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Original Article

Correlation between serum bone remodeling biomarkers and CTX-1 levels among patients with rheumatoid arthritis: A cross-sectional study at a provincial referral hospital in Indonesia

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Abstract

Rheumatoid arthritis (RA) is associated with accelerated bone loss, partly mediated by dysregulation of the receptor activator of nuclear factor-κB (RANK)/RANK ligand (RANKL)/osteoprotegerin (OPG) pathway, which regulates osteoclast activity. Carboxy-terminal cross-linked telopeptide of type I collagen (CTX-1) is a biochemical marker of bone resorption and may reflect increased skeletal turnover in RA. Although previous studies have evaluated RANKL, OPG, and the RANKL/OPG ratio in relation to bone mineral density, osteoporosis, and fracture risk, the correlations of circulating RANK, RANKL, and OPG with CTX-1 remain insufficiently characterized in patients with RA. The aim of this study was to evaluate the correlations of serum RANK, RANKL, and OPG levels with serum CTX-1 levels in patients with RA. An analytical cross-sectional study was conducted at a provincial referral hospital in Padang, Indonesia, from July to December 2024, during which patients with RA were recruited through consecutive sampling. Serum RANK, RANKL, OPG, and CTX-1 concentrations were measured using enzyme-linked immunosorbent assays. Correlations were assessed using Pearson's correlation analysis. The mean age of the patients was 40.30±5.08 years. The mean serum concentrations of RANK, RANKL, OPG, and CTX-1 were 5.20±2.83, 6.55±3.14, 0.17±0.09, and 2.10±1.10 ng/mL, respectively. Serum RANK and RANKL levels showed very strong positive correlations with CTX-1 levels (r=0.928 and r=0.929, respectively; both p<0.001). Serum OPG levels also showed a strong positive correlation with CTX-1 levels (r=0.786; p<0.001). These findings suggest that circulating components of the RANK/RANKL/OPG pathway are associated with biochemical bone resorption in patients with RA. However, a larger longitudinal study incorporating disease activity, treatment exposure and bone mineral density is required to determine their clinical relevance.

Keywords: Rheumatoid arthritis, RANK, RANKL, OPG, CTX-1

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Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by persistent synovial inflammation and progressive cartilage and bone damage. When inadequately controlled, RA may lead to irreversible joint destruction, disability, reduced quality of life, and premature mortality [1]. The disease affects approximately 0.5–1% of the global population, with a higher frequency among women and a peak incidence during middle age [1,2]. Although

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nationally representative data for Indonesia remain limited, available estimates and health-service records indicate a substantial burden of RA and other inflammatory joint disorders [3].

Osteoporosis and fragility fractures are important complications of RA. Bone loss may occur both locally, near inflamed joints, and systemically, reflecting the combined effects of chronic inflammation, reduced physical activity, disease-related disability, and treatment exposures. The prevalence of osteoporosis among patients with RA has been estimated at approximately 30% and may be considerably higher among postmenopausal women [2]. Moreover, fracture risk in RA may be associated with disease activity and the extent of systemic inflammation [4].

Bone homeostasis is maintained through a tightly regulated balance between osteoclast-mediated bone resorption and osteoblast-mediated bone formation. A central regulator of this process is the receptor activator of nuclear factor-κB (RANK)/RANK ligand (RANKL)/osteoprotegerin (OPG) pathway. Binding of RANKL to RANK promotes osteoclast differentiation, activation, and survival, whereas OPG acts as a soluble decoy receptor that prevents RANKL–RANK interaction and thereby limits osteoclastogenesis [5]. In RA, pro-inflammatory cytokines produced within the synovium may enhance RANKL expression and osteoclast activity, contributing to periarticular erosion and generalized bone loss [6,7].

Carboxy-terminal cross-linked telopeptide of type I collagen (CTX-1) is released during the degradation of type I collagen and is widely used as a biochemical marker of bone resorption. Since type I collagen is the principal organic component of bone, circulating CTX-1 concentrations may reflect the intensity of osteoclastic activity and skeletal turnover [6,8]. Bone turnover markers may complement bone mineral density assessment by providing information on ongoing changes in bone remodeling and may assist in evaluating skeletal deterioration in patients with RA [8,9].

Previous studies have primarily examined RANKL, OPG, and the RANKL/OPG ratio in relation to bone mineral density, osteoporosis, and fracture risk [8,10]. However, the relationships of circulating RANK, RANKL, and OPG with CTX-1 remain insufficiently characterized in patients with RA. Therefore, this study aimed to evaluate the correlations of serum RANK, RANKL, and OPG levels with serum CTX-1 levels in patients with RA.

