Serum Uric Acid - a Potential Marker of Inflammation in Rheumatoid Arthritis

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ABSTRACT

Introduction: Serum uric acid (SUA) has been associated with inflammation in metabolic disorders as well as infections. Its role in autoimmune diseases like Rheumatoid Arthritis (RA) is not well established. Our study aims to evaluate the association of serum uric acid and inflammation in patients of RA. Aims and Objectives: To estimate the prevalence of hyperuricemia in RA patients, and correlation of serum uric acid levels with disease activity scores and already established inflammatory markers Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP).

Material and methods: 150 RA patients as per sample size calculation fulfilling the inclusion and exclusion criteria were taken into the study and evaluated with respect to disease activity, current treatment, inflammatory markers ESR and CRP, and their SUA levels measured. Data was recorded in MS Excel sheet and statistical analysis done by JASP software.

Results: Patients with hyperuricaemia had higher disease activity scores and higher levels of CRP. SUA levels correlated positively and significantly with CRP levels and clinical disease activity index (CDAI) and positively but not significantly with ESR. SUA levels didn't differ between genders, serological status of RA, or between different treatment groups.

Conclusion: SUA by itself has the potential to be an independent marker of inflammation in patients of RA

Keywords: CRP, CDAI, Hyperuricaemia, Rheumatoid Arthritis, Serum Uric Acid

MeSH Terms: Hyperuricaemia, Inflammation, C-Reactive Protein, Rheumatoid Arthritis

INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic, systemic, autoimmune inflammatory polyarthritis of the small joints along with a variety of extraarticular manifestations. Measurement of disease activity is a cornerstone in treatment and is measured by various scores which incorporate clinical parameters and/or levels of markers of inflammation. Commonly used scores include Disease Activity Score 28 (DAS28) and Clinical Disease Activity Index (CDAI), and commonly used markers of inflammation include Erythrocyte Sedimentation Rate (ESR) in 1st hour, and C-Reactive Protein (CRP).

Uric Acid (UA) has been found to be a mediator of systemic inflammation by activation of the NF-kB pathway and increased levels in serum (SUA) correlates with various inflammatory markers including CRP[1] in cardiovascular and metabolic diseases. SUA is also thought to be a contributor to inflammation induced by P.falciparum[2]. Its role in RA is still controversial[3,4], though it has been proposed to be a diagnostic marker of Interstitial Lung Disease associated with RA (RA-ILD)[5].

This study intends to evaluate the prevalence of hyperuricaemia in patients of RA in the Indian population and evaluate its role as a marker of inflammation.

MATERIAL AND METHODS

A cross-sectional observation study of one hundred and fifty adult RA patients of either gender, the minimum sample size of 101 cases being calculated by the formula for prevalence using power of study of 80% and 95% confidence interval, based on previous study on prevalence of hyperuricaemia in RA patients[6] was undertaken. Exclusion criteria included patients having Diabetes Mellitus, hypertension, chronic kidney disease (CKD), hypothyroidism, chronic alcoholics, patients on diuretics like thiazides and loop diuretics, and those taking steroids since last 1 month. Patients were assessed as to disease activity by number of swollen and tender joint counts (SJC and TJC), ESR, CRP, and DAS28 and CDAI were calculated. Rheumatoid Factor (RF) and Anti Citrullinated Cyclic Peptides (Anti CCP) status, blood counts, renal and hepatic function tests, and current and previous treatments, were noted. Data was entered in MS Excel worksheet and statistical analysis carried out by JASP software. Continuous variables were represented as Mean ± Standard Deviation (SD) or Medians with Inter-quartile range (IQR). Categorical variables were represented as number and percentage (%). Correlation coefficient was used to find out the strength of correlation between two variables. P value less than 0.05 was taken as level of significance. SUA levels ≥7 mg/dL was defined as hyperuricaemia. The patients were divided into normouricaemic and hyperuricaemic groups and compared with each other across various parameters. Correlation of SUA with inflammatory markers and with disease activity scores was also evaluated in the whole cohort.

RESULTS

9 out of 150 cases (6%) had SUA ≥7 mg/dL and hence

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Parameter	Hyperuricaemic	Normouricaemic	P value
Age (in years)	48 (IQR: 42-52)	46 (IQR: 40-55)	0.971
Male: Female	2:7	14:127	0.246
CRP (mg/dL)	5.52 ± 3.68 4.12 (IQR: 3.2-8.3)	2.8 ± 3.64 1.1 (IQR: 0.6-4.3)	0.008
ESR 1st hr (mm)	56.7 ± 19	42.9 ± 19.6	0.054
Serum UA (mg/dl)	7.21 ± 0.22	4.61 ± 1.14	< 0.001
TJC	7 (IQR: 2-12)	2 (IQR: 0-8)	0.163
SJC	4 (IQR: 2-4)	0 (0-2)	0.014
CDAI	23 (IQR: 15-24)	9 (IQR: 3-16)	0.08
DAS28-ESR	5.8 (IQR: 5-6)	3.8 (IQR: 3-5.2)	0.089
DAS28-CRP	5.15 (IQR:4.68-5.67)	3.29 (IQR: 2.29-4.69)	0.028

Table-1: Comparison between the hyperuricaemic and normouricaemic groups of patients of RA.

