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Effect of the Period of Glucocorticoid Administration on Bone Quality in Patients with Autoimmune Inflammatory Rheumatism Disease (AIIRD)

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ABSTRACT

Introduction
Inflammatory autoimmune rheumatic disease (AIIRD) such as rheumatoid arthritis, systemic lupus erythematosus, and Sjogren's syndrome often requires long-term glucocorticoid therapy. Despite its effectiveness, glucocorticoids are recognized to cause decreased bone quality and increase the risk of osteoporosis. This study aims to evaluate the effect of the period of glucocorticoid administration on bone quality parameters in AIIRD patients.

Methods
This study was an observational analytical study with a cross-sectional design. A total of 28 female patients with AIIRD were divided into two groups based on the period of glucocorticoid administration: less than 24 months and more than 24 months. The parameters to be measured included bone mineral density (BMD), Collagen Type I C-Telopeptide (CTX), Vitamin D3 levels, and Calcium Ions. Data analysis was conducted using the Mann-Whitney test and the unpaired t-test with a significance level of $p<0.05$.

Results
There was no statistically significant difference between the two groups on all measured parameters. The mean BMD in the group of less than 24 months was 0.9471 kg/m², while in the group of more than 24 months it was 0.8920 kg/m² ($p>0.05$). The mean CTX also did not differ significantly between the two groups (0.2474 vs. 0.2508 ng/mL; $p>0.05$). Vitamin D3 and Calcium Ion levels showed similar results in the absence of significant differences (Vitamin D3: 15,596 vs. 16,255 ng/mL; Calcium Ion: 1,075 vs. 1,040 mmol/L; $p>0.05$).

Conclusions
The period of glucocorticoid administration does not show a significant effect on bone quality in AIIRD patients in this study. Nonetheless, regular monitoring and an individualized approach are still necessary to prevent bone complications in patients receiving long-term glucocorticoid therapy.

Keywords: AIIRD, bone mineral density, bone quality, glucocorticoids, osteoporosis

Introduction

Autoimmune Inflammatory Rheumatic Disease (AIIRD) is a collection of various disorders that, although different, have similar clinical, laboratory, and immunological manifestations. A basic finding in the pathology of AIIRD is an excessive increase in immune response, is auto-reactive, and is triggered by the presence of certain antigens (Hayter & Cook, 2012)AIIRD can be classified into three groups based on the presence or absence of a proinflammatory response, namely: autoinflammatory, such as ankylosing spondyloarthritis; autoimmune, such as systemic lupus erythematosus (SLE) and Sjogren's Syndrome; as well as conditions with overlapping characteristics, such as rheumatoid arthritis. Regardless of the type of disease, the affected organs are generally infiltrated by auto-reactive immunocytes and pro-inflammatory cytokines. (Yap et al., 2018)Epidemiological studies related to AIIRD in Southeast Asia are still limited. However,

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in East Asia, the most common AIIRD are rheumatoid arthritis (AR), SLE, and Sjogren's Syndrome. In Korea, the prevalence of AR was recorded at 188.5 per 100,000 population, while the prevalence of SLE and Sjogren Syndrome was 38 per 100,000 and 23.5 per 100,000 population, respectively. (Han et al., 2023); (Kim et al., 2018)

Glucocorticoids remain one of the top choices in AIIRD therapy due to their anti-inflammatory and immunosuppressive effects. However, long-term use of glucocorticoids can lead to a decrease in the rate of bone formation, a decrease in the number of osteoblasts, and a decrease in the number and activity of osteocytes. In addition, glucocorticoids increase RANK-ligand expression and suppress osteoprotegerin expression in stromal and osteoblastic cells (Kim et al., 2020) (Den Uyl et al., 2011). Long-term use of glucocorticoids can increase osteoclastic activity and suppress osteoblast activity, thereby increasing the risk of osteoporosis. In patients with rheumatoid arthritis (RA), the use of glucocorticoids at a dose of <2.5 mg/day for 12 months increases the risk of osteoporosis by 1.6 times compared to patients who do not undergo glucocorticoid therapy. Meanwhile, higher doses of glucocorticoids can increase the risk of osteoporosis by up to 6.5. (Hayat & Magrey, 2020)A study at the rheumatology polyclinic of Hasan Sadikin Hospital indicated that 9% of all new rheumatic cases in 2000–2002 experienced osteoporosis side effects due to the use of glucocorticoids. The prevalence of glucocorticoids-induced osteoporosis (GIOP) is estimated to reach 0.9% of the total adult population and increase to 2.5% in the population over 70 years of age.