Methods

Study design and setting

This analytical cross-sectional study was conducted at the Rheumatology Outpatient Clinic of Dr. M. Djamil General Hospital, Padang, Indonesia, from July to December 2024. The study evaluated the correlations of RANK, RANKL, and OPG levels with serum CTX-1 levels in patients with RA.

Sample and criteria

Patients were eligible if they met the American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) classification criteria for RA, were newly diagnosed or had established RA while receiving prednisone at a dose of ≤5 mg/day or an equivalent corticosteroid dose for at least three months, and provided written informed consent.

Patients were excluded if they were postmenopausal or had systemic lupus erythematosus, mixed connective tissue disease, systemic sclerosis, a glomerular filtration rate (GFR) of <60 mL/min/1.73 m², obesity defined as a body mass index (BMI) of >30 kg/m², malignancy, or an acute infection.

Sample size and sampling method

The sample size was calculated for a two-sided Pearson correlation test, assuming an anticipated correlation coefficient of 0.50, a statistical power of 80%, and a significance level of 0.05. The calculation yielded a minimum requirement of 29 participants, which was rounded to 30 patients with RA. Eligible patients were recruited using consecutive sampling, whereby all patients who met the eligibility criteria were enrolled sequentially until the required sample size was reached.

Study variables

The primary study variables were serum RANK, RANKL, OPG, and CTX-1 levels. Serum RANK, RANKL, and OPG levels were considered the independent variables, whereas serum CTX-1 level was the outcome variable reflecting bone resorption. Participant characteristics included age, sex, BMI, corticosteroid dose, disease-modifying antirheumatic drug (DMARD) use, and GFR.

Data collection and study procedure

Potential participants were screened for eligibility through interviews and medical-record review. Menopausal status, coexisting autoimmune diseases, renal function, BMI, malignancy, acute infection, corticosteroid use, and DMARD therapy were assessed during screening. Eligible patients were consecutively enrolled after providing written informed consent.

Venous blood was collected from each participant and centrifuged at room temperature to obtain serum. Serum RANK, RANKL, OPG, and CTX-1 concentrations were measured using enzyme-linked immunosorbent assay (ELISA) kits produced by Bioassay Technology Laboratory, Shanghai, China, according to the manufacturers' instructions. The kits used were the Human RANK ELISA kit, Human RANKL ELISA kit, Human OPG ELISA kit and Human CTX-1 ELISA kit. Briefly, 50 µL of serum was added to each designated well, followed by 50 µL of antibody cocktail. The plate was incubated for 1 hour at room temperature with shaking at 400 rpm and subsequently washed three times using 500 µL of wash buffer. Next, 100 µL of tetramethylbenzidine substrate was added, and the plate was incubated in the dark for 10 minutes with shaking at 400 rpm. The reaction was terminated by adding 100 µL of stop solution. Absorbance was measured using an ELISA microplate reader, and biomarker concentrations were expressed in ng/mL.

Data analysis

Categorical variables were summarized as frequencies and percentages, whereas continuous variables were presented as means and standard deviations. The normality of continuous variables was assessed using the Shapiro–Wilk test. Because serum RANK, RANKL, OPG, and CTX-1 levels were normally distributed, the correlations of RANK, RANKL, and OPG levels with CTX-1 levels were evaluated using Pearson's correlation analysis. Correlation coefficients were interpreted according to their absolute values as weak (r<0.40), moderate (r=0.40–0.59), strong (r=0.60–0.79), or very strong (r≥0.80). All statistical tests were two-sided, and p<0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics, version 27.0.1 (IBM Corp., Armonk, NY, USA).

Results

Characteristics of research respondents

A total of 30 patients with RA were included, and their characteristics are presented in **Table 1**. All patients were women, with a mean age of 40.30 (5.08) years. Most patients received methylprednisolone at a dose of 4 mg/day (70.0%), whereas 10.0% each received methylprednisolone 2 mg/day, prednisone 2.5 mg/day, or prednisone 5 mg/day. Methotrexate was the most commonly used DMARD (86.7%), followed by leflunomide (13.3%). The mean BMI was 22.28 (3.16) kg/m², with most patients classified as having normal weight (73.3%), followed by overweight (20.0%) and underweight (6.7%). The mean GFR was 100.23 (24.01) mL/min/1.73 m², and 76.7% of patients had a GFR of >90 mL/min/1.73 m².

