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Serum uric acid as a risk factor for hypertension in Rheumatoid Arthritis patients

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ABSTRACT:
Background: Rheumatoid arthritis (RA) is a chronic autoimmune disease associated with chronic inflammatory arthritis and extraarticular manifestations. Hypertension is a common cardiac manifestation which is often associated with RA. Serum uric acid has been associated with cardiovascular disorders. In this study we aim to determine whether serum uric acid is associated with hypertension in patients of RA.
Methods: It is a case control study from a tertiary care center in South India which included 78 patients diagnosed with Rheumatoid Arthritis satisfying the inclusion and exclusion criteria. The patients were divided into 2 groups with equal number of patients. Group 1 had patients of RA with hypertension and Group 2 had patients of RA without hypertension. Patients of both groups were evaluated for serum uric acid levels. Statistical analysis was performed using IBM SPSS version 20.0 software.
Results: In our study, number of hyperuricemic Rheumatoid Arthritis patients with hypertension were 5 out of total 39 and in the normotensive group 4 had hyperuricemia out of 39 patients. Comparison of mean uric acid levels of both the groups showed no statistical significance with a p value of 0.189. The mean Uric acid levels in the Hypertensive group was 4.91 mg/dl and mean uric acid levels in the normotensive group was 4.57 mg/dl.
Conclusions: Serum uric acid levels are not associated with hypertension in Rheumatoid Arthritis patients in Indian Population.

I. INTRODUCTION

"Rheumatoid arthritis (RA) is an autoimmune disease with chronic systemic symptoms characterized by inflammatory arthritis and extra-articular involvement"(1). It is a persistent inflammatory disease of unknown etiology mainly involving synovial joints. RA usually begins in small peripheral joints, is often bilaterally symmetrical, and evolves to engage proximal joints in advanced stages(1).About 0.24 percent of people in the world are known to have RA(2). The prevalence of RA in Indian population is described as 0.75%(3).

RA is linked with some extraarticular cardiovascular disorders like myocardial infarction, hypertension and heart failure(4). In patients of RA some circulating inflammatory markers are implicated including "Interleukin -6 and TNF-α, Acute phase reactants, immune complexes and altered lipid particles" that can increase endothelial damage and lead to unstabilized atheromatous plaques(5). Among the patients of Rheumatoid arthritis, hypertension is one of the frequently observed extraarticular manifestation but it can occur spontaneously as well as due to long term administration of drugs like glucocorticoids used in the treatment of RA. Hypertension also sometimes referred as systemic arterial Hypertension and it is described by constantly increased blood pressure in systemic arteries(18). Currently hypertension is defined as "systolic blood pressure(SBP) of 130mmHg or more and diastolic blood pressure(DBP) of more than 80mmHg"(6).

Most cases of Hypertension are idiopathic but some studies have shown that increased sodium consumption is a risk factor for development of hypertension(7).The disease burden of hypertension is massive, almost 3.5 billion of adult population globally have an average systolic Blood Pressure (110-115 mmHg) and about one fourth of those adult population have increased systolic Blood Pressure (≥140 mmHg), therefore almost one fourth of all adults have hypertension(8). In a normal individual, blood pressure (BP) is regulated by multiple cardiac parameters including: blood volume, cardiac output and balance of arterial tone, which is influenced by intravascular volume and neurohumoral system which includes "renin-angiotensin-aldosterone system (RAAS); natriuretic peptides and the endothelium, the sympathetic nervous system (SNS) and the immune system". Any disruption is the BP regulating mechanisms can coherently or discursively lead to

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variation in average BP, which ultimately results in end organ damage and other cardiovascular disorders(9).Multiple previous researches based on patients of RA have shown that RA is associated with subclinical atherosclerosis and it is a significant predictor of Cardiac disease with a relative risk of1.49 - 4.3(10).Patients with rheumatoid arthritis have a documented prevalence of hypertension that ranges from 3.8% to 73%(11). Serum uric acid (SUA) levels are often seen to be high in patients of hypertension. As it is seen in few studies that blood pressure values may improve by Uric acid lowering drugs which supports a possible link between SUA and CVD(cardio vascular disease)(12). Hyperuricemia occurs if the uric acid levels are above the normal range, on an average if the uric acid levels are >6.8mg/dl it is considered as hyperuricemia. Thethreshold level for male and female are different to be labelled as hyperuricemia, in males it is >7.0 mg/dl and in females it is >5.7mg/dl(13). Serum uric acid has both beneficial functions (as an anti-oxidant) and damaging effect (triggers vascular smooth muscle cell multiplication and lead to endothelial dysfunction)(14).

