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Research Article

Serum Magnesium and Uric Acid Levels in Patients with Rheumatoid Arthritis: A Case-Control Study

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disease, characterized by joint pain, stiffness, and deformity. Both environmental determinants and genetic factors play a role in RA development and progression. Oxidative stress due to reactive oxygen species (ROS) can aggravate these symptoms. Studies on trace elements such as magnesium (Mg) and uric acid (UA) suggest that these can be potential treatment targets. Therefore, we designed this study to compare Mg and UA levels in patients with RA and healthy individuals.
Methods: This was a case-control study with 43 patients with RA and 43 healthy controls. Patients with RA were diagnosed based on ACR/EULAR criteria and were categorized by Disease Activity Score 28 (DAS28). Blood samples were collected for laboratory tests, including UA, Mg, C-reactive protein (CRP), and anti-cyclic citrullinated peptide (anti-CCP) antibody levels.
Results: The study found no significant difference in serum UA levels between patients with RA and healthy controls. However, Mg levels were significantly lower in patients with RA. Mg levels were not significantly different according to DAS. A significant inverse correlation was found between Mg levels and CRP serum levels. A receiver operating characteristic (ROC) curve analysis revealed that anti-CCP had high sensitivity for RA diagnosis, with an optimal cut-off point of 32.5 U/ml.
Conclusion: Low Mg levels should be expected in patients with RA. Supplementing Mg may be a helpful treatment approach in this group. In contrast, UA does not appear to be influenced by RA, but its antioxidant properties cannot be entirely disregarded. Moreover, anti-CCP shows high sensitivity as a diagnostic tool for RA.

Keywords: Rheumatoid Arthritis; Magnesium; Uric Acid; Anti-Citrullinated Protein Antibodies; Oxidative Stress

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Background

As a chronic autoimmune disease, rheumatoid arthritis (RA) may cause debilitating musculoskeletal consequences if left untreated (1). This condition can have systemic manifestations and involve other organs such as the kidneys, heart, lungs, and liver (2). Its prevalence ranges from 0.5% to 1%, but can be staggeringly higher in some communities due to genetic predisposition (3). Patients diagnosed with RA may suffer from joint pain, stiffness, and deformity, and tend to have a reduced quality of life (4).

Both genetic and environmental factors are implicated in the development of RA (5). At a molecular level, the symptoms may be aggravated by oxidative stress and free radicals. Oxidative stress is characterized by the accumulation of reactive nitrogen species (RNS) and reactive oxygen species (ROS). These reactive species are also produced under physiological conditions, where they are scavenged and eliminated by antioxidant molecules (6). A reduction in antioxidant activity or an overproduction of these reactive species can cause oxidative stress (7). Accordingly, antioxidant molecules in inflammatory conditions like RA and systemic lupus erythematosus (SLE) can be used as potential treatment targets (8). For example, uric acid (UA), the end product of purine metabolism, is produced in ischemic reperfusion conditions and is considered a biomarker of oxidative stress. Furthermore, recent studies have demonstrated that UA is a scavenger of free radicals (9).

Recently, growing interest has emerged in investigating serum levels of trace elements such as zinc, copper, and magnesium (Mg) in inflammatory conditions (10). Mg is an essential mineral involved in various biochemical processes within the body, including nerve function, muscle contraction, and protein synthesis (11). This element is an obligatory cofactor for an enzyme called gamma-glutamyl transpeptidase (GGT), which plays a key role in glutathione synthesis and is considered the most substantial antioxidant in our bloodstream (12). Despite Mg's anti-inflammatory properties, its effectiveness in treating RA and its exact role in RA's pathogenesis remains uncertain (13, 14).

So far, this study is one of the few in our country that evaluates Mg and UA serum levels in patients with RA. In this study, we aim to compare the serum levels of Mg and UA in patients with RA with those of healthy controls. Our secondary objective is to find possible correlations with other inflammatory biomarkers including C-reactive protein (CRP) and anti-cyclic citrullinated peptide (anti-CCP) antibody.

Methods

Study Design and Participants: The current study was designed as a case-control study, with patients recruited from the outpatient rheumatology clinic of Shahid Beheshti Hospital, Kashan University of Medical Sciences,

Iran, between March 2020 and April 2021. Overall, 43 patients with a definitive diagnosis of RA and 43 healthy controls were enrolled. Controls were similar to cases in terms of ethnicity, cultural background, and sociodemographic characteristics such as age, income, and occupation. The RA diagnosis was based on ACR/EULAR 2010 RA classification criteria. Patients with malignant conditions or regular consumption of supplements were excluded. We used the Disease Activity Score 28 (DAS28) to categorize disease activity into the following: inactive (2.6), mild (2.6-3.2), moderate (3.2-5.1), and high (> 5.1). The Mg level reported in a study by Chavan et al. was used for sample size calculation (15).

In this study, mean Mg level in patients with RA and healthy controls was 1.73 ± 0.46 and 2.12 ± 0.25 mg/dl, respectively. We assumed a type I error (α) of 0.05, and a power (1 - β) of 0.8. Subsequently, the calculated sample size for each group was 22 individuals.