Table 1. Demographic and clinical characteristics of patients with rheumatoid arthritis included in the study

Characteristics	Frequency (%)
Gender	
Male	0 (0.0)
Female	30 (100.0)
Age (years), mean±SD	40.30±5.08
Corticosteroid dosage	
Methylprednisolone 2 mg	3 (10.0)
Methylprednisolone 4 mg	21 (70.0)

Characteristics	Frequency (%)
Prednisone 2.5 mg	3 (10.0)
Prednisone 5 mg	3 (10.0)
Disease-modifying antirheumatic drug (DMARD)	
Leflunomide	4 (13.3)
Methotrexate	26 (86.7)
Body mass index, mean±SD	22.28±3.16
Underweight	2 (6.7)
Normoweight	22 (73.3)
Overweight	6 (20.0)
Glomerular filtration rate (GFR), mean±SD	100.23±24.01
60–89 mL/min/1.73 m²	7 (23.3)
>90 mL/min/1.73 m²	23 (76.7)

Levels of RANK, RANKL, OPG, CTX-1 in rheumatoid arthritis patients

The serum concentrations of RANK, RANKL, OPG, and CTX-1 in patients with RA are presented in **Table 2**. The mean serum RANK level was 5.20±2.83 ng/mL, while the mean RANKL level was 6.55±3.14 ng/mL. The mean serum OPG concentration was 0.17±0.09 ng/mL, and the mean serum CTX-1 concentration was 2.10±1.10 ng/mL. Among the evaluated biomarkers, RANKL had the highest mean serum concentration, whereas OPG had the lowest.

Table 2. Serum concentrations of RANK, RANKL, OPG, and CTX-1 in patients with rheumatoid arthritis

Serum biomarker (unit)	Mean (SD)
Receptor activator of nuclear factor-κB (RANK) (ng/mL)	5.20 (2.83)
RANK ligand (RANKL) (ng/mL)	6.55 (3.14)
Osteoprotegerin (OPG) (ng/mL)	0.17 (0.09)
Carboxy-terminal cross-linked telopeptide of type I collagen (CTX-1) (ng/mL)	2.10 (1.10)

Correlations of serum RANK, RANKL, and OPG levels with CTX-1 levels in patients with rheumatoid arthritis

Pearson's correlation analysis demonstrated significant positive correlations between each serum biomarker and CTX-1 levels (**Table 3**). Serum RANK levels showed a very strong positive correlation with CTX-1 levels (r=0.928; p<0.001), indicating that patients with higher RANK concentrations tended to have higher CTX-1 concentrations. A similarly very strong positive correlation was observed between serum RANKL and CTX-1 levels (r=0.929; p<0.001) (**Table 3**). Among the evaluated biomarkers, RANKL showed the highest correlation coefficient with CTX-1, although its magnitude was nearly identical to that of RANK.

Serum OPG levels were also significantly and positively correlated with CTX-1 levels, with a strong correlation coefficient (r=0.786; p<0.001) (**Table 3**). Although the association between OPG and CTX-1 was weaker than those observed for RANK and RANKL, it remained statistically significant. Overall, these findings indicate that higher serum RANK, RANKL, and OPG levels were associated with higher serum CTX-1 levels in patients with RA.

Table 3. Correlations of serum RANK, RANKL, and OPG levels with serum CTX-1 levels in patients with rheumatoid arthritis

Serum biomarker	Carboxy-terminal cross-linked telopeptide of type I collagen (CTX-1)	
	r	p-value
Receptor activator of nuclear factor-κB (RANK)	0.928	<0.001
RANK ligand (RANKL)	0.929	<0.001
Osteoprotegerin (OPG)	0.786	<0.001

Discussion

This study demonstrated very strong positive correlations of serum RANK and RANKL levels with CTX-1 levels and a strong positive correlation between OPG and CTX-1 levels in patients with RA. These findings indicate that higher circulating concentrations of components of the RANK/RANKL/OPG pathway were associated with greater biochemical evidence of type I

collagen degradation. However, because of the cross-sectional design, these correlations should not be interpreted as evidence that these biomarkers directly caused increased bone resorption.

All participants were premenopausal women, with a mean age of approximately 40 years. The female predominance and age distribution are broadly consistent with previous Indonesian and international studies of RA, although the proportions of women and clinical characteristics have varied across populations [11-17]. The predominance of women may reflect the established sex disparity in RA, which has been partly attributed to hormonal and immunological differences [18]. Nevertheless, the inclusion of women only limits the generalizability of the findings to men and older or postmenopausal populations, who may have different patterns of bone turnover. Most patients received low-dose corticosteroids and methotrexate. Although low-dose glucocorticoids may support short-term disease control, their skeletal effects depend on the dose, duration, and individual risk profile [19,20]. Treatment exposure is particularly relevant because both glucocorticoids and DMARDs may affect systemic inflammation and bone turnover. Previous studies have also shown that bone turnover, treatment response, hypertension, difficult-to-control disease, and the broader comorbidity burden contribute to clinical heterogeneity among patients with RA [21-24]. Therefore, the observed biomarker correlations may have been influenced by treatment-related and disease-related factors that were not included in the analysis.

