Relationship between Disease Activity and Calcium Levels with Bone Mineral Density in Rheumatoid Arthritis Patients

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ABSTRACT

Background: Arthritis rheumatoid (AR) is a chronic inflammatory disease that mainly affects the joints. Decreased bone mass and osteoporosis are its complications. Several factors such as dietary calcium, disease activity, physical activity, vitamin D levels, steroids can affect bone mineral density values. **Aim:** The purpose of this study was to determine the relationship between disease activity, calcium levels and bone mineral densitometry in patients with arthritis rheumatoid. **Methods:** 23 AR patients based on the 2010 ACR criteria including the inclusion criteria with a cross sectional study approach that had bone mineral densitometry (BMD) data for the last 1 year. Blood samples were also taken to check the total calcium level, the characteristics of the baseline data were collected, and the disease activity was examined using the DAS 28 LED. The relationship between these factors and the bone mass density was analyzed using the Spearman test. The analysis result was considered significant if $p < 0.05$. **Results:** The results showed that the basic characteristics of the subjects were 45,87 years old, body mass index 24,51 kg / m², duration of illness 3,96 years, steroid dose 3,48 mg, disease activity 4.35 (moderate disease activity), anti CCP 333,87 U / ml, rheumatoid factor (RF) 10,18 IU / ml, methotrexate 12,17 mg, leflunomide 20 mg. There was no significant relationship between serum calcium levels and disease activity with BMD. However, there was a significant relationship between age and BMI with BMD in the femur neck ($p = 0,043$), lumbar 3 ($p = 0,017$) and lumbar 4 ($p = 0,048$). **Conclusion:** There is no relationship between disease activity and calcium levels with bone mass density values in AR patients except for age and BMI.

Keywords: Artritis reumatoid, disease activity, BMD, calcium

INTRODUCTION

Rheumatoid arthritis (AR) is an autoimmune disease of the joints characterized by chronic and progressive systemic

inflammation in which joint synovium are the main targets. Decreased bone mass and osteoporosis are complications in patients with AR. ^[1-4] Systemic chronic inflammation in AR has

a major role in decreasing bone mass and osteoporosis in patients with AR.^[5-8] In AR, there is an overexpression of several inflammatory cytokines tumor necrosis factor (TNF- α), IL-1, IL-6 and IL17 triggering osteoclast activation, differentiation and proliferation induced by receptor activator of nuclear factor K β -Ligand (RANKL) where activation osteoclasts will cause bone mineral reabsorption. Chronic systemic inflammation increases RANKL expression and reduces osteoprotegerin (OPG).^[9-12] OPG is a soluble feed receptor for RANKL that inhibits both osteoclast differentiation and function. In chronic inflammation, inhibition of osteoclast activity occurs through the mechanism of decreasing OPG expression.^[7, 10]

It is known that localized and generalized reduction in bone mineral densitometry (BMD) is the main effect of increased osteoclast activity in AR. Dual-energy X-ray absorptiometry (DXA) is the gold standard for measuring BMD. DXA is a widely used technique to assess general and periarticular reduction in bone mineral density. DXA is able to measure the bone mineral density of integral cortical and trabecular areas of bone.^[13-15]

In patients with AR, calcium administration is very beneficial in maintaining bone health. It is widely known that in AR there is impaired calcium absorption. In addition, the long-term use of steroids results in decreased intestinal calcium absorption and increased renal excretion of calcium. In previous studies, it was found that calcium metabolism disorders in AR patients caused a decrease in blood calcium levels.^[16, 17]

In patients with AR, measurement of disease activity is very important because it reflects the patient's results and response to the therapy given. Persistently high disease activity

can lead to permanent joint damage, disability, and even decreased life expectancy. Tightly controlled disease activity will improve the inflammatory process associated with AR and improve bone metabolism to form normal bone structure again not only in joints but also throughout the body.^[18]

METHODS

This study was conducted with a cross-sectional study approach, conducted on AR patients aged 18-55 years who were diagnosed based on the 2010 ACR criteria for at least 1 year and the steroid dose used was less than 7,5 mg per day in the last 3 months, and the patient had already been done. BMD within a maximum of 1 year and have agreed to the informed consent to participate in the study. The exclusion criteria included having malignancy, chronic kidney disease, systemic lupus erythematosus, chronic liver disease, diabetes mellitus, or having thyroid dysfunction. This research has received ethical permission from the Hospital Research Ethics Commission of dr. Saiful Anwar, General Hospital Malang.