Laboratory Tests: A trained laboratory technician obtained blood samples from all the participants in both groups after 12 hours of fasting. These samples were collected in plain tubes and were delivered to our facility for measurements. We determined the serum UA level (mg/dl) with a calorimetric method using phosphotungstic acid reduction (Pars Azmoon Co., Iran). Serum Mg level (mg/dl) was measured via atomic absorption spectrophotometry (Shimadzu ASC-6100, Japan). We used the enzyme-linked immunosorbent assay (ELISA) to quantify CRP (on a qualitative scale of 1 to 4) and anti-CCP (U/ml) levels. These laboratory tests were performed as part of standard diagnostic procedures at our center, and no extra cost was imposed on patients.

Statistical Analysis: We used descriptive statistics to explore our variables' frequency, mean, and standard deviation (SD). Serum levels of UA and Mg were compared between the two groups by independent samples t-test. To compare UA and Mg levels among patients with different disease activity, an analysis of variance (ANOVA) test was conducted, and analysis of covariance (ANCOVA) was used to adjust for covariates. The Kolmogorov-Smirnov test was used to determine if the continuous variables had normal distribution. For normally distributed variables, we utilized the aforementioned parametric tests; otherwise, their non-parametric equivalent was used. We used chi-square test to detect any association between categorical variables. To adjust for imbalanced observations between the two groups, we developed a logistic regression model and included the potential confounders along with the main predictor of interest. Finally, to assess the predictive value and validity of anti-CCP, we plotted the receiver operating characteristic (ROC) curve. The SPSS software (version 23, IBM Corporation, Armonk, NY, USA) was used for statistical analysis.

Results

A total of 86 individuals (43 patients with RA and 43 healthy subjects) were enrolled in the study. The mean age was not significantly different between the two groups, but the sex distribution differed. The mean age of patients with RA and healthy individuals was 51.00 ± 11.90 and 51.09 ± 11.70, respectively (P = 0.97). The female-to-male ratio in the RA group was 36:7, while it was 26:17 in healthy controls (P = 0.03). Patients with mild, moderate, and high DAS accounted for 8 (18.6%), 26 (60.5%), and 9 (20.9%) cases in the RA group. CRP and rheumatoid factor (RF) were reported on an ordinal scale of 1 to 4, and 1 to 3, respectively, and both of these biomarkers were negative in all participants in the control group. The mean anti-CCP levels in the RA group and healthy controls were 223.18 ± 243.75 U/ml and 9.06 ± 14.01 U/ml, respectively, and the difference was statistically significant (P < 0.001). The baseline characteristics of patients, including age, gender, DAS, and lab results, are summarized in table 1.

Table 1. Baseline characteristics of patients and controls

Variables	Patients with RA	Healthy controls
Age (mean ± SD)	51.00 ± 11.90	51.09 ± 11.70
Gender (F:M)	36:7	26:17
DAS [n (%)]		
Mild	8 (18.6)	-
Moderate	26 (60.5)	-
Severe	9 (20.9)	-
Magnesium level (mg/dl) (mean ± SD)	2.18 ± 0.15	2.27 ± 0.24
Uric acid level (mg/dl) (mean ± SD)	5.39 ± 1.60	5.55 ± 1.50

RA: Rheumatoid arthritis; DAS: Disease Activity Score; SD: Standard deviation

The mean serum level of UA was not significantly different between the two groups (5.39 ± 1.60 in patients with RA vs. 5.55 ± 1.50 in controls, P = 0.62), even after adjusting for sex (P = 0.57). Based on DAS, UA level was not statistically different among patients with RA (P = 0.79). Furthermore, we did not observe an association between UA level and anti-CCP levels (P = 0.33). In contrast to UA, serum levels of Mg were significantly lower in patients with RA compared to healthy controls after adjusting for sex (2.18 ± 0.15 vs. 2.27 ± 0.24, respectively, P = 0.02). On the other hand, Mg levels were not associated with disease activity (P = 0.26). Moreover, we found a significant correlation between Mg and CRP levels according to Spearman's rank correlation test (r = -0.224, P = 0.04). However, we could not detect a significant correlation between anti-CCP levels and Mg levels (P = 0.44). Ultimately, we plotted an ROC curve based on anti-CCP levels for RA diagnosis, which resulted in a statistically significant model with an area under the curve (AUC) of 0.857. The optimal cut-off point for anti-CCP was 32.5 U/ml with a sensitivity of 0.651 and specificity of 0.90. The ROC plot is depicted in figure 1.

