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Role of uric acid in predicting renal dysfunction in patients with rheumatoid arthritis

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ABSTRACT

Objective: Recent epidemiologic studies provide evidence for hyperuricemia as a potential independent risk factor for the development of kidney disease as well as in its progression. Recent evidence supports the hypothesis that uric acid (UA) may take on a direct pathogenic role in multiple diseases, including renal disease. Previous reports have indicated that patients with rheumatoid arthritis (RA) also have considerable incidence of renal disease. Therefore, in this study, we investigate the potential association of UA with renal dysfunction in patients with RA.

Methods: In this hospital-based cross-sectional study, 100 newly diagnosed cases of RA were included. Three millilitre of blood sample was collected from the patients, separated, and stored at −20°C until analysis. Serum UA (SUA) was estimated by the uricase-peroxidase method. Serum creatinine was measured by Jaffe's method. Pearson's correlation and Spearman's Rho were used for the correlation. Linear regression analysis was performed to predict the outcome variable in the patients. SPSS version 18 was used for the statistical analysis of the data.

Results: A total of 97 RA patients were recruited, out of which, 55 were males and 42 were females. Mean age of the patients was 48.64 ± 12.35 and body mass index (BMI) was 28.20 ± 3.41. SUA and creatinine level were 8.0 ± 1.38 mg/dl and 1.42 ± 0.81, respectively. The mean estimated glomerular filtration rate (eGFR) of the patients was 67.28 ± 28.05 ml/minutes/1.73 m2. Based on eGFR there were 23% with normal renal function, 31% had a mild renal impairment, 41% had moderate renal impairment, and 5% had severe renal impairment. Linear regression model showed age and UA was strongly associated with eGFR (β = −0.324, P = 0.004; β = −0.472, P < 0.001) and predicts the incidence of altered kidney function.

Conclusion: This study shows that age and UA is an independent predictor of renal dysfunction in patients with RA.

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that affects most of body tissues leading to joint destruction and other major morbidity and mortality. In particular, previous reports have indicated that patients with RA also have considerable incidence of renal disease [1,2]. Renal disease in patients with RA is clinically important because it not only restricts the management of primary disease, but also increases mortality. In one study, RA patients with renal disease had significantly increased mortality compared to those with normal renal function, with a hazard ratio (HR) of 2.77–4.45 [2].

Uric acid (UA) is the final breakdown product of purine, which is excreted mainly by kidney [3]. In recent years, it has been proposed that UA itself plays a causal role in the pathophysiology of chronic kidney disease (CKD) and possibly in acute kidney injury. Evidences from different studies have demonstrated a significant and independent

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association between serum UA (SUA) levels and the progression of CKD [4–6].

Renal dysfunction in patients with RA has been attributed to multiple factors, including the use of nephrotoxic medication, the presence of comorbidities such as hypertension and atherosclerosis and complications such as vasculitis or amyloidosis [7,8]. There has been recent epidemiologic and experimental evidence supporting the hypothesis that UA, regardless of crystal deposition, may play a direct pathogenic role in multiple diseases, including renal disease [9,10].

However, few research studies have yielded conflicting evidence regarding the causal linkage between SUA concentration and the incidence and progression of CKD [11]. Studies have identified high levels of UA as a significant predictor of the development of kidney disease [12]. One prospective study conducted among 21,457 seemingly healthy subjects found that the odds of new-onset kidney disease increased 1.74-fold with slightly elevated SUA (7.0–8.9 mg/dl) and 3.12-fold with elevated SUA (≥ 9.0 mg/dl) relative to normal SUA (< 7.0 mg/dl) [4]. Conversely, other reports have not supported the hypothesis that SUA contributes to CKD, including a cohort study of 5,808 elderly participants in which SUA showed a significant association with prevalent but not incident kidney disease [13].

A growing amount of evidence from prospective large-scale epidemiologic studies has proved the strong link between UA and renal dysfunction in the general population. UA was shown to be a powerful independent predictor of prevalent renal dysfunction but was also a significant predictor of progression of renal disease [14,15]. In a recent meta-analysis of the prospective studies addressing the role of hyperuricemia as a predictor of future renal disease among patients with normal glomerular filtration rate (GFR), conducted in the past 20 years, it was shown that most studies found that UA was an independent predictor [12].

However, the previous studies have focused mainly on the association of UA with kidney disease. Only few literatures are there to support the role of UA in predicting renal disorder in RA patients. Therefore, in this study, we investigate the potential association of UA with renal dysfunction in patients with RA and explore whether such an association is independent or mediated through other comorbidities.