Most participants had normal weight and preserved renal function. This relatively restricted population may have reduced the influence of obesity and severe renal impairment on the measured biomarkers. Obesity has been associated with RA risk, inflammatory activity, and altered cytokine production [25-27]. Renal function is also clinically important because impaired clearance may alter circulating concentrations of bone turnover markers. Previous studies have reported variable frequencies and determinants of renal dysfunction among patients with RA [28-30]. Although patients with a GFR below 60 mL/min/1.73 m^2 were excluded, residual variation in renal function may still have contributed to differences in CTX-1 levels.

The very strong correlations of RANK and RANKL with CTX-1 are biologically plausible. RANKL binding to RANK promotes osteoclast differentiation, activation, and survival, thereby increasing bone resorption and the release of CTX-1 from type I collagen. In RA, inflammatory mediators produced within the synovium and other tissues may enhance RANKL expression and osteoclastogenesis, contributing to both local bone erosion and systemic bone loss [31]. Previous research has linked CTX-1 with the clinical and treatment-related characteristics of RA, although direct evidence regarding the correlations of circulating RANK and RANKL with CTX-1 remains limited [32]. These findings therefore provide preliminary evidence that the circulating RANK/RANKL axis is closely associated with biochemical bone resorption in this population.

The positive correlation between OPG and CTX-1 requires more cautious interpretation. OPG is a decoy receptor that inhibits RANKL–RANK binding and is generally considered protective against excessive osteoclastogenesis. Therefore, a positive relationship between OPG and CTX-1 does not necessarily indicate that OPG promotes bone resorption. Instead, higher OPG concentrations may represent a compensatory response to increased RANKL activity, inflammation, or accelerated bone turnover. The circulating OPG concentration alone may also inadequately reflect the balance of the pathway because the RANKL/OPG ratio was not evaluated. Furthermore, renal impairment and systemic inflammation may influence both OPG and bone turnover markers [33,34].

The present findings are consistent with evidence that suppression of inflammation may alter the RANKL/OPG pathway and reduce biochemical markers of bone resorption in RA [34,35]. Nevertheless, CTX-1 is not specific to RA-related joint damage and may reflect systemic skeletal turnover or other clinical processes [36]. Consequently, the correlations observed in this study should not be interpreted as establishing the diagnostic performance of these biomarkers for osteoporosis, fracture risk, or radiographic joint damage. Such applications would require comparison with reference standards such as bone mineral density, fracture-risk assessment, or imaging findings.

This study has some limitations. The sample was small, obtained from a single center, and restricted to premenopausal women without obesity or advanced renal impairment. Disease duration, disease activity, inflammatory markers, autoantibody status, cumulative corticosteroid exposure, DMARD duration, smoking, physical activity, dietary factors, and menopausal

hormone profiles were not assessed. The analyses were also unadjusted, preventing evaluation of whether the observed correlations were independent of potential confounders. In addition, bone mineral density was not evaluated.

Conclusion

Serum RANK and RANKL levels showed very strong positive correlations with serum CTX-1 levels, and serum OPG showed a strong positive correlation with CTX-1 in patients with RA. These findings suggest that circulating components of the RANK/RANKL/OPG pathway may be associated with biochemical bone resorption. However, given the small sample size and cross-sectional design, the findings should be interpreted cautiously and confirmed in larger longitudinal studies incorporating disease activity, treatment exposure, bone mineral density, and fracture outcomes.

Ethics approval

The study protocol has been approved by the Health Research Ethics Committee of Dr. M. Djamil Padang Hospital, Padang, Indonesia (DP.04.03/D.XVI.XI/274/2024).

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Conflict of interest

All authors declare no conflict of interest.

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Underlying data

The data underlying the results of this study can be obtained from the corresponding author upon request.

Declaration of artificial intelligence use

We hereby declare that no artificial intelligence (AI) tools or methodologies were utilized throughout the conduct of this study, including during data collection, analysis, visualization, or manuscript writing. All research activities and outputs were carried out solely by the authors without support from AI-based tools or systems.

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