)	<0.0001
CRP at 24^{th} months	29.00 (21.7—32.25)	23.00 (16.75—31.00)	0.112

Table 3:Baseline clinical characteristics of disease for Patient with RA (without Prednisolone or with Prednisolone)

Baseline parameters			Patient without Prednisolone (n=30)median (IQR)	Patient on Prednisolone (n=45)median (IQR)	*P* Value
Duration of symptoms (years)			4.5 (2.5—6.0)	3.00 (2.00—6.25)	0.582
Duration of RA Diagnosis (Days)			150 (27.5—365)	60.00 (30.00-365)	0.838
Morning Stiffness (minutes)			45.00 (30.00-60.00)	30.00 (30.00—60.00)	0.516
Rheumatoid (%) Factor (RF)		Positive	83.3	63.0	0.057
		Negative	16.7	37.0	
RA Diagnosis (%)	Total Joint Involvement (%)	1-3 small joints	7.1	4.7	0.393
		4-10 small joints	64.3	55.8	
		≥10 small joints	28.6	39.5	
	Serology Parameter	Negative RF and CCP	0	2.4	0.455
		Low titer positive	32.1	21.4	
		Higher titer positive	67.9	76.2	
X-ray hand -joint space narrowing (JNS) (%)		JSN present	36.7	28.3	0.575
		JSN in Radiocarpal	53.3	65.2	
		JSN absent	10	6.5	
Joint erosion (%)		Absent	46.7	87	<0.0001
		Present	53.3	13	
Total tender joints counts (TJC)			4.00(2.00—9.00)	5.00(3.00—9.00)	0.628
Total swollen joints counts (SJC)			4.00(2.00—7.00)	3.5(2.00—6.00)	0.664
PGH (%)			50 (20.00—60.00)	50 (20.00—60.00)	0.940
Active co-morbidity (%)		Diabetes	3.3	9.4	0.093
		Hypothyroidism	10	6.5	
		Tuberculosis	3.3	8.7	
		Hypertension	7.9	26.1	

Table 4:Drug treatment profile of total 76 RA patients (without Prednisalone or with Prednisolone)

Treatment profile	Dose/Frequency	Patient without Prednisolone (n=30) median (IQR)	Patient on Prednisolone (n=45) median (IQR)	*P* Value
Methotrexate (%)	7.5 mg once/week	63.3	69.6	0.572
	7.5 mg twice/week	36.7	30.4	
Hydroxychroroquine (%)	200 mg /OD	20	15.2	0.622
	300 mg /OD	36.7	14.8	
	400 mg/OD	43.3	37	
Prednisalone (%)	80mg IM once/ 3 month	0	54.3	NA
	80 mg IA once/ 3 month	0	45.7	
NSAIDs (%)	90 mg/OD	60	54.3	0.871
	120 mg/OD	23.3	28.3	
	500 mg/OD	16.7	17.4	
Vitamin D (%)	60,000 IU once/month	53.3	63.1	0.542
	60,000 IU once /week	46.7	37	
Antidepressants (%)	In various strength /OD	83.3	71.7	0.245
Calcium (%)	500 mg/ OD	70	78.3	0.416
	1000 mg/ OD	30	21.7	

Table 5:Adiposity Assessment comparison in Patient with RA (without Prednisalone or with Prednisolone)

Baseline parameters	Patient without Prednisolone (n=30)median (IQR)	Patient on Prednisolone (n=45)median (IQR)	*P* Value
Total fat mass (kg)	3.340 (2.391—4.524)	2.435 (1.784—4.244)	0.121
Total lean mass (kg)	1.827 (1.557—2.190)	2.230 (1.784—21.950)	0.015
Android Fat (kg)	34.225 (29.40—45.065)	29.40 (2.308—45.140)	0.097
Gynoid fat (kg)	4.270 (3.459—7.800)	3.950 (3.198—4.270)	0.060
Total BMC	1.929 (1.775—2.404)	1.857 (1.670—2.146)	0.391
Total Fat Percent	38.10 (32.90—42.87)	38.15 (32.90—43.15)	0.899

Table 6:Bone characteristics at baseline and change up to one years in controls and patients with RA (without Prednisolone or with Prednisolone)