The use of glucocorticoids is often associated with the risk of side effects in the form of osteoporosis and fractures. Population-based epidemiological studies show that 30–40% of individuals who use glucocorticoids in the long term will develop fractures. Fractures can occur in all types and parts of bone, but they are most common in trabecular bones, especially in the vertebral corpus. A glucocorticoid dose equivalent to ≥5 mg of prednisone per day is closely related to osteoporosis due to an imbalance in the bone remodelling process. In most cases, the risk of fracture increases significantly within the first 3 months of glucocorticoid therapy and continues over time.(Adami & Saag, 2019)
It is significantly affected by the dose and period of glucocorticoid use. Patients taking glucocorticoids in a high dose daily (≥15 mg prednisone) or cumulatively (≥1 g prednisone) had a higher risk of fracture compared to patients taking lower doses. Increased dose and period of glucocorticoid administration are closely related to an increased occurrence of osteoporosis.

This study aims to determine the effect of the period of corticosteroid administration on the bone quality parameters of AIIRD patients, namely CTX levels, Vitamin D3 Levels, Calcium Ions, and BMD. The urgency of this study is to discover when in the period bone loss occurs so that prevention can be carried out as early as possible toward AIIRD patients who are treated with glucocorticoids

Method

This study was a cross-sectional observational analytic study with *a* multistage purposive sampling method. The study was located at the Rheumatology Polyclinic of the Medical Staff Group of the Internal Medicine Hospital dr. Moewardi Surakarta. The population in this study was outpatients at dr Moewardi Hospital. The inclusion criteria of this study were women aged 18-50 years or had not reached menopause, diagnosed with AIIRD (Rheumatoid Arthritis according to the ACR/EULAR diagnosis criteria in 2021, SLE according to the ACR EULAR diagnosis criteria in 2019, and Sjogren's Syndrome according to the ACR EULAR diagnosis criteria in 2016), willing to participate in this study, receiving Glucocorticosteroid therapy equivalent to Methyl Prednisolone at a dose of more than 4 mg/day. Exclusion criteria were patients with routine antiosteoporosis therapy, Metastases to the bones, with severe chronic disease comorbidities. It obtained 28 study subjects who were divided into groups of <24 months and >24 months. Each group was measured for their level of CTX, Vitamin D3, and Calcium Ions, BMD *(*Bone Mass Densitometry *).* The data were depicted in the form of demographic data with mean + standard deviation. Difference tests before and after treatment were performed at the end of the study with normal and homogeneous data t-tests; if they were not homogeneous and normal, then the Mann-Whitney test would be used. P would be significant if $p < 0.05$.

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Result

This study obtained 28 study subjects consisting of 14 people in the <24 months and >24 months groups. The subjects of the test group in the study were patients with AIIRD (SLE, AR, and Sjögren's Syndrome) at the dr. Moewardi Regional General Hospital Surakarta, and met the inclusion and exclusion criteria in this study. The characteristics of the study subjects can be seen in Table 1.

Table 1. Characteristics of Study Subjects

Characteristic	Frequency	Average	%
Gender			
- Female	28	9	100
- Age		36,82	
Diagnosis			
- SLE	13		46.42
- AR	10		35.70
- SLE + AR	0		06
- SLE + Sjogren's	5		17.85
- AR + Sjogren's	0		0

In Table 1. the average age of the subjects in this study was 32.3 ± 4.1 years. The ages of the youngest and oldest subjects in this study were 19 and 49 years, respectively. In this study, 100% of the subjects were female. Of the entire study sample, 13 subjects (46.62%) were patients with SLE diagnosis, 10 subjects (35.70%) were AR patients, while 5 subjects (17.85%) were patients with SLE and Sjogren's Syndrome.