In some experimental animal based studies, uric acid has been linked to hypertension, it was shown that the potential mechanism of uric acid induced hypertension occurs due to generation of oxidative stress, reduction in Nitric oxide (NO) and increased plasma renin activity and increased angiotensin activity which leads to vasoconstriction of renal arteries and ischemia in kidney which triggers immune cell activation in kidney leading to salt sensitive hypertension(15). In these mice afferent arteriolopathy like renal changes and endothelial cell damage were observed, which resembles the changes in a human patient of hypertension.It has been seen that the uric acid lowering drugs like Allopurinol have shown beneficial role in animal models of hypertension, as they reduces the BP and prevents vascular damage(16). It has been seen in a previous cross sectional researches that hyperuricemia is a strong indicator of CVD in cases matched for other cardiac risk factors, patients with the highest SUA showed 6.5 times risk of developing CVD(17). In a cross sectional research, the relation of hyperuricemia and RA and hypertension was shown,

The association of uric acid in hypertensive patients of Rheumatoid arthritis has been demonstrated in past study based on British Caucasian patients of RA with hypertension, in that study it was found that serum uric acid levels were higher in the patients of RA who had hypertension as compared to normotensive RA patients(18). It also demonstrated that with every 1mg/dl increase the uric acid levels, the odds to develop hypertension increased 1.6 times

But there is only limited data available in Indian patients, thus forms the basis of this study.

II. METHODS

I. Selection and description of participants

This is a case control study with the study setting being the General Medicine Department ofAmrita Institute of Medical Sciences, conducted during the year 2021 until 2022. Thisresearchwasapprovedbybothdissertationreviewcommitteeandethicalcommittee. Subjects attending the outpatient clinic and inpatient in Departments of General Medicine, Rheumatology departments at Amrita Hospital were enrolled in the study. The selected patients were studied in detail, history was taken and physical examination was done. Blood samples were collected obtained from the patient to evaluate the Serum Uric Acid Levels.

- The inclusion criteria of the study were:

Patients with Rheumatoid Arthritis satisfying 2010 ACR Criteria for Rheumatoid Arthritis(19)

- The exclusion criteria of the study were:
  - Patients having other risk factors for hypertension
  - Renal dysfunction
  - Patients on high dose prednisolone (more than 15 mg /day)
  - Pregnancy

- Sample size

Based on the mean and SD of Serum uric acid value in the hypertensive group (5.44 ± 1.6mg/dl) and in the normotensive group (4.56 ± 1.1) in the patients with rheumatoid arthritis observed in the earlier publication ("Serum Uric Acid is independently associated with hypertension in patients with Rheumatoid arthritis, Journal of Human Hypertension,2008") and with 80% power and 95% confidence, the minimum sample size comes to 38 per group and totalling to be 76 rheumatoid arthritis patients.

II. Technical information

- Primary objective of the study: To compare Serum uric acid value in hypertensive versus normotensive Rheumatoid Arthritis patients.

- Methods of the study :Rheumatoid Arthritis patients satisfying ACR 2010 Criteria were matched for Age, Sex, Type 2 Diabetes

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Mellitus and Dyslipidemia. Patients were then divided into 2 groups

- Rheumatoid Arthritis with systemic hypertension
- Normotensive Rheumatoid Arthritis
- Serum Uric acid levels were evaluated in patients of both the groups using Enzymatic Calorimetry principle via Cobas C702 instrument after obtaining a written informed consent from the patients. Along with that other specifications and details were collected like Age, Gender, Blood Pressure, history of uric acid lowering drugs, duration of the disease, family history of the disease and history of oral steroid intake.

III. Statistical analysis

Statistical analysis was performed using IBM SPSS version 20.0 software. Categorical variables were expressed using frequency and percentage. Continuous variables were presented using mean and standard deviation. Independent sample t test was used to study the statistical significance of the comparison of all continuous variables between two groups. Chi-square test was used to study the statistical significance of the comparison of all categorical variables between two groups/Chi-square test with continuity correction in the case where expected cell count was less than 5. A p value of <0.05 was considered to be statistically significant.

III. RESULTS:

Among the total 78 patients, the number of female normotensive patients were 33 and normotensive males were 6 out of 39, whereas female hypertensive patients were 26 and male hypertensive patients were 13 ; With a p value of 0.065 showing no significant difference of gender between the 2 groups. The mean age of normotensive patients was 62.85±7.84 and mean age of hypertensive patients were 63.21 ±9.51 and the p value of 0.856, which shows that there is no significant difference of age between the 2 groups. The mean duration of RA in normotensive patients is 6.46 ±5.871 years and mean duration of RA in hypertensive patients is 7.51± 6.641. The p value is 0.461, showing no significant difference between the 2 groups.

Out of 39 normotensive patients, 35 patients had uric acid within normal range and only 4 had elevated uric acid, whereas in hypertensive group out of 39 patients 34 had normal uric acid and only 5 had hyperuricemia with a p value of 1.00 which determines that there is no significance difference between the uric acid values of the 2 groups.

Uric acid levels in hypertensive patients was 4.91 ±1.04 and in normotensive patients was 4.57± 1.16 with a p value of 0.189 which shows that there is no significant difference between the 2 groups.

IV. DISCUSSION

Rheumatoid Arthritis is a chronic inflammatory autoimmune disease which occur more commonly in women with a peak age of incidence in 6^{th}-7^{th} decade. During this age, patient is at risk to develop other comorbidities like hypertension. Hypertension in such patients can occur idiopathically or due to lifestyle changes like lack of physical exercise and cigarette smoking and alcohol consumption. Other than these factors, Hypertension can also occur as an extraarticular manifestation of Rheumatoid Arthritis. Other risk factors or the markers for cardiac abnormalities in RA patients include positive RF(rheumatoid factor) and anti CCP(cyclic citrullinated peptide), elevated inflammatory markers like ESR and CRP and severe RA(20). The occurrence of extraarticular manifestation in patients of Rheumatoid Arthritis and hypertension together can lead to reduction in quality of life of patient. Along with that the financial burden can also increase for taking medications for multiple disorders. So it is extremely important to identify hypertension and other Rheumatoid arthritis related complication and to start early treatment.

In this case control study conducted in 78 patients, our objective was to to compare Serum uric acid value in hypertensive versus normotensive Rheumatoid Arthritis patients.

A similar study published in 2008 by “VF Panoulas, KMJ Douglas, HJ Milionis, P Nightingale, MD Kita1, R Klocke, GS Metsios, A Stavropoulos-Kalinoglou, MS Elisaf and GD Kitas”; which was based on patients of RA in UK described the association of serum uric acid withhypertension in patients of RA . In that study, a total of 400 of British Caucasian RA patients fulfilling the ACR criteria were enrolled(18). Among the total patients, 282 were hypertensive and rest were non hypertensive. It was seen that RA patients with hypertension had significantly higher level of mean uric acid (5.44± 1.6 mg /dl) whereas RA patients without hypertension had a mean uric acid (4.56±1.1 mg/dl) with an odds ratio of 1.6 showing a positive association of serum uric acid in hypertension and rheumatoid arthritis. Whereas in the study performed at our centre based on Indian patients of RA fulfilling the ACR criteria a total of

78 patients were enrolled, out of which 39 were with hypertension and 39 were without hypertension. Serum uric acid in the hypertensive group was 4.91±1.04mg/dl and in the normotensive group was 4.57±1.16 mg/dl with a p value of 0.189. The mean serum uric acid levels in the hypertensive patients which was observed in this study are relatively lower than the levels observed during a study based on effect of allopurinol and low fructose diet on reducing the blood pressure, in that study the mean serum uric acid levels were 6.2mg/dl(21). The possible reason for such difference between the findings of the 2 studies could be the low number of hyperuricemia patients observed in this study, which may have lowered the mean value of Serum Uric Acid.

The mean age of patients in this study was 62.85 years in normotensive group and 63.21 years in hypertensive group which was similar to study by PanoulasVF et al who observed the mean age of patients to be 62 ± 12. In this study, the total number of hyperuricaemia patients were 9 out 78 whereas in the previous study by byPanoulas VF et al they found 37 patients of hyperuricemia out of total 400 patients. The sample size of the study conducted in UK by byPanoulas VF et al, had a large sample size of 400 patients,possibly because the study period was of 2 years, whereas in this study, study period is 1 year and almost half of the one conducted earlier.

The study conducted at our centre was first of its kind in Indian patients of RA but unlike the study performed on RA patients in UK it does not shows a direct correlation between serum uric acid in hypertension in Rheumatoid arthritis patients.These results can possibly be explained by the difference in the lifestyle of Caucasian population and South Indian population. There is a possibility of the difference in the genetical composition between the two populations, which is a matter of further detailed genetical studies which will add on to the validation of our theory.Serum uric acid has been shown to influence the hypertension as shown in past researches but in this study it was not found to be very common in the patients of hypertension, which suggest further studies to find more predictors and markers of hypertension in RA and other disorders.

As discussed earlier, hypertension can occur idiopathically as well and there could be other causative agents as well but it should be screened every time a patient of Rheumatoid Arthritis visits the OPD because often patient is unaware of his hypertension status, and in this case it can affect the treatment plan. As some drugs like corticosteroids are often used in the management of Rheumatoid Arthritis at a low dose but for a long period of time, such cases are more prone to develop adverse effects of corticosteroids.

Although in this study, it is seen that serum uric acid levels are not a direct indicator of hypertension in patients of Rheumatoid Arthritis, other makers of hypertension in RA patients should be explored.

Strength of the study

- This study contradicts with the existing theory of serum uric acid levels can independently influence the hypertension risk in a patient of Rheumatoid Arthritis.
- This study specifically focuses on South Indian Population, thus forming a base for the further analysis.

Limitations of the study

- It is a single centred study; in future we need multiple multicentric studies with large sample size involving patients of different geographical area.

Conclusion of the study:

- In our study total of 78 patients were taken out of which 39 were of Rheumatoid Arthritis with hypertension and 39 were of Rheumatoid arthritis with normal blood pressure.
  In our study, number of hyperuricemic Rheumatoid Arthritis patients with hypertension were 5 out of total 39 and in the normotensive group were 4 out of 39.
- There was no significant statistical difference between the number of hyperuricemia patients in both groups.
- The mean uric acid levels in hypertensive group was 4.91 mg/dl with a SD of 1.047 and in normotensive group it was 4.57 mg/dl with SD of 1.169.
- The difference in mean uric acid values in both groups was also not statistically significant.
- Uric acid levels are not associated with hypertension in Rheumatoid arthritis patients in Indian Population.

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