Sl No	Group	Sub group	SUA levels (mg/dL)	P value
	Gender	Male: n= 16 Female: n=134	5.08 ± 1.5 4.73 ± 1.24	0.29
	RF	RF +ve: n= 142 RF -ve: n= 8	4.79 ± 1.24 4.22 ± 1.63	0.211
	Anti CCP	Anti CCP +ve: n=65 Anti CCP -ve: n= 84	4.78 ± 1.37 4.77 ± 1.18	0.788
	Treatment (current)	Methotrexate: n= 119 Leflunomide: n= 10 Both: n= 12 Others: n= 9	4.76 ± 1.23 4.08 ± 1.30 5.28 ± 1.67 4.83 ± 0.93	0.176

Table-2: Comparison of SUA levels across different subgroups of patients of RA in our study.

Sl No	Parameter	R value	P value
1	ESR	0.111	0.176
2	CRP	0.203	0.013
3	CDAI	0.177	0.03
4	DAS28-ESR	0.157	0.055
5	DAS28-CRP	0.221	0.007

Table-3: Correlation of SUA with inflammatory markers and disease activity scores.

defined as hyperuricaemic. 134 of the 150 cases (89.3%) were females. The cases were grouped into normouricaemic and hyperuricaemiac and various parameters were compared across the groups. The results are tabulated in Table 1.

The groups did not differ significantly in age or gender. The hyperuricaemic group had significantly higher levels of CRP, and SJC and hence DAS28-CRP, but not ESR, TJC, or DAS28-ESR. CDAI did not differ significantly between the two groups.

SUA was then compared between different subgroups of patients of RA in our study based on gender, presence or absence of RF and anti-CCP, and current treatment. The findings are summarised in Table 2. The correlation of SUA with other markers of inflammation and disease activity scores are summarised in Table 3.

DISCUSSION

Our study focussed on the questions of prevalence of hyperuricemia in RA patients, and whether levels of SUA correlate with inflammatory markers such as ESR, CRP, and also with disease activity scores.

Our study defined SUA level of 7 mg/dL as threshold for defining hyperuricaemia. Different studies define different levels of SUA as hyperuricaemia, like Meriem et al [6] in Morocco as 7 mg/dL in males and 6 mg/dL in females, Nada et al[4] in Egypt as 7.5 mg/dL and 6.2 mg/dL in males and females respectively, and Chiou et al[7] in USA as 6.8 mg/dL in either gender. Using the thresholds of studies by Meriem, Nada, and Chiou, the prevalence in our cohort would be 16.6%, 11.3%, and 6.6% respectively. However, our laboratory defines hyperuricaemia as 7 mg/dL, and the same has been used in our study.

Both the normouricemic group and the hyperuricemic group were similar in age with most of the cases being between the ages of 40 and 60 years, with 60.3% in the former and 77.77% in the later. Both the groups though similar in gender distribution had overwhelmingly female preponderance.

In conformity with the treatment algorithm in our institution, most of our patients were on Methotrexate (79.33%) with few on Leflunomide (6.67%) or combined methotrexate and leflunomide (8%). However, there were no significant difference in SUA in between the three groups. This assumes importance in view of the fact that Lefunomide is supposed to be uricosuric and decreases SUA independent of its disease modifying activity[3].

SUA had a positive and statistically significant correlation with CDAI, though CDAI did not vary significantly between the hyperuricaemic and normouricaemic groups. However, closer examination reveals that the hyperuricaemic group had a median CDAI of 23 and the normouricaemic group a median CDAI of 9. A CDAI of 23 places the patient in high

disease activity group and a CDAI of 9 places the patient in the low disease activity group. Thus, it can be inferred that hyperuricaemic patients have clinically significant higher disease activity.

SUA correlated significantly with CRP and by extension DAS28-CRP, while with ESR and DAS28-ESR, it showed a positive but non-significant correlation. This is in conformity with CRP being a better marker of inflammation compared to ESR[8,9].

SUA did not differ between those positive for RF and those negative. The same held true for Anti CCP. Thus, serological status of RA patients did not influence SUA levels.

The strengths of our study were the incorporation of disease activity scores as well as RF and Anti-CCP status of the patients for purposes of comparison with SUA. The limitation is the small number of hyperuricaemic patients in our cohort. However, considering that RA is well known to have a female preponderance, and SUA levels are lower in females and in those less than 50 years, the lower prevalence in our hyperuricaemia in our cohort is expected.

We conclude that hyperuricaemic RA patients have higher levels of inflammatory marker CRP and that SUA levels in patients of RA correlate positively and significantly with both CDAI and CRP. The presence of higher SUA levels is regardless of the treatment regimen or seropositivity status of patients. Thus, SUA by itself has the potential to be an independent marker of inflammation in patients of RA. More studies to evaluate whether raised SUA is the cause or the effect of inflammation are warranted.

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