The normality test using the Shapiro-Wilk test showed that both the BMD and CTX variables have a significance value of less than 0.05, indicating that the data for both variables are not normally distributed. Meanwhile, in the variables Osteocalcin and Vitamin D3, a value of sig > 0.05 was obtained, which means that the two data are distributed normally. The homogeneity test obtained p> 0.05 in all groups, which shows homogeneous data. To see the comparison between BMD and CTX in the control and therapy groups, the Mann-Whitney test was used. An unpaired T-test was used to compare Ca Ion and Vitamin D3 levels in the control and therapy group.

***Bone Marrow Density* (BMD)**

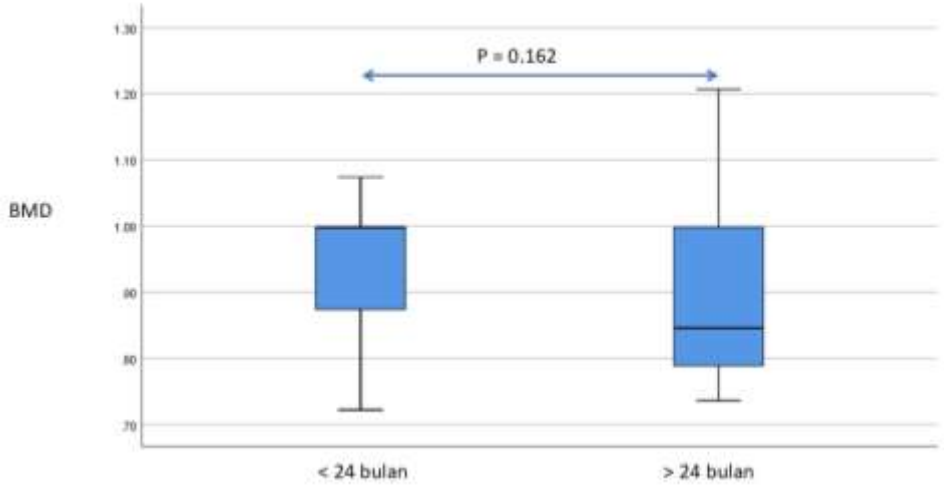

Figure 1. Bone Marrow Density Graph

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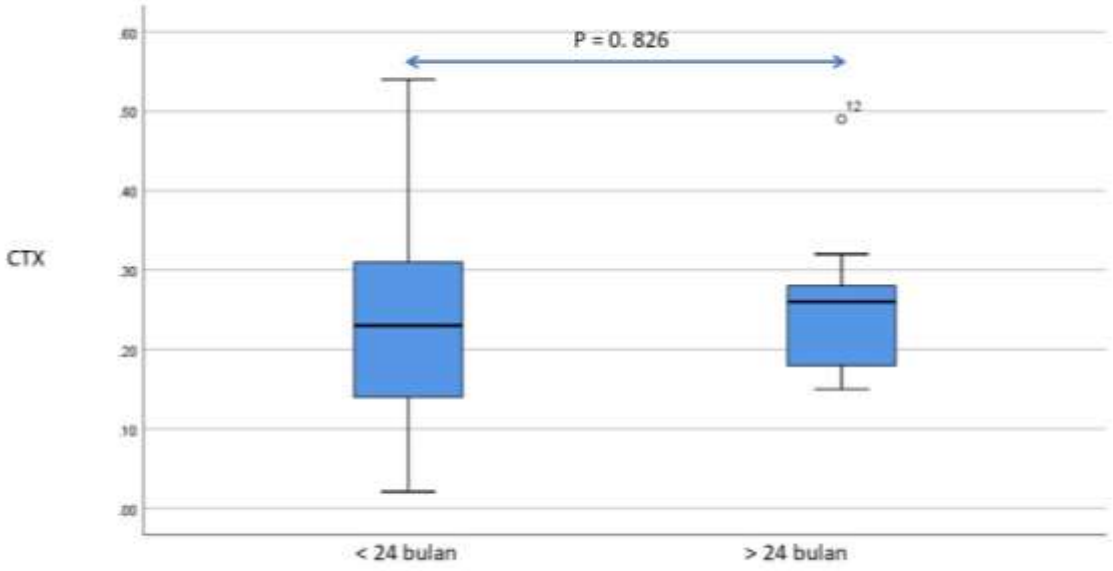
From the results of the Mann Whitney's Difference test a p > 0.05 was obtained which showed that there was no statistically significant difference between the BMD results in the control and therapy groups. The average <24-month group was 0.9471 kg/m2 higher than the >24-month group, which was 0.8920 kg/m2.