Characteristics of the patient's baseline data were taken consisting of name, age, weight, height, body mass index (BMI), duration of AR illness, rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP), steroid dosage used, the dosage and type of DMARD treatment used by the patient. Disease activity was measured using a disease activity score 28 LED (DAS 28 LED). AR disease activity level was defined as low (DAS 28 $\leq$ 3,2), moderate (3,2 < DAS 28 $\leq$ 5,1), or high (DAS 28 > 5,1). Then, routine biochemical and blood tests were carried out to determine the calcium level and sedimentation rate (ESR).

All samples were examined enzymatically using an auto-analyzer located in the clinical pathology laboratory of Saiful Anwar General Hospital Malang. The serum level of biochemical parameters is determined by standard laboratory procedures. Serum calcium is considered normal 8,6–10,2 mg / dL. The serum calcium used was not adjusted according to the findings in previous studies. ^[20] Bone mass density (g/cm²) was measured by means of a DXA instrument at lumbar 1, lumbar 2, lumbar 3, lumbar 4, lumbar 1-4, and proximal femur (femoral neck, Ward's triangle, and femoral trochanter). Based on the World Health Organization (WHO) criteria, the T-score for bone density is at -1,0 to -2,5 osteopenia, a T-score $\leq$ -2,5 is called osteoporosis and a T-score $\geq$ -1,0 is called normal. ^[21]

All data are presented as means and standard deviation if the data is normally distributed or median and interquartile ranges if the data are not normally distributed. The relationship between data was tested with Pearson's or Spearman's correlation coefficient. A p value $<0,05$ was considered statistically significant. All statistical analyzes were performed with SPSS version 26 software.

RESULTS

The total research subjects who were the subjects were 23 people. With 18-55 years of age, those diagnosed with AR are at least 1 year old, with a steroid dose that is not more than 7,5 mg/day for the last 3 months. There is no chronic liver disease, diabetes mellitus, chronic renal impairment, hyperthyroidism, malignancy and systemic lupus erythematosus.

Based on **Table 1** about the characteristics of the subject above, it is known

that the mean age was $45,87 \pm 12,77$ years and the body mass index was obtained a mean of $24,51 \pm 4,55$ kg / m² which is included in the normal range. The mean serum calcium level was $9,20 \pm 0,36$ mg / dL which is still within the normal range of calcium values. For the mean duration of AR illness suffered was $3,96 \pm 2,46$ years. The average dose of methotrexate drug consumed was $12,17 \pm 4,15$ mg per week. The average dose of steroid consumed per day was $3,48 \pm 1,38$ mg. Meanwhile, the average dose of leflunomide per week was $20 \pm 8,44$ mg. The patient's AR disease activity measured by the DAS 28 LED formula obtained a mean of $4,35 \pm 1,42$ which can be classified as moderate disease activity.

Table 1. Characteristics of Subject

Characteristics	Subject (N=23)
Age (years)	$45,87 \pm 12,77$
IMT (Kg/m ²)	$24,51 \pm 4,55$
Calcium Level (mg/dL)	$9,20 \pm 0,36$
Duration of RA (Years)	$3,96 \pm 2,46$
Methotrexate dosage (mg)	$12,17 \pm 4,15$
Steroid Dosage (mg)	$3,48 \pm 1,38$
Leflunomide Dosage (mg)	$20 \pm 8,44$
Anti-CCP Level (U/ml)	$338,87 \pm 433,91$
Patient with CCP (+)	61,11 %
Patient with CCP (-)	38,89%
Rheumatoid Factor (IU/ml)	$10,18 \pm 28,33$
Patient with RF (+)	21,73 %
Patient with RF (-)	78,26 %
Activity of AR	$4,35 \pm 1,42$

Based on **Table 2**, the results of the proportion value classification of the BMD value based on the T-score on the femur neck were found to be normal patients as much as 0%, patients with osteopenia as much as 91,3%, and osteoporosis patients as much as 8,7%. The value of the proportion of classification of BMD values based on the T-score in lumbar 1-4 was obtained by 0% normal classification patients, 65,22% osteopenia patients, and 34,78% osteoporosis patients.