Materials and Methods

Study design and setting

This was a hospital-based cross-sectional study conducted in the Department of Biochemistry in collaboration with Orthopedics Department.

Participants and sample

A total of 97 diagnosed cases of RA patients were enrolled in the study after taking their informed consent. Patients taking medicine that alters UA metabolism were excluded. Three millilitre of blood was collected via standard venipuncture technique. Serum was separated by centrifugation at 3,000 rpm for 10 minutes and samples were stored at −20°C until the biochemical analysis.

Analysis of sample

SUA was estimated by the uricase-peroxidase method. It is based on the principle that uricase converts UA into allantoin and hydrogen peroxide. Peroxidase releases nascent oxygen from hydrogen peroxide which oxidizes a phenolic chromogen to a red color compound. The red color represents the amount of the UA present in the serum and is measured at 510 nm. Serum creatinine was measured by Jaffe's method. It is based on the principle that picric acid in an alkaline medium reacts with creatinine to form quantitatively an orange colored pigment. The color was measured in auto analyzer at a wavelength of 520 nm.

Statistical analysis

Data are represented as mean±SD, frequency, and percentage as a descriptive statistics. To test the normality of the data, Kolmogorov–Smirnov's test was used. Pearson's correlation or Spearman's Rho was used for the correlation analysis. Linear regression model was used to find the association of independent variables; age, UA, disease duration, and BMI with estimated GFR.(eGFR) SPSS version 18 was used for the statistical analysis of the data. *P* value of <0.05 was set as statistical significance.

Results

A total of 97 patients were included in the study. It was carried out for the period of 1 year. Out of total patients, 55 were males and 42 were females (Table 1). Majority of the patients were in 40–60 years of age. Table 2 shows the clinical

Table 1. Basic characteristics of the patients.

Characteristics	Values*
Age (years)	48.64 ± 12.35
Gender	
Male (*n*)	55
Female (*n*)	42
Height (m)	1.57 ± 0.49
Weight (kg)	66.17 ± 5.11
BMI (kg/m²)	28.20 ± 3.41

*Expressed as mean±SD.

characteristics like RA duration, UA, creatinine, and eGFR of the participants.

Mean SUA was 7.53 ± 1.18 mg/dl (448.4 ± 70.22 µmol/l). Forty-eight participants were hyperuricemic as defined by UA levels of greater than 8.4 mg/dl for men and of greater than 6.7 mg/dl for women. eGFR was calculated by modified diet in renal disease formula: (ml/minutes/1.73 m^2) = 175 × $(Scr)^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female). Based on the eGFR, patients were categorized into five stages of CKD based on the Renal Association. eGFR ≥ 90 ml/minutes/1.73 m^2 under stage 1 (normal), eGFR between 60 and 89 ml/minutes/1.73 m^2 under stage 2 (mild), eGFR between 30 and 59 ml/minutes/1.73 m^2 under stage 3 (moderate), eGFR between 15 and 29 ml/minutes/1.73 m^2 under stage 4 (severe), and eGFR < 15 ml/minutes/1.73 m^2 under stage 5 (renal failure).

Table 3 depicts the comparison of different variables with the stages of CKD. We observed a statistically significant difference of age, UA, and creatinine in different stages of CKD. Also, we noticed that the advance age patients are more prone to severe CKD so as higher UA level. In correlation of the different variables with eGFR, we found age, BMI, UA, and creatinine were negatively correlated and statistically significant (Table 4).

Table 2. Clinical characteristics of the patients.

Variables	Values*
Disease duration (years)	4.91 ± 2.09
UA (mg/dl)	8.0 ± 1.38
Creatinine (mg/dl)	1.42 ± 0.81
eGFR (ml/minutes/1.73 m²)	67.28 ± 28.05

*Expressed as mean±SD.

The independence of the strong association between UA and GFR was evaluated using linear regression. A multiple linear regression analysis was performed between variables age, UA, disease duration, BMI, and dependent variable eGFR. Age and UA were the only strongest correlate of eGFR (β = −0.324, P = 0.004; β = −0.472, P < 0.001) whereas duration and BMI does not contribute significantly (Table 5).