***C-Telopeptide* (CTX)**



Gambar 4.2. Grafik CTX

From the results of the test for the mean difference using the Mann-Whitney, a p > 0.05 was obtained, indicating that there was no statistically significant difference between the CTX results at <24 months and >24 months; nor was there statistically significant difference in CTX changes. The mean <24-month group was 0.2474 ng/mL lower than the >24-month group, which was 0.2508 ng/mL.

Vitamin D3

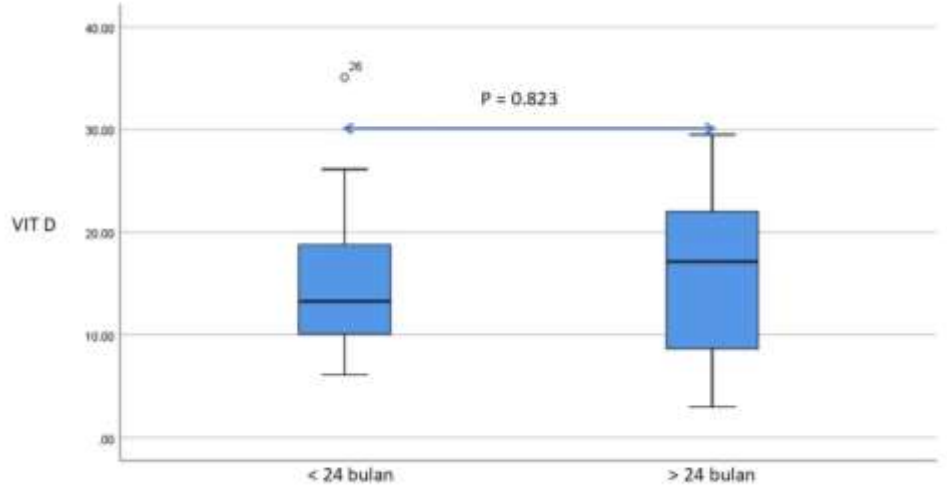


Figure 4.2. Vitamin D3 Graph

From the results of the average difference using the Unpaired T-Test, the result was p> 0.05, showing that there was no statistically significant difference between the results of

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Vitamin D3 in the <24 months and >24 months groups. The average < 24-month group was 15,596 ng/ml, lower than the >24-month group, which was 16,255 ng/ml.

Ca Ion

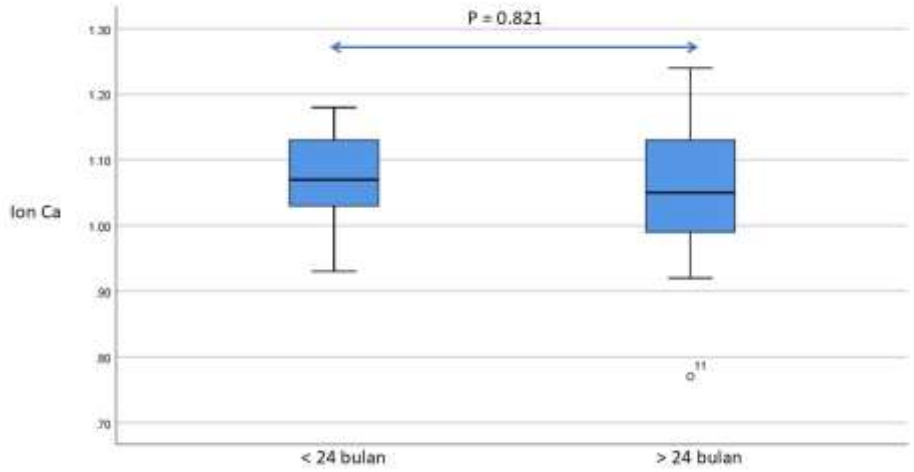

Figure 7. Ca Ion Graph

From the results of the average difference test using the Unpaired T-Test, a result of p > 0.05 was obtained, showing that there was no statistically significant difference between the results of Ca Ions in the <24 Months and >24 Months groups. The average <24 months group was 1,075 mmol/l, higher than the >24-month group, which was 1,040 mmol/l.