Table 2. Percentage of BMD Classification

Classification of BMD	Percentage of BMD Result (N=23)
Normal	0%
Osteopenia	65,22%
Osteoporosis	34,78%

From the analysis of the correlation test between disease activity and calcium levels with BMD values in lumbar 1, lumbar 2, lumbar 3, lumbar 4, lumbar 1-4, and proximal femur (femoral neck, Ward's triangle, and femoral trochanter), there was no significant correlation. However, there was a significant correlation between age and BMD value on the femur neck ($p = 0,043$) and lumbar 4 ($p = 0,048$) with a negative correlation coefficient. There was a significant correlation between steroid dose and BMD value on the femur neck ($p = 0,025$) with a positive correlation coefficient.

DISCUSSIONS

AR is a chronic systemic autoimmune disease that primarily affects the joints. Decreased bone mass is one of the complications that occur.^[22] The occurrence of osteoporosis and decreased BMD resulted in osteoporosis and decreased BMD was found in the spine and hips by 11% and 25% in AR patients, respectively.^[14] The risk of osteoporosis in AR is 2 times higher than that of controls. The prevalence in various parts of the world is reported to be between 22% and 36%.^[23]

In this study, it was found that there were no normal BMD in the patient both on the femur neck and at L1-4, osteopenia as much as 65,22% and osteoporosis as much as 34,78%, although from the patient's basic characteristics, the mean age of the patient was 45,87 years. This indicates a decrease in bone mass and osteoporosis. A substantial decrease in bone

mass usually occurs around age 65 in men and 50 years in women. Women can maintain their peak bone mass density until menopause.^[24-26] These results are consistent with existing literature that AR increases the risk of decreased bone mass and osteoporosis.^[22, 27]

The osteoporosis rate was 34,78% and subjects who had osteopenia were 100% a high number. Several factors influenced the results, including the high disease activity, where in this study the disease activity of patients was $4,35 \pm 1,42$ who were included in the moderate disease activity. Disease activity in this study has not yet reached the target, so inflammation that continues to eat will increase the risk of decreasing bone mass. Negative RF can also affect disease progression and activity in AR, negative RF is often associated with disease activity and higher progressivity so that the risk of decreased bone mass and osteoporosis increases.^[28] Where in this study the research subjects had a negative dominant RF. The dominant anti-CCP factor was positive in this study, where anti-CCP based on previous studies correlated with the progression of AR disease.^[29-32]

In this study, there was no significant relationship between disease activity and BMD values in patients. This is different from the hypothesis that the higher the disease activity, the lower the BMD value. Several factors influence the results of this study. Among them is a research design that uses a cross sectional study approach where disease activity and bone mineral density are measured at the same time. Changes in bone density take a long time while disease activity is a condition that can change in a short time. The change in BMD in AR patients who did not receive adequate therapy was 0.2% -1.2% per year.^[27] In AR patients who have

normal BMD results at the beginning will change to osteopenia around 2-7 years.^[21] This is different from the disease activity which can change every month. Several factors that affect bone mass in AR such as calcium supplementation, vitamin D levels, administration of bisphosphonate drugs, serum estradiol levels, and parathyroid hormone levels in this study cannot be controlled.^[16, 33]

In this study, there were no significant results between calcium levels and BMD values. This is different from the hypothesis where AR patients are suspected of having decreased calcium, thus affecting the low BMD value. These results are not in accordance with our hypothesis because the normal calcium levels in this study are caused by a process of calcium balance and homeostasis which is played by the 3 main mechanisms of intestinal absorption, renal reabsorption, and bone turnover. The main mechanism above is regulated by the interaction of parathyroid hormone, 1,25-dihydroxyvitamins, calcium ions and their receptors in the intestines, kidneys. The homeostasis process aims to maintain normal plasma calcium levels. Intestinal and renal absorption of calcium stimulates bone formation and remodeling. On the other hand, if the absorption rate is reduced, it will stimulate bone reabsorption.^[34, 35] The results of this study are consistent with previous studies where serum calcium levels did not affect the value of BMD.^[35-37]