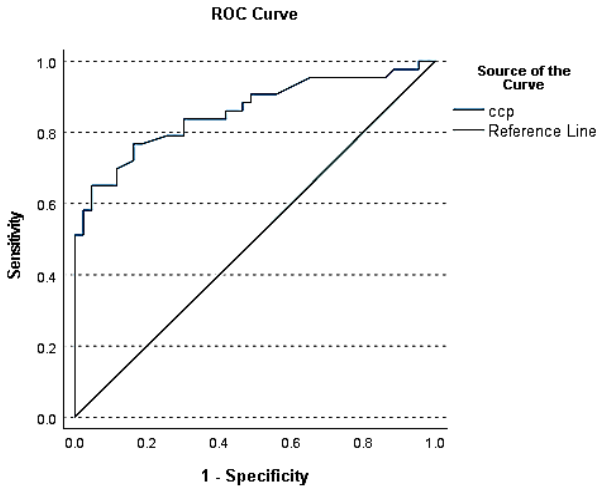

Figure 1. Receiver operating characteristic (ROC) curve of anti-cyclic citrullinated peptide (anti-CCP) antibody to differentiate between patients with rheumatoid arthritis (RA) and healthy controls

Discussion

This study aimed to assess serum levels of Mg and UA in patients with RA and compare them with a group of healthy controls. We showed that serum levels of Mg were

significantly lower in patients with RA. Furthermore, serum Mg levels had an inverse correlation with serum CRP levels. However, we did not detect lower Mg levels in patients with severe disease compared to those with mild disease activity. In contrast to Mg, our results showed that the mean UA level was not statistically different between patients with RA and healthy controls. The ROC analysis revealed that anti-CCP could be a sensitive diagnostic test for RA, but the cut-off point was much higher than the laboratory's upper limit of normal.

There are few studies on Mg and its association with RA, and the results are inconsistent (16). Additionally, the relationship between disease activity, symptom severity, and Mg level remains unclear. In a study on 100 human subjects, patients who consumed less Mg than the estimated average requirement had a higher body mass index (BMI) and CRP level. In this placebo-controlled trial, Mg supplementation reduced CRP levels in those with a baseline CRP level greater than 3 mg/dl (17). This is congruent with our results, as we found an inverse relationship between Mg concentrations and CRP levels. Since CRP is an acute phase reactant that surges in inflammatory processes, this finding may reflect the anti-inflammatory properties of Mg. Similar to our findings, Chavan et al. detected significantly lower Mg levels in patients with RA compared to healthy individuals (15). This is also corroborated by another study, although the observed difference was not statistically significant (14). A lower Mg level in patients with RA suggests that Mg could have a therapeutic effect on treating arthritis. For instance, intra-articular injection of Mg relieves postoperative pain after knee arthroscopy (18). Furthermore, Kuang et al. suggested that Mg and probiotics might have a synergistic effect in preventing and/or treating osteoarthritis (OA) (19). In another study, Mg supplementation in patients with RA appeared to reduce fasting blood sugar (FBS) levels, and was thus proposed as an alternative method for preventing type 2 diabetes in patients with RA (20).

Our findings on UA are in line with those of previous studies. A meta-analysis including 19 studies found no significant alterations in serum levels of UA in patients with RA. However, allantoin, a product of UA oxidation, was significantly higher in patients with RA (21). Despite this lack of alteration, it remains unclear whether UA is protective against RA through its antioxidant activity. For instance, a study on the association between lipid peroxidation and plasma urate suggested that UA could act as a protective agent against lipid peroxidation during physical activity (22). On the other hand, UA has been associated with increased expression of CRP, fibrinogen, and complement C3 in a dose-dependent manner (23). Moreover, an animal study showed that mild hyperuricemia in rats led to increased blood pressure and endothelial dysfunction (24).

Anti-CCP antibody is a serological biomarker that can be used for early diagnosis to monitor disease activity and treatment response (25). Anti-CCP test, used along with RF, can be beneficial in primary care setting, as it increases the positive likelihood of RA and obviates the need for extra laboratory tests (26). Various assays are available to measure anti-CCP. In a study by Cho et al., four anti-CCP assays were compared in terms of their analytical and clinical performance. The AUC ranged from 0.888 to 0.914 (27). This is slightly better and more accurate than our model (AUC = 0.857), which can be attributed to our limited sample size and different care settings. According to a recent study, the proposed anti-CCP cut-off value to reach optimal sensitivity and specificity is 6.95 U/ml (28). We set this value at 32.5 U/ml. The fact that we did not recruit the patients early in their disease course (incident cases) and the retrospective design of our study may explain this discrepancy.

Limitations: We faced several limitations in the present study. First of all, we did not follow up with the patients longitudinally. Thus, we could not establish any causal relationships. The two groups in our study were not sex-matched; therefore, we made adjustments to our analysis. However, we could not adjust for other possible confounding variables such as BMI and physical activity, due to missing data. Furthermore, the level of other trace elements such as zinc and copper was not measured. The controversies mentioned previously highlight the need for high quality randomized controlled trials (RCTs) and molecular studies to further elucidate the relationship between RA, trace elements, and UA.

Conclusion

Our findings suggest that a low Mg level is expected in patients with RA; thus, the administration of Mg supplementation in this patient population may be beneficial. Unlike Mg, the UA level does not seem to change in patients with RA, but its antioxidant activity cannot be ruled out. Lastly, anti-CCP can be a reliable diagnostic test for RA with high sensitivity.

Conflict of Interest

The authors declare no conflict of interest in this study.

Acknowledgements

This study was a retrospective analysis of anonymized data, and was not subject to obtaining informed consent from the patients.

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