Table 2. Statistcal Analisis

Parameter	P-Value
Bone Marrow Density	0.162[a]
C-Telopeptide (CTX)	0.826[a]
Vitamin D3	0.823[b]
Ca Ion	0.821[b]

a Mann-Withney test, b Unpaired T-Test, CI 95% Significat p<0.05

Discussion

The results of this study showed no statistically significant differences in bone mineral density (BMD), Collagen Type I C-Telopeptide (CTX), Vitamin D3, and Calcium Ion levels between patients who received glucocorticoid therapy for less than 24 months compared to those with more than 24 months. This indicates that long-term use of glucocorticoids does not necessarily lead to decreased bone quality in patients with inflammatory autoimmune rheumatic disease (AIIRD). The absence of significant changes in BMD is in line with previous studies that suggest that glucocorticoid use, even for a long duration, does not necessarily have an impact on bone loss in certain populations. For example, a study in rheumatoid arthritis patients discovers no significant difference in BMD between long-term and short-term glucocorticoid users (Fiehn, 2020). Similar to the results of this study in a study by Kuniyil et al, in 2021, there is a significant decrease in BMD and BMC in pediatric patients who receive steroid therapy for 2-6 weeks. In another similar study, the administration of GC in RA triggers CTX and BMD levels to decrease, and improves after the administration of anti-RANKL (Denosumab) through 2 subcutaneous administrations .

This suggests that the effects of glucocorticoids on bones can be affected by a variety of factors, including the level of inflammation, dosage, and characteristics of the patient.

The findings in CTX also support previous study showing that glucocorticoid therapy does not necessarily have a significant impact on markers of bone resorption. Rodan et al. (2020) states that the activity of osteoclasts and osteoblasts can be compensated, so that the stability of bone remodelling is maintained even though bone formation is inhibited by glucocorticoids. This mechanism highlights the variation in biological responses between individuals to glucocorticoid therapy. Similar results are found in Vitamin D3 and Calcium Ions, where long-term glucocorticoid therapy does not cause clinically significant changes. This is contrary to a previous study that stated that glucocorticoids could inhibit calcium absorption and decrease the activity of Vitamin D3. Long-term administration of GC caused osteoblast and osteocyte apoptosis as well as increased osteoclastogenesis, thus causing an imbalance of bone remodelling. The final result was a decrease in bone density to osteoporosis (Den Uyl et al., 2011)

In long-term GC administration, it causes the activation of hydrolase so that the vitamin D level decreases. The administration of GC also decreases the absorption of calcium in the intestines and resorption in the kidneys so that the levels in the blood decrease. A decrease in calcium levels will spur the parathyroid hormone to be produced more, so that osteoclastic activity increases so and calcium levels will become normal. However, this study has some limitations that need to be considered. Small sample sizes can limit the statistical power of detecting minor differences between groups. In addition, the cross-sectional design of the study does not allow the determination of cause-and-effect relationships, so it is necessary to be cautious in interpreting the results.

The study was also conducted in one research center, so it did not reflect regional variations in treatment approaches or differences in patient demographic characteristics. Multi-centre studies involving larger and more diverse populations are urgently needed to ensure the validity and generalization of these findings. In addition to these limitations, it is important to consider that glucocorticoid therapy must be carried out with a personalized approach. Monitoring osteoporosis risk factors, such as age, gender, and comorbidities, is essential to prevent long-term complications. Calcium and Vitamin D3 supplementation, as well as osteoporosis therapy if needed, can be a mitigation strategy to prevent glucocorticoid side effects on bones.

Overall, this study provides new insights into the impact of glucocorticoid therapy on the bone quality of AIIRD patients. Although the results show that this therapy does not significantly impair bone quality, preventive interventions are still needed to protect patients from more serious complications in the future.

Conclusion

There is an increase in CTX levels and a decrease in Ca Ion and Vitamin D levels in AIIRD patients with the use of glucocorticoids for more than 24 months compared to less than 24 months. There is a decrease in bone density in AIIRD patients with the use of glucocorticoids for more than 24 months compared to less than 24 months. Meanwhile is no significant difference in bone density and bone turnover between the administration of glucocorticoids for less than 24 months and more than 24 months.

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