In this study, there was a significant relationship between age and BMD values for Femur Neck ($p = 0,043$), Lumbar 3 ($p = 0,017$), and Lumbar 4 ($p = 0,048$) even though the patient's average age was 45,87 years. With a negative correlation direction, which indicates that the higher the age, the lower the BMD value. It is

known that there is no substantial reduction in bone mass in men up to age 65 and women until menopause.^[24-26] The results of this study are consistent with previous studies that in newly diagnosed AR patients with symptom duration <2 years, 11.3% showed osteoporosis and 24,7% had decreased bone mass density, even in younger AR patients aged 20-49 years, 2,4% had osteoporosis and 21,6% had low bone mass density.^[21, 38] These results are consistent with the existing literature that AR increases the risk of decreased bone mass and osteoporosis.^[22, 27]

In this study, there was a significant relationship between BMI and bone mass density at the femur neck ($p = 0,045$) and the great trochanter ($p = 0,018$) with the r value at both locations which indicates that the greater the BMI value, the greater the value of BMD. These results are consistent with the literature that ideal BMI is associated with a good BMD value, this is because BMI itself is an independent risk factor for osteoporosis.^[39] In addition, a study states that the ideal BMI is related to a healthy diet where nutrients such as calcium, protein, and other nutrients are consumed in sufficient quantities so that in the end, results in good BMD values.^[40] In patients with AR, a chronic inflammatory disease, inflammatory mediators such as (TNF- α) and interleukin 6 (IL-6) are known to play a role in muscle proteolysis, mitochondrial muscle dysfunction, and insulin resistance. And TNF- α and IL-6 inhibition in AR patients will increase muscle mass and body weight.^[41, 42] The results of this study are consistent with another study in which half of the patients with AR are likely to experience rheumatoid cachexia, a condition significantly associated with activity. disease and low hip BMD values.^[43]

Table 3. The correlation coefficient between bone mass density values and disease activity, calcium levels, duration of AR, BMI, age and steroid dose (n = 23)

Variable	Femur Neck			Ward			Great Trochanter			L1			L2			L3			L4			L1-L4		
	r	p		r	p		r	p		r	p		r	p		r	p		r	p		r	p	
Disease Activity	0,136	0,536		0,023	0,918		-0,029	0,896		-0,061	0,783		-0,262	0,228		0,049	0,823		-0,073	0,740		0,040	0,856	
Calcium	0,318	0,140		0,224	0,304		0,008	0,970		0,017	0,937		-0,038	0,862		0,111	0,615		0,098	0,657		0,209	0,339	
Age	-0,426	0,043		-0,331	0,123		0,036	0,869		-0,353	0,099		-0,295	0,172		-0,492	0,017		-0,416	0,048		-0,401	0,058	
Steroid	0,467	0,025		0,311	0,148		0,380	0,074		0,282	0,192		-0,156	0,478		-0,068	0,757		-0,058	0,791		0,117	0,595	
Duration of AR	-0,230	0,291		-0,345	0,107		-0,115	0,601		-0,130	0,554		-0,003	0,989		0,063	0,776		0,038	0,862		-0,152	0,488	
BMI	0,422	0,045		0,319	0,138		0,489	0,018		-0,189	0,387		-0,261	0,229		-0,162	0,460		-0,056	0,798		0,054	0,805	
Anti CCP	-0,137	0,589		-0,278	0,265		0,027	0,915		0,180	0,476		0,090	0,723		0,120	0,635		0,242	0,333		0,253	0,311	
RF	-0,028	0,899		-0,107	0,625		-0,044	0,841		0,056	0,801		0,253	0,243		0,258	0,235		0,232	0,288		0,174	0,426	

CONCLUSION

There was no correlation between disease activity and calcium levels and BMD values in AR patients. There was a correlation between age and BMI with BMD values in AR patients. (As shown in the Table 3)

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