Baseline parameters		Patient without Prednisolone (n=30)median (IQR)	Patient on Prednisolone (n=45)median (IQR)	*P* Value
At Baseline	BMD score (g/cm^2)(L 1- L4)	0.427 (-0.320—0.450)	0.401(0.363—0.460)	0.691
	T score (L 1- L4)	-0.90 (-2.90— -0.400)	-1.55 (-2.52— -4.50)	0.931
	Z score (L 1- L4)	-0.90 (-2.90— -0.400)	1.45 (-2.52— -2.75)	0.965
	BMD score (g/cm^2)(Total Femur)	0.768 (0.700—0.807)	0.772 (0.746— -0.832)	0.332
	T score (Total Femur)	-1.40 (-1.60— -0.85)	-1.20 (-1.52— -0.60)	0.279
	Z score (Total Femur)	1.40 (-1.60— -0.85)	-1.20 (-1.50— -0.60)	0.219
	BMD score (g/cm^2)(Radius total)	0.600 (0.565—0.633)	0.598 (0.568—0.664)	0.564
	T score (Radius total)	-1.300 (-1.90— -0.70)	-1.400 (-1.90— -0.37)	0.628
	Z score (Radius total)	-0.80 (-1.70 — -0.10)	-1.35 (-1.825— -0.37)	0.202
	BMD score (g/cm^2)(Radius UD)	14.98 (12.085—23.93)	23.93 (12.43—28.98)	0.94
	T score (Radius UD)	28.98 (26.71—31.29)	27.30 (1.91—29.90)	0.015
	Z score (Radius UD)	1.461 (0.97—2.66)	1.911(1.12—3.00)	0.102
At 12th month	BMD score (g/cm^2) (L 1- L4)	1.088 (0.99—1.10)	1.06 (0.93—1.09)	0.181
	T score (L 1- L4)	-0.90 (-1.70— -0.60)	-1.40 (-2.00— -7.00)	0.262
	Z score (L 1- L4)	-0.65 (-1.20— -0.10)	0.60 (-1.32— -0.20)	0.418
	BMD score (g/cm^2) (Total Femur)	0.926 (0.724—0.102)	0.871 (0.772— -0.393)	0.346
	T score (Total Femur)	-0.60 (-2.0— -0.10)	-1.00 (-1.90— -0.50)	0.337
	Z score (Total Femur)	-0.40 (-1.45— -0.50)	-0.80 (-1.50— -0.00)	0.651
	BMD score (g/cm2) (Radius total)	0.819 (0.699—0.936)	0.809 (0.730—0.853)	0.524
	T score (Radius total)	-1.60 (-2.30— -0.70)	-1.65 (-2.20— -1.30)	0.448
	Z score (Radius total)	-1.00 (-1.60 — -0.40)	-1.05 (-1.50— -0.670	0.917
	BMD score (g/cm^2) (Radius UD)	0.694 (0.573—0.749)	0.652 (0.571—0.721)	0.465
	T score (L 1- L4) (Radius UD)	-1.40 (-2.40— -0.50)	-1.70 (-2.40— -1.17)	0.391
	Z score (L 1- L4) (Radius UD)	-0.90 (-1.85— -0.25)	-1.00 (-1.80— -0.57)	0.789

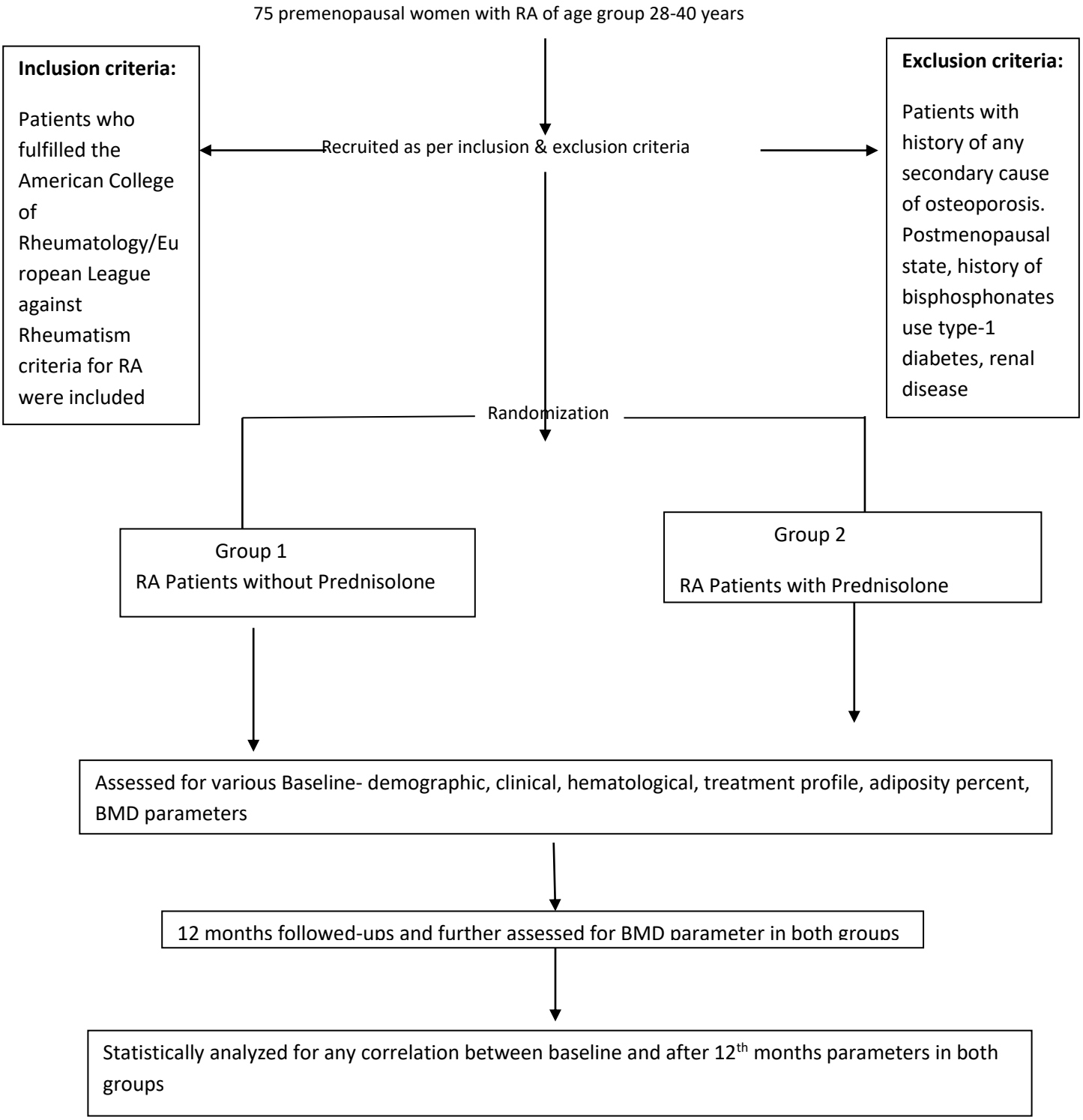

Fig 1:Inclusion and exclusion criterias

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