Discussion

This study has shown that UA is an independent and strong predictor of GFR in patients with RA, even after adjustments for most of the potential confounding factors. Age also has shown to be a good predictor of GFR. GFR in the present study was not assessed by direct measurement and this is a potential limitation. Radioisotopes methods that use chromium ethylene diamine tetra-acetic acid are considered gold standard, but not generally

Table 3. Comparison of the variable with different stages of CKD.

CKD stages	Age (years)	BMI (kg/m²)	RA duration (years)	UA (mg/dl)	Creatinine (mg/dl)
1 (*n* = 24)	42.04 ± 10.66	27.46 ± 3.44	4.50 ± 1.74	4.50 ± 1.74	0.76 ± 0.02
2 (*n* = 32)	49.66 ± 10.7	27.44 ± 3.21	4.75 ± 1.85	4.75 ± 1.85	1.00 ± 0.04
3 (*n* = 41)	49.95 ± 11.88	29.34 ± 3.30	5.02 ± 2.29	5.02 ± 2.29	1.93 ± 0.09
***P* value* between groups**	0.015	0.021	0.588	<0.001	<0.001

*One-way ANOVA; P < 0.05 considered as statistically significant between the different groups.

Table 4. Correlation analysis of the variables with eGFR.

Variables	*R* value	*P* value*
Age	−0.313	0.001
BMI	−0.214	0.030
RA duration	−0.174	0.079
UA	−0.537	<0.001
Creatinine	−0.919	<0.001

*Pearson's correlation; P < 0.05 is considered statistically significant.

Table 5. Multiple linear regression model for the independent association of variables with eGFR.

Model 1 variables	Coefficient β	Standard error	*P* value
Age	−0.324	0.248	0.004*
UA	−0.472	1.79	0.000*
RA duration	0.144	1.553	0.215
BMI	−0.472	1.79	0.267

*P < 0.05 is considered statistically significant.

used in the hospital setup due to financial, technical, and time constraints. eGFR from predictive equations GFR (ml/minutes/1.73 m^2) = 175 × $(Scr)^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) are generally accurate [16]. Specifically with respect to RA patients, predictive equations have shown a very good correlation with direct GFR measurements, despite the initial concerns that muscle wasting, a common feature of RA, could lead to overestimation of GFR.

The association between the UA levels with renal dysfunction in the general population is well known, but was attributed solely to the fact that UA is excreted mainly through the kidneys and a decline of GFR increases its level [5,6]. Generally speaking, the lowered GFR can be attributed to the increased levels of UA in plasma; hence, UA could serve as a biomarker for early detection of glomerular filtration of patients with RA.

Clinical studies also suggest an association of UA with renal dysfunction. A large-scale study of 6,400 people from the general population with normal renal function revealed that UA was a powerful and independent predictor for developing renal impairment in 2 years [17]. In some prospective study, UA was the second strongest predictor of renal impairment after hypertension [18]. The above study provides UA as an independent predictor of renal dysfunction in the general population and in this study, we prove the association in RA patients as well.

Bellomo et al. showed higher SUA levels were associated with a greater likelihood of eGFR decrease in both women and men (HR, 1.13 [95% CI, 1.04–1.39] per each 1-mg/dl increase in UA level) [19]. The study done in Japanese population by Yamada et al. has shown that SUA were associated with increased risk of CKD in both sexes. The odds ratio with 95% confidence interval for 1 increment of SUA were 1.42 and 1.28 to 1.58 in men and 1.32 and 1.12 to 1.56 in women, respectively [20]. Satirapoj et al. evaluated the independent association between SUA levels with increased prevalence of CKD in the Southeast Asian population [21].

The association of UA levels with renal dysfunction in the general population is well known but was attributed solely to the fact that UA is excreted mainly through the kidneys and a decline in GFR increases its level. However, the fact that UA was the strongest predictor and was independent of all the traditional risk factors for renal disease suggests that, in this population, the UA may indeed play a direct pathogenic role in the development of renal dysfunction.

Our study suggests that such an association also occurs in patients with RA. Even if this simply reflects a decline in glomerular function, serial measurement of UA could serve as a biomarker for the early detection of subtle changes in the glomerular function of patients with RA and helps to identify patients at risk of developing renal impairment. Referable to the cross-sectional nature of our study, this interpretation can be made only with great caution and prospective studies are needed before any definite conclusions are drawn.

Conclusion

To conclude, this work shows that UA is an independent predictor of renal dysfunction in patients with RA. Its possible direct pathogenic role and potential clinical use as an early biomarker of future renal dysfunction in this group of patients need to be investigated in prospective studies designed specifically for the